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ASSESSMENT OF OUTCOMES OF HIV-EXPOSED INFANTS ENROLLED IN
PREVENTION OF MOTHER-TO-CHILD TRANSMISSION (PMTCT) OF HIV
FOLLOW-UP CARE IN EMBU DISTRICT, KENYA

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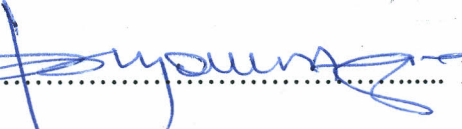
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DEDICATION

In memory of children who have died due to HIV in Kenya.

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ABBREVIATIONS AND ACRONYMS

AIDS	-	Acquired Immunodeficiency Virus
ART	-	Anti Retroviral Therapy
ARV	-	Anti Retro Viral
CD4	-	Cluster of differentiation 4
CI	-	Confidence Interval
DNA	-	Deoxyribose Nucleic Acid
E.I.D	-	Early Infant Diagnosis
HAART	-	Highly Active Antiretroviral Therapy
HIV	-	Human Immunodeficiency Virus
KDHS	-	Kenya Demographic Health Survey
KNBS	-	Kenya National Bureau of Statistics
MTCT	-	Mother-to-Child Transmission
NACC	-	National AIDS Control Council
NASCOP	-	National AIDS and STI Control Program
PCR	-	Polymerase Chain Reaction
PMTCT	-	Prevention of Mother-to-Child Transmission
RR	-	Relative Risk

- UNAIDS** - Joint United Nations Programme on HIV/AIDS
- UNGASS** - United Nations General Assembly on AIDS Special Session
- WHO** - World Health Organization

ABSTRACT

HIV infection transmitted from an infected mother to her child during pregnancy, labour, delivery and breastfeeding is known as mother-to-child transmission (MTCT). HIV infection through this route has become a major killer of children globally. In Kenya, there were about 141,000 HIV-exposed infants in 2007 with 22,000 of them getting HIV infected. Though the PMTCT services have been at the forefront of HIV prevention among HIV-exposed infants since 1998, outcomes of these infants in Kenya are rarely documented. This leaves an important PMTCT intervention aimed at eliminating paediatric HIV largely unmeasured. The purpose of this study was to therefore establish the outcomes achieved among HIV-exposed infants enrolled in the PMTCT as a way of evaluating the efficacy of the program in Embu District. This was done through a descriptive retrospective study by reviewing HIV-exposed infants' registers in four health facilities in Embu District. The study population comprised HIV-exposed infants enrolled in PMTCT follow-up care in the district. Descriptive statistics used were proportions of HIV-exposed infants who received antiretroviral drugs for PMTCT, underwent early infant diagnosis of HIV, were HIV-positive, were lost-to-follow-up and were deceased. Analytic statistics calculated were the relative risk (RR) of HIV transmission and the RR of mortality associated with antiretroviral prophylaxis for PMTCT. The RR of loss-to-follow up among the infants associated with their HIV status was also calculated. The study found that the median infant age of enrolment into the follow-up care was 7 weeks. The uptake rate of infant and maternal antiretroviral prophylaxis was 81.7% and 86.8% respectively. Some 87.7% of the HIV-exposed infants underwent the first early infant diagnosis test for HIV at a median age of 8 weeks. The percentage of HIV-exposed infants who had early infant diagnosis of HIV conducted within the recommended six weeks of age was only 32%, while those who had it conducted by 12 weeks of age was 56%. Only 11.5% of the HIV-positive infants were put on paediatric highly active antiretroviral therapy (HAART) during the period of follow-up. The HIV transmission rate, when the first early infant diagnosis test for HIV was conducted, was 7%. For those infants whose mothers received antiretroviral prophylaxis for PMTCT, HIV transmission was reduced by 92% compared to those who did not (RR [95% CI] 0.08[0.03-0.14]). The cumulative HIV transmission rate at the end of follow-up was 7.3%. For those HIV-exposed infants who received ARV prophylaxis at birth, HIV transmission reduced by 90% by the end of follow-up compared to those who did not receive (RR [95% CI] 0.096 [0.087-0.109]). Cumulative infant mortality rate by the end of the 18-month follow-up was 14.8%; the median time of death was 4 months. Although not statistically significant, there was a 54% mortality reduction among HIV-exposed who received ARV prophylaxis compared to those who did not (RR [95% CI] 0.46 [0.13-1.09]). HIV-exposed and infected infants had 53.8% mortality compared to a lower 13.1% mortality rate among the HIV-exposed but negative infants. Cumulative loss-to-follow-up rate among the HIV-exposed infants was 14.8%. HIV-exposed and infected infants were 14 times more likely to be lost to follow-up than those who were uninfected (RR [95% CI] 14.0 [2.4-18.9]). The 18-month HIV-free survival was 68%. These results show that the PMTCT program in Embu District reduced mother-to-child transmission of HIV and improved the HIV-free survival of the HIV-exposed infants. However, late enrolment of the infants, delay in conducting early infant diagnosis of HIV, poor uptake of paediatric HAART and loss-to-follow-up posed a threat to successful program implementation. The study recommends measures to facilitate early conduction of infant HIV virologic diagnosis, eliminate missed opportunities in ARV prophylaxis for PMTCT, further reduce MTCT, improve paediatric HAART uptake and reduce the high loss-to-follow-up.

CHAPTER ONE

INTRODUCTION

1.1 Background

Globally, HIV/AIDS has become one of the major killers of children, responsible for up to two thirds of all under-five deaths in some high prevalence countries. The HIV infection transmitted from an HIV-infected mother to her child during pregnancy, labour, delivery or breast-feeding is known as mother-to-child transmission (MTCT). This is the most important source of HIV infections in children, accounting for about 430,000 new infections every year globally. Without any intervention, one third of these children will die by their first birthday and half by their second birthday. Hence preventing mother-to-child transmission (PMTCT) of HIV has been a fundamental advance in the AIDS response for the past decade. PMTCT is a highly effective intervention and has huge potential to improve both maternal and child health (WHO^d, 2010).

Preventing mother-to-child transmission of HIV has been at the forefront of global HIV prevention activities since 1998. Infection rates among children born to mothers living with HIV have dropped significantly in recent years, from mean of 500 000 (320 000–680 000) in 2001 to mean of 370 000 (230 000–510 000) children infected with HIV in 2009. Globally an estimated 33 million (30 million - 36 million) people were living with human immunodeficiency virus type-1 (HIV) in 2007. Children less than 15 years old accounted for approximately 2.0 million (1.9 million - 2.3 million) of those living with HIV with an estimated 370 000 (330 000 - 410 000) children less than 15 years newly infected in 2007 (UNAIDS, 2010).

Sub-Saharan Africa is at the core of the epidemic, home to 90% of the HIV burden worldwide. In non-breast-feeding populations, the combined risk of transmission without any interventions is

15-30%. In breast-feeding populations, the combined risk of transmission in the absence of prevention of mother-to-child transmission interventions is 35% (Filteau, 2010). The risk of continued HIV transmission through breastfeeding is directly related to the duration of breastfeeding. In developed countries where combinations of interventions are available, vertical transmission of HIV occurs in 1-2% of infants born to HIV infected women. In Africa, where prolonged breastfeeding for 18-24 months is commonplace, HIV transmission through breast milk may contribute a further risk of 10-15% (WHO^d, 2010). The provision of a package of interventions that include antiretroviral prophylaxis given to the mother and her baby, safe infant delivery and infant feeding counseling and support could reduce the risk of MTCT by 90% or more. This lower rate of mother-to-child transmission means that the number of HIV-exposed children being born will rise and even dwarf even the staggering number of children infected with HIV. Any health problems that these HIV- exposed children may have will thus be of enormous public health importance. Furthermore, these children are crucial to their countries' economic and social future, not only because of their own work and other contributions to their societies but also because they are likely to shoulder much of the burden of care of their HIV-infected relatives (Filteau, 2010).

Access to PMTCT interventions still remains a challenge in Africa. According to the WHO, in 2008 an estimated 34% of eligible HIV-infected women received either PMTCT antiretroviral drugs prophylaxis or highly active antiretroviral therapy for their own health, 32% of infants received antiretroviral prophylaxis for PMTCT, and 15% of children born to infected mothers received an HIV test within 2 months of birth for early infant diagnosis (WHO^d, 2010). A multicentre sub-Saharan study measuring nevirapine in neonatal cord blood from HIV-infected mothers and observing nevirapine administration showed that only 51% had taken the drugs

correctly. Such attrition at each stage of the PMTCT testing and treatment cascade means that ultimately only a small proportion of HIV-infected women and their infants received optimum care in Africa (The PEARL study group, 2010). This situation therefore puts at risk the intended outcome of PMTCT interventions of reducing MTCT of HIV.

Kenya is among the African countries with a large number of pregnant women living with HIV and with 30-40% chance that an HIV-positive breastfeeding mother will pass HIV to her child in the absence of PMTCT services (WHO^b, 2010). There were about 81,000 HIV positive pregnancies in 2009 and as a result there are approximately 22,000 children infected every year. In 2009, about 58,591 HIV positive pregnant women received antiretroviral prophylaxis to reduce the risk of mother-to-child transmission of HIV. There were 81,000 HIV positive women in need of PMTCT services, giving coverage 72.32% for HIV positive pregnant who received antiretroviral prophylaxis to reduce the risk of MTCT. Of these, 11% of HIV-infected pregnant mothers received highly active antiretroviral therapy (HAART) for their own health. With regards to access to antiretroviral therapy for HIV-exposed infants, only 49% of them received antiretrovirals for MTCT. While for early infant diagnosis of HIV, 79% of HIV-exposed infants received HIV DNA polymerase chain reaction (PCR) within 12 months; there was no data available for those who underwent the test within 6 weeks and 3 months. An estimated 141,000 HIV-exposed infants were delivered in Kenya in 2007 as shown in table 1.1 below (NASCO, 2009). The overall national mother-to-child transmission rate was estimated at 27% (NACC^b, 2010).

The PMTCT services in Kenya are free and integrated into Maternal and Child Health services. These include various interventions, such as HIV counseling and testing, preventive treatment with antiretroviral (maternal and infant), support for appropriate infant feeding, access to safe

obstetric care and family planning services. Health facilities offering PMTCT services have increased from about 2000 in 2007 to 3000 in 2008 and 3,397 in 2009. Thus, about 50% of the health facilities in the country are offering PMTCT services (NASCO, 2009).

Table 1.1: Estimated magnitude of MTCT in Kenya, 2007 (NASCO, 2009).

Population (Estimates 2007)	37.2 million
Births per annum	1.73 millions
HIV prevalence in mothers	6.7%
Total number of HIV-exposed infants	141,101
Number of HIV positive infants per annum in Kenya assuming 40% transmission	56,440

The PMTCT program was started in Embu District in 2002 with the aim of having as many pregnant women as possible counseled and tested for HIV and initiated on PMTCT interventions to minimize the risk of MTCT. To date a total of 35 health facilities in the district provide PMTCT services from an initial four. The district has an estimated number of 12,000 births per annum and with an estimated HIV prevalence of 5.1% among pregnant women; there are about 441 HIV-exposed children delivered in Embu every year (Unpublished, 2010).

1.2 Problem statement

Though PMTCT services have been at the forefront of HIV prevention activities in Kenya, its associated outcomes are seldom documented. Embu District for example, has about 441 HIV-exposed infants enrolled in PMTCT care every single year but their eventual outcomes remain

largely unknown. Outcome indicators like infant HIV transmission, HIV-free survival and mortality rates among HIV-exposed infants that could provide information on the efficacy of PMTCT interventions are not measured and reported on in Kenya on a regular basis. Consequently, there is lack of adequate information on the outcomes associated with PMTCT interventions in Kenya and leaving an important intervention aimed at eliminating paediatric HIV largely unmeasured on routine basis. The purpose of the study was therefore to establish the outcomes achieved in HIV- exposed infants as a way of evaluating the efficacy of the PMTCT program in Embu District.

1.3 Justification

The outcomes associated with HIV-exposed children in Kenya are rarely established due to lack regular measurement of PMTCT program performance. By assessing these outcomes, this study has therefore provided information on benefits, effectiveness and challenges of PMTCT in real practise and made recommendations that will be useful for PMTCT programs operating in similar resource-limited settings. Embu District was selected on the basis of having an established PMTCT program for the past nine years with access to a laboratory network for conducting early infant diagnosis of HIV.

1.4 Research questions

- (i) What proportions of HIV-exposed infants enrolled in PMTCT care in Embu District underwent early infant diagnosis of HIV, received antiretroviral drugs prophylaxis for PMTCT and highly active antiretroviral therapy?

- (ii) What was the HIV transmission rate amongst HIV-exposed infants enrolled in follow-up care in Embu District?
- (iii) What were the mortality, HIV-free survival and loss-to-follow up rates amongst HIV-exposed infants enrolled in PMTCT follow-up care in Embu District?

