ADDIS ABABA UNIVERSITY

COLLEGE OF HEALTH SCIENCE

SCHOOL OF PUBLIC HEALTH DEPARTMENT OF PREVENTIVE MEDICINE

SURVIVAL AND MORBIDITY OF BREASTFEEDING VERSUS FORMULA FEEDING INFANTS AND YOUNG CHILDREN OF HIV-INFECTED WOMEN WHO ARE ON PMTCT FOLLOW UP ON SELECTED HOSPITALS IN ADDIS ABABA, ETHIOPIA, 2013. A RETROSPECTIVE COHORT STUDY

By

MEKONNEN ASSEFA (BSc)

Advisor:

ALEMAYEHU WORKU (PhD)

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Approved by the examining board **Signature**

Chairman, Department Graduate Committee

_____ _____

Advisors:

Dr. Alemayehu Worku _____

Examiners:

Dr. Solomon Shiferaw _____

Dr. Nugussie Deyassa _____

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LIST OF ACRONYMS AND ABREVATIONS

AACAHB	Addis Ababa City Administration Health Bureau
AAU	Addis Ababa University
ADIS	Acquired Immune Deficiency Syndrome
ART	Anti Retro viral treatment
ARV	Antiretroviral
BHITS	Breastfeeding and HIV International Transmission Study
CD4	Subgroup of T-lymphocytes carrying CD4 antigens
CPT	Cotrimoxazole Prevented Treatment
C/S	Cesarean Section
DNA	Deoxyribonucleic acid
EDHS	Ethiopia Demographic and Health Surveys
EBF	Exclusive Breast Feeding
FMOH	Federal Ministry of Health
HAART	Highly Active Anti-Retroviral therapy
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
ICAP	International Center for AIDS Care and Treatment Programs
IRR	Incident rate ratio
NVP	Nevirapine
PCR	Polymerase Chain Reaction
PLWHA	Peoples Living with HIV /AIDS
PMTCT	Prevention of Mother to Child Transmission (of HIV infection)
SPSS	Statistical Package for the Social science
SVD	Spontaneous Vaginal Delivery

RNA	Ribonucleic acid
UNAIDS	United Nations Program on HIV/AIDS
UNICEF	United Nations Children's Fund
WHO	World Health Organization
ZDV	Zidovudine

ABSTRACT

BACKGROUND: Nearly 90% of the almost half a million children who yearly become infected with HIV through their mothers live in sub-Saharan Africa. Infant feeding in the context of HIV is complex because of the major influence that feeding practices and nutrition have on child survival. HIV-infected mothers face a dilemma regarding how to feed their newborn infants due to the competing risk of HIV transmission associated with breast-feeding and the risk of increased morbidity and mortality associated with formula feeding.

OBJECTIVE: To compare the survival and health benefits of breast feeding and formula feeding infants and young children of HIV infected women followed the PMTCT programs**.**

Method: A retrospective cohort study design was employed to compare the HIV free survival of exposed infants and young children who were on breast fed and formula fed. Data was extracted from PMTCT registration book and exposed infants follow up card. Data were entered in Epi info (version 3.5.3 software) and exported into SPSS version 16 and STATA version11 statistical software for analysis. Infants and young children morbidity and HIV infection (i.e., the complement of HIV-free survival) were compared by using Kaplan- Meier time-to-event method and long rank test was used to compare HIV free survival between the two groups. Cox regression analysis was used to assess the determinant factors.

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 PMTCT intervention had five fold risk to transmit HIV infection to their infants (Adjusted HR=4.8, 95%CI; 1.1-22.5). There was no statistical significant different risk of developing any types of morbidity between the two groups (log rank statistics =0.92, df=1, p=0.34). There were totally seven deaths of infants in both cohorts.

Conclusion and recommendations: the 18 month cumulative probability of HIV free survival was significantly lower in the breast feeding infants and young children as compared to formula fed infants and young children. Using formula feeding or Breastfeeding and receiving ARVs prophylaxis should be the one that will most likely give infants the greatest chance of HIV-free survival.

1. INTRODUCTION

1.1. BACKGROUND

At the end of 2010, an estimated 34 million people [31.6 million–35.2 million] were living with HIV worldwide and there were 2.7 million [2.4 million–2.9 million] new HIV infections in 2010 ,including an estimated 390 000 [340 000–450 000] among children.(1). Globally, there were 3.4 million children living with HIV in 2011, 330,000 new infections among children and 230,000 AIDS deaths(2). Worldwide, 2.5 million children younger than 15 years were living with HIV in 2009, and more than 90% had been infected via mother to child transmission (MTCT) of HIV during pregnancy, delivery and breastfeeding (3). Pediatric HIV infection remains a substantial problem worldwide, with close to 400,000 new infections occurring yearly primarily as a result of maternal to child transmission(4).

Sub-Saharan Africa remains the region most heavily affected by HIV. In 2010, about 68% of all people living with HIV resided in sub-Saharan Africa , and also this region accounted for 70% of new HIV infections in 2010(1). In 2008, sub-Saharan Africa accounted for 67% of HIV infections worldwide, 68% of new HIV infections among adults and 91% of new HIV infections among children. The region also accounted for 72% of the world's AIDS-related deaths and an estimated 390 000 [210 000–570 000] children were infected in sub-Saharan Africa(5). Nearly 90% of the almost half a million children who yearly become infected with HIV through their mothers live in sub-Saharan Africa. The region has the highest indicators of food insecurity, highest prevalence of adult and pediatric HIV infection, the highest incidence of AIDS and AIDS related morbidity and death, and the highest proportion of HIV and AIDS affected households(6). With an estimated 1.1 million people living with HIV, Ethiopia has one of the largest populations of HIV infected people in the world. However, HIV prevalence among the adult population is lower than many sub- Saharan African countries(7).Approximately 1.3 million child deaths per year (13% of deaths of children aged less than 5 years) could be prevented if universal coverage of exclusive breastfeeding were increased to 90% among infants aged less than 6 months(8). In Ethiopia, the first PMTCT guidelines were developed in 2001, incorporating early recommendations by the WHO on HIV counseling and testing, ARV prophylaxis regimen, infant feeding counseling, infant HIV diagnosis algorithm, partner testing and referring HIV positive pregnant women for treatment, care and support(9)

1.2. STATEMENT OF THE PROBLEM

Infant feeding in the context of HIV is complex because of the major influence that feeding practices and nutrition have on child survival. Depending on the availability of interventions to reduce HIV transmission during pregnancy and delivery, HIV transmission through breastfeeding is responsible for between 30-60% of all HIV infections in children. However, in many resource-limited settings, infants who do not breastfeed are up to six times more likely to die from malnutrition, pneumonia and diarrheal illnesses. The dilemma has been to balance the risk of infants being exposed to HIV through breastfeeding with the risk of death from causes other than HIV if infants are not breastfed(10). HIV-infected mothers face a dilemma regarding how to feed their newborn infants due to the competing risk of HIV transmission associated with breast-feeding and the risk of increased morbidity and mortality associated with formula feeding (11). Exclusive breastfeeding carries a lower risk of HIV transmission over the first 6 months of life but is infrequently practiced by mothers or ineffectively supported by health systems. Replacement feeding avoids all postnatal HIV transmission but carries the risk of death when given in household circumstances that are not ideal(12). Although not commonly measured in programmes, child survival without HIV infection, rather than avoidance of HIV infection alone, has emerged as the most important measure of PMTCT effectiveness (12).

Promotion of exclusive breastfeeding (EBF) has been a cornerstone of public health measures to promote child survival for several decades. Despite the well-established benefits of EBF in the absence of HIV, initial findings from Durban, South Africa, that the risk of post-natal HIV transmission was lower with EBF than with non-EBF were met with some skepticism (13). National and local recommendations for infant feeding by HIV-infected mothers in resource-poor countries have been confounded by the scarcity of accurate estimates of the risk of HIV acquisition through different infant feeding practices and the associated survival risks and benefits(14). Postnatal transmission was prevented by advising against breastfeeding; the alternative was replacement feeding with formula milks as these could be safely prepared, were affordable, and were culturally acceptable (15). The risks associated with formula feeding children living in resource-limited settings with high background rates of infant morbidity and mortality, outweigh the benefits of reduced HIV transmission(16). Breastfeeding has several advantages including improved nutrition, growth and development, anti-infective properties and improved child survival. Other benefits not well quantified include improved cognitive and

psychosocial development, social and economic benefits to the mother and family. Balancing the risks of possible HIV transmission against the risks of not breastfeeding remains a major public health dilemma for programs providing PMTCT and HIV care and treatment services to children and their families in resource-limited settings (10, 16).

In resource-limited settings with high prevalence of HIV, health workers face a dilemma on how best to advise HIV-infected mothers on infant-feeding practices.(17). Unfortunately, most at risk infants are in the developing world where breast feeding is the pillar of child survival, associated with reduced morbidity and mortality from infectious diseases and providing inexpensive nutrition(18). Despite expanding access to highly active antiretroviral therapy (HAART) in resource-limited settings, it is estimated that less than half of those in need are currently receiving treatment. Major gaps remain inadequate coverage of MTCT services as well as HAART access in sub-Saharan Africa for women and their infants, highlighting the need for continued studies to examine the impact of HIV infection on infant health outcomes (11). Duration of mother's ARV regimen, mother's CD4 cells/mm3 and low birth weight were associated with early MTCT. By 12 months, mixed feeding, prematurity and low birth weights were associated with children's risk of progressing to infection or death (19).

Maternal RNA viral load in plasma has been strongly associated with the risk of MTCT. However, although the risk of transmission increases substantially with increasing viral load, transmission of the virus to the fetus or infant can occur, even with very low, or undetectable, viral load levels. Nevertheless, women with a low CD4 cell count near the time of delivery (below 200 cells per mm3) and those who have been diagnosed with severe clinical disease are approximately three times as likely to transmit the virus than those who are less severely affected by HIV infection (20). The increased risks of mortality among HIV-exposed uninfected infants due to artificial feeding might be justifiable if a net benefit in terms of HIV-free survival could be accomplished. In the clinical trial in Botswana, there was no net benefit of artificial feeding on HIV-free survival. The reduced risk of HIV transmission as a result of formula feeding was outweighed by the increased risk of mortality among uninfected children(21). The prevention of HIV transmission should be balanced against the risk of other morbidity and mortality risks, including malnutrition. The reduction of HIV transmission through the breastfeeding period is one of the most pressing public health dilemmas confronting researchers, health-care professionals, health policy-makers and HIV-infected women in many areas of the world,

especially in developing countries. Prevention of HIV transmission during breastfeeding should be considered in a broad context that takes into account the need to promote breastfeeding of infants and young children within the general population.

Countries need to develop (or revise) comprehensive national feeding policies of infants and young children to consider the risks of HIV transmission during infant feeding, while continuing to protect, promote and support breastfeeding for infants of HIV-negative women and women whose HIV infection status is unknown(18). The new WHO guidelines that expand treatment criteria to include all pregnant women with CD4 counts <350 cells/mm3 go a long way to also reduce postnatal transmission. Programs that have proactively initiated treatment among pregnant women with low CD4 counts have also consistently reported low rates of postnatal transmission(21).

RATIONALE OF THE STUDY

The goal of prevention of mother to child HIV transmission is to reduce HIV related child mortality, to reduce risk of vertical transmission of HIV and hence increasing HIV free survival of uninfected children. However Infant feeding by HIV-infected mothers in resource-poor countries have been confounded by the scarcity of accurate estimates of the risk of HIV acquisition through different infant feeding practices and the associated survival risks and benefits(14). In Ethiopia, there is a shortage of data on mortality and HIV free survival of infants and young children of HIV infected women and the risk-benefit of breastfeeding and replacement feeding to improve HIV-free survival of HIV-exposed infants. Therefore, this study will try to bring scientifically sound data on the aforementioned gaps and will have paramount importance for evaluation of the various feeding programs.

2. LITERATURE REVIEW

Infant feeding policies for HIV-infected women in developing countries differ from policies in developed countries. Artificial feeding can prevent a large proportion of mother-to-child HIV transmission but also is associated with increases in morbidity and mortality among both exposed-uninfected and HIV-infected children(21). The objective of any PMTCT strategy must be to optimize overall child survival, including that of children of HIV-uninfected women. Central to this decision is determining the risk of morbidity and death associated with both breast-feeding and not breast-feeding, and what impact the recommendation and/or provision of formula milk or other replacement feeds to HIV-infected women will have on the feeding practices of uninfected mothers (22).

2.1 Cumulative risk of mother to child transmission and HIV free survival in breast feeding and formula feed infants and young children.

The risk of an HIV-infected mother passing the virus to her infant during pregnancy, labour and delivery or in the postnatal period is 1 in 3 if nothing is done to reduce this risk. In other words, out of 100 infants born to women with HIV/AIDS and without intervention, 60-75 of them will not be infected. Of the one-third who become infected, about 5-10 babies will be infected during pregnancy, 15 will be infected during labour and delivery while 5-15 will be infected during breastfeeding, largely being dependent on breastfeeding practices and on the duration of breastfeeding(23). Breast milk transmission of HIV in sub-Saharan Africa is estimated to be responsible for 40% of perinatally acquired HIV infections and over a third of women of childbearing age are HIV infected (11). The prevalence of HIV infection varies considerably from region to region. Women and children in sub-Saharan Africa are disproportionately affected, with nearly eight in every 10 HIV-infected women worldwide, and nine in every 10 newly-infected children living in this region(20). Developed countries have achieved remarkable progress in the prevention of MTCT (PMTCT) by scaling up access to highly active antiretroviral therapy (HAART), elective caesarean section, and formula feeding as a replacement to breastfeeding, leading to a dramatic decrease in the MTCT rate (below 2%) . Yet MTCT remains a major challenge in developing countries, particularly in sub-Saharan Africa where more than 90% of new pediatric HIV infections occur each year(3). With a national adult HIV prevalence of 2.1%, Ethiopia is one of the countries most severely hit by the epidemic. Besides the dominant heterosexual transmission, vertical virus transmission from mother to child

accounts for more than 90% of pediatric AIDS (24). Several African studies have suggested that exclusive breast-feeding could decrease the cumulative risk of HIV transmission while maintaining the benefits of breast-feeding, but the risk of HIV infection does not exist if breast exposure is completely avoided (11, 25).

It is logical that the post-natal transmission rate increases with breastfeeding duration, as infections accumulate with each month of additional exposure. It is more difficult, however, to quantify the instantaneous hazard or force of infection during early or later periods of breastfeeding. A combined analysis of selected studies concluded that hazards were constant over time. But several cohort studies with tighter intervals for determining the timing of transmission have reported declining hazards as the child becomes older (21). The overall risk of mother-to-child HIV transmission in non-breastfeeding populations is 15-25% (without interventions to reduce transmission) and in breastfeeding populations 20-45%. The risk can be reduced to less than 2% by antiretroviral prophylaxis during gestation, birth and the neonatal period together with elective caesarean section and avoidance of breastfeeding. An individual patient meta-analysis estimated that the cumulative probability of late postnatal transmission between 4 weeks and 18 months of age was 9.3%, or about 9 HIV infections per 100 child years of breastfeeding, and that the risk of transmission was constant throughout breastfeeding and approximately 42% of all HIV infections were attributable to breastfeeding (26). By 18 months an estimated 21% (19%–23%) of children born to HIV infected mothers would have acquired HIV infection. Combined, the overall probability of remaining free from HIV infection and death by 18-month was 0.76 (0.73–0.78). The overall estimated risk exposure for breastfeeding over the 18 month period was 9.1 cases per 100 child years of breastfeeding (95%CI: 5.8–12.5)(12). The proportion of HIV infected infants at one month were 13.0% among the breast-fed compared to 4.4% among the formula-fed infants (P-value = 0.06) (3). In a trial in Nairobi, Kenya where infants were randomized to breastfeed or formula-feed, most of the cumulative difference in HIV infection rates between breastfed and formula-fed infants had occurred by 6 weeks of age: the difference between groups was 10% at 6 weeks and 16% at 24 months(27). The probability of breast-feeding transmission of HIV was estimated to be 9.3% at 18 months, and the overall risk of breast-feeding transmission was estimated as8.9 transmissions/100 child years of breast-feeding, which is interpreted as a monthly risk of 0.74% per month of breast-feeding(12, 22, 25, 28). The risk of HIV transmission through breastfeeding is 3 to 10 times higher among women

with CD4 count <200 cells/ml than above this threshold (12). Studies have consistently shown a relationship between maternal CD4+ cell count around the time of delivery and risk of postnatal HIV transmission. The crude analysis of 18-month HIV transmission or death showed that the type of scARV regimen, low maternal CD4 count, advanced maternal clinical staging, maternal eligibility for ART, high maternal plasma viral load at inclusion, longer duration of pre-partum scARV prophylaxis, higher gestational age, home delivery, and low-birth weight, were significantly associated with HIV-infection or death(29). The MASHI study in Botswana Cumulative HIV transmission rates at 7 months were 5.6% in the formula-fed group and 9.0% in the breastfed plus ZDV group(8). By 18 months an estimated 21% (19%–23%) of children born to HIV infected mothers would have acquired HIV infection. Combined, the overall probability of remaining free from HIV infection and death by 18-month was 0.76 (0.73–0.78) (4). The probability of HIV-free survival was significantly lower in children who were breastfed for more than 6 months than in the combined group of children replacement fed or breastfed for less than 6 months (0.91 (0.88–0.93) vs. 0.96 (0.93–0.98), p=0.001). Overall, breastfeeding beyond 6 months increased the risk of HIV acquisition (AHR 3.3; CI: 1.0–10.5, p=0.05) compared with durations of breastfeeding less than 6 months (12). Exclusive breastfeeding (EBF) with early cessation and FF are two conceivable alternatives to prevent postnatal HIV transmission. Mothers with CD4 < 200 had a 2-5 fold increased risk of postnatal transmission compared to those with CD4 > 500, acute maternal infection during pregnancy or lactation also increases the risk of postnatal transmission. Infant feeding patterns influence transmission: mixed feeding and prolonged breastfeeding can lead to higher risk of PNT. Breast problems such as cracked nipples, breast abscesses, clinical and subclinical mastitis have been shown to increase postnatal transmission (16, 30) . Several studies from low-income countries have reported postnatal transmission rates of less than 2% using alternatives to BF without a higher overall mortality rate. However, in operational settings, these alternatives have shown a worrying increase in overall mortality among FF children, probably due to the lack of access to clean water, incorrect dilution of formula, and inadequate access to formula or postnatal follow-up(31).

2.2 Morbidity status of breast feeding and formula feeding HIV exposed infants and young children.

Breastfeeding is a significant protector against diarrheal disease, respiratory disease and other infections. Breastfeeding tends to result in better nutritional outcomes, including protecting against obesity in over-fed and against wasting in under-fed populations(21) . The highest rates of serious gastroenteritis events were 16.2 events per 1000 child-months at 3 - 4 months and 15.0 events per 1000 child-months at 7 - 8 months and thereafter remained relatively high up to 17 months (32). A significant reduction in the incidence of gastrointestinal infections was observed during the period from three to six months in the six month group (adjusted incidence density ratio: 0.35 [0.13, 0.96]), but there were no significant differences in risk of respiratory infections outcomes or atopic eczema. Exclusive breastfeeding for six months was associated with a lower risk of gastrointestinal infection and no demonstrable adverse health effects in the first year of life in a general population with low HIV prevalence(18).

A randomized trial study in Nairobi, Kenya the incidence of diarrhea during the first two years of life was also similar in both groups: 155 and 149 per 100 child-years of follow-up in the formula and breastfeeding groups respectively, while the incidence of pneumonia was identical at 62 per 100 child-years of follow-up. Infants in the breastfeeding arm tended to have better nutritional status than those in the formula arm (p=0.06 overall), significantly so during the first six months of life (p=0.003). After adjusting for HIV infection status, infants in the breastfeeding arm had significantly better nutritional status than those in the formula arm over the two-year period (p=0.04). In this trial, there was substantial movement between arms, and many in the formula arm left the study before follow-up (18, 27). In a small study from Durban, South Africa, HIV-infected infants who were never breastfed had a poorer outcome than breastfed HIV-infected children: 60% of 15 never-breastfed infected infants had three or more morbidity episodes in the first 18 months of life compared to 32% of 47 breastfed HIV-infected infants. During the first two months of life, never-breastfed infants, regardless of their HIV status, were nearly twice as likely to have had an illness episode as compared to breastfed infants (OR 1.91, p=0.006). Two earlier studies from South Africa compared 90 partially breastfed and exclusively formula-fed HIV-infected infants; both groups had similar frequencies of failure to thrive, episodes of diarrhea and pneumonia, as did 43 uninfected infants born to HIV-positive mothers(18).

The proportion of infants with severe underweight who received formula feeding was higher in the first two months of life, reaching a pick of 40% at two months, but it was reduced notably

afterwards. The proportion of infants with severe underweight who received breastfeeding experienced progressive reduction over time (33). Factors resulting in disruption of the integrity of infants' mucous membranes, such as oral thrush, may be associated with an increased risk of transmission through breastfeeding. However, the direction of any causality is difficult to establish since early HIV infection may also be associated with thrush (Ekpini et al. 1997; Embree et al. 2000). Infant oral thrush can also lead to maternal nipple thrush and fissures. Feeding with cow's milk, allergic reactions to complementary foods and infectious illness can all result in intestinal damage, which could also be a risk factor for transmission. It has also been hypothesized that the intestinal permeability of the young infant may be affected by mode of feeding, with infants who receive only breast milk having a less permeable and therefore healthier lining of the gut than those who also receive other foods(18).

2.3 Mortality rate of breast feeding and formula feeding HIV exposed infants and young children.

One of the key principles in the WHO guidelines in infant feeding in the context of HIV infection is balancing HIV prevention with protection from other causes of child mortality(34). Infants aged 0–5 months who are not breastfed have seven-fold and five-fold increased risks of death from diarrhea and pneumonia respectively, compared with infants who are exclusively breastfed. At the same age, non-exclusive rather than exclusive breastfeeding results in a more than two-fold increased risk of dying from diarrhea and pneumonia(8). For infants and young children 6-23 months of age not breastfeeding resulted in an excess risk of diarrhea mortality as compared to breastfeeding. The estimated relative risk of all-cause mortality was higher when comparing not breastfed (RR: 3.69) to breastfed infants and young children 6-23 months of age(35). Exclusive breast-feeding with abrupt weaning at six months of age has also been associated with high rates infant morbidity and mortality and WHO has updated guidelines to allow for more prolonged breastfeeding (17).

The mortality rate among HIV-infected infants (0.72 per 1000 child-days) was eight times higher than among HIV-uninfected infants (0.09 per 1000 child-days) ($p<0.0001$). The difference in overall probability of remaining alive between HIV-infected and HIV uninfected infants was also significant ($p<0.0001$)(11). In settings where antiretroviral prophylaxis and free infant formula were provided, the combined risk of HIV infection and death by 18 months of age was similar in infants who were replacement fed from birth and infants breastfed for 3 to 6 months. Early

cessation of breastfeeding (before 6 months) was associated with an increased risk of infant morbidity (especially diarrhea) and mortality in HIV-exposed children(36). The cohort study in Rakia Uganda, the 12-month cumulative probability of death was 18% (95% CI =11%–29%) among the formula-fed compared to 3% (95% CI =1%–9%) among the breast-fed (unadj. HR=6.1(95% CI, 1.7–21.4, P value, 0.01). In this study Infant mortality among formula-fed infants born to HIV infected mothers was over six times higher compared to mortality of breast-fed infants. However, the excess mortality associated with formula feeding in this rural setting is substantially greater than that reported in the earlier urban studies. This suggests that the risk of mortality with formula-feeding could be much greater in rural populations with limited access to clean water and medical care. findings from this study also suggest that formula-feeding may be particularly hazardous for HIV-infected infants, since all infants HIV infected by one month of age in the formula-feeding group died by twelve months, compared to none in the breast-feeding group(17).

The Mashi trial evaluated the efficacy and safety of breastfeeding and ZDV prophylaxis in infants for six months compared to formula feeding from birth and one month of ZDV prophylaxis of the infant for reducing postnatal transmission of HIV. There were significantly higher rates of mortality (mainly related to diarrheal disease and pneumonia) in formula-fed than in breastfed children in the first six months of life. The cumulative incidence of infant death was significantly higher in the formula-fed group than in the breastfed plus ZDV group at age seven months (9.3% versus 4.9%, p=0.003); however, this difference diminished beyond seven months, such that the mortality through 18 months of age was not significantly different (10.7% in the formula-fed arm versus 8.5% in the breastfed arm, p=0.21) (18).

In conclusion infant feeding in the context of HIV infection is balancing HIV prevention with protection from other causes of child mortality. Several studies from low-income countries have reported postnatal transmission rates of less than 2% using alternatives to BF without a higher overall mortality rate. Even if the above mentioned studies are methodologically strong they are conducted in different setting and have different follow up time and hence they brought with discrepancy outcomes. And also in our set up data comparing survival of formula-fed to breast-fed infants in programmatic settings are limited. So, this study will try to bring scientifically sound data to fill the above mentioned information gaps. **(See annex-1)**

3. OBJECTIVES

3.1 GENERAL OBJECTIVE

To compare the survival and benefits of breast feeding and formula or replacement feeding in infants and young children of HIV infected women followed under the prevention of mother to child transmission of HIV (PMTCT) programs.

3.2 SPECIFIC OBJECTIVES

1. To determine the cumulative risk of HIV infection and HIV free survival in breast feeding and formula feeding infants and young children.

2. To describe the mortality rate of infants and young children in breast feeding and formula fed groups.

3. To compare the morbidity status of infants in formula fed to in infants and young children of breast fed.

4. METHODOLOGY

4.1 Study Setting

Addis Ababa, located about 2,408m above sea level at 9.02° N 38.44° E, is the capital city of Ethiopia. According to CSA July 2013 projection, Addis Ababa has total population of 3,103,673, consisting of 1,478,890 men and 1,624,783 women. It is estimated that presently there are no rural parts to the city, so 100% of the inhabitants are considered urban dwellers; 24% of all urban dwellers in Ethiopia are in Addis Ababa(37). The city is administratively divided into 10 sub-cities. The HIV prevalence among adults (15-24 years) in the city is estimated to be 8.8% were the majority of the infections occur through hetro-sexual contact (38).

According to the 2011 Ethiopian Demographic and Health Surveys HIV prevalence in Addis Ababa is 6% (39). In total 59 health facilities were providing PMTCT services, where 25 were public health centers. The health services were fairly accessible with a median distance to the nearest referral centre being less than 5 km. About 90% of the pregnant women in the city had antenatal visit at least once and about 90% of these attended public health facilities. In 2009 alone 54 698 women attended PMTCT programs across the city, about 79% received HIV counseling and testing and 4.6% were HIV positive(24, 40). The first national PMTCT guidelines were developed in 2001 and incorporated an opt-in HIV counseling and testing approach. Two years following the development of the guidelines, PMTCT programs were launched in selected public health facilities across the country. In 2007, when the PMTCT guidelines were revised, the HIV testing approach shifted from opt-in to routine opt-out(24). From early 2008, the routine opt-out HIV testing has become the standard of practice in public health facilities. In private health facilities by contrast, opt-in HIV testing remained the standard of practice since the launching of the PMTCT programs in 2007 (38)

4.2. Study Design

A retrospective cohort study design was employed to compare the HIV free survival of exposed infants and young children who were on breast fed and formula fed and the cumulative risk of HIV infection throughout the duration of breast feeding. Infants and young children feeding practice who were born from HIV infected mothers were considered as exposure, and infants and young children HIV free survival, cumulative risk of HIV transmissions, mortality and morbidity were the outcome variables.

4.3. Population

4.3.1. Source Population

All HIV exposed infants and young children who were on PMTCT program and age <= 18 months

4.3.2. Study population

All HIV exposed infants and young children, whose feeding practice is determined or known immediately after birth, started PMTCT follow up and end up at 18 months with one of the follow up outcomes.