1.5 Null Hypotheses

- (i) Antiretroviral prophylaxis given to the mother and HIV-exposed infant for PMTCT did not reduce mother-to-child transmission rate of HIV.
- (ii) Antiretroviral prophylaxis given to the mother and HIV-exposed infant for PMTCT had no influence on mortality and HIV-free survival of the HIV-exposed infants.
- (iii) Infant exposure to maternal HIV had no influence on mortality.

1.6 Objectives

1.6.1 General objective

To establish the effectiveness of the PMTCT program in Embu District through the determination of the outcomes realized among HIV-exposed infants enrolled in prevention of mother-to-child transmission follow-up care.

1.6.2 Specific objectives

- (i) To determine the proportions of HIV-exposed infants enrolled in PMTCT care in Embu District who underwent early infant diagnosis of HIV, received antiretroviral drugs prophylaxis for PMTCT and highly active antiretroviral therapy.

- (ii) To determine the HIV transmission rate among HIV-exposed infants enrolled in the PMTCT follow-up care in Embu District.
- (iii) To establish the infant mortality, HIV-free survival and loss-to-follow-up rates amongst the HIV-exposed infants enrolled in the PMTCT follow up care in Embu District.

1.7 Limitations

- (i) The four facilities where the study was conducted were purposively and not randomly selected therefore affecting the external validity of the results. To this extent, findings may therefore not be fully generalizable to other PMTCT settings.
- (ii) The loss-to-follow-up among HIV-exposed infants enrolled in the program was significant (14.8%). This may have introduced measurement bias since their HIV status and mortality outcomes could not be established.
- (iii) Uptake of PMTCT interventions and outcomes could not be determined in some HIV-exposed infants due to missing entries in the registers.
- (iv) Data extraction from the records was laborious because they were not stringently kept and were sometimes in a fragmented format with no central coordination.

1.8 Delimitations

- (i) The HIV-exposed infants in the four study health facilities were randomly selected into the study.

- (ii) Though the HIV-exposed infants register was main source document, it was complimented by the electronic ARV register otherwise known as the Health Facility Drug Management System, antenatal and post-natal registers. Missing entries on ARV prophylaxis for mother or infant in the HIV-exposed infants register were checked up in the electronic antiretroviral register available in the health facility pharmacy and comprehensive care clinic.
- (iii) The four facilities selected for this study represented most the levels of health service provision in Embu District; a government health centre, a private faith-based hospital, a government district hospital and a government provincial hospital.

1.9 Assumption

The outcomes among HIV-exposed infants were not stratified by infant feeding methods and duration of breast-feeding. Therefore the influence of this variable on the eventual findings of HIV transmission and mortality could not be determined. It was therefore assumed that by randomization, the potential confounding effect of this variable was equally distributed in all comparison sub-groups.

1.10 Conceptual framework

Effective prevention of mother-to-child transmission involves simultaneous support for several strategies that work synergistically to reduce the odds that an infant will become infected as a result of exposure to the virus from the mother. The prevention of mother-to-child transmission strategy is composed of four prongs namely primary prevention of HIV infection in women, prevention of unintended pregnancy among HIV-infected women, interventions to reduce

transmission from HIV-infected pregnant and lactating women to their children and care and support of women, children and families infected and affected by HIV and AIDS. This study focuses on the outcomes of the third and partly fourth prong of the broader package of services to prevent mother-to-child transmission. Ideally a woman who intends to get pregnant should know her HIV status before conception. Thereafter, those who are identified as HIV negative can be counseled on how to remain HIV uninfected during the pregnancy. Those who are identified as HIV infected can receive care that can almost eliminate the risk of transmission of HIV from the mother to the child. Care of the HIV-exposed newborn must then focus on reducing the risk of infection with post-exposure prophylaxis, monitoring for signs and symptoms of HIV infection, and following the recommended testing schedule to confirm the absence of infection in the vast majority of infants or confirm infection and begin treatment as soon as possible. The intended outcomes are:

- (i) There is increased up-take of the prevention of mother-to-child transmission interventions including antiretroviral prophylaxis, safe infant feeding methods in HIV-exposed infants and early infant diagnosis of HIV with provision of paediatric highly active antiretroviral therapy for those HIV positive.
- (ii) Mother-to-child HIV transmission is reduced
- (iii) Infant and child mortality for HIV exposed children is reduced
- (iv) Consequently, HIV-free survival of the exposed infants is increased (Chetty *et al.*, 2010).

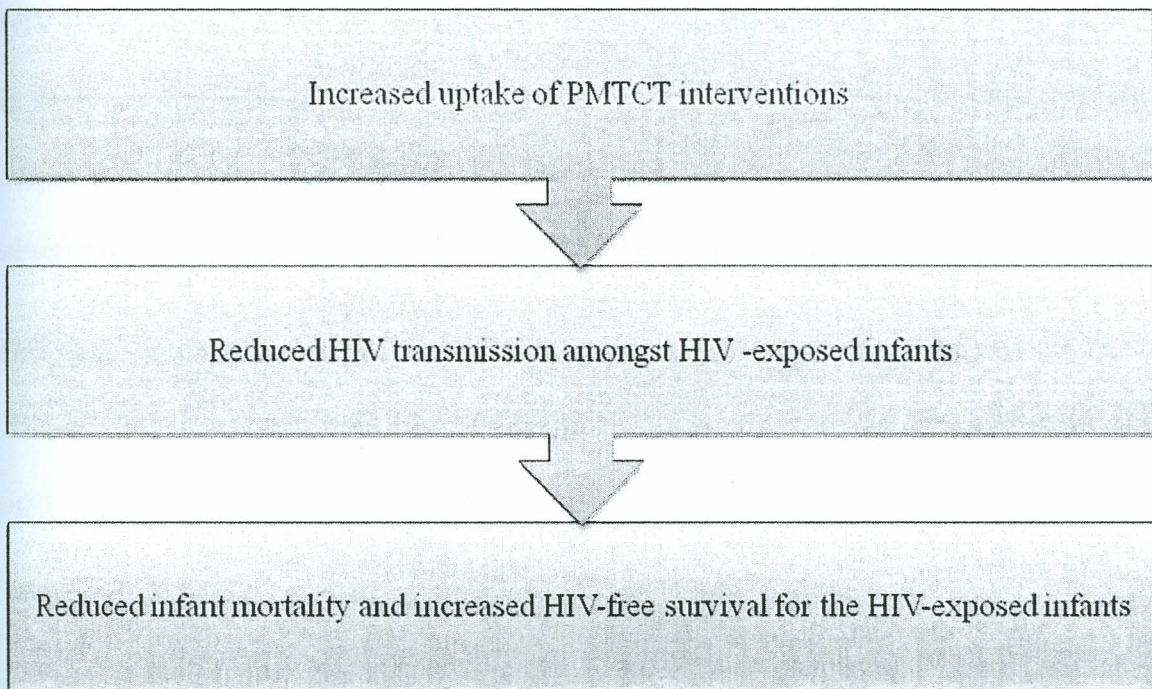


Figure 1.2: Flow diagram of the conceptual framework (Chetty *et al.*, 2010).

1.11 Operational Definition of Terms

Outcomes in HIV-exposed infants: the medium term results among HIV-exposed infants realized in the course of their follow-up till 18 months of age. For this study they were HIV transmission, loss to-follow-up, mortality and HIV-free survival among the infants.

Early infant diagnosis of HIV: refers to the making of HIV diagnosis in infants and young children before 18 months of age since routine serological antibody tests can only determine exposure to maternal antibodies. Infant DNA polymerase chain reaction (PCR) testing is the current recommended method for early infant diagnosis of HIV in Kenya.

HIV-exposed infants: children up to 18 months of age whose biological mothers were HIV-positive.

HIV DNA polymerase chain reaction (PCR): a diagnostic tool used to detect the presence HIV in the blood; it identifies viral genetic material by highlighting sequences of the virus within the subject's deoxyribonucleic acid (DNA). This is achieved via nucleic-acid amplification testing to observe the resulting polymerase chain reaction, hence the acronym (PCR).

HIV-free survival: infants born to HIV-infected mothers who were alive and uninfected with HIV at a given point in time (for this thesis HIV-free survival was reviewed at 18 months of age).

PMTCT interventions: antiretroviral prophylaxis for the mother during pregnancy, labour and delivery, antiretroviral prophylaxis for infant after birth, early infant diagnosis through HIV DNA polymerase chain reaction (PCR) and provision of paediatric HAART for those HIV-positive. Infant feeding methods were not included because of the poor record keeping with regard to this variable.

Loss-to-follow-up: any HIV-exposed infant who missed the follow-up clinic for duration equal to or exceeding six months.

CHAPTER TWO

LITERATURE REVIEW

2.1 Care for HIV-exposed infants

Follow-up clinical care of the human immunodeficiency virus (HIV)-exposed infant involves important management considerations that are intended to reduce the risk of transmission of HIV infection from mother-to-child. To obtain the maximal reduction in transmission, care for the HIV-exposed infant begins well before delivery. A woman who intends to get pregnant should know her HIV status before conception. Thereafter, those who are identified as HIV negative are counseled on how to remain HIV uninfected during the pregnancy. Those who are identified as HIV infected receive care that can almost eliminate the risk of transmission of HIV from the mother to the child. Care of the HIV-exposed newborn then focuses on reducing the risk of infection with post-exposure ARV prophylaxis, monitoring for signs and symptoms of HIV infection, and following the recommended testing schedule to confirm the absence of infection in the vast majority of infants or confirm infection and begin treatment as soon as possible in the small percentage of infants who continue to be diagnosed with perinatal HIV infection (Lisa-Gaye and Aracelis, 2010).

Optimal care of the HIV-exposed infant involves first identifying that the infant has, in fact, been exposed to HIV. Once exposure has been reasonably established, subsequent management considerations aim to reduce the transmission of HIV from the mother to the child and eventually determine the HIV status of the exposed infant. Prenatally, the HIV-infected mother receives special prenatal care that includes the receipt of potent combination antiretroviral therapy.

Postnatally, a thorough maternal and delivery history taking helps establish the level of risk of transmission for the infant. The physical examination in the newborn may not be revealing for stigmata of HIV. Prophylaxis against HIV should be started immediately after birth, followed by prophylaxis for pneumocystis jirovecii at 6 weeks of age, as recommended by current national guidelines (WHO^a, 2010).

The pertinent history of a newborn is the maternal history. For HIV-exposed infants, the maternal history helps establish whether the transmission risk is high and close to the natural transmission rates for mother-infant dyads who received no intervention or approaches the low transmission rate for mother-baby dyads who received all recommended interventions to reduce transmission. This history includes obstetric history, sexually transmitted disease history, date of maternal HIV diagnosis, timing of initiation of antiretrovirals in the mother, maternal antiretroviral regimen, adherence to regimen, resistance testing of maternal HIV virus, maternal viral load (particularly close to the time of delivery), maternal CD4 count, maternal clinical status, prematurity, mode of delivery, length of rupture of membranes, and use of intra-partum monitoring that may have breached the newborn's skin. In most cases, recommended prenatal HIV testing that identified infant exposure to HIV would have been determined by the health provider of the infected mother. However, if during acquisition of the maternal history for any newborn it is determined that prenatal HIV testing has not been done, a rapid HIV antibody testing of the mother and/or infant is recommended as soon after birth as possible (Lisa-Gaye and Aracelis, 2010).

2.2 ARV prophylaxis for PMTCT

The efficacy of antiretroviral drugs in preventing mother-to-child transmission of HIV varies with the type of regimen used and the duration over which it is given. Combination regimens which include different types of antiretroviral drugs are more efficacious than monotherapies. Monotherapies are also prone to building antiretroviral resistance in the virus, which may limit future therapeutic options when treatment is needed. According to the 2010 WHO treatment guidelines it is recommended that pregnant women living with HIV and their exposed infants receive combination therapy rather than single-dose Nevirapine. Antiretroviral prophylaxis is also recommended during breast-feeding in settings where breast-feeding is judged to be the safest infant feeding option. In addition, all women eligible for treatment under WHO guidelines should receive an appropriate combination therapy for their own health. In the 59 low- and middle-income countries that provided disaggregated data for their prevention of mother-to-child regimens around 30% of pregnant women received single dose Nevirapine, while 54% received a combination regimen to avoid mother-to-child transmission of HIV. About 15% of all mothers received ongoing antiretroviral therapy (highly active antiretroviral therapy) based on eligibility criteria for treatment (WHO^b, 2010).

In Kenya, HIV-exposed infants receive postnatal zidovudine to reduce the transmission of perinatal HIV infection. For the maximal effect, zidovudine should be started as close to birth as possible but certainly within 12 hours of birth. Zidovudine should be continued through day 42 of life (6 weeks). They should also receive single dose nevirapine within 72 hours and lamivudine for 1 week (NASCO, 2009). Antiretroviral prophylaxis is discontinued immediately

if any of the newborn's HIV DNA polymerase chain reaction results are positive, and these infants referred for possible initiation of highly active antiretroviral therapy. Continuing antiretroviral monotherapy in an HIV-infected infant leads to the development of resistance. HIV-exposed infants who present for initial care more than 48 hours after birth would not benefit from post exposure prophylaxis (WHO^c, 2010).

2.3 Challenges in uptake of PMTCT interventions in Africa

The first clinical trials of antiretroviral (ARV) drug prophylaxis for women and infants were conducted in Europe and the United States of America, where most HIV-infected women have access to good prenatal and delivery care, a range of laboratory tests and replacement feeding. Effectiveness - defined as the prophylactic benefit of a prevention of mother-to-child transmission intervention when implemented in real practice - closely approximates clinical trial efficacy in these settings because of strong supporting health-care infrastructure, low HIV seroprevalence and near-universal service coverage. Paediatric AIDS has been all but eradicated in Europe and the USA by ensuring high service coverage and by systematically targeting each risk factor. The situation in most developing countries differs dramatically. Although the risk factors for transmission remain the same, there are far fewer options for most women: few have access to completely suppressive antiretroviral regimens, elective caesarean or safe alternatives to breast-feeding and even basic antenatal service access is far from universal. Because of this, most studies in developing countries have focused on simpler and more cost-effective regimens that can be deployed widely. In addition, breast-feeding remains an important route of

transmission; however, benefits of replacement feeding in Africa are becoming less clear due to competing co-morbidities (Stringer *et al.*, 2008).

In a random sampling of more than 40 treatment sites in Cameroon, Côte d'Ivoire, South Africa, and Zambia that provide treatment against mother-to-child transmission of HIV, only 51% of infants born to mothers infected with HIV actually received HIV prophylaxis (Palombi *et al.*, 2010). Successful prevention of mother-to-child HIV transmission requires each mother–infant pair to negotiate a critical path that begins with the offering of an HIV test and proceeds through post-test counseling to drug adherence and beyond. These findings indicate that despite the known efficacy of PMTCT interventions, programmatic failures are common along the implementation path may pose challenge to the realization of the intended outcomes. Though PMTCT interventions are a critical move toward global paediatric AIDS control, they hold only half the key. The other half lies in service coverage of the PMTCT interventions in order to realize favourable outcomes in HIV-exposed infants. Even the most potent interventions will not protect those infants who do not receive them (The PEARL Study Group, 2010). Yet without these interventions, over one-third of infants will be infected with HIV by two years of age, half of which as a result of breast-feeding (Palombi *et al.*, 2010).

Even in those PMTCT programs that provide good service coverage for the interventions other programmatic challenge arise. Despite diagnosis of HIV having been made by early infant diagnosis, infants accessing treatment in sub-Saharan Africa remain low (Namukwaya *et al.*, 2011). Among those HIV-exposed children who test HIV positive, access to paediatric

antiretroviral therapy remains a challenge in many settings in sub-Saharan Africa. In Kenya for example, there are approximately 150,000 HIV infected children, out of whom nearly 60,000 are in need of antiretroviral therapy and about 25,000 are currently accessing treatment. This is in spite of numerous concerted efforts to raise the number of children on antiretroviral therapy through increased availability of early infant diagnosis and strengthening provider-initiated counseling and testing in health facilities. Survival of HIV infected children in Kenya and similar settings may be improved as more children access highly active antiretroviral therapy (Wamalwa *et al.*, 2010).

This inability to provide highly active antiretroviral therapy for HIV-positive infants continues to be an important limitation in HIV treatment programs. In a study to describe outcomes for young children receiving antiretroviral therapy in resource-limited settings for 48 HIV treatment programs in Africa and Asia it was found that only 9% of the children initiated on highly active antiretroviral therapy were under 12 months, 50% were 12 to 35 months, and 41 percent were 36 to 59 months of age. The median time for treatment initiation was 12 months. In view of these findings of late initiation of antiretroviral therapy (after 12 months), the study recommended improvement in early infant diagnosis to enable early initiation of treatment (Sauvageot *et al.*, 2010).

2.4 Lack of regular measurement of PMTCT program performance

With ambitious goals set for paediatric AIDS control, including a 50% reduction in new infections by 2010, there is however lack of clarity and consensus on how to monitor the

effectiveness of programs to prevent mother-to-child HIV transmission (Chopra, 2008). In Kenya for instance, the data on outcomes in HIV-exposed infants are not routinely collected and reported making it difficult for policy-makers to mount a coordinated response.

1.3.3 Coverage

Previous evaluations of PMTCT programs impact used program coverage as a surrogate marker for program effectiveness, i.e. the proportion of HIV infected/exposed mother/infant pairs in a population that receive a PMTCT intervention. This measure assumes that the benefits of a PMTCT intervention will accrue to a population of mothers and infants who access the intervention appropriately. Coverage is defined as the product of a critical pathway of events that must be in place for the prophylaxis to be delivered. This critical pathway called the PMTCT cascade can be constructed from process indicators that are collected routinely with varying success by PMTCT programmes and health-care facilities (Stringer *et al.*, 2008).

1.3.4 Attrition

Attrition along each step of the cascade can be significant. For example, the acceptability of HIV testing strategies varies greatly in many high-HIV-prevalence settings, with significant proportions declining HIV testing or failing to return to collect test results. Even after a woman is diagnosed with HIV, there is no guarantee that she will agree to PMTCT ARV drug prophylaxis. Studies in Kenya, Burkina Faso and Côte d'Ivoire have found that up to 40–60% of HIV-infected women decline short-course zidovudine prophylaxis in pregnancy once diagnosed, although this experience is not universal. Though most HIV control programs including the Kenya National AIDS and STI control program (NASCO) have not incorporated outcome

indicators; infant infections prevented, infant deaths prevented and HIV-free survival are being widely proposed as ideal measures in resource limited settings (Stringer *et al.*,2008).

2.5 Enrolment into early infant diagnosis of HIV

Early infant diagnosis (EID) refers to the determination of HIV status in infants and young children before 18 months of age. The EID gives an opportunity for early identification of HIV infected infants and early linkage to care and treatment. It is a fact that HIV antibody testing among children aged 18 months or more is able to determine whether a child is infected or not. During pregnancy, mothers give their babies antibodies to infections they have experienced and these antibodies wane with time. Antibody testing in children aged less than 18 months identifies children who have been exposed to their mothers' HIV infection or who may be truly infected and are making HIV antibodies. Currently, there is no test to differentiate the mother's antibodies from those produced by the baby.

In order to identify the HIV-infected child aged less than 18 months, a second test is required for all babies testing positive on antibody testing or known to be HIV-exposed (mother is HIV-positive). Infant DNA polymerase chain reaction (PCR) testing is the current recommended method for early infant diagnosis of HIV. Since most babies lose maternal antibodies by 12 months, a negative antibody test will identify uninfected babies as long as they are not still breastfeeding. A positive antibody test at 12 months, although highly likely to be diagnostic, may still be due to passively carried maternal antibodies. Such tests need to be confirmed by PCR testing or repeat antibody test at 18 months (NASCO, 2009).

Several studies give varying observations on the uptake rates of this important intervention that is the first step in a cascade of events that are supposed to eventually ensure that the HIV-exposed and infected infants are put on highly active antiretroviral therapy at the earliest opportunity. In a prospective study to determine continuity of care and outcomes of PMTCT services with regard to early infant diagnosis in Malawi, it was found that 53.7% of the HIV-exposed received HIV DNA polymerase chain reaction (PCR) testing with 13.8% being HIV infected. However, the late infant diagnosis was found to have eventually delayed paediatric highly active antiretroviral therapy initiation among those who tested positive (Braun *et al.*, 2011).

In Tanzania, from October 2006 to March 2007, 510 HIV-exposed infants were identified from four health facilities. Of these, 87% of the infants had an HIV DNA polymerase chain reaction test at a median age of 4 months and 17% were HIV positive. The study concluded that early infant diagnosis through HIV DNA PCR can be implemented in resource limited settings and it introduces systems for identification of HIV-exposed infants (Nuwagaba-Biribonwoha *et al.*, 2010). Another study in western Kenya reported that only 40% of the HIV-exposed infants enrolled in care before three months of age underwent HIV DNA polymerase chain reaction test for early infant diagnosis (Nyandiko *et al.*, 2010). In a study in Coast Province Kenya, it was reported that early infant diagnosis of HIV is not routinely carried out in infants, and yet rapid diagnosis could improve access to lifesaving interventions especially paediatric HAART (Khamadi *et al.*, 2010).

2.6 HIV transmission rates and antiretroviral drugs prophylaxis for PMTCT

Various studies in Africa give differing rates for mother-to-child HIV transmission depending on which health care settings they were conducted, type of antiretroviral prophylaxis regimen used and the duration for which it was given. Two salient factors arose from review of these studies; First the differences in HIV transmission in exposed infants in different locations were underlined by respective differences in uptake rates of antiretroviral drugs prophylaxis for PMTCT i.e. where the uptake rate of prophylactic ARVs was high the HIV transmission rate was low and vice-versa. Secondly, most of the studies were conducted in intensely monitored well funded conditions that actively enrolled HIV-exposed infants and provided conditions superior to those you would generally find in real PMTCT practise in Africa. Very few studies are therefore available to determine the generalizabilty of these observed findings to real PMTCT practice in resource-limited health care settings (Chopra, 2008).

2.6.1 Mother-to-child transmission rates of HIV in East Africa

In a study in Mulago Hospital Uganda, 62.3% of HIV-infected women received combination antiretrovirals, including the highly active antiretroviral prophylaxis therapy. Early HIV infection rates were highest among infants with no maternal antiretroviral prophylaxis at 36.4% and only single dose nevirapine at 11.2%. Lower transmission rates were observed for the group that took short-course antiretroviral regimen of zidovudine and single dose nevirapine at 4.6%; and the lowest rates for those that took triple antiretroviral combination at 1.7%. The overall infection rate was found to be 5%. These findings indicate low rates of infant infection for mothers receiving combination antiretrovirals and demonstrate that provision of combinations of

antiretroviral drugs for PMTCT is feasible and effective in resource-limited settings (Namukwaya *et al.*, 2011). In a study in Tanzania, it was found that 17% of HIV-exposed children tested HIV DNA polymerase chain reaction positive on their first test. The possible explanation of this high transmission rate was that 35% of the infants and 53% of mothers were recorded as not having received any antiretroviral drug prophylaxis. Among the 282 tested babies who were exposed to either maternal and/or infant PMTCT antiretroviral drugs, 12.8% tested HIV positive, compared to a higher transmission of 25.3% for those where neither the mother nor the infant received antiretroviral drugs for PMTCT. Where PMTCT programs are better resourced and more efficacious PMTCT regimens are given, the proportion of HIV-exposed infants testing PCR positive is less than half what was observed here. The challenge in Tanzania as revealed by this study was to increase uptake of antiretroviral drugs for PMTCT and implement PMTCT programs utilizing multi-drug antiretroviral therapy regimens which are more effective in reducing HIV transmission to infants. In addition, 6.7% of the previously HIV negative infants at first test who returned for confirmation of infection status after weaning were HIV positive further, highlighting the imperative need to offer effective interventions to prevent postnatal transmission (Nuwagaba-Biribonwoha *et al.*, 2010).

2.6.2 Mother-to-child transmission rates of HIV in West Africa

In the MTCT-Plus Initiative in Abidjan, Côte d'Ivoire pregnant women received either highly active antiretroviral therapy for their own health or short-course antiretroviral PMTCT regimens according to their clinical and immunological status. Plasma HIV-RNA viral load was measured to diagnose peri-partum infection when infants were 4 weeks of age, and HIV final status was

documented either by rapid antibody testing when infants were aged $>$ or $=$ 12 month or by plasma viral load earlier. The Kaplan-Meier method was used to estimate the rate of HIV transmission and HIV-free survival. One hundred and seven women began highly active antiretroviral therapy (HAART) at a median of 30 weeks of gestation, 102 of them with zidovudine (ZDV), lamivudine (3TC), and nevirapine (NVP) and they continued treatment postpartum; 143 other women received short-course antiretroviral for prevention of mother-to-child transmission, 103 of them with short course zidovudine and lamivudine (ZDV+3TC) with single-dose nevirapine during labour. Overall, the rate of peri-partum HIV transmission was 2.2% (95% confidence interval [CI] 0.3%-4.2%) and the cumulative rate at 12 months was 5.7% (95% CI 2.5%-9.0%). The study found the overall probability of infant death or infection with HIV was 4.3% (95% CI 1.7%-7.0%) at four weeks of age and 11.7% (95% CI 7.5%-15.9%) at 12 months of age (Tonwe-Gold *et al.*, 2010).

2.6.3 Mother-to-child transmission rates in South Africa

In Khayelitsha, South Africa HIV-exposed infants were located and tested for HIV using polymerase chain reaction (PCR) for early diagnosis, with a documented transmission rate of 8.8% at six weeks of age. In Cameroon, infants were followed up in a nevirapine-based prevention of mother-to-child transmission programme and exposed infants tested for HIV infection at 6–8 weeks and then again at 5–6 months. The transmission rate was 13/123 (10%) at six weeks and 16/123 (13%) at 5–6 months (Chopra, 2008).