End points: Both the exposed (breast feeding) and non exposed (formula feeding) infants and young children were followed for 18 months until any one of the aforementioned follow up outcomes are observed in the course of PMTCT program.

Inclusion Criteria: Any HIV exposed infants and young children with breast or formula feeding, 18 or less month of age that have completed the PMTCT follow up were part of the study. Unknown follow up status were as well the study subjects.

Exclusion Criteria: Death before the first HIV test, infants and young children who transferred out and those who started PMTCT follow up after 60 days were not part of the study.

4.4. Sample size determination

Sample size was determined using two-population proportion formula, taking type one error to be 5%, and 80 % power

$$n_1 = \frac{\left[z_{\alpha/2}\sqrt{(1+1/r)\bar{p}\bar{q}} + z_{\beta}\sqrt{p_1q_1 + p_2q_2/r} \right]^2}{(p_1 - p_2)^2}, \; n_2 = r \times n_1$$

Where;

- n_1= number of HIV exposed infants and young children with breast feeding (Exposed)
- n_2= number of HIV exposed infants and young children with formula feeding (non exposed)
- r= the ratio of non exposed to exposed infants and young children = 1
- $\bar{p} = \frac{p_1 + r \times p_2}{r+1}$; $\bar{q} = 1 - \bar{p}$
- P_1= proportion of HIV free survival in breast feeding infants and young children
- P_2=proportion of HIV free survival in formula feeding infants and young children
- α =Type one error(0.05)
- $z_{\alpha/2}$= Critical value at 95 % level of significance
- $z_{1-\beta}$= standard normal distribution value corresponding to power

Sample size was calculated for different infant and young children feeding outcome variables (cumulative risk of HIV transmission, death, HIV free survival). Since there was no study conducted in Ethiopia to accurately estimate these issues, proportion of feeding outcomes from a study conducted in Kenya on effects of breast feeding and formula feeding for transmission of HIV-1 (a randomized clinical trial) was considered (27).

Table 1: Sample size determination

Follow up outcome variables	**Proportion(%) in**		**Sample Size for**		**Total sample size**
	Exposed	**Non Exposed**	**Exposed**	**Non Exposed**	
Cumulative risk of HIV transmission	36.7	20.5	134	134	268
Mortality	24.4	20.0	1445	1445	2890
HIV free survival	58	70	267	267	534*1.5=801

NB: The sample size calculated from the proportion of HIV free survival which is the second largest sample size was considered. Because of time and others resource limitation the maximum sample size calculated from the proportion of mortality in breast and formula feeding infants and young children were not considered**.** Therefore the calculated total sample size from second largest outcomes and taking the design effect of 1.5 was 801 and considering 10 % incomplete or inconsistent data , the resulting minimum sample size was 882 (441 HIV exposed breast feeding infants and young children and 441 HIV exposed formula feeding infants and young children)

The final sample size **(N)** = **882** with, $\mathbf{n_1=n_2=441}$

4.5. Sampling procedures

From 59 federal and Addis Ababa city administrative hospitals and clinics which give PMTCT services five government hospitals and one private (WWO) clinics were randomly selected and then based on the follow up card and PMTCT registration book the required study subjects were recruited from these hospitals. All HIV exposed infants and young children who were on breast feeding or formula feeding and fulfilling the inclusion criteria were included in the study. HIV exposed infants and young children on breast feeding (exposed) and on formula feeding (none exposed) was selected using simple random sampling. And the number of infants and young children was allocated to each hospital proportionally to their total number of follow up. **(See annex-III)**

4.6. Data Collection

4.6.1. Study variables

4.6.1.1 Dependent variables

Cumulative risk of HIV infection and its complement HIV free survival, Mortality and Morbidity

4.6.1.2. Independent variables

Socio-demographic variables:

-Age, marital status, religions, educational status, employment status

-Family size, source of water, Number of rooms' in house hold

Maternal and infants characteristics

Place of delivery	CD4 count at delivery
Sex	Breast conditions
Birth weight	WHO clinical stage
CPT prophylaxis	Duration on HAART/ARV
Mode of delivery	HIV/ART care enrollment
Infants ARV prophylaxis's	Disclosure status
Types of feeding	PMTCT intervention

Duration of breast feeding	No of ANC visit
Gestational age or term of pregnancy	Maternal survival
Immunization	

4.7. Data Collection procedures

Data collection form which helps to extract necessary information from PMTCT registration book and infant and young children cards was prepared by the principal investigator as shown in **(Annex -VI)**. To ensure the quality of data, nurses who have been providing PMTCT, exposed infants follow up and recording exposed infants' information on PMTCT registration book were recruited and trained as data collectors on how to extract data from PMTCT registration book and infant and young children card and filled out on data collection form. First, exposed infants and young children from the PMTCT registration book and their cards was identified as exposed (breast fed) or none exposed (formula fed), and then the outcome of infants and young children on follow up was sought forward as presented in (**annex –IV).**

4.8. Data quality management

Several data quality measures were considered to keep the validity of the study. The data collection instrument; data extraction form, was pre-tested on 2 % of the eligible study subjects from bole17 health center which was not included in this study and modifications have been made based on the findings. One day training was given to data collectors to be familiar with the objective, the procedures of retrieving the data from the infants' card and registration books and mothers' card and on how to relate infants and mothers information to make the extraction process consistent. Data extraction form was prepared in English based on the exposed infant follow up card and mothers' card to retrieve data. The data extraction process was closely monitored by supervisors and the principal investigator; as a result errors were corrected. And also during data management, storage, cleaning and analysis consistency and completeness were checked.

4.9. Data Processing and Analysis

Data were entered in Epi info for window version 3.5.3 software and exported into SPSS version 16 and STATA version11 statistical software for cleaning and analysis.

Frequency was run to describe the data in the study followed by assessing the difference between breast fed and formula fed groups with respect to various variables by using X^2 test. T-test statistics for independent sample test was used to compare the maternal age between the two groups. The HIV free survival status of infants and young children were presented by using actuarial life table analysis. Infants and young children morbidity and HIV infection (i.e., the complement of HIV-free survival) in the two feeding groups were compared by using Kaplan-Meier time-to-event methods. HIV free Survival was compared among subjects with breast feeding and formula feeding, HIV exposed infants and young children with the use of the log-rank test.

Before adjusting the covariates the association between HIV infection and infant feeding type was done by using bivariate Cox proportional hazards regression analysis. And to see the effect of infants and young children feeding on the developments of morbidity, bivariate Cox regression analysis was done without adjusting for other covariates.

Potential interactions among exposure variables i.e. infants and young children feeding type and other determinants were assessed. Multivariate Cox regression analysis was performed to see the independent effects of determinant variables after the Cox proportional hazard assumption was checked.

All variables with p-value less than 0.2 during the bivariate Cox regression analysis were included on the multivariate Cox regression model. Hazard ratios with 95% confidence interval (CI) were used to test the significance of the association after multivariate Cox regression analysis.

4.10. Operational Definitions

According to the ICAP (international center for AIDS care and treatment programs) HIV and infant feeding approach to improve HIV free survival:

Exclusive breastfeeding (EBF)-infant receives only breast milk and no other Liquids or solids including water, tea and commercial formula, except prescribed medications such as vitamins, mineral supplements or medicine.

Formula feeding (FF)- use of commercial infant feeding which is formulated Industrially in accordance with applicable Codex Alimentarius standards to satisfy the nutritional requirements of the first months of life until the introduction of complementary foods.

Replacement feedings- feeding infants with commercial infant formula or home modified animal milk instead of breastfeeding until the child is fully fed on family food.

Mixed feeding or partial breastfeeding:- feeding breast milk and other liquids and or solids prior to six months of age.

Complementary feeding- the addition of any food, whether manufactured or locally prepared, to breast milk or formula when breast milk/formula becomes insufficient to satisfy all the nutritional requirements of the infant. This usually occurs around 6 months of age.

Postnatal transmission (PNT):-mother-to-child-transmission of HIV occurring after delivery through breastfeeding.

HIV-free survival- child is alive and does NOT acquire 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 with dehydration, pneumonia or lower respiratory tract infection (LRTI), otitis media or hepatomegaly during the follow up time

Any types of Breast conditions –if the mothers develop any types of breast problems while she is on breast feeding which includes; cracked nipple, breast abscess, and mastitis.

4.11. Ethical Consideration

We obtained ethical approval from research ethics committee of AAU School of Public Health. Following the endorsement by the research ethics committee, AACAHB and the two federal hospitals were informed about the study through a support letter from AAU School of Public Health. Then written permission was obtained from research ethics committee of AACAHB and the committee wrote support letter for each facilities where this study was conducted and verbal permission had been obtained from respective health facilities.

Following the endorsement by AACAHB, the selected Hospitals were informed about the objective of the study through a support letter from the School of Public Health, AAU and written permission was obtained from the respected Hospital administration. As the study was conducted through review of medical records, the individual child was not subjected to any harm as far as the confidentiality is kept. Assent was obtained from mothers or care takers who happen to be in the hospital during record review. To preserve the confidentiality, nurses working in PMTCT clinic, in the selected hospital extracted the data from the medical records. Moreover, no personal identifiers were used on data collection form. The recorded data was never accessed by a third person except the principal investigator, and was kept with a firm confidentiality in a secured place.

5. RESULTS

5.1 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, of which 70 (8.2%) of infant records were incomplete. The mean (± SD) age of the mothers were 29(± 4.4) among breast fed group and 29.4 (± 3.9) among formula fed group. The number of people living in 157 (52.9%) households in breast fed and 88 (60.3%) households in formula fed group were two –three persons. And 147(57.2%) and 75(63.6%) of the mother were lived in >= 2 rooms in breast fed and formula fed groups respectively.

Majority of the mothers 373 (79.2%) in breast fed group and 180(80.4%) in formula fed group were married and198 (55.5 %) and 61(34.5%) of mothers were unemployed in breast fed and formula fed group respectively. From the total of 608 women, more than a third in breast fed and more than half in formula fed group had secondary level of education, 154 (37.7 %) and 105(52.5%) respectively. In both cohort the majority of mothers were orthodox; 296 (65.6%) in breast fed and 155(78.7%) in formula fed group respectively.

In this study 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 (X^2=24.9, P= 0.0001 and X^2 = 18.0, P=0.0001) respectively.

Table 1: Socio-demographic characteristics of mothers on selected government and private health facilities in Addis Ababa, september2009-may2013.

Variables	Breast fed n(%)	Formula fed n(%)	X^2,df	p-value
Age of mother				
n(Mean ±SD)	482(29±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/ windowed	37(7.9%)	26(11.6%)		
Mothers employment status			24.9,2	**0.0001***
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	**0.0001***
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 **a=0.05**, ▲ T- test statistics for independent sample test used, **HH**=house hold

When we see the parent's clinical characteristics, there was no statistically significant difference on each attributes of clinical characteristics of both cohorts. Among the study subjects half of mothers were WHO clinical stage I at time of delivery; 223(49.7%) in breast fed and 112 (51.6%) in formula fed groups respectively. Of the total study subjects more than half of the mothers disclosed their HIV status to their partners; 348(61.7%) in breast fed and 170(58.4) formula fed cohorts respectively. More than two third of the mothers had less than four ANC visits 381(67.3%) in breast fed group and 205(70.4%) of them were in formula fed groups. Two third of mothers were on HAART and one fourth of mothers were on triple antiretroviral drugs for prevention of mother to child transmission of HIV; 364(66.7%), 132(24.2%) in breast fed groups and 186(65.0%), 70(24.5%) in formula fed groups respectively. More than half of the mothers hand a CD4 count >350 cells/ul during delivery 169(55.2%) in breast fed and 80(52.3%) in formula fed groups respectively. Of the total husbands 17.5 % of them had discordant HIV status 92(17.6%) in breast fed and 46 (17.5 %) formula fed group were HIV negative respectively.

Table 2: Clinical characteristics of parents in government and private health facilities in Addis Ababa, September 2009- may 2013

Variables	Breast fed n(%)	Formula fed n(%)	X2,df	p- value
Mother WHO clinical stage			0.3,2	0.8
Stage I	223(49.7%)	112(51.6%)		
Stage II	134(29.8%)	64(29.5%)		
Stage III or IV	92(20.5%)	41(18.9%)		
Disclosure status			0.9,1	0.4
Disclosure to husband	348(61.7%)	170(58.4%)		
Disclosure to others [a]	216(38.3%)	121(41.6%)		
No of ANC visit			0.9,1	0.4
1-3 visit	381(67.3%)	205(70.4%)		
>=4 visit	185(32.7%)	86(29.6%0		
Mothers PMTCT intervention			4.3,4	0.4
None	14(2.6%)	3(1.0%)		
Sd NVP	8(1.5%)	5(1.7%)		
AZT+ Sd NVP+3TC	132(24.2%)	70(24.5%)		
HAART	364(66.7%)	186(65.0%)		
Others [b]	28(5.1%)	22(7.7%)		
Duration of HAART			1.8,1	0.2
<=2 months	24(7.9%)	7(4.5%)		
>2 months	281(92.1%)	148(95.5%)		
Duration of ARV			0.4,1	0.5
<= 1 month	27(28.1%)	13(23.2%)		
>1 months	69(71.9%)	43(76.8%)		
CD4 count during delivery			0.4,1	0.6
<=350 cell/ul	137(44.8%)	73(47.7%)		
>350 cell/ul	169(55.2%)	80(52.3%)		
Father HIV status			0.002,2	0.9
HIV negative	92(17.6%)	46(17.5%)		
HIV positive	315(60.3%)	159(60.5%)		
Unknown	115(22.0%)	58(22.1%)		
Father enrollment to HIV /ART care			2.0,1	0.2
Enrolled	248(90.2%)	111(85.4%)		
Not enrolled	27(9.8%)	19(14.6%)		

a- disclosure to parents, brother/sisters, friends, relatives and neighbors **b**- AZT

5.2. Delivery and clinical characteristics of infants and young children

When we see the infant delivery characteristics in both cohorts there was a statistically significant difference only on place of delivery and mode of delivery (X^2 = 5.6, df -1, p= 0.02 and X^2 =8.7, df-1, p = 0.003) respectively. Majority of the infants 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. More than three fourth of infants; 353(80.8%) and 164(75.2%) in breast fed and formula fed groups had gestational age of >=37 weeks 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 no statistically significant difference on growth and development of infants and young children between the two cohorts. The median duration of follow up time in the exposed infant clinic was 10.6 months with the IQR of 3 months and the duration of breast fed ranges from 1.2 month to 21.5 months with median duration of 7.3 month and IQR of 3.8 months.