Women with HIV infection who were breast-feeding infants were enrolled in a randomized, trial in Blantyre, Malawi. At birth, the infants were randomly assigned to one of three regimens: single-dose nevirapine plus 1 week of zidovudine (control regimen) or the control regimen plus daily extended prophylaxis either with nevirapine (extended nevirapine) or with nevirapine plus zidovudine (extended dual prophylaxis) until the age of 14 weeks. The results showed that the control group had consistently higher rates of HIV infection from the age of 6 weeks through 18 months. At 9 months, the estimated rate of HIV infection (the primary end point) was 10.6% in the control group, as compared with 5.2% in the extended-nevirapine group ($P < 0.001$) and 6.4 percent in the extended-dual-prophylaxis group ($P = 0.002$). The study therefore concluded that extended prophylaxis with nevirapine or with nevirapine and zidovudine for the first 14 weeks of life significantly reduced postnatal HIV infection in 9-month-old infants (Kumwenda *et al*, 2008).

In a study in Zambia, samples of 8237 babies between 0 and 12 months were analyzed, with 84 percent of the mothers having ever breastfed their children. The observed transmission rate was 6.5% (5.1% - 7.8%) among infants aged 0-6 weeks when both mother and infant received prevention of mother-to-child transmission interventions compared with 20.9% (12.3% - 29.5%) where no intervention was given to either mother or baby. Observed HIV transmission with single-dose nevirapine was 8.5% (5.9% - 11.0%) among infants aged 0-6 weeks, whereas zidovudine with single dose nevirapine and highly active antiretroviral therapy were associated with observed transmission rates of 6.8% (4.5% - 9.1%) and 5.0% (3.0% - 7.0%), respectively; whereas these estimates were not significantly different from one another, they were all significantly lower than no intervention for which the estimated rate was 20.9%. Regardless of

the intervention, the observed transmission rates were higher among infants aged 6-12 months (Torpey *et al.*, 2010).

2.6.4 Mother-to-child transmission rates of HIV in South America

In a study in Brazil to determine impediments to the effective reduction of maternal-infant transmission of HIV, a municipality town that followed up pregnant HIV positive mothers and their children showed that the rate of maternal-infant transmission of HIV was 7.7%. Variables that were found to show significant association with maternal-infant transmission of HIV were the non-utilization of antiretrovirals for prophylaxis or treatment during pregnancy and diagnosis of maternal disease after pregnancy. The study identified following as impediments to the effective reduction of maternal-infant transmission of HIV: low prenatal screening coverage of maternal HIV infection, impairing maternal treatment or prophylaxis; and the incorrect use of the rapid screening test at admission for delivery (Fernandes *et al.*, 2010).

2.6.5 Mother-to-child transmission of HIV and type of ARV regimen given

The ongoing Kesho Bora study whose objective is to compare efficacy and safety of triple-antiretroviral and short-antiretroviral MTCT-prophylaxis with regard to HIV transmission and child mortality; pregnant women with CD4 counts 200-500 cells/mm³ at 28-36 weeks of pregnancy were randomized to receive either maternal highly active antiretroviral therapy (zidovudine + lamivudine + lopinavir/ritonavir) for six months after delivery or breastfeeding cessation if earlier) or short- course zidovudine plus single-dose nevirapine in labour. Done in

five study sites in Kenya, Burkina Faso and South Africa, infants received single-dose nevirapine post partum. The interim results show HIV transmission rates to be almost identical. Overall the investigators concluded that receiving maternal highly active antiretroviral therapy as prophylaxis and stopping after breastfeeding did no harm compared to short course zidovudine plus single dose nevirapine. The other important conclusion from the analysis is that the high rate of progression to CD4 <200 cells/mm³ in both arms among women with <350 cells/mm³ at entry, reinforces WHO guidance to treat from 350 cells/mm³ and emphasizes the importance of early treatment initiation in pregnant women or women desiring pregnancy (The Kesho Bora Study Group, 2010).

In a systematic review that focused on antiretroviral therapy for treating HIV infection in eligible pregnant women in Africa different results were reported on mother-to-child HIV transmission rates achieved using different drug regimens. The use of a triple drug regimen of zidovudine, lamivudine and lopinavir/ritonavir starting at 28-36 weeks gestation in a breast-feeding population reduced infant HIV-transmission or death at 12 months compared to a short-course regimen ARV regimen in a study conducted in rural Uganda in 2007. Starting zidovudine, lamivudine, and nevirapine at 34 weeks in a mixed-feeding population reduced infant HIV-transmission or death at 7 months compared to a short-course regimen (RR 0.39, 95% CI: 0.12-0.85) as observed in one study done in Zambia in 2008. But in a South African study conducted in 2009, no difference was observed in mother-to-transmission of HIV at six months between the three drug regimen of zidovudine, lamivudine and lopinavir/ritonavir combination and zidovudine lamivudine on the other hand (Sturt *et al.*, 2010).

2.6.6 Mother-to-child transmission of HIV in Kenya

A retrospective study to compare rates of mother-to-child transmission of HIV and infant survival in women-infant dyads receiving different interventions covering 18 clinics in Western Kenya was conducted between February 2002 and July 2007 and 2477 HIV-exposed children were registered for care before 3 months of age. Results show that one thousand (40%) underwent HIV DNA Polymerase Chain Reaction virologic test at a median age of 8.3 weeks: 5 percent were HIV infected, 89% uninfected, and 6% were indeterminate. HIV transmission rate by the end of 18 month follow-up was 15.6% (Nyandiko *et al.*, 2010).

Interim results from an ongoing study entitled Evaluation of Effectiveness of PMTCT Services Kenya showed that nevirapine was the most used PMTCT antiretroviral intervention at 33.2%, HAART at 27%, nevirapine with zidovudine at 17.3% and zidovudine alone at 5.7%. The study also reported that 88.8% of mothers interviewed had been prescribed ARV drugs for PMTCT in pregnancy or during labour. The overall Kenyan mother-to-child transmission rate from infant HIV DNA polymerase chain reaction results was found to be 7.6%. However, there were wide regional variations in the HIV transmission rate in Kenya; Eastern Province had the highest at 15% while Central Province had the lowest at 2.8% (Kiarie *et al.*, 2011).

2.7 Mortality in HIV-exposed infants

There is conflicting evidence reported by various studies on the effect of maternal HIV-exposure on infant mortality. This is further compounded by losses-to-follow-up in PMTCT programs

studied, making it difficult to determine the exact mortality rates since the outcomes in the defaulted infants remain largely unknown. However, there is some evidence that HIV-exposed children are at increased risk of mortality, morbidity and slower early growth than their HIV-unexposed counterparts. A likely major cause of this impaired health is less exposure to breast milk as mothers are either less able to breastfeed or stop breast-feeding early to protect their infant from HIV infection. Other contributing factors are parental illness or death resulting in reduced care of the children, increased exposure to other infections and possibly exposure to antiretroviral drugs. Equally, disease progression in HIV infected infants is fast, with a high mortality rate greater than 50% by two years of age. The median age of death in the first two years is six months (WHO³, 2010).

In a study in Zimbabwe to determine morbidity in HIV-exposed but un-infected, HIV infected and HIV un-exposed infants found that HIV-infected infants made 2.8 times more all-cause sick clinic visits and required 13.3 times more hospitalizations compared with not-exposed infants ; they had 7.2 times more clinic visits and 23.5 times more hospitalizations for lower respiratory tract infection after the neonatal period and were 159.9 times more likely to be hospitalized for malnutrition during the second half of infancy. Compared with not-exposed infants, sick clinic visits were 1.2 times more common among HIV-exposed infants. It therefore concluded that morbidity is higher among HIV-exposed infants (Konyangi *et al.*, 2011).

HIV leads to poor infant outcomes as a consequence of both HIV per se and HIV infectious complications. A recent large mother-to-child transmission trial in Zimbabwe included HIV-uninfected women and found that mortality within the first two years was significantly higher

among HIV-exposed children than among HIV-unexposed children. Risk factors for death among HIV-exposed children were lower birth weight, male sex, maternal death, low maternal CD4 count, severe maternal anaemia, single or widowed mother and low household income (Marinda *et al.*, 2007).

Other mortality information has come from longitudinal community surveillance. A pooled analysis of three such studies from Uganda, Tanzania and Malawi found that both maternal HIV infection and maternal death increased the risk of child death. Several cohort studies distinguished mortality among HIV-exposed children from among HIV-unexposed ones. In Botswana, mortality was significantly higher among HIV-exposed children compared with HIV-unexposed children with discontinuation of breast-feeding the strongest predictor of illness (Shapiro *et al.*, 2007). In Uganda cumulative mortality rate at 12, 18 and 24 months tended to be higher, statistically significantly so only at 18 months, among HIV-exposed children than among HIV-unexposed children (Chopra, 2008).

However, some studies show that HIV-exposed children do not have a higher mortality than their unexposed counterparts. In Gambia, it was found that under-5 mortality hazard of HIV-exposed children was not significantly higher than that of HIV-unexposed children and maternal death was a major risk factor for child death, irrespective of maternal or child HIV status. Another study in Malawi which analyzed mortality between ages 12 and 36 months, found no significant difference between HIV-exposed and unexposed children. In Zambia, mortality between 9 and 36 months of age among HIV-exposed children was slightly, but not significantly, higher than

among HIV-unexposed children. In Rwanda, there was no observed difference in child mortality between HIV-exposed and unexposed children (Chopra, 2008).

2.8 Factors associated with mortality in HIV-exposed infants

Although data are limited, it seems that the mortality of HIV-exposed children is generally greater than that of HIV-unexposed children. In addition to relatively small sample sizes and numbers of deaths, it is likely that both underlying child mortality rates and causes in the geographical area and availability of medical care contribute to differences among studies. In Malawi, it was reported that infants born to HIV-positive mothers had an almost three-fold increased risk of death compared to infants born to HIV-negative mothers. The excess risk of infant death associated with the death of a mother was 3.9. However, these studies have relatively little information concerning other distal factors such as socio-economic and educational levels of mothers or more proximal biological factors related to mortality such as maternal viral load of HIV and/or infant HIV status. The more proximal biological factors related to mortality have been identified by a recent pooled analysis of clinical studies from African trials to assess the efficacy of short course antiretroviral medicine to reduce mother to child transmission of HIV (Chopra,2008).

It was that found the annual rate of death in infants who became HIV-infected was much higher than in those infants who stayed HIV-free (35.2% compared to 4.9%). In addition to infant HIV infection, mortality in this analysis was associated with geographical region, maternal death,

CD4+ cell count, and timing of infection, but was not associated with ever breast-feeding or infant gender (Chopra, 2008).

A more recent study from Kenya followed HIV-infected infants identified in order to determine predictors of mortality during the first two years of life. One of the predictors of infant mortality in addition to biological factors, such as low birth weight, was formula feeding. All deaths amongst the non-breastfed infants occurred during the first six months of life and these infants were more likely to be of low weight for age at age one month compared to breastfed infants. These results have been important in delineating risk factors for HIV exposed infants. However, they have important drawbacks with respect to informing public health decision-making prevention of mother to child transmission of HIV in Africa (Nyandiko *et al.*, 2010).

A meta-analysis of seven PMTCT studies from sub-Saharan Africa estimated a cumulative mortality of 110 per 1000 live births at one year. The high mortality is occurring in the context where the underlying infant mortality rate amongst HIV unexposed infants is much lower (37 per 1000 live births). The excess mortality is occurring almost completely amongst HIV infected infants who had a nine fold increased risk of mortality compared with HIV exposed but HIV negative infants. The vast majority (81.3%) of infected infants who died in this cohort had contracted early infection (i.e. were infected by 3 weeks of age) and they suffered a rapid decline in survival, with a mortality risk of 39.7% (27 out of 68 infants with early HIV infection) by 36 weeks, compared to 19.3% (6/31) for those who acquired infection after 3 weeks. The hazard ratio (HR) of mortality at 36 weeks of age in HIV-infected children compared with exposed but

HIV negative children was 8.9 (95% CI 6.7-11.8). There was no significant difference in 36 week survival rates between those HIV exposed but uninfected infants and those who were not HIV exposed, Hazard ratio 0.7 (95% CI 0.3-1.5). In univariate analyses infant death amongst HIV exposed infants was strongly associated with infant positive HIV status at 3 weeks, maternal viral load greater than 100 000 and inappropriate formula feeding. In a Cox regression analysis amongst HIV exposed infants the only independent risk factor for infant death was the infant testing HIV-positive at three weeks of age. Other factors were low socio-economic score and low birth weight (Chopra, 2008).

In a Malawian study it was found that initiation of antiretroviral therapy increased the likelihood of survival seven-fold in HIV-infected children. However, it noted that the separate nature of the maternal and infant HIV prevention and care services was associated with high attrition rates of HIV-exposed and HIV-infected infants, elevated levels of mother-to-child transmission, late infant diagnosis, delayed pediatric antiretroviral therapy initiation, and high HIV-infected infant mortality. Antiretroviral therapy increased HIV-infected infant survival, emphasizing the urgent need for improved service coordination and strategies that increase access to infant HIV diagnosis, improve patient retention, and reduce antiretroviral therapy initiation delays (Braun *et al.*, 2011).

2.9 Loss-to-follow up and HIV-free survival

There are a few studies in Kenya on this subject to date. The studies mostly report on loss-to-follow-up with only one recent study in western Kenya reporting on infant mortality while

another reported on infant HIV-free survival. In a study to compare rates of mother to child transmission of HIV and infant survival in women-infant dyads in a prevention of mother-to-child transmission program in Western Kenya; by three months of age, 31 of 2477 infants (1.3%) were dead and 183 (7.4%) were lost to follow-up. By 18 months of age 41 (3.4%) were deceased and 329 (27.4%) were lost to follow-up (Nyandiko *et al.*, 2010). A study in Kilifi, Kenya on dynamics and constraints of early infant diagnosis, found a 65% drop-out before follow-up to 18 months old with 43 percent of them occurring within 2 months of age. Maternal factors that were found to be associated with infant drop out were maternal loss-to-follow-up and younger maternal age. Others were service provider related (inadequate training, knowledge and understanding of PMTCT follow-up) and social-economic (poverty and lack of social support). Also included were challenges in accessing early infant diagnosis of HIV through DNA polymerase chain reaction test (Hassan *et al.*, 2011).

A study on retention of HIV-infected and HIV-exposed children in comprehensive HIV clinical care in western Kenya found that the overall lost-to-follow-up was 18.4% of all enrolled infants. Among HIV-infected children, 15.2 percent and 14.1% became lost-to-follow-up pre- and post-pediatric highly active antiretroviral drugs initiation, respectively. Among the HIV-exposed children, 20.1% became lost-to-follow-up. Loss to follow-up in both groups was associated with being orphaned at enrolment (Braitstein *et al.*, 2011).

In another study done in Kenya, Songok used two-year HIV-free survival as the effectiveness outcome of a zidovudine-based PMTCT programme and found that HIV-exposed infants whose

mothers took short-course zidovudine had a significantly higher 24-month HIV-free survival (59%) than those whose mothers did not take the PMTCT regimen (30%; $P < 0.001$). Unfortunately, follow-up losses were significant in both of these programmatic settings, introducing biases that could not be quantified (Songok *et al.*, 2006).

CHAPTER 3

METHODOLOGY

3.1 Study Design

This was a descriptive retrospective study utilized prospectively collected information. Data for the study was collected by review of HIV-exposed infants', paediatric antiretroviral, postnatal and antenatal registers. The primary source document was the HIV exposed infants' register complimented with the paediatric ART registers, post-natal and antenatal registers. The paediatric ART registers were kept in the HIV care clinics and pharmacy in electronic format otherwise referred to as Health Facility Drug Management System while the registers for HIV-exposed children were located in either the laboratory, maternal child health clinic or HIV care clinics depending on the convenience of the health facility.

3.2 Variables

The independent variables were the PMTCT interventions conducted among the HIV-exposed infants i.e. early infant diagnosis, antiretroviral drugs prophylaxis and paediatric highly active antiretroviral therapy (for the HIV-positive exposed infants). The outcome measures (dependent variables) were:

- (i) The HIV transmission rate among the HIV- exposed infants at the conduct of the first HIV early infant diagnosis test and at the end of the 18-month follow-up.
- (ii) The 18-month HIV-free survival rate among the HIV-exposed infants.
- (iii) The infant mortality rate by the end of the 18-month follow-up.

- (iv) Loss-to-follow-up rate during the 18-month duration of the care of the HIV-exposed infants.

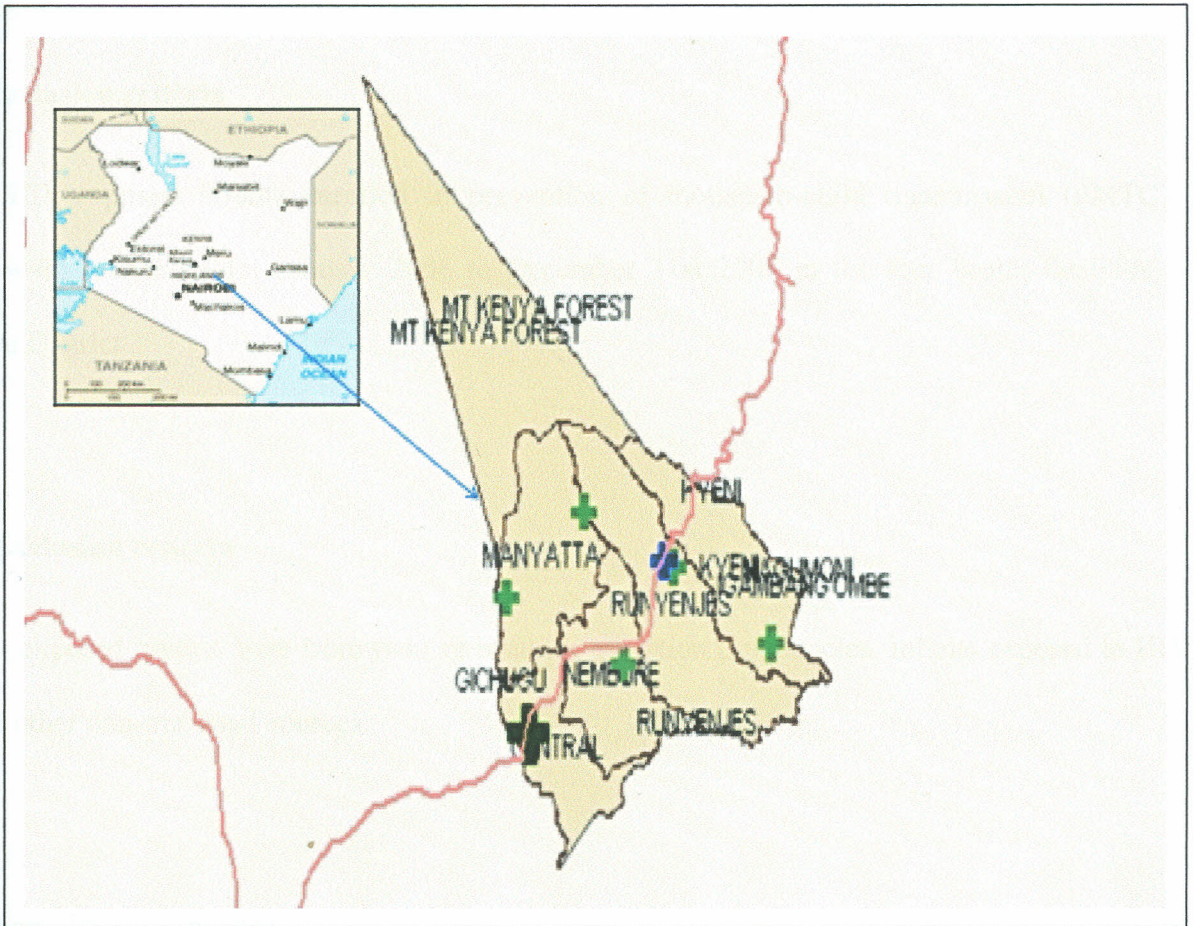
3.3 Location of the study

The study was conducted in four health facilities in Embu District; Embu Provincial General Hospital; Kyeni Mission Hospital; Runyenjes sub-District Hospital and Karurumo Health Centre. These health facilities have been offering prevention of mother-to-child transmission of HIV (PMTCT) services from 2004 and provide long-term follow-up of HIV-exposed infants till they attain 18 months of age. They used HIV DNA polymerase chain reaction for early infant diagnosis of HIV by sending dried infant blood samples to the HIV Reference Laboratory in Nairobi for the test. The final HIV status at 18 months of age was determined by rapid antibody testing. The sites were purposively chosen to reflect the different levels of health service provision in the district. Embu Provincial General Hospital is a government owned referral health facility for Eastern Province located within the urban settings of Embu Municipality, Kyeni Mission Hospital is a faith-based hospital situated in a rural part of Embu District. Runyenjes District Hospital is a middle level government health facility situated in the peri-urban Runyenjes Municipality while Karurumo Health Centre is a government health centre providing mainly primary health care services and located in the rural parts of Embu District.

These four facilities cumulatively account for just over 50 percent of the PMTCT workload in the district. Embu District is a highland agricultural area mainly growing tea, coffee and horticulture with a population of 304,000 people (KNBS^b, 2010). It is situated on the northern slopes of Mount Kenya. The population of women of reproductive age group is 80,582 with 9,328 deliveries annually. Embu District has an infant mortality rate of 37 per 1000 live births

and an under-five mortality rate 61 per 1000 live births (Unpublished, 2010). The adult (15-49 years) HIV prevalence is estimated at 4.2% (KNBS^a, 2010), while the prevalence of HIV amongst women attending antenatal clinics is 5.1% (Unpublished, 2010).

Fig 3.1 : Map of the study area showing Embu District and inset Kenya



3.4 Study population

Target population was all infants whose biological mothers were HIV-positive (HIV-exposed infants). The number of HIV-exposed infants born in Kenya in 2007 was 141,101 (NASCO, 2008).

2009), while in Embu District it is estimated that 441 HIV-exposed infants are delivered annually (Unpublished, 2010). The study population comprised HIV-exposed children enrolled in PMTCT follow-up care in Embu District while the sample population was derived from HIV-exposed children enrolled in PMTCT follow-up from 1st January 2006 to December 31st 2008 in the four health facilities in Embu District.

3.5 Inclusion criteria

All HIV-exposed infants enrolled in prevention of mother-to-child transmission (PMTCT) follow-up care from 1st January 2006 to December 31st 2008 in the four health facilities in Embu District.

3.6 Exclusion criteria

HIV- exposed infants born from twin or multiple gestation pregnancies. Infants exposed to HIV from other non-maternal sources.

3.7 Sampling techniques

The total sampling frame of 679 HIV-exposed infants was constructed from all the entries in the HIV-exposed children register at the four health facilities for the duration from 1st January 2006 to 31st December 2008. In each facility using the HIV-exposed infants' register in chronological order, the first infant was selected using a random number picked from the last digit on a

currency note (this was the readily available method to generate a random number), thereafter a sampling interval of two was utilized (the total sampling frame of 679 HEI was divided by the required sample of 357 HEI to get the sampling interval) till the required sample of 357 HIV-exposed infants was achieved.

3.8 Sample size

The sample size was calculated using the formula as used by Fisher *et al* 1998; based on the total number of expectant mothers who have accessed HIV testing for PMTCT in Embu District in the last five years.

$$n = \frac{N \cdot Z^2 \cdot p(1-p)}{d^2(N-1) + \{Z^2 \cdot p(1-p)\}}$$

$$d^2(N-1) + \{Z^2 \cdot p(1-p)\}$$

Where N = the total number of expectant mothers who accessed HIV testing for PMTCT in Embu district from 2006 to 2008 (11,021)

Z = z value for 95% confidence interval [1.96]

d = level of precision [0.05]

p = proportion of HIV positive expectant mother who transmit the virus to their infants without PMTCT intervention [0.4]

$$\text{Hence } n = \frac{11,021 \times 1.96^2 \times 0.4(0.6)}{0.05^2(11,021 - 1) + \{1.96^2 \times 0.4(0.6)\}}$$

$$= 357$$

Hence the sample size comprised of 357 HIV-exposed infants

3.9 Construction of Research Instruments

A standardized data extraction form was developed using the study objectives as the guide. It captured key information on provision of antiretroviral prophylaxis of PMTCT (both maternal and infant), early infant diagnosis of HIV through HIV DNA polymerase chain reaction including the time when it was conducted. Other items included were the final outcome of the infant at the end of follow-up in terms of their HIV status, whether they were alive, dead or lost-to-follow-up. Also included were the HIV- exposed infants' socio-demographic data on age and gender. It was structured in logical sequence to the entries in HIV-exposed infants register to make it user-friendly to the research assistants. Provisions were also made in the data collection tool for missing entries in the registers that had been earlier detected by the pilot study.

3.10 Pilot Study

The data collection tool was piloted in Kianjakoma sub-District Hospital and Kibugu Health Centre in Embu District. A sample of thirty five HIV-exposed infants was used for this pilot study. The summary description of the collected data is shown in a filled out dummy tables in figure 3.1 and 3.2 below. The pilot study determined that the data available had enough information to explore the objectives of the study. However, the data were found to have several missing entries. The final tool was hence amended to cater for these inadequacies by having options for missing entries on the variables under study.