Table 3: Delivery and clinical characteristics of infants and young children in government and private health facilities in Addis Ababa, September 2009- may 2013

Variable	Breast fed n(%)	Formula fed n(%)	X^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 grams	64(12.8%)	40(15.3%)		
>=2500 grams	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 [e]	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			0.1,1	0.7
Normal growth	544(96.1%)	281(96.6%)		
Growth flatter	22(3.9%)	10(3.4%)		

***** Significant at **a=0.05** **a-** Private clinic, on the street, **C/S**= cesarean section, **SVD**= spontaneous vaginal delivery **e=zdv**

5.3. Cumulative risk of HIV infection in breast fed and formula fed infants and young children.

All 857 study subjects had contributed a total of 270075 infant days. Of which 179173 infant days were from breast fed infants and 90902 infant days were from formula fed infants and young children. The proportion of HIV infection in breast fed infants and young children was 7.1% and it was 2.7% among formula fed infants with their respective incidence rate of HIV infection 0.22per 1000 infant days and 0.088 per 1000infant days respectively. There was a statistically significant difference in transmission of HIV between the two cohorts with incident rate ratio of 2.54 (95%CI 1.2-6.3, p=0.009). About sixty percent 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 1000 infant days.

Based on the actuarial life table analysis majority of HIV infection occurred in the first 90 days of the follow up time with the cumulative proportion of surviving 97 % in breast fed and 98 % in formula fed infants respectively. The cumulative probability of HIV free surviving in the first 180 and 360 days of infants on the breast fed cohort were 95% and 93% respectively but in the formula fed cohort the cumulative probability of HIV free surviving in the two above mentioned time was 97%.

The 18 months cumulative probability of HIV free survival in breast fed and formula fed infants and young children were 84% and 97% respectively. And the 18 month cumulative probabilities of the compliment of HIV free survival i.e. HIV infection was 16% and 3% on breast fed and formula fed infants and young children respectively. The mean HIV free survival time of breast fed infants and young children was 606 days while it was 921 days for formula fed infants and young children. Combined, the overall probability of remaining free from HIV infection by 18-month was 88%.

Table 4 a: Actuarial life table analysis of HIV infection of breast fed infants and young children on selected government and private health facilities in Addis Ababa, September 2009- may 2013

Infant Feeding Types	Time interval in days	Number entering interval	Number withdrawing during interval	Number exposed to risk	Number of HIV infection	Probability of not developing infection	Cumulative probability of not developing HIV infection
BF	0	566	5	563.5	4	0.99	0.99
	30	557	9	552	9	0.98	0.98
	60	537	6	536	4	0.99	0.97
	90	529	4	527	6	0.99	0.96
	120	519	8	515	3	0.99	0.95
	150	508	11	502.5	3	0.99	0.95
	180	494	8	490	1	1.00	0.95
	210	485	27	471.5	3	0.99	0.94
	240	455	41	434.5	0	1.00	0.94
	270	414	69	379	0	1.00	0.94
	300	345	124	283	2	0.99	0.93
	330	219	67	185.5	0	1.00	0.93
	360	152	23	140.5	0	1.00	0.93
	390	129	21	118.5	2	0.98	0.92
	420	106	10	101	0	1.00	0.92
	450	96	18	87	1	0.99	0.91
	480	77	38	58	0	1.00	0.91
	510	39	25	26.5	2	0.92	0.84
	540	12	7	8.5	0	1.00	0.84
	570	5	3	3.5	0	1.00	0.84
	600	2	1	1.5	0	1.00	0.84
	630	1	1	0.5	0	1.00	0.84

Table 4 b: Actuarial life table analysis of HIV infection of formula fed infants and young children on selected government and private health facilities in Addis Ababa, September 2009-may 2013

Infant Feeding Types	Time interval in days	Number entering interval	Number withdrawing during interval	Number exposed to risk	Number of HIV infection	Probability of not developing infection	Cumulative probability of not developing HIV infection
FF	0	291	1	290.5	1	1.00	1.00
	30	289	5	286.5	5	0.98	0.98
	60	279	2	278	1	1.00	0.98
	90	276	9	271.5	0	1.00	0.98
	120	267	2	266	1	1.00	0.97
	150	264	6	261	0	1.00	0.97
	180	258	6	255	0	1.00	0.97
	210	252	17	243.5	0	1.00	0.97
	240	235	20	225	0	1.00	0.97
	270	215	40	195	0	1.00	0.97
	300	175	70	140	0	1.00	0.97
	330	105	41	84.5	0	1.00	0.97
	360	64	12	58	0	1.00	0.97
	390	52	4	50	0	1.00	0.97
	420	48	13	41.5	0	1.00	0.97
	450	35	4	33	0	1.00	0.97
	480	31	15	23.5	0	1.00	0.97
	510	16	10	11	0	1.00	0.97
	540	6	5	3.5	0	1.00	0.97
	570	1	0	1	0	1.00	0.97
	600	1	0	1	0	1.00	0.97
	630	1	0	1	0	1.00	0.97
	660	1	1	1	0	1.00	0.97
	690	1	0	1	0	1.00	0.97
	720	1	0	1	0	1.00	0.97
	750	1	0	1	0	1.00	0.97
	780	1	0	1	0	1.00	0.97
	810	1	0	1	0	1.00	0.97
	840	1	0	1	0	1.00	0.97
	870	1	0	1	0	1.00	0.97
	900	1	0	1	0	1.00	0.97
	930	1	1	0.5	0	1.00	0.97

The Kaplan Meier analysis and log rank test were used to compare the survival probabilities of the two groups. There is a significant difference on HIV free survival time between the two groups (log rank test statistics =6.13, df=1, p=0.013) i.e. Overall probability of HIV free survival in formula fed cohort was significantly greater than breast fed groups.

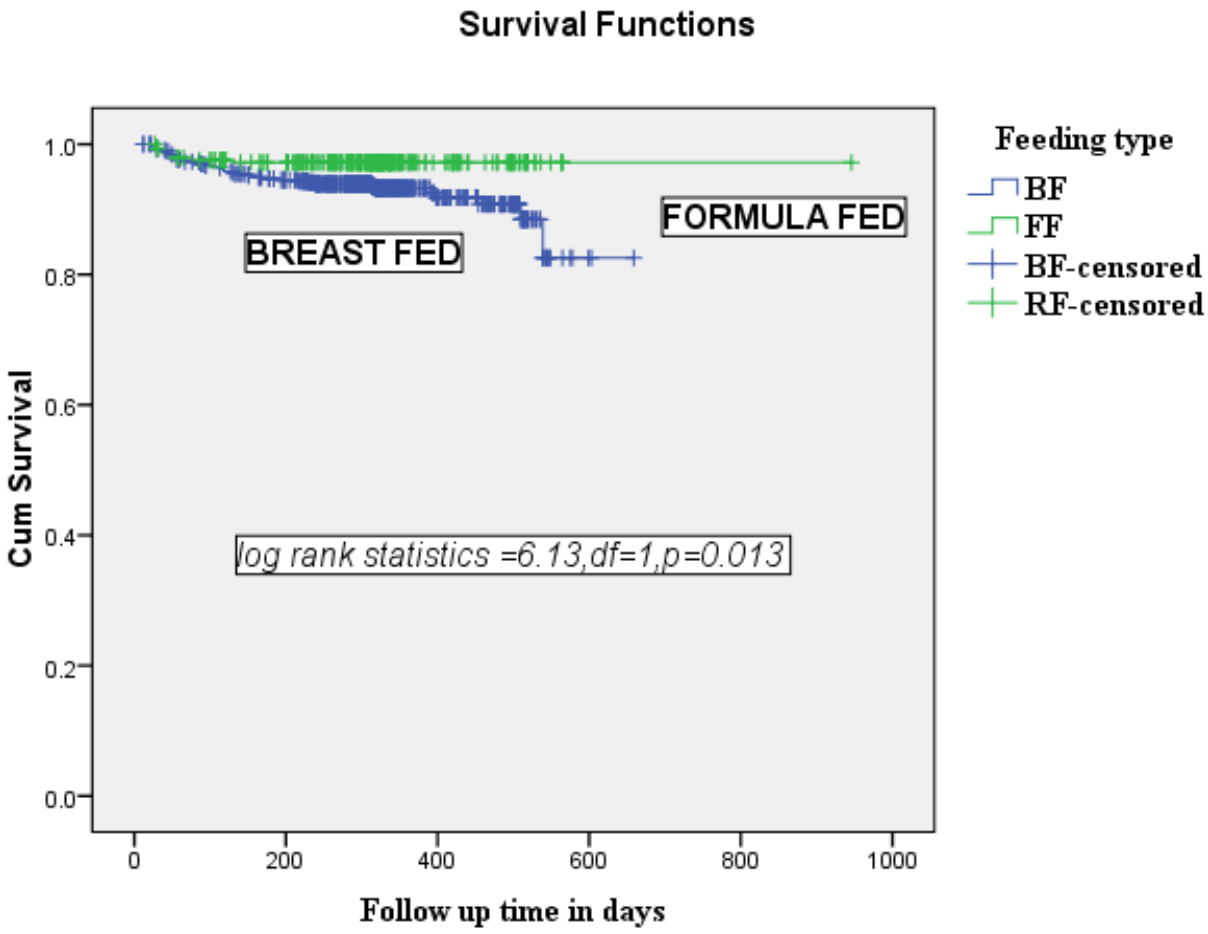

Figure 1: Kaplan Meier estimate of HIV free survival among HIV exposed infants and young children during their breast fed and formula fed follow up time in the HIV exposed infant clinic in the selected government and private health facilities, September 2009- may 2013

5.4. Determinants of cumulative risk of HIV infection for infants and young children.

Bivariate Cox regression model was used to assess the relationship between the selected determinants and the risk of transmission of HIV infection. Before fitting the covariate into the model Cox proportional hazard assumption was checked by schoenfield residuals test and graphically by –ln(-ln) survival probability. Those variables with p< 0.2 on the bivariate Cox regression were fitted to the multi variate Cox regression model. Since the number of variables with p< 0.2 on the bivariate Cox regressions from maternal socio demographic condition, parent's clinical condition and infants clinical and delivery characteristics were few one final model was developed.

Based on the bivariate Cox regression analysis infants whose mother were dead had 11.6(95%CI 2.8-48.8, P=0.001) times higher hazard to acquiring HIV infection as compared to the reference group. And infants whose mother were not enrolled on HIV/ART care were 4.6 (95%CI 1.9-11.0, P=0.001) times more likely to acquire HIV infection as compared to infants from mothers enrolled on HIV/ART care. Infants from mothers who did not have any prevention of mother to child transmission of HIV had a risk of 13.6 (95%CI 6.0-30.8, P=0.0001) than the reference group for the transmissions of HIV.

Infants who delivered at home had 5.8(95%CI 1.7-18.9, P=0.003) times higher hazard in acquiring HIV infection as compared to hospital delivered infants. As compared to infants on sd NVP+AZT for 7 days ARV prophylaxis, infants who did not take any types of ARV prophylaxis had 8.7(95%CI 3.0-25.1, P=0.0001) more risk for the acquisition of HIV infection. Infants and young children under the red flags of developmental milestone were 4.3 (95%CI 1.5-12.1, p=0.006) times higher risk of acquiring HIV infection as compared to the reference groups. The transmission risk of HIV infection among breast fed infants and young children were 2.5 (95%CI 1.2-5.4, p=0.014) higher than those formula fed infants and young children. Infants and young children who breast fed less than six months were 2.9 (95% CI 1.5-5.8,P=0.002) times higher risk to acquire HIV infection than those infants and young children who breast fed more than six months. **(See table 5, 6& 7)**

Table 5: Bivariate Cox regression analysis for determinants of HIV infection of selected maternal socio-demographic characteristics on selected government and private health facilities in Addis Ababa, September 2009- may 2013

Variables	HIV INFECTION		Crude HR (95% CI)	P- value
	YES(n)	NO (n)		
Source of drinking water				
Pipe water	1	6	2.7 (0.3-19.9)	0.3
Running water	24	424	1	
Mothers employment status				
Working full time	9	147	1	
Working part time/not working due to ill	6	105	0.9(0.3-2.7)	0.9
Unemployed/others [a]	18	249	1.2(0.5-2.6)	0.6
Mothers levels of education				
No education	7	58	1.1(0.3-3.8)	0.8
Primary	15	231	0.6(0.2-1.7)	0.3
Secondary	10	249	0.4(0.1-1.2)	0.09
Tertiary	4	34	1	
Mothers marital status				
Married	5	74	1	
Never married	32	521	0.9(0.4-2.4)	0.9
Separated/divorced /windowed	5	58	1.2(0.4-4.3)	0.7
Mothers status				
Alive	45	793	1	
Dead	2	4	**11.6(2.8-48.8)**	**0.001***

***-** significant at **a=0.05** **a**-house wife

Table 6: Bivariate Cox regression analysis characteristics of parents on selected government an private health facilities in Addis Ababa, September 2009- may 2013