Table 3.1: Summary description of the data collected from the pilot study in Embu District N=35

Variable	Number of HIV-exposed infants	
Infants who underwent EID	21	
Timing of early infant diagnosis	within 6 weeks	8
	6-12 weeks	12
	after 12 weeks	7
	missing entries	8
HIV status of infants at early infant diagnosis	positive	1
	negative	28
	indeterminate	0
	missing entries	6
ARV prophylaxis for the infant's mother	number who received	19
	did not receive	10
	no record	6
Type of maternal ARV regimen administered for PMTCT	HAART	0
	zidovudine and nevirapine	8
	single dose nevirapine only	9
	no record	2
Infant ARV prophylaxis for PMTCT	number who received	23
	did not receive	8
	missing entries	4

Table 3.2: Summary data of outcomes in HIV- exposed infants in Embu District from the pilot study

Outcome status of the infants at end of follow-up	Number alive	19
	Number deceased	9
	Number lost-to-follow-up	7
HIV status of the infants at end of follow-up	Number HIV positive	8
	Number HIV negative	28
	Number with no recorded HIV results	1

3.10.1 Validity

To reduce threats to internal validity, the research assistants underwent an intensive training to ensure standard and consistent application of data collection. Content validity was ensured by designing the data collection tool with all relevant items as per the study objectives. The paediatrician at Embu Provincial Hospital who is also the clinician in-charge of PMTCT services reviewed the data collection tool to ensure conformity of the items included to the study objectives. Use of systematic random sampling ensured internal validity by making the sample population as representative of the target population as possible. The major extraneous variable of infant feeding on mother-to-child transmission of HIV was not included as dependent variable in this study (due to poor recording in the health facilities). However, by use of probability sampling, the chosen sample of 357 infants was as representative in the infant feeding practices as the target population. To reduce the threat to external validity introduced by the purposive selection of the study sites, the selection of health facilities was done to represent all levels of

health care facilities thus a public health center, a private faith based hospital, a public district hospital and a provincial general hospital making the findings as generalizable to the target population as possible.

3.10.2 Reliability

The reliability of the data collection tool was ascertained by administering it on a selected sample of 35 infants selected from the HIV-exposed infants register. The resultant data was then analyzed. This activity was repeated a week later on the same sample. The two data sets were analyzed and the results compared. The results were found to be similar hence establishing the reliability of the data collection tool.

3.11 Data Collection techniques

During the data collection exercise, descriptive data on the HIV-exposed infants were collected from HIV-exposed infants' records. HIV-exposed infants register was the primary source document. Data on missing entries in HIV-exposed infants register was collected from the electronic antiretroviral therapy register located in the pharmacy, ante-natal and post-natal registers. For each HIV-exposed infant, data on socio-demographic variables (gender, age at enrolment), outcome status (alive, dead, lost-to-follow-up), uptake of various PMTCT interventions (early infant diagnosis of HIV, antiretroviral drugs prophylaxis for mother and infant) and highly active antiretroviral therapy for HIV- infected infants was recorded.

3.12 Methods of data analysis

The data was checked for completeness, cleaned, validated and entered in epi-info version 3.5.1 of 2008 for analysis. Descriptive statistics calculated include infant male-female ratio and median age of enrolment into follow-up care. Also calculated were the infants' median age at which the first test for early infant diagnosis of HIV was conducted and the infant death occurred. Others were proportions of HIV-exposed infants who received antiretroviral drugs for PMTCT, underwent early infant diagnosis of HIV, were HIV-infected, were lost-to-follow-up and were deceased. Analytical statistics calculated were the relative risks (RR) of HIV transmission and mortality associated with PMTCT antiretroviral prophylaxis. The RR of loss-to-follow up associated with the infant HIV status was also calculated. The 95% confidence intervals (CI) were used to determine statistical significance of the RR values. If number "1" was included in the range of the 95% confidence interval of the relative risk, then the observed difference was not considered statistically significant.

3.13 Logistical and ethical considerations

Approval for the study was granted by the Department of Public Health and the Graduate School of Kenyatta University. Permission to access the health facilities was sought from and granted by the District Medical Officer of Health, Embu. No personal identifier information like names was collected to ensure confidentiality and anonymity.

CHAPTER FOUR

RESULTS AND DISCUSSION

4.1 Age at enrolment and gender of HIV-exposed infants

The study enrolled 357 HIV-exposed infants from Embu District. The median age at enrolment into the PMTCT follow-up care was 7 weeks (range 1-39 weeks). Faith-based and government hospitals had a later age of enrolment (median 9 weeks) while the infants in the government health center enrolled at a much earlier age (median 5 weeks). There were no differences in age at enrolment by gender.

Figure 4.1: The sex ratio of the HIV-exposed infants enrolled in the study in Embu District



HIV-exposed infants should ideally be enrolled in care soon after birth to allow for subsequent care interventions like early infant diagnosis and provision of paediatric HAART for those who test HIV-positive to be carried out timely (WHO^b, 2010). The delayed enrolment observed in this study (median age of 7 weeks) could be a contributory cause to the eventual delay observed in conducting early infant diagnosis of HIV and initiating paediatric HAART. A study in western Kenya on outcomes of HIV-exposed children in resource-constrained settings (Nyandiko *et al.*, 2010) recorded similar findings with regard to age of enrolment (median age of enrolment 6.1 weeks), suggesting that just like in Embu District there may exist possible barriers to timely enrolment in PMTCT follow-up care in other PMTCT programs in Kenya. The higher age of enrolment found in the hospitals (median 9 weeks) compared to health centers (median 5 weeks) may be partially explained by the easy accessibility of the lower level health centers compared to hospitals, however, a further health systems audit may be needed to fully inform the circumstances regarding this apparent delay for enrolment to care for the hospitals.

4.2 Uptake rates of infant and maternal antiretroviral prophylaxis for PMTCT

Two hundred and ninety one (81.5%) HIV-exposed infants received ARV prophylaxis for PMTCT, 63 (17.6%) did not receive any kind of prophylaxis, while 4 infants (1.1%) had no record of prophylaxis. Of the 291 HIV-exposed infants who received ARV prophylaxis for PMTCT at birth, 128 (44%) were on short course double-antiretroviral drugs regimen of zidovudine and nevirapine, while 160 (55%) were on single drug antiretroviral prophylaxis of nevirapine. However, for 3 (1%) HIV-exposed infants there were no records of the type of ARV

prophylaxis given. There were no major differences in enrolment rate into ARV prophylaxis according to the type of health facility as shown in table 4.1 below.

Table 4.1: Uptake rate of infant antiretroviral prophylaxis at birth stratified according to type of health facility in Embu District

Type of health facility	Infants who received ARV prophylaxis	95% confidence intervals
Faith based hospital	84.4%	76.8%-90.4%
Government health centre	83.8%	75.8%-89.9%
Government hospitals	76.9%	68.2%-84.8%

Three hundred and nine (86.6 %) mothers of the HIV-exposed infants received antiretroviral drugs prophylaxis for PMTCT during pregnancy, labour and delivery; 3 (0.8%) had missing entries with regards to maternal antiretroviral prophylaxis given while 45 (12.6%) did not receive any kind prophylaxis for PMTCT during pregnancy, labour and delivery. Of these 309 mothers of HIV-exposed infants who were recorded as having received maternal antiretroviral prophylaxis for PMTCT, 36 (11.8 %) received single dose nevirapine drug in labour and delivery, 23 (7.4 %) were on a triple drug regimen of highly active antiretroviral therapy (HAART) and 250 (80.8 %) were on short course double antiretroviral drug regimen of zidovudine and nevirapine starting in the third trimester of pregnancy up to labour and delivery.

This high uptake rate of antiretroviral therapy for prevention of mother-to-child transmission (81.7 % for infant prophylaxis and 86.8 % for maternal prophylaxis) adds to the growing evidence that this PMTCT intervention can be up-scaled in resource-limited settings like Embu District to attain universal access. However, these encouraging findings should be interpreted

with caution due to the fact that the study considered only those HIV-exposed infants who were enrolled in prevention of mother-to-child transmission care in health facilities with the likelihood that some infants and HIV-positive expectant mothers were not enrolled in the formal health sector and were not accessing antiretroviral prophylaxis for PMTCT. Nevertheless, the high uptake rate of antiretroviral drugs for prevention of mother-to-child transmission among the mothers of HIV-exposed infants demonstrates that the PMTCT program in Embu has performed considerably well, considering that it has exceeded the Kenya national target as set out in Kenya National AIDS Strategic Plan III (KNASP III) of ensuring that 80 % of HIV-positive pregnant women receive antiretroviral medicine to reduce the risk of mother-to-child transmission by the year 2012 (NACC^a, 2009). This uptake rate of antiretroviral therapy for prevention of mother-to-child transmission is also higher than that found by National AIDS Control Council (NACC) in 2009 of a 44 % uptake rate of prophylactic nevirapine drug in maternity and 11 % infant nevirapine uptake rate in Eastern Province, Kenya (NACC^c, 2009).

Studies from elsewhere in the sub-Saharan region also post different observations with regards to percentage of infants enrolled in PMTCT care and their mothers who received antiretroviral prophylaxis. In Uganda, a study at the referral Mulago hospital reported that 62.3 % of the HIV-exposed infants enrolled in PMTCT follow-up received antiretrovirals for prophylaxis (Namukwaya *et al.*, 2011), while in Tanzania only 35 % of the HIV-exposed and 53 % of the their mothers did not receive antiretroviral prophylaxis for PMTCT (Nuwagaba-Biribonwoha *et al.*, 2010). The PEARL study group in 2010 found a 51 % uptake rate of infant antiretrovirals for PMTCT in 40 sites sampled across sub-Saharan Africa. These differences in uptake of antiretroviral prophylaxis between this study and the three others mentioned here may be a further pointer to the earlier observation that different PMTCT programs in similar resource-

limited environments may have marked differences in uptake rates of interventions and the data usually presented as national averages of PMTCT indicators may frequently mask these variations in performance. The high uptake of antiretrovirals for PMTCT in all the types of health facilities helps to demystify earlier held perceptions against use of these drugs (ARVs) in health centers (due to unavailability of medical doctors at this level) and demonstrates that antiretroviral drugs can be provided in lower level health facilities like health centers, hence providing avenues for enhancing service access to PMTCT services.

Three types of maternal antiretroviral regimens were used for prevention of mother-to-child transmission in Embu District; the majority (80.8 %) was on double ARV regimen of zidovudine from 28 weeks of gestation and single dose nevirapine during labour, while 11.8 % were on single dose nevirapine during labour. This latter situation may be explained by circumstances where expectant mothers had their HIV positive status determined very late in pregnancy or during labour and therefore missed out on prophylactic antiretroviral medicine administered during pregnancy. Only 7.4% of the mothers of HIV-exposed infants received highly active antiretroviral therapy (HAART) for their own health, which is lower than 11 % Kenyan national average (NACC^b, 2010). Nevertheless, it demonstrates that the recommended two key PMTCT approaches of lifelong treatment for HIV positive women in need of treatment and short term provision of antiretroviral drugs to prevent mother -child-transmission were being implemented in Embu District PMTCT program. It also provides opportunity to increase the proportion of expectant mothers on HAART by providing for them further specialized evaluation to determine their eligibility for HAART.

4.3 Uptake rate and timing of early infant diagnosis of HIV among HIV-exposed infants enrolled in care

Overall, 313 (87.7%) of the HIV-exposed infants enrolled in care in Embu District underwent the first HIV DNA polymerase chain reaction for early infant diagnosis of HIV at a median age of 8 weeks (range 6 – 17 weeks). There were no differences in percent uptake of early infant diagnosis according to type of health facility as shown in table 4.3 below. With regard to timing of the test, only 114 (32 %) of the HIV-exposed infants had the first HIV DNA polymerase chain reaction test for early infant diagnosis of HIV conducted within the recommended six weeks of age, while 198 (56%) had it conducted by 12 weeks of age.

Table 4.2: Infant enrolment rate into early infant diagnosis according to type of health facility in Embu District

Type of health facility	Percent uptake of early infant diagnosis of HIV
Government hospitals	88.9%
Government health center	86.1%
Faith-based hospital	86.1%

If early infant diagnosis of HIV was to be seen as the first step in the critical pathway to the eventual care of the HIV-exposed infants who will test HIV-positive, then this high uptake rate of the first HIV DNA polymerase chain reaction in Embu District was an encouraging accomplishment in this journey. Considering the observation that early infant diagnosis of HIV is not routinely done in Kenya (Khamadi *et al.*, 2010), it may be argued that the uptake rate of this procedure may therefore vary from one location to another. This uptake rate is also twice as high

as that observed by Nyandiko *et al.* (2010) in western Kenya (40%) and Braun *et al.* (2011) in Malawi (53.7%), but similar to that of Nuwagaba-Biribonwoha *et al.* (2010) in Tanzania (87%).

These glaring differences in the percent of infants who underwent the first HIV DNA polymerase chain reaction test by the four studies all carried out in rural resource-limited locations may probably be explained by factors related to the underlying health care infrastructure. This test requires sophisticated equipment and highly trained health personnel to conduct, in most settings in Africa it is conducted in a centralized HIV reference laboratory usually hundreds of kilometers away through sending of packaged dried blood samples from the HIV-exposed infants. In circumstances where there is an established laboratory network as reported by Nuwagaba-Biribonwoha *et al.* (2010) in the Tanzanian study, the turn-around time for the test is reduced hence improving the test uptake rate. This demonstrates that a supporting health care infrastructural system is of critical importance in aiding the successful implementation of PMTCT interventions especially the uptake rate of early infant diagnosis. The finding in this study that there was no difference in terms of percentage of HIV exposed children who underwent the first early infant diagnosis of HIV test between the different types of health facilities in Embu District may attest to the capacity of lower level health facilities like health centers to perform dry blood samples required for the test from the infants.

These results add new knowledge, albeit at district level, with regard to the proportion of HIV-exposed infants who underwent early infant diagnosis within six weeks (32%) and three months respectively (58%) since there is no Kenya national or regional data on these indicators (NACC³, 2010). The timing of early infant diagnosis is important. When conducted at the recommended time of 6 weeks of infant age, it gives an opportunity for early identification of HIV-infected infants and subsequent linkage to care and treatment. Therefore the delay in testing reported by

this study may have deferred definitive diagnosis and put the HIV-infected infants at the risk of disease progression and death. The median age when the test was performed as reported by this results (8 weeks) is similar to the one found by Nyandiko *et al.* (2010) in western Kenya, but twice as high as the 4 weeks reported by Nuwagaba-Biribonwoha *et al.* (2010) in Tanzania. This delay in conducting the first HIV DNA polymerase chain reaction beyond the recommended 4-6 weeks among 68 % of the infants in this study may be mitigated by the fact that WHO and the Ministry of Health in Kenya allows for some flexibility in timing as may be influenced by prevailing local circumstances and program related challenges.

4.4 Uptake rate of paediatric highly active antiretroviral therapy

There were 26 HIV-exposed infants who were HIV-positive by the end of the 18 month follow-up. Only 3 (11.5 %) were put on paediatric highly active antiretroviral therapy. All the 3 children were from the two government hospitals (one from Runyenjes District Hospital and two from Embu Provincial Hospital).

This results show one of the under achievements in the care of HIV-exposed infants in Embu District was the low uptake rate of paediatric highly active antiretroviral therapy among the HIV-exposed and positive infants. Though this study did not explore the causes, it requires urgent strategies to tackle since all infants with confirmed HIV infection should be started on HAART, irrespective of the clinical or immunological stage (WHO², 2010). In an article 'Easier Said than Done': World Health Organization Recommendations for Prevention of Mother-to-Child-Transmission of HIV: Areas of Concern Possible (Palombi *et al.*, 2010) alludes to possible causes in similar resource constrained settings. It is suggested in the article that the low uptake of

paediatric HAART in HIV-exposed infants who test HIV-positive in many PMTCT programs sub-Saharan Africa could be because HIV care and treatment clinic and early infant diagnosis/PMTCT clinics are run as separate programs (this is indeed true in most health facilities in Kenya). This would in turn create challenges and delays in referrals of HIV-exposed and infected infants from the PMTCT care to HIV care clinics. Sauvageot *et al.*(2010) further illustrates this difficulty in initiating HIV-positive infants on highly active antiretroviral therapy when he observes that in resource limited settings only 9 % of eligible children below 12 months of age are put on this life saving drugs in an analysis of HIV treatment programs in Africa.

The Southern African CHER trial of early versus delayed initiation of highly active antiretroviral therapy (HAART) in HIV-infected infants indicates that early initiation of HAART before 12 weeks of age and before clinical and immunological deterioration achieved a 76 % reduction in infant mortality and a 75 % reduction in HIV disease progression (Violari *et al.*, 2007). This evidence therefore suggests that regardless of the prevailing circumstances, impediments to paediatric HAART uptake like the lack of capacity by health care workers, fears of toxicities, lack of caregivers etc need be urgently identified and solved so that the HIV-exposed and infected infants in Embu District and elsewhere access these life saving drugs at the earliest opportunity and further mortality is averted in this group.

4.5.1 HIV transmission rate among the exposed infants who underwent early infant diagnosis for HIV

When the first HIV DNA polymerase chain reaction was conducted, 22 (7%) out of the 313 infants who underwent the test turned out HIV-positive as shown in table 4.4 below. However,

15 infants (4.8 %) who underwent the test did not have a record of their HIV status. In regard to HIV transmission rate at the time of early infant diagnosis, it was twice as high among infants enrolled in the faith based hospital compared to other types of health care facilities as shown in the table 4.4 below.

Table 4.3: HIV status amongst the 313 HIV-exposed infants who underwent early infant diagnosis in Embu District

HIV status	Frequency	Percent	95% confidence intervals
Indeterminate	8	2.6%	1.1%-4.9%
Negative	268	85.6%	81.8%-89.6%
Not recorded	15	4.8%	2.7%-7.6%
Positive	22	7.0%	4.6%-10.4%

Table 4.4: HIV transmission rates when the first HIV DNA polymerase chain reaction test was conducted stratified according to health facility type in Embu District

Type of health facility	HIV transmission at first early infant diagnosis	95% confidence intervals
Faith based hospital	12%	5.4%-17.2%
Government hospitals	6%	2.1%-11.9%
Government health center	5%	1.5%-10.7%

4.5.2 HIV transmission rate among the exposed infants at end of 18-month follow-up

The cumulative HIV transmission rate at the end of follow-up was 7.3% (95% CI 4.9% -10.6%) as illustrated by table 4.6 below. There was an increase in proportion of infants with no record of their HIV status by 8.7 % (from 4.8% to 13.5%) between the first HIV DNA polymerase chain reaction test at early infant diagnosis and end of follow-up HIV status done by rapid serological testing.

Table 4.5: HIV status of the infants at the end of follow-up in Embu District

HIV status at end of follow-up	Frequency	Percent	95% confidence intervals
Negative	283	79.2%	74.6%-83.3%
Not recorded	48	13.5%	10.2%-17.6%
Positive	26	7.3%	4.9%-10.6%
Total	357	100%	

4.5.3 Maternal ARV prophylaxis and HIV transmission

Table 4.6: HIV status at early infant diagnosis among 39 infants whose mothers did not receive ARV prophylaxis in pregnancy and labour in Embu District

Infant HIV status	Frequency	Percent	95% confidence intervals
Indeterminate	1	2.6%	0.1%-13.5%
Negative	23	59.0%	42.1%-74.4%
Not recorded	1	2.6%	0.1%-13.5%
Positive	14	35.9%	21.2%-52.8%

The HIV transmission rate, when the first HIV DNA polymerase chain reaction test was conducted among those infants whose mothers received antiretroviral prophylaxis was 3.1 % compared to 35.9 % among those infants whose mothers did not receive any kind of antiretroviral prophylaxis for PMTCT as shown in tables 4.7 (above) and 4.8 (below). For those infants whose mothers received antiretroviral prophylaxis for PMTCT, HIV transmission was reduced by 92% compared to those who did not (RR [95% CI] 0.08[0.03-0.14]).

Table 4.7: HIV status at early infant diagnosis among 309 infants whose mothers received antiretroviral prophylaxis in Embu District

Infant HIV status	Frequency	Percent	95% CI limits
Indeterminate	7	2.4%	0.1-13.5%
Negative	259	90.6%	42.1-94.4%
Not recorded	34	3.8%	0.1-5.5%
Positive	9	3.1%	1.2-5.2%

As shown in table 4.7 above, HIV results from early infant diagnosis were recorded for only 275 out of the total 309 HIV-exposed infants whose mothers had received antiretroviral prophylaxis for PMTCT in pregnancy, labour and delivery (HIV status results were not available for 34 infants due to missing entries in all the registers).

4.5.4 Type of maternal ARV prophylaxis and HIV transmission

The HIV transmission, when early infant diagnosis was conducted among infants whose mothers were on dual antiretroviral drug combination of nevirapine and zidovudine for PMTCT

prophylaxis was lower than those on the three-drug highly active antiretroviral therapy (HAART) as shown in the table 4.9 below.

Table 4.8: HIV transmission rates at early infant diagnosis stratified according to type of maternal antiretroviral prophylaxis in Embu District

Type of maternal antiretroviral prophylaxis	HIV transmission	95% C I limits
Nevirapine and zidovudine (n=231)	3%	1.2-6.1%
HAART (n=23)	4.5%	1.1-22.8%

4.5.5 Infant ARV prophylaxis and HIV transmission

The rapid serological HIV test (done at 18 months of age) results showed that the HIV-exposed infants who received antiretroviral prophylaxis for PMTCT at birth (n=291) had a much lower HIV transmission rate of 2.7% (95% CI 1.2% - 5.3%) by the close of follow-up at 18 months of age. For those HIV-exposed infants who received ARV prophylaxis at birth, HIV transmission reduced by 90% by the end of follow-up compared to those who did not receive (RR [95% CI] 0.096 [0.087-0.109]). However, 38 infants who received antiretroviral prophylaxis at birth did not have a record of their HIV status at the end of 18 month follow-up due to loss-to-to follow up.

The cumulative mother-to-child transmission rate of 7.3 % at the end of follow-up is four times lower than the Kenya national estimate of 27 % mother-to-child transmission rate for 2008 (NACC², 2010) and six times lower than the 30-40 % transmission reported in breast-feeding populations without any PMTCT intervention (Filteau, 2009). This is a demonstration that

mother-to-child transmission rate was reduced among the HIV-exposed infants in Embu District. The cumulative HIV transmission rate when the infants underwent first HIV DNA polymerase chain reaction was 7 %. Compared to the HIV transmission at the end of follow-up (7.3%), these findings may suggest that there was no on-going transmission among the infants in the duration of the follow-up. A higher transmission rate is generally expected at the end the follow-up period due continued HIV infection risk posed by breast-feeding. This argument is supported by the findings of the western Kenya study that 5 % of the infants were HIV-positive at median age of 8.3 weeks when the first early infant diagnosis was conducted and a much higher 15.6 % were HIV-positive at 18 months age (Nyandiko *et al.*, 2010). In Tanzania, 6.7 % of the previously HIV-negative infants at first test who returned for confirmation of infection status after weaning were HIV-positive according to a study in Tanzania (Nuwagaba-Biribonwoha *et al.*, 2010). In this study similar transmission rates at the beginning and the end of follow-up may be explained by the 48 infants lost-to-follow-up and whose final HIV status was not recorded leading to an increase in infants without recorded results HIV from 4.8 % to 13.5 % between the two times and introducing some measurement bias.

The finding that 7 % of the HIV-exposed infants were HIV-positive when the first HIV DNA polymerase chain reaction test is similar to that of 8.8 % HIV transmission rate at six weeks of age in Khaliyelitsha, South Africa (Chopra, 2008) in a prospective follow-up of the infants enrolled in PMTCT care. In Blantyre, Malawi, a HIV transmission of 6.5 % was reported in HIV-exposed infants who had received both infant and maternal antiretroviral drugs prophylaxis (Kumwenda *et al.*, 2008). In Tanzania, a much higher mother-to-child HIV transmission rate of 17 % was recorded from the first HIV DNA polymerase chain reaction test. The marked differences between the early transmission rates found in Embu District (this study), South

Africa and Malawi on one hand and in Tanzania on the other hand may be explained by the extent of the antiretroviral prophylaxis for PMTCT for the mother and infants (relative proportions of infants who did not receive antiretroviral drug prophylaxis). This argument is supported by the finding in this study that HIV transmission rates among infants whose mothers did not receive and received PMTCT antiretroviral prophylaxis during pregnancy and delivery was 35.9 % and 3.1 % respectively. This demonstrates that missed opportunities in PMTCT antiretroviral prophylaxis may be opening the window for otherwise preventable HIV transmission which may be as high as 36.4 % of all infants who missed both maternal and infant prophylaxis in Mulago Hospital (Namukwaya *et al.*, 2011). Therefore, efforts to ensure that all mothers and infants enrolled in PMTCT care receive antiretroviral drugs prophylaxis may close off the HIV transmission that is seemingly 'slipping through the net' and hence significantly reduce paediatric HIV infection.

An enigma in these study findings was the higher HIV transmission rate (4.5 %) observed in infants born to mothers who were on highly active antiretroviral therapy (n=23) compared to that of 3 percent for those who were on short term dual prophylaxis of zidovudine and nevirapine (n=231). A more beneficial effect of highly active antiretroviral therapy on mother-to-child transmission of HIV is expected as documented in the following studies. In Zambia, among infants aged 0-6 weeks, zidovudine and single dose nevirapine and highly active antiretroviral therapy were associated with observed transmission rates of 6.8 % and 5.0 % respectively. In Mulago Uganda, the HIV transmission rate at 18 months of age in HIV-exposed infants whose mothers were on the three-drug regimen highly active antiretroviral therapy was 1.7 % compared to 4.6 % among those who were on the dual combination of zidovudine and nevirapine. However, the ongoing Kesho Bora Study in its interim report finds near similar transmission rates from these

two arms of treatment (Kesho Bora Study Group, 2010). The rather small sub-sample of HIV-positive women on highly active antiretroviral therapy (n=23) in this study in Embu District could have introduced some measure of bias in these findings and hence the apparent higher transmission rate among the infants whose mothers were on highly active antiretroviral therapy may not be actually real.