Variables	HIV INFECTION		Crude HR (95% CI)	P- value
	YES (n)	NO (n)		
Mother HIV disclosure status				
Disclose to husband	30	488	1	
Disclose to others [c]	18	319	0.9(0.5-1.6)	0.7
No of ANC visit				
1-3 visit	38	548	1.8(0.9-3.7)	0.08
>= 4 visit	10	261	1	
Mothers HIV/ART care enrollment				
Enrolled	36	741	1	**0.001***
Not enrolled	6	27	**4.6(1.9-11.0)**	
Mothers WHO clinical stage				
Stage I	13	322	1	
Stage II	10	188	1.3(0.6-2.9)	0.6
Stage III or IV	8	125	1.4(0.6-3.5)	0.4
Mothers PMTCT intervention				
HAART	22	528	1	
AZT+SDNVP+3TC	7	195	0.9(0.4-2.1)	0.8
SD NVP	2	11	3.9(0.9-16.8)	0.06
None	8	9	**13.6(6.0-30.8)**	**0.0001***
Others [a]	4	46	2.1(0.7-6.0)	0.2
Duration of ARV prophylaxis				
<= 1 month	4	36	3.7(0.6-21.7)	0.1
>1 month	2	110	1	
Duration of HAART				
<= 2 months	3	28	3.0(0.9-10.5)	0.08
>2 months	14	415	1	
CD4 count during delivery				
<=350 cell/ul	10	200	1.7(0.7-4.6)	0.3
>350 cell/ul	7	242	1	
Fathers status				
Alive	41	769	1	
Dead	4	9	**7.0(2.5-19.8)**	**0.0001***
Fathers HIV status				
Negative	5	133	1	
Positive	19	455	1.1(0.4-2.8)	0.9
unknown	15	158	2.2(0.8-6.2)	0.2
Father HIV/ART care enrollment				
Enrolled	14	345	1	
Not enrolled	4	42	2.5(0.8-7.8)	0.1

*- significant at a=0.05 **a-** AZT **c-** disclosure to parents, brothers/sisters, friends, relatives and neighbors

Table 7: Bivariate Cox regression analysis of characteristics of infants and young children on selected government and private health facilities in Addis Ababa, September 2009- may 2013

Variables	HIV INFECTION		Crude HR (95%CI)	P- value
	YES(n)	NO (n)		
Infant place of birth				
Hospital	40	756	1	
Home	3	9	**5.8(1.7-18.9)**	**0.003***
Health center	3	25	2.4(0.7-7.8)	0.1
Others [a]	2	12	2.4(0.6-10.3)	0.2
Mode of delivery				
C/S	7	154	1	
SVD	41	598	1.5(0.7-3.3)	0.3
Infant sex				
Male	22	421	1	
female	26	384	1.3(0.7-2.3)	0.3
Infant birth weight				
<2500 grams	6	98	1.2(0.5-2.9)	0.6
>= 2500 grams	31	628	1	
Gestational age				
<37 weeks	7	131	1.3(0.5-3.0)	0.5
>=37weeks	21	496	1	
Infants ARV prophylaxis				
SD NVP+AZT for 7 days	29	599	1	
AZT for 7 days	4	115	0.8(0.3-2.2)	0.6
SD NVP	3	18	**4.2(1.2-13.9)**	**0.02***
None	4	9	**8.7(3.0-25.1)**	**0.0001***
Others [e]	2	38	1.3(0.3-5.6)	0.6
Immunization status				
Not immunized	5	118	0.6(0.3-1.6)	0.3
>=1immunization	43	691	1	
Growth pattern				
Normal growth	44	781	1	
Growth flatter	4	28	2.5(0.9-7.0)	0.08
Developmental milestones				
No red flags	44	793	1	
Red flags	4	16	**4.3(1.5-12.1)**	**0.005***
Infant feeding type				
Breast fed	40	526	**2.5(1.2-5.4)**	**0.01***
Formula fed	8	283	1	

Maternal breast condition				
Normal	47	776	1	
Any breast problems	1	33	0.5(0.07-3.7)	0.5
Duration of breast fed				
<=6 months	26	233	2.9(1.5-5.8)	**0.002***
>6 months	12	289	1	

***-** significant at **a=0.05** **C/S** = cesarean section, **SVD** = spontaneous vaginal delivery **a**= private clinic, on the street **e= zdv**

Those variables with p< 0.2 on the bivariate Cox regression analysis were entered into Multivariate Cox regression model after the multi co linearity assumption was assessed. Infant breast fed duration, mothers' duration on HAART, mothers' duration on ARV prophylaxis and father HIV/ART care enrollments were excluded from the multivariate Cox regression even if these variables had a p- value < 0.2 on bivariate Cox regression to transmission of HIV. Because there were only 560 valid cases of infants on duration of breast fed, 460 valid cases of mothers on duration HAART, 152 valid cases of mothers on duration ARV prophylaxis and 405 valid cases of fathers HIV /ART care enrollments; so the number of missing values were high and this may reduce the power of the study if they are included in the analysis.

Based on the multivariate Cox regression 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 for the transmission of HIV to their infants and young children as compared to infants and young children from mothers on HAART intervention. Breast fed infants and young children were 3.8 (95%CI 1.3-11.1) times higher risks to acquire HIV infection as compared to formula fed infants and young children.

Table 8: Multivariate Cox regression analysis for determinants of HIV transmissions in infants and young children on selected government and private health facilities in Addis Ababa, September 2009- may 2013

Variables	HIV INFECTION		Crude HR (95%CI)	Adjusted HR (95%CI)
	YES(n)	NO (n)		
Mothers status				
Alive	45	793	1	1
Dead	2	4	11.6(2.8-48.8)	0.0
Fathers status				
Alive	41	769	1	1
Dead	4	9	7.0(2.5-19.8)	1.0(0.08-12.1)
No of ANC visit				
1-3 visit	38	548	1.8(0.9-3.7)	1.6(0.7-3.7)
>=4 visit	10	261	1	1
Mothers HIV/ART care enrollment				
Enrolled	36	741	1	1
Not enrolled	6	27	4.6(1.9-11.0)	3.2(0.7-13.2)
Mothers PMTCT interventions				
HAART	22	528	1	1
AZT+ sd NVP+3TC	7	195	0.9(0.4-2.1)	0.5(0.2-1.5)
SD NVP	2	11	3.9(0.9-16.8)	3.2(0.6-17.1)
NONE	8	9	13.6(6.0-30.8)	**4.8(1.1-22.5)***
Others [a]	4	46	2.1(0.7-6.0)	1.4(0.3-6.1)
Infant place of birth				
Hospital	40	756	1	1
Home	3	9	5.8(1.7-18.9)	1.5(0.2-9.9)
Health center	3	25	2.4(0.7-7.8)	0.6(0.09-5.2)
Others [b]	2	12	2.4(0.6-10.3)	0.2(0.01-3.5)
Infants ARV prophylaxis				
SD NVP+AZT for 7 days	29	599	1	
AZT for 7 days	4	115	0.8(0.3-2.2)	0.5(0.1-1.6)
SD NVP	3	18	4.2(1.2-13.9)	2.5(0.6-10.2)
None	4	9	8.7(3.0-25.1)	1.6(0.2-9.8)
Others [c]	2	38	1.3(0.3-5.6)	0.7(0.1-5.6)
Infant feeding type				
Breast fed	40	526	**2.5(1.2-5.4)**	**3.8(1.3-11.1)***
Formula fed	8	283	1	1
Developmental milestones				
No red flags	44	793	1	1
Red flags	4	16	**4.3(1.5-12.1)**	3.6(0.8-15.7)
Growth pattern				
Normal growth	44	781	1	1
Growth flatter	4	28	2.5(0.9-7.0)	0.9(0.2-4.8)

*****-significant at **a=0.05, a=AZT**, **b**= private clinic, on the street, **c=ZDV**

5.5. Cumulative risk of development of any types of morbidity in breast fed and formula fed infants and young children.

Both cohorts contributed a total of 270075 infant days with an incident rate of any type of morbidity 0.7 per 1000 infant days. Of which 179173 infant days contributed from breast fed infants and young children and 90902 infant days were from formula fed infants and young children with their corresponding incident rate of any types of morbidity were 0.75 per 1000 infant days and 0.6 per 1000 infant days respectively. 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 cumulative probability of not developing any types of morbidity for the first 6 months of follow up time for both breast fed and formula fed infants and young children were 97%. The cumulative morbidity free survivals of infants and young children for the first 360 days were 75% and 76% for breast fed and formula fed infants respectively. The cumulative probabilities of not developing any types of morbidity at 540 days for breast fed infants were 33% and it was 48% for formula fed infants and young children. The median time to develop any types of morbidity for breast fed infants and young children was 506 days and it was 565 days for formula fed infants and young children.

Table 5 9 a: Actuarial life table analysis of developments of any types of morbidity for breast fed infants and young children on selected government and private health facilities in Addis Ababa, September 2009- may 2013

Infant Feeding Types	Time interval in days	Number entering interval	Number withdrawing during interval	Number exposed to risk	Number of morbidity	Probability of not developing morbidity	Cumulative probability of not developing morbidity
BF	0	566	9	561.5	0	1.00	1.00
	30	557	16	549	2	1.00	1.00
	60	537	6	536	4	0.99	0.99
	90	529	8	525	2	1.00	0.99
	120	519	7	515.5	4	0.99	0.98
	150	508	12	502	2	1.00	0.97
	180	494	6	491	3	0.99	0.97
	210	485	26	472	4	0.99	0.96
	240	455	32	439	9	0.98	0.94
	270	414	50	389	19	0.95	0.89
	300	345	99	295.5	27	0.91	0.81
	330	219	51	193.5	16	0.92	0.75
	360	152	20	142	3	0.98	0.73
	390	129	17	120.5	6	0.95	0.69
	420	106	9	101.5	1	0.99	0.69
	450	96	12	90	7	0.92	0.63
	480	77	23	65.5	15	0.77	0.49
	510	39	17	30.5	10	0.67	0.33
	540	12	5	9.5	2	0.79	0.26
	570	5	3	3.5	0	1.00	0.26
	600	2	1	1.5	0	1.00	0.26
	630	1	1	0.5	0	1.00	0.26

Table 6: Actuarial life table analysis of developments of any types of morbidity for formula fed infants and young children on selected government and private health facilities in Addis Ababa, September 2009- may 2013

Infant Feeding Types	Time interval in days	Number entering interval	Number withdrawing during interval	Number exposed to risk	Number of morbidity	Probability of not developing morbidity	Cumulative probability of not developing morbidity
FF	0	291	2	290	0	1.00	1.00
	30	289	8	285	2	0.99	0.99
	60	279	1	278.5	2	0.99	0.99
	90	276	5	273.5	4	0.99	0.97
	120	267	3	265.5	0	1.00	0.97
	150	264	6	261	0	1.00	0.97
	180	258	5	255.5	1	1.00	0.97
	210	252	17	243.5	0	1.00	0.97
	240	235	15	227.5	5	0.98	0.95
	270	215	30	200	10	0.95	0.90
	300	175	60	145	10	0.93	0.84
	330	105	33	88.5	8	0.91	0.76
	360	64	11	58.5	1	0.98	0.75
	390	52	2	51	2	0.96	0.72
	420	48	12	42	1	0.98	0.70
	450	35	3	33.5	1	0.97	0.68
	480	31	9	26.5	6	0.77	0.53
	510	16	9	11.5	1	0.91	0.48
	540	6	4	4	1	0.75	0.36
	570	1	0	1	0	1.00	0.36
	600	1	0	1	0	1.00	0.36
	630	1	0	1	0	1.00	0.36
	660	1	1	1	0	1.00	0.36
	690	1	0	1	0	1.00	0.36
	720	1	0	1	0	1.00	0.36
	750	1	0	1	0	1.00	0.36
	780	1	0	1	0	1.00	0.36
	810	1	0	1	0	1.00	0.36
	840	1	0	1	0	1.00	0.36
	870	1	0	1	0	1.00	0.36
	900	1	0	1	0	1.00	0.36
	930	1	1	0.5	0	1.00	0.36

The Kaplan Meier analysis and log rank test were used to compare the survival probabilities of the two groups. There were no significant different risk of developing any types of morbidity in breast and formula fed groups **(log rank statistics =0.92, df=1, p=0.34).**

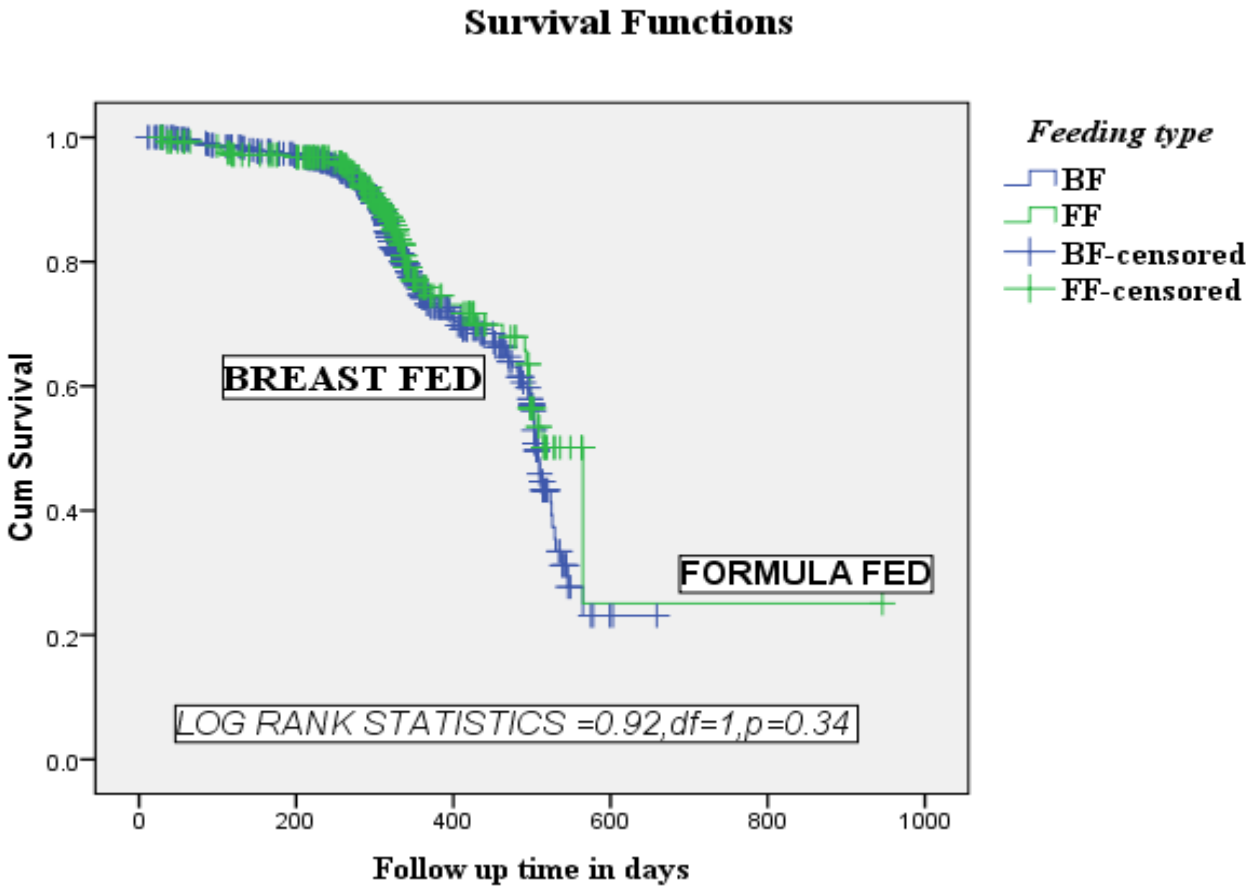

Figure 2: Kaplan Meier estimate of survival among HIV exposed infant and young children during their breast fed and formula fed follow up time in the HIV exposed infant clinic in the selected government and private health institution, September 2009- may 2013

5.6. Determinants of development of any types of morbidity on HIV exposed infants and young children during their follow up period.

Bivariate Cox proportional model was used to assess the relation between the selected determinants and the risk of development of any types of morbidity. Before fitting the covariate into the model Cox proportional hazard assumption was checked by schoenfield residuals test and graphically by –ln(-ln) survival probability. Those variables with p< 0.2 on the bivariate Cox regression analysis were fitted to the multivariate Cox regression model after the multi colliniarity were assessed by using tolerance and variance inflation factor test.

Based on the bivariate Cox regression analysis infants on sd NVP ARV prophylaxis were 5.1(95%CI 2.0-12.6, P= 0.001) times higher risk than the reference groups to develop any types of morbidity .As compared to infants on SD NVP+AZT for 7 days ARV prophylaxis, infants who didn't take any types of ARV prophylaxis were 5.4(95% CI 2.5-11.6, P=0.0001) times higher risk to develop any types of morbidity. Infants and young children under the red flags of developmental miles stone was 2.2(95% CI 1.0-4.5, p=0.02) time higher hazard risk than those under the no red flags of developmental milestone. Based on the bivariate Cox regression analysis all maternal socio demographic variables, parents clinical characteristics and infants' delivery and clinical characteristics except infants' developmental milestone and infants ARV prophylaxis were not statistically significantly associated to the development of any types of morbidity. In fact the basic exposure variables i.e. the infants feeding type were also not statistically significant association to the development of any types of morbidity on the follow up time. **(See Annex-V)**

Variables in bivariate Cox regression with a p- value < 0.2 were included in the multivariate Cox regression after the multi co linearity were assessed. Mothers ARV prophylaxis and infants duration of breast fed were excluded from the analysis due to high number of missing values and this may reduce the power of the study if they are included in the analysis.

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. Based on the multivariate Cox regression analysis infants and young children from mothers who disclosed their HIV status to other than their husband to others were decrease 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 ARV 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 the reference groups, infants on others forms of ARV prophylaxis had a hazard ratio of 5.8(95%CI 3.5-9.8).

Table 10: 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 2009- may 2013

Variables	MORBIDITY		Crude HR (95%CI)	Adjusted HR (95%CI)
	YES (n)	NO (n)		
Mothers HIV disclosure status				
Disclose to husband	122	396	1	1
Disclose to others [c]	68	269	0.7(0.5-1.0)	**0.7(0.5-0.9)***
No of ANC visit				
1-3 visit	136	450	1.3(0.9-1.7)	1.3(0.9-1.8)
>=4 visit	55	216	1	1
Mothers PMTCT Intervention				
HAART	130	420	1	1
AZT+SDNVP+3TC	42	160	0.9(0.6-1.4)	1.0(0.7-1.4)
SD NVP	3	10	1.1(0.4-3.5)	1.8(0.5-6.1)
None	6	11	1.6(0.7-3.7)	0.9(0.4-2.5)
Others	6	44	0.5(0.2-1.2)	0.6(0.2-1.4)
Infants place of birth				
Hospital	180	616	1	1
Home	3	9	0.0	0.9(0.2-4.6)
Health center	3	25	4.5(1.0-19.6)	0.8(0.2-2.6)
Others [a]	2	12	2.8(0.3-21.5)	0.5(0.1-2.1)
Infants ARV prophylaxis				
SD NVP+AZT for 7 days	128	500	1	1
AZT for 7 days	27	92	1.3(0.8-2.0)	1.3(0.8-1.9)
SD NVP	5	16	5.1(2.0-12.6)	**4.8(1.9-12.0)***
None	7	6	5.4(2.5-11.6)	**3.8(1.3-10.6)***
Others [e]	19	21	5.5(3.4-8.9)	**5.8(3.5-9.8)***
Growth pattern				
Normal growth	179	646	1	1
Growth flatter	12	20	1.8(0.9-3.2)	1.3(0.6-2.7)
Developmental milestone				
No red flags	183	654	1	1
Red flags	8	12	2.2(1.0-4.5)	1.5(0.6-3.6)

***significant at **a=0.05**, **c-** Disclosure to parents, brothers/sisters, friends, relatives and neighbors, **a**= private clinic, on the street. e- zdv

5.7. Describing the mortality rate of infants and young children in breast fed and formula fed groups

Both cohorts had the contribution of 270075 infant days, of which 90902 infant days were from formula fed and 179173 infant days were from breast fed infants. There were totally seven deaths of infants and young children in the two groups of cohorts with a total rate of mortality incidence in infants and young children of breast and formula fed groups were 0.025 per 1000 infant days. The incident rate of mortality of breast fed and formula fed infants and young children were 0.016 per 1000 infants' days and 0.044 per 1000 infants' days respectively.

There were no statistically significant differences of mortality of infants and young children from the two groups of cohorts with their incident rate ratio of 0.38 (95%CI 0.06-2.2, p-0.2). This may be due to it small no of cases and due to this reason we were unable to do further statistical analysis.

Table 11: The incident rate of mortality of infants and young children in the selected government and private health facilities in Addis Ababa, September 2009- may 2013

Feeding type	Infant days	Death	Incident rate /1000 infants and young children	Incident rate ratio (95%CI)	P- value
Breast fed	179173	3	0.016	0.38(0.06-2.2)	0.22
Formula fed	90902	4	0.04		

6. DISCUSSION

This study assessed the HIV free survival and health benefits of breast and formula fed infants and young children of HIV infected mothers which is an overwhelming problem and a dilemma for choosing a feeding type to balance the risk of infants being exposed to HIV through breast feeding with risk of death and morbidity from causes other than HIV if infants are not breast fed.

Results of this study suggested that those breast fed infants and young children were about four times more likely to acquire HIV infection than formula fed infants and young children. There was statistically significant difference on the incidence rate of HIV infection for breast and formula fed infants and young children with their incident rate ratio of 2.54. As a result the 18 month HIV free survival of formula fed infants and young children were higher (97%) than breast fed infants (84%).There was no statistically significant difference in the developments of any types of morbidity between breast and formula fed infants and young children; the incident rate of any types of morbidity for breast fed and formula fed infant were 0.75/1000 infants days and0.6/1000 infants days respectively. Only seven deaths of infants and young children were reported in this study with the incident rate of 0.025 per 1000 infant days.

In this study the 18 month cumulative probability of HIV free survival was significantly lower in the breast feeding infants and young children than formula fed infants and young children (84%vs 97%).This is comparable with the study conduct in Kenya (RCT) which showed that the rate of HIV free survival at two years was significantly lower in breast fed arm than formula fed groups (58%vs70%) (27). The study conducted in kuazulu Natal, South Africa also stated that probability of HIV free survival at 18month was significantly lower in children who breast fed for more than 6 months than in the combined group of children replacement fed or breast fed for less than 6 months (91% vs. 96%) (12). It is also consistent with the other study conducted in Coˆte d'Ivoire (25). But it is inconsistent with the study done in rakai Uganda which shows the 12 months cumulative probabilities of HIV free survival were no statistically significant different by feeding choice (86% in the formula-fed compared to 96% in breast-fed group (Adjusted HR= 2.8(95%CI = 0.67–11.7, P-value = 0.16) this may be due to high number of infants death in formula fed group within the 12 month follow up period which may be confounded with lack of adequate and safe water supply because it was community cohort study (17). The result of the current study is not also in line with the study done in Rwanda which shows HIV-free survival

by nine months was 95% (95% CI 91–97%) in the BF group and 94% (95% CI 91–96%) for the FF group (P=0.66), with no significant difference in the adjusted analysis (adjusted hazard ratio for BF: 1.2 (95% CI 0.5–2.9%) (31).There are also others studies which is inconsistent with this result (8, 31, 33).

Another important finding was the cumulative risk of HIV infection, i.e. the complement of HIV free survival, in the two forms of infants feeding modalities. Based on our findings the probabilities of cumulative risk of HIV transmissions from infected mother to their child during the follow up period was 16% for breast fed infants and 3% for formula fed infants and young children. And 60% of risk difference in the breast fed infants and young children were contributed from mothers' breast milk. This results were in line with the study done in Kenya even though it shows a significantly different risk of HIV infection; the estimated cumulative risk of HIV infection at 24 months in both cohort were high (36.7% in the breast feeding arm and 20.5% in the formula arm) (27). This may be due to the antiretroviral naïve pregnant women were involved in this study. These findings were also similar with the study done in HIV-infected pregnant women attending rural and semi-urban antenatal clinics in KwaZulu Natal, Durban South Africa (12). But this result was inconsistent with the other studies conducted in developing countries in Africa ((17, 31) and a study conducted in India which shows the effects of formula feeding and breast feeding on child growth, infant mortality and HIV transmission in children born to HIV infected pregnant women (33).

In this study the median duration of breast feeding was 7.3 months with IQR of 3.8 months which is inconsistent with other studies (12, 25, 27, 32) this is because of all these study had different duration of breast fed and follow up time. According to the Ethiopia demographic and health survey 2011reports the median duration and the mean duration of any breastfeeding in Ethiopia are 25 months. The median duration of exclusive breastfeeding is 2.3 months, and the mean duration of exclusive breastfeeding is 4.2 months (39). Majority of HIV infection occurred in the first six month of breast fed time with un adjusted hazard ratio of 2.9 than infants who breast fed more than 6 months, which is consistent with others studies (17, 27). But another study suggested that the risk of transmission of HIV increase with duration of breast fed (28). Studies also determined that there was a constant hazard risk of transmissions of HIV throughout breast fed time (26) .Compared to formula fed infants and young children, breast fed infants and young children had an adjusted hazard ratio of 3.8 (adjusted HR =3.8, 95%CI 1.1-11.1) for HIV

infection which was adjusting by mothers PMTCT interventions, mothers HIV/ART enrolments, mothers status, no of ANC visit, infants ARV prophylaxis, Infants place of birth, infants and young children developmental milestone and infants and young children growth pattern.

In this study it was difficult to determine the effect of mothers CD4 count at 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 there were only 459(53%)of mothers had CD4 count during delivery. But Studies have consistently shown a relationship between maternal CD4 cell count around the time of delivery and risk of postnatal HIV transmission. In the BHITS meta-analysis, a strong association was observed between risk of postnatal infection after 4 weeks of age and maternal CD4+ cell count: transmission increased 8 times at counts less than 200 x 106 cells/L and 3.5 times at counts between 200 and 500 x 106 cells/L compared with the reference group of CD4+ cell count greater than 500 x 106 cells/L (26). Low plasma CD4+ counts have been associated with detection of HIV DNA in breast milk *(29)*. The study done in Kwa Zulu Natal also showed that antenatal maternal CD4 count below 200cells/ml was associated with a 3.6-fold increased risk of HIV infection or death (12, 14). Infants born to mothers with CD4-cell counts less than 200 per μL were almost four times more likely to acquire HIV or die than were those born to mothers with CD4-cell counts greater than 500 per μL, and those born to mothers with CD4-cell counts between 200 and 500 cells per μL were 2.2 times more likely to acquire HIV or die (14). The rate of late postnatal transmission increased 2.6-fold for every one log10 increase in plasma RNA viral load (measured in late pregnancy)(18). In a study conducted in Durban, South African women with detectable RNA viral load in breast milk at any time during the first six months postpartum were more likely to transmit than those with undetectable RNA viral load (18).

Use of prevention of mother to child transmissions of HIV intervention during pregnancy, delivery and the postnatal period was very important to reduce the risk of vertical transmission of HIV to their infants. Based on our findings infants and young children from mothers who were not initiated to any types of PMTCT intervention had an adjusted hazard ratio of 4.8(95%CI 1.1-22.5) than those infants and young children whose mother was on highly active antiretroviral therapy (HAART) intervention for the acquisition of HIV. This result is consistent with the study done in Rwanda which showed that children born to HIV positive women who received HAART

during pregnancy were 60% less likely to be infected with HIV when compared with children whose mothers did not take any ARV during pregnancy (AOR: 0.4, 95% CI: 0.1-0.96) (3).

Another important issue was the development of any types of morbidity. 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). This result is consistent with other studies conducted in South Africa and cote devoir (11, 25).

But there are studies with inconsistent findings, a systematic review mad on breast feeding and the risk for diarrhea morbidity and mortality shows the results of random effects meta-analyses of eighteen included studies indicated varying degrees of protection across levels of breastfeeding exposure with the greatest protection conferred by exclusive breastfeeding among infants 0-5 months of age and by any breastfeeding among infants and young children 6-23 months of age. Specifically, not breastfeeding resulted in an excess risk of diarrhea mortality in comparison to exclusive breastfeeding among infants 0-5 months of age (RR: 10.52) and to any breastfeeding among children aged 6-23 months (RR: 2.18) (35). For HIV-exposed infants in South Africa, Coutsoudis et al. observed a 2-fold increase in risk of morbidity (e.g. diarrhea, lower respiratory tract infection, ear infection) among those who had never breastfed compared those who had reported ever breastfeeding (34). In a study in Brazil, the risk of hospital admissions for pneumonia was increased 17-fold in infants who were not being breastfed (odds ratio, OR, 16.7, 95% CI 7.7– 36.0) compared to those being breastfed (18). In contrast In the United States of America, a nationally representative cross-sectional home survey conducted from 1988 to 1994 documented an increased risk of respiratory tract infections, including pneumonia and recurrent otitis media, in children who were fully breastfed for four versus six months (18).

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 were not statistically significantly association with the development of morbidity which is supported by other studies (11, 25). In this study infants and young children from mothers who disclose their HIV status to parents, brother/ sisters, friends, relatives and neighbors' were decrease the risk of developments of any types of morbidity by 30% which was adjusted for no ANC visit, mothers PMTCT interventions, infants place of birth, infants ARV prophylaxis, growth pattern and developmental milestones.

7. STRENGTH

This study was considered censored observation with multivariate analysis.

8. LIMITATIONS

-HIV test done only at 45 days, 12 months and 18 months to confirm their HIV status which is difficult to exclude the intra and peri partum transmission of HIV infection, so in this study it was difficult to determine the actual timing of HIV transmission.

-There were some missing values and some variables with high missing values are excluded in the analysis.

9. CONCLUSION

- The cumulative risk of HIV transmissions during the infants feeding period from infected mother 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 feeding infants and young children as compared to formula fed infants and young children.
- The majority of HIV infection occurs in the early period of breast fed duration before 6 months.
- In this study there was 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. And those mothers who disclose their HIV status for their parents, brothers/sisters, friends and neighbors had significantly lower risk of development of any types of morbidity for their infants.
- There were a total of seven deaths for breast fed and formula fed infants and young children.

10. RECOMMENDATIONS

Addis Ababa City Administration Health Bureau and FMOH

- ✓ Programs for the prevention of mother to child transmission (PMTCT) should re-enforce ARV intervention for HIV positive mothers which can drastically reduce the risk of HIV transmissions through breast fed.
- ✓ Formula feeding or Breastfeeding with ARVs prophylaxis is likely to give infants the greatest chance of HIV-free survival.

Health professional working on PMTCT clinic

- ✓ All HIV positive pregnant mothers should be properly counseled and supported to enable them to choose the best feeding option and balancing the risk and benefits of breast feeding and formula /replacement feedings.

Future research

- ✓ Future prospective and /or community based study is recommended to address the limitation of this study and to determine the effects of patterns of breast feeding for the transmission of HIV.

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12. ANNEXES

ANNEX –I CONCEPTUAL FRAMEWORK

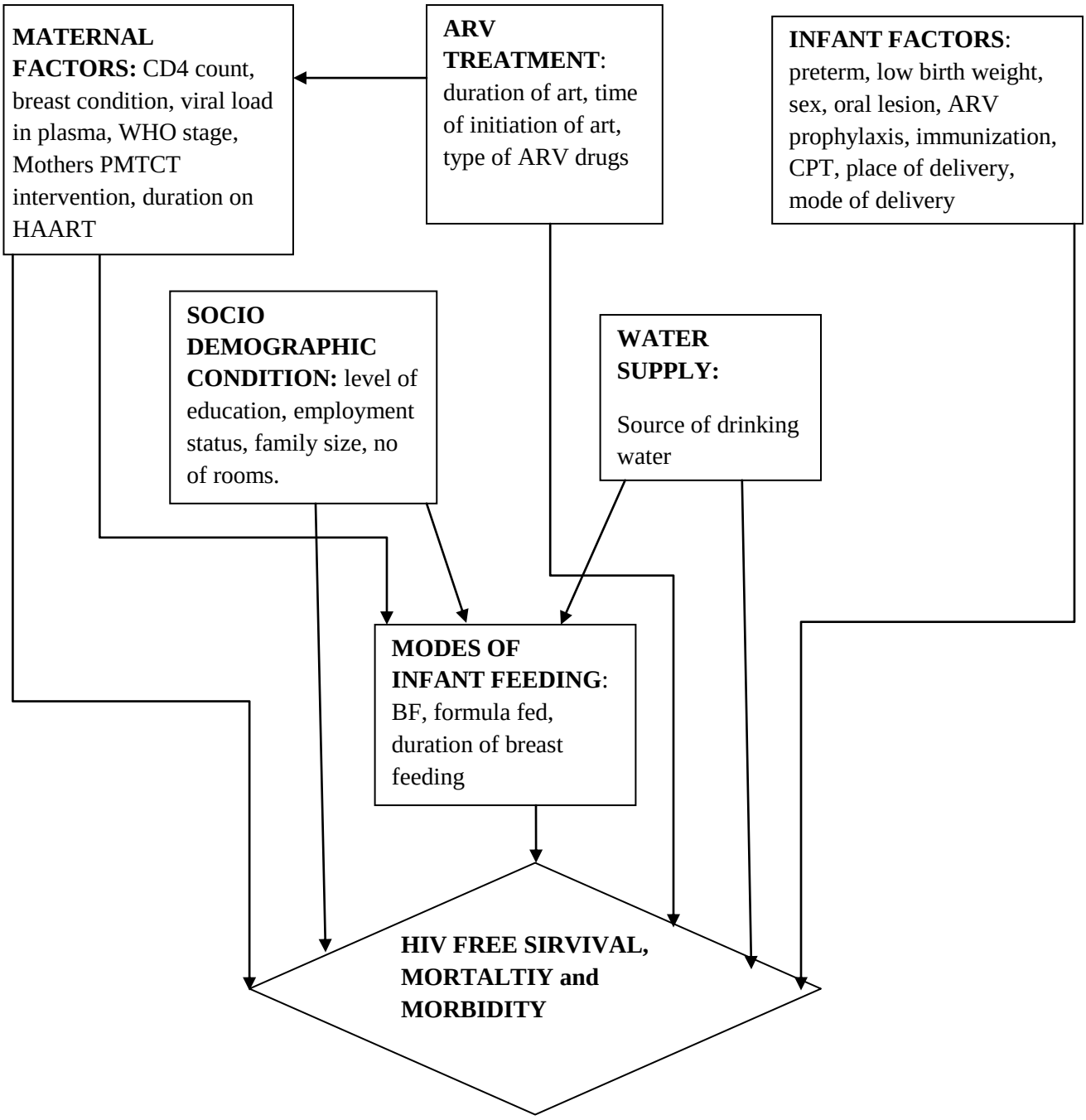
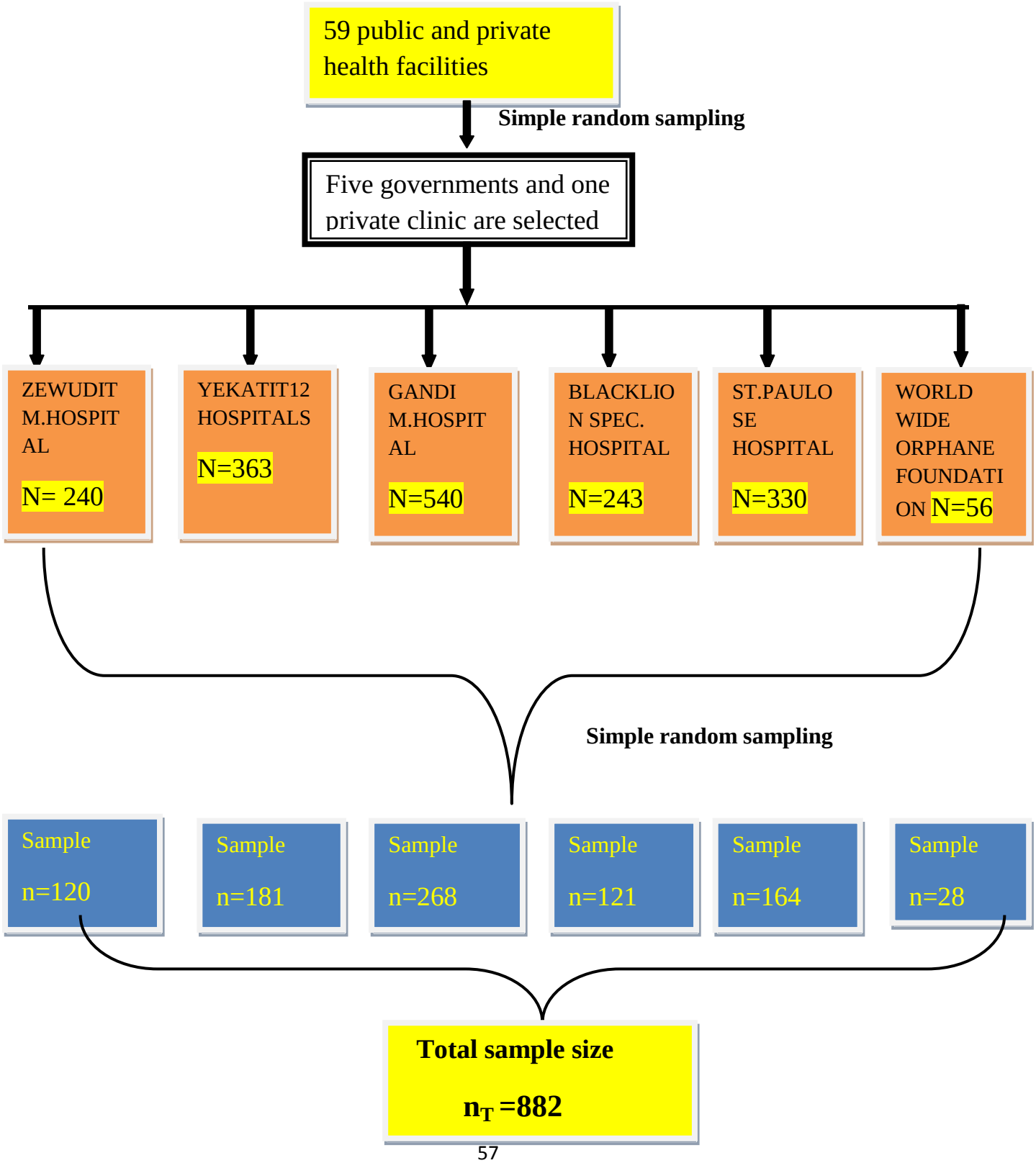


Figure 3: Conceptual frame work on determinants factors for HIV free survival of HIV exposed infants which was developed by reviewing International Center for AIDS Care and Treatment Programs , Columbia University Mailman School of Public Health, A review on HIV transmission through breast feeding and Randa J. Saadeh etal , infants feeding and HIV transmission**.**

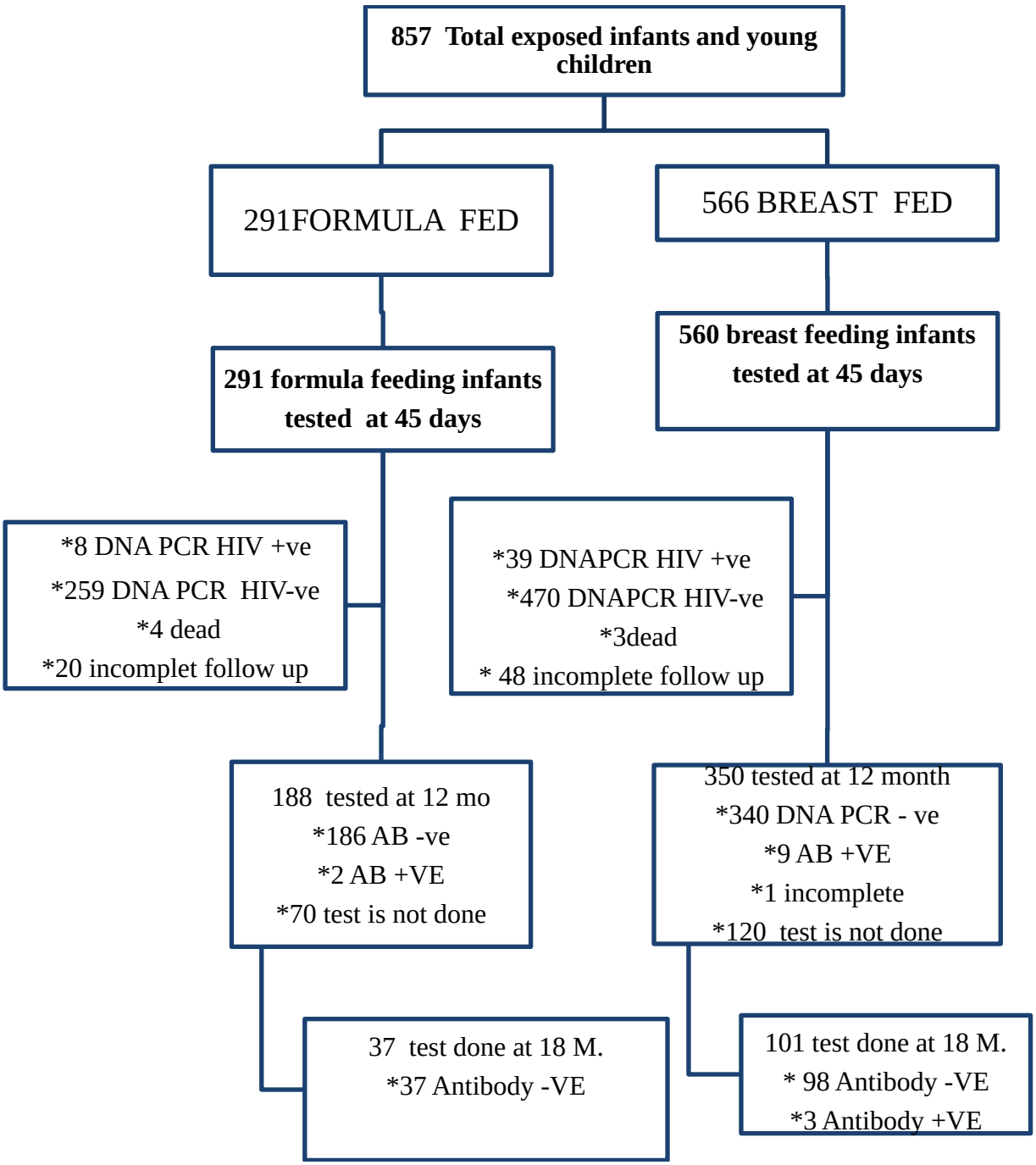
ANNEX-II: SAMPLING PROCEDURES

Figure 4: Sampling procedure



ANNEX –III: ANALYSIS FRAMEWORK

Figure 5: Analysis framework



ANNEX-IV: DETERMINANTS OF DEVELOPMENT OF MORBIDITY

Table 1: Bivariate Cox regression analysis on selected socio demographic characteristics of mothers on selected government and private health facilities in Addis Ababa, September 2009-may 2013

Variables	MORBIDITY		Crude HR (95%CI)	p- value
	YES (n)	NO (n)		
Source of drinking water				
Pipe water	0	7	1	
Running water	82	366	20.6(0.0-1.4E5)	0.5
Mothers employment status				
Working full time	33	123	1	
Working part time / Not working due to ill	23	88	1.0(0.6-1.7)	0.9
Unemployed /others [a]	59	208	1.0(0.7-1.6)	0.8
Mothers levels of education				
No education	12	53	1.2(0.4-3.1)	0.7
Primary	58	188	1.2(0.5-2.5)	0.7
Secondary	53	206	1.0(0.4-2.3)	0.9
Tertiary	7	31	1	
Mothers marital status				
Married	17	62	1	
Never married	134	419	1.2(0.7-1.9)	0.6
Separated /divorced/windowed	9	54	0.7(0.3-1.5)	0.3
Mother status				
Alive	187	651	1	
Dead	1	5	1.7(0.2-12.3)	0.5

a= house wife

Table-2: Bivariate Cox regression analysis on parents clinical characteristics on selected government and private health facilities in Addis Ababa, September 2009- may 2013.

Variables	MORBIDITY		Crude HR (95%CI)	P-value
	YES (n)	NO (n)		
Mothers HIV disclosure status				
Disclose to husband	122	396	1	
Disclose to others [c]	68	269	0.7(0.5-1.0)	0.05
No of ANC visit				
1-3 visit	136	450	1.3(0.9-1.7)	0.1
>=4 visit	55	216	1	
Mothers HIV/ART care enrollment				
Enrolled	174	600	1	
Not enrolled	9	24	1.5(0.7-2.9)	0.2
Mothers WHO clinical stage				
Stage I	71	264	1	
Stage II	54	144	1.2(0.8-1.8)	0.2
Stage III or IV	28	105	0.7(0.5-1.2)	0.3
Mothers PMTCT Intervention				
HAART	130	420	1	
AZT+SDNVP+3TC	42	160	0.9(0.6-1.4)	0.8
SD NVP	3	10	1.1(0.4-3.5)	0.8
None	6	11	1.6(0.7-3.7)	0.2
Others	6	44	0.5(0.2-1.2)	0.1
Duration of ARV Prophylaxis				
<= 1 month	5	35	0.5(0.2-1.2)	0.1
>1 month	24	88	1	
Duration on HAART				
<=2 months	8	23	0.9(0.4-1.9)	0.9
>2 months	103	326	1	
CD4 count during delivery				
<=350 cell/ul	39	171	0.9(0.6-1.4)	0.7
>350 cell/ul	47	202	1	
Fathers status				
Alive	176	634	1	
Dead	0	13	0.05(0.0-13.4)	0.3
Fathers HIV status				
Negative	27	111	1	
Positive	105	369	0.9(0.7-1.5)	0.9
Unknown	33	140	0.7(0.4-1.2)	0.2
Fathers HIV/ART care enrollment				
Enrolled	81	278	1	
Not enrolled	11	35	1.2(0.7-2.3)	0.5

c- Disclosure to parents, brothers/sisters, friends, relatives and neighbors

Table 3: Bivariate Cox regression analysis of characteristics of infants and young children on selected government and private health facilities in Addis Ababa, Septem2009-may 2013

Variables	MORBIDITY		Crude HR (95% CI)	P-value
	YES (n)	NO (n)		
Infants place of birth				
Hospital	180	616	1	
Home	3	9	2.7(0.9-8.5)	0.09
Health center	3	25	0.6(0.2-1.9)	0.4
Others [a]	2	12	0.4(0.1-1.7)	0.2
Mode of delivery				
C/S	39	122	1	
SVD	137	502	1.2(0.8-1.7)	0.3
Infant sex				
Male	104	339	1	
Female	85	325	0.9(0.7-1.2)	0.6
Infant birth weight				
<2500 grams	23	81	1.3(0.8-1.9)	0.3
>=2500 grams	136	523	1	
Gestational age				
<37 weeks	26	112	0.8(0.5-1.3)	0.4
>=37 weeks	124	393	1	
Infants ARV prophylaxis				
SD NVP+AZT for 7 days	128	500	1	
AZT for 7 days	27	92	1.3(0.8-2.0)	0.2
SD NVP	5	16	**5.1(2.0-12.6)**	**0.0001***
None	7	6	**5.4(2.5-11.6)**	**0.0001***
Others	19	21	**5.5(3.4-8.9)**	**0.0001***
Immunization status				
Not immunized	40	83	1.2(0.8-1.7)	0.3
>=1immunization	151	583	1	
Growth pattern				
Normal growth	179	646	1	
Growth flatter	12	20	1.8(0.9-3.2)	0.05
Developmental milestone				
No red flags	183	654	1	
Red flags	8	12	**2.2(1.0-4.5)**	**0.02***
Infant feeding type				
Breast fed	136	430	1	
Formula fed	55	236	0.8(0.6-1.2)	0.3
Mothers breast condition				
Normal	181	642	1	
Any breast problems	10	24	1.6(0.8-3.0)	0.16
Duration of breast fed				
<=6 months	60	199	1.3(0.9-1.8)	0.1
>6 months	75	226	1	

*significant at **a=0.05** **a**= private clinic, on the street **C/S** = cesarean section, **SVD** = spontaneous vaginal delivery

ANNEX-VI: ENGLISH VERSION DATA EXTRACTION /COLLECTION FORMAT

General information for mothers or care takers

My name is _____, I am health professional working here in -------hospital PMTCT clinic and now I am collecting data from HIV exposed infants registration books for the research being conducted to determine Survival and Health Benefits of Breastfeeding Versus formula or Replacement feedings for Infants and young children born to HIV-Infected Women who are on PMTCT follow up on selected hospitals in Addis Ababa.

In resource-limited settings with high prevalence of HIV, health workers face a dilemma on how best to advise HIV-infected mothers on infant-feeding practices. Unfortunately, most at risk infants are in the developing world where breast feeding is the pillar of child survival, associated with reduced morbidity and mortality from infectious diseases and providing inexpensive nutrition. The objectives of this study is to compare the survival and health benefits of breast feeding and formula feeding in infants and young children of HIV infected women followed under the prevention of mother to child transmission of HIV (PMTCT) programs.

Your child is selected as one of study subject by chance. The investigator employed me (from this PMTCT clinic) for this data collection to maintain your data strictly confidential, i.e. not to let others outside of this clinic to access your child's name and other identifiers. We believe that findings of this study have had paramount importance on mortality and HIV free survival of infants and young children of HIV infected women and the risk-benefit of breastfeeding and replacement feeding to improve HIV-free survival of HIV-exposed infants.

Information which is necessary for the study will be taken from exposed infant registration books. As the study was conducted through review your medical records alone, it will not inflict any harm as far as the confidentiality is kept. The information will be taken when you give permission, participation is totally voluntary. Your willingness for your child's record information to be utilized in this study will help us to achieve the stated benefits of the study. Your child's name and other personal identifiers were not being recorded on data collection form and the information that you give us will be kept confidential and will also be used for this study

purpose alone. You have full right not to let your child's information on exposed infants' registration book to be consumed for this study. But the information that would be taken was quite useful for the study. Your child will not face any problem if you do not allow the information to be taken from your records and your child will not also be denied of getting any medical services from the hospital. If you have any questions about this study you may ask me or the principal investigator Mekonnen Assefa (Tel: +251-9-12-87-30-43or E-mail: mekonnen.as@gmail.com)

Are you willing to let your child's information to be utilized for this study?

1. Yes 2. No

Signature of the interviewer which shows that the respondent has consented (verbally) to take part in the study _____

Data Collection Format

Sr. No	**Variable**	**Description**	**Remark**
PART I MATERNAL SOCIO- DEMOGRAPHIC CONDITION			
1. Living condition (no of rooms)	---------- rooms		
2. Family size (no of people in the house hold)	---------- peoples		
3. Source of water	1. Pipe water 2. Running water 3. Others (specify)--------		
4. Marital status	1. Never married 2. Married 3. Separated 4. Divorced 5. Windowed		
5. Employment status	1. Working full time 2. Working part time 3. Not working /studying due to ill health 4. Un employed 5. Others (specify)------		
6. Level of education	1. No education 2. Primary 3. Secondary 4. Tertiary		

7. Religions	1. Orthodox 2. Protestant 3. Muslims 4. Catholic 5. Others (specify)--------		
PART II MATERNAL CHARACTERISTICS			
1. mothers unique ART and MRN number	Unique ART No ----------	MRN No ----------	
2. Age of the mother	---------- years		
3. Maternal WHO clinical Stage of HIV at birth	1. Stage I 2. Stage II 3. Stage III 4. Stage IV	Based on WHO clinical staging	
4. Disclosure status of the mother	1. Husband 2. Brothers/sisters 3. Friends 4. Parents 5. Neighbor 6. Others (specify)---------		More than one answers is possibe
5. Mother Status	1. Alive 2. Dead		
6. If the mother is alive	1. enrolled in HIV/ART care 2. Not enrolled in HIV/ ART care		
7. Mothers PMTCT intervention	1. None 2. sd NVP 3. AZT+ sdNVP + 3TC 4. HAART 5. others , specify-------		
8. ANC visit date (DD/MM/YYYY)	1. First visit----/----/---------- 2. Second visit----/----/--------- 3. Third visit -----/-----/--------- 4. Fourth visit -----/----/-------- 5. Others visit -----/-----/-----		
9. Duration of pre partum ARV prophylaxis or HAART	ARV ---------- months HAART---------- months		
10. If mother on HAART specify the regimen	1. Regimen---------- 2. Date started (dd/mm/yyyy ------/------/------		
11. Cd4 count during delivery (DD /MM/YYYY)	1. ---------- (cells/mm^3) Date ------/-------/---------	take the nearest cd4 count	
PART III FATHER'S CHARACTERISTICS			

1. Father status	1. Alive 2. Dead		
2. Father HIV status	1. positive 2. negative 3. unknown		
3. If the father HIV positive	1. enrolled in HIVART care 2. not enrolled in HIV/ART care		
PART IV INFANT CHARACTERISTICS			
1. HIV exposed infants unique ID ----------			
2. Infants date of birth	DD / MM/ YYYY ----------/----------/--------		
3. Place of birth	1. home 2. Hospital 3. health center 4. Other specify-----		
Delivery summary			
4. Mode of delivery	1. SVD 2. cesarean section (C/S) 3. vacuum 4. forceps 5. episiotomy		
5. new born	1. single 2. multiple		
6. Infant sex	1. Male 2. female		
7. Infants birth weight	1. ---------- kilograms (kg)		
8. Gestational age (Terms of gestation)	1. Preterm (--------weeks) 2. Term(----------weeks) 3. post term (------weeks)	Preterm < 37wks Term 37- 42 wks Postterm>42wks	
9. Infants ARV prophylaxis	1. none 2. sd NVP 3. sd NVP+AZT for7 days 4. other; specify (Regimen& Duration)		
10. Infants Immunization status	1. BCG 2. OPV (0) (1) (2) (3) 3. DPT (1) (2) (3) 4. Pentavalent (1) (2) (3) 5. Measles 6. Not immunized		
11. first visit date on HIV exposed infant follow up clinic (entry date)	Date -----/---------/--------- Age at first visit--------(days)		

12. Infant feeding practice for infants less than 6 months	1. Exclusive breast feeding 2. Exclusive replacement feeding	If the answer for question no 12 is 2 skip question no 14	
13. Infant feeding for older than 6 months	1. Breast feeding and complementary feeding 2. Infants weaned off breast feeding 3. replacement feeding with complementary feeding		
14. Duration of breast feeding if a child breast fed older than 6 months.	When the infant stop breast feeding. Date -----/------/----		
15. HIV test done at 45 days	1. Test Date (dd/mm/yyyy) ---------/----- 2. HIV test is not done		
16. HIV test result at 45 days.	1. Sample collected 2. DNA PCR negative 3. DNAPCR positives 4. test result indeterminate		
17. HIV test done at 12 months.	1. test Date (dd/mm/yyyy) --------/-----------/----------- 2. HIV test is not done		
18. HIV test result at 12 months.	1. rapid anti body test negative 2. rapid anti body test positives 3. test result is indeterminate		
19. HIV test done at 18 months.	1. test date(dd/mm/yyyy) --------/-----------/----------- 2. HIV test is not done		
23. HIV test result at 18 months.	1. rapid anti body test negative 2.anti body test positives 3. test result is indeterminate		
24. follow up conclusion (DD/MM/YYYY) --------/-------/-----------	0 = no clinical or laboratory evidence of HIV 1= clinical evidence of HIV 2= laboratory evidence of HIV 3= loss to follow up 4= died 5= other specify ---------		
25. If they are died or infected	Last visit date (DD/ MM/YY) --------/---------/---------		
26. The last visit date if they are complete the 18 months follow up visit.	Last visit date (DD/MM/YY) ----------/-------/----------		

PART V: Extraction of infants' characteristics from the follow up card

Date of follow up visit		Age	Anthropometric measurements			Growth pattern (0/1)	Dev't milestone Red flags (0/1)	Infants feeding practice (1/2/3/4/5/6)	Maternal breast condition if she is breast feeding (0/1/2/3/4)	Abnormal findings or diagnosis that may suggest HIV infection (0/1/2/3/4/5/6/7/8/9)	Cotrimoxazole prophylaxis adherence (G/F/P)	follow up conclusion (0/1/2/3/4/5) if (5) specify ----------
Visit	Date		Wt kg	L cm	HC cm							
First visit(enrollment date)												
6 weeks												
10 weeks												
14 weeks												
4 months												
5 months												
6 months												
9 months												
12 months												
15 months												
18 months												