Despite the high uptake rate of PMTCT interventions of early infant diagnosis and short-term prophylactic antiretrovirals in all the types of health care facilities the study was conducted, there were differences in the observed HIV transmission rates between the faith-based hospital on one hand (12%) and government hospitals (6%) and health centers (5%) on the other hand. These differences despite use of same prevention of mother-to-child transmission protocols and similarity in health infrastructure are difficult to explain. The low HIV transmission rate among mother-infant dyads that received antiretroviral therapy for prevention of mother-to-child transmission in Embu District compared to those who did not supports the findings by other previous studies that antiretroviral medicines do indeed reduce the risk of mother-to-child transmission of HIV. Given that some HIV-exposed infants did not receive maternal and infant antiretroviral drugs for PMTCT prophylaxis, the potential for further reductions in perinatal transmission is therefore evident and was not fully utilized, given this low transmission rate among HIV-exposed infants who received.

4.6 Mortality rate amongst HIV-exposed infants during the follow-up

By the end of the follow-up, 53 (14.8%) infants were deceased as shown in table 4.9 below. This translates to a mortality rate of 148 infants per 1000 live births. Only 17 infants (32%) had record

of time of death; and the median time of death was 12 weeks. Government hospitals had the highest death rate at 205 per 1000 live births; faith based hospital 123 per 1000 live births and health centers at 119 per 1000 live births. Although not statistically significant, mortality among HIV-exposed infants who received ARV prophylaxis reduced by 54% compared to those who did not receive (RR [95% CI] 0.46 [0.13-1.09]). The mortality was higher among the HIV-positive infants (n=26); with 53.8 percent mortality by end of 18 month follow-up compared to a much lower 13.1 percent mortality rate among those HIV-exposed infants who were HIV negative as shown in table 4.10 below. However, the median age of death (12 weeks) was the same in both groups of HIV positive and HIV negative infants.

Table 4.9: Outcome status of the HIV-exposed infants at the end of 18 month follow-up in Embu District

Status of the infants at the end of follow-up	Frequency	Percent	95% confidence Limits
Alive	251	70.3%	63.3-75.0%
Deceased	53	14.8%	11.4-19.1%
Lost-to-follow up	53	14.8%	11.4-19.1%
Total	357	100%	

All the HIV positive infants started on paediatric highly active antiretroviral therapy (n=3) were alive by the end of the follow-up. However, 60 % (14/23) of those HIV positive infants that were not started on paediatric highly active antiretroviral therapy were deceased by the end of the follow-up.

Table 4.10: End of follow-up outcomes for the 26 HIV infected infants

Outcome status	Frequency	Percent	95% confidence interval
Alive	8	30.8%	14.3-51.8%
Deceased	14	53.8%	33.4-73.4%
Lost-to-follow up	4	15.4%	4.4-34.9%

Considering that the infant and under five mortality rates in Kenya in 2008 were 81 and 128 per 1000 live births respectively (KNBS^a, 2010), the observed mortality rate of 148 deaths per 1000 live births in this study suggests that HIV-exposed children in Embu District (and probably elsewhere in Kenya) had an higher risk of death compared to their HIV-unexposed counterparts in the whole of Kenya. Similar evidence of this marked disparity in death rates between HIV-exposed and unexposed infants is seen in prospective studies in Botswana (Shapiro *et al.*, 2007) and Zimbabwe (Marinda *et al.*, 2007) among others that demonstrated that HIV-exposed infants had much higher death rates. However, findings of studies in Gambia, Rwanda and Malawi suggested otherwise by finding no significant difference in mortality rates between HIV-exposed and unexposed infants. The study in western Kenya on outcomes of HIV exposed children reported a much lower mortality of 3.4 %, but all the deaths were reported to have occurred within the first six months of life (Nyandiko *et al.*, 2010). All these studies however, had a small sample and hence the fewer resultant number of deaths that may deter conclusive inferences.

The HIV-exposed but uninfected infants had a higher mortality rate (13.1 % for this study) than among HIV-unexposed infants in the general population, a finding also supported by Shapiro and Lockman, 2010. To fully address this maternal HIV-exposure related mortality, more information is needed about the specific causes of mortality in HIV-exposed and uninfected

infants and about the nature of their vulnerability of that makes mortality higher than their unexposed infants. This will enable the identification of potential modifiable mortality risk factors in HIV-exposed but uninfected infants and assist in establishing strategies to stem them.

The findings with regard to mortality in HIV-exposed children in general also suggest an association with two factors. Firstly is age; younger HIV-exposed infants are more likely to succumb to the disease as established by this study. The median age of infant death in this study was 4 months while all the deaths in the study in the western Kenya study occurred within the first 6 months of life. Secondly, the provision of paediatric HAART for the HIV-exposed infants who turn HIV-positive is an urgent matter. The low paediatric HAART uptake of 11.5 % (3 out of 26 infants) may be associated with the 60 % mortality among the HIV positive infants before their eighteenth month birthday. These findings are also supported by WHO guidelines advice that without immediate treatment, half of HIV positive infants are unlikely to survive beyond two years (WHO^c, 2010). However, the extent to which the results of mortality in this study can be generalized to other settings is also unknown, because background mortality and underlying causes of death vary in different areas. Further, this study did not consider infant feeding practices used which are likely to have an impact on mortality. This includes the duration of breast-feeding with longer breast-feeding likely to increase mother-to-child transmission and HIV associated mortality while shorter breast-feeding may increase mortality from childhood illness. Other factors which affect infant mortality that this study did not consider is maternal death. Maternal survival is critical to the survival of young infants. Infants whose HIV-positive mothers received antiretroviral therapy had a 75 % reduction in mortality rates by the age of 5 years compared with those of HIV-positive mothers who were not on treatment, as a result of the improved survival of HIV-infected mothers (Nyandiko *et al.*, 2008).

4.7 Loss-to-follow-up

Cumulatively, 14.8 % of all the HIV-exposed infants enrolled had defaulted from care by the end of the follow-up. There was higher loss to follow-up rate among the infants who were both HIV-exposed and positive compared to the HIV-exposed but negative infants (15.4% and 1.1% respectively). HIV-exposed and infected infants were 14 times more likely to be lost to follow-up than those who were uninfected (RR [95% CI] 14.0 [2.4-18.9]).

4.8 Eighteen month HIV-free survival

The overall 18-month HIV-free survival rate was 68 % (242 out of the 357 HIV-exposed infants evaluated were alive and HIV negative by the end of follow-up) as shown in table 4.12 below. The HIV-exposed infants who missed PMTCT - ARV prophylaxis (both maternal and infant) had a worse 18-month HIV-free survival rate at 31.2 % (95% CI 19.4%-43.6%) compared to 74.2 % (95% CI 68.8%-79.2%) for those who received. A combined total of 104 (29.13%) HIV-exposed infants had adverse outcomes by 18-months of age if a positive HIV status, death and loss-to-follow up were all to be classified as such.

Table 4.11: Outcome status among 282 HIV-exposed but uninfected infants at the end of 18 month follow-up in Embu District

Outcome status of HIV negative infants	Frequency	Percent	95% confidence interval
Alive	242	85.8%	81.2-89.7%
Deceased	27	13.1%	9.4-17.6%
Lost-to-follow up	3	1.1%	0.2-3.1%
Total	282	100%	

The 14.8 % of HIV-exposed infants enrolled in PMTCT follow-up care in Embu District who were lost-to-follow-up may limit the generalization of these results to other PMTCT programs since it was not possible to determine such outcomes as death and final HIV status in this group. However, the finding that those HIV-exposed infants who were HIV-positive when the first early infant diagnosis test was conducted were 2.4 times more likely to default from care than their HIV-negative counterparts may suggest that about half of the ones who defaulted could as well have been dead. This suggestion is supported by the 53.8% mortality observed in the HIV-exposed and positive infants in this study. Moreover, in a study in Zambia it was found that the reasons for the loss to follow-up are not completely understood, although a proportion may be due to unreported transfers and deaths (Sutcliffe *et al.*, 2010). Inability to retain HIV-exposed infants in care has increasingly become a familiar story with PMTCT programs in Kenya. In the western Kenya study, by 3 months of age 7.4 % of the infants had been lost-to-follow-up with a 27.4 % defaulter rate by 18 months of age (Nyandiko *et al.*, 2010). An even more worrying drop-out rate of 65 % by 18 months of age was reported in the Kilifi, Kenya study with half of them occurring within the first 2 months (Hassan *et al.*, 2011). The study in Kilifi associated this attrition with maternal deaths and lack of local support networks alluding that factors outside the core PMTCT mandate may need to be addressed to forestall this situation. This evidence suggests that there is need for resources to be directed towards retention of HIV-exposed infants in PMTCT follow-up to ensure that all infants remain in care and are appropriately monitored.

CHAPTER 5

SUMMARY, CONCLUSION AND RECOMMENDATIONS

5.1.1 Summary

Though PMTCT services have been at the forefront of HIV prevention activities for HIV-exposed infants since 1998, outcomes associated with these infants are seldom documented in Kenya. The purpose of this study was therefore to establish the outcomes achieved among HIV-exposed infants as a way of evaluating the efficacy of the PMTCT program in Embu District. This was done through a descriptive retrospective review of the relevant patient records. Thereafter the uptake rates of PMTCT interventions (ARV prophylaxis, early infant diagnosis) and outcomes (HIV transmission, mortality, loss-to-follow up and 18-month HIV free survival) realized among HIV-exposed infants enrolled in PMTCT follow-up care in the district were determined. The main findings according to the study objectives were:

- i) Early infant diagnosis of HIV was conducted for 87.7 % of HIV-exposed infants. However, in 68 % of the enrolled infants, it was conducted beyond the recommended time of six weeks. Overall, 81.7 % of the infants and 86.8 % of their mothers received antiretroviral drug prophylaxis for PMTCT of HIV. Only 11.5 % of the HIV-exposed infants who were HIV-positive received paediatric HAART.
- i) The HIV transmission rate among the HIV-exposed infants at the end of the 18-month follow-up was 7.3 %. For those infants whose mothers received antiretroviral prophylaxis for PMTCT, HIV transmission was reduced by 92 % compared to those who did not (RR [95% CI] 0.08[0.03-0.14]). For those HIV-exposed infants who received ARV prophylaxis at birth,

HIV transmission was reduced by 90% compared to those who did not receive (RR [95% CI] 0.010 [0.087-0.109]).

- ii) The cumulative 18-month mortality rate among HIV-exposed infants was 14.8 %. Although not statistically significant, the reduction in mortality among HIV-exposed infants who received ARV prophylaxis was by 54 % compared to those who did not receive (RR [95% CI] 0.46 [0.13-1.09]). Mortality in HIV-exposed but uninfected infants was at 13.1 percent and 14.8 percent of all HIV-exposed infants had been lost-to-follow-up by the end of 18 months. HIV-exposed and infected infants were 14 times more likely to be lost to follow-up than their uninfected counterparts (RR [95% CI] 14.0 [2.4-18.9]).
- iv) The HIV-free survival rate was 68%. The HIV-exposed infants who missed PMTCT ARV prophylaxis (both maternal and infant) had a worse 18-month HIV-free survival rate at 31.2 % (95% CI 19.4%-43.6%) compared to 74.2 % (95% CI 68.8%-79.2%) for those who received.

5.1.2 Implications of the findings

- (i) The low HIV transmission rate among infants who received both maternal and infant ARV prophylaxis implies that by strengthening uptake rates of PMTCT interventions like maternal and infant antiretroviral drugs prophylaxis in Kenya, the mother-to-child transmission of HIV can be reduced to levels similar to those witnessed in the developed world.
- (ii) The high HIV transmission rate among HIV-exposed infants who missed maternal and infant ARV prophylaxis demonstrates that missed opportunities in providing PMTCT interventions may be opening the window for otherwise preventable HIV paediatric infections.

- i) The high uptake rate of PMTCT antiretroviral prophylactic drugs and early infant diagnosis test for HIV in Embu District despite the low national averages on these indicators may point to marked differences in performance of PMTCT programs in different locations in Kenya.
- 7) The finding of a high mortality in HIV-exposed but uninfected infants may imply that exposure to maternal HIV increases mortality in infants even when the absence of HIV infection has been confirmed.
- 7) For HIV-exposed infants, priority and emphasis should be laid on confirmation of their HIV status and for those positive the initiation of paediatric highly active antiretroviral therapy fast-tracked since the deaths are likely to occur at much younger ages.
- i) Resources have to be directed towards ensuring retention of HIV-exposed infants in care and putting HIV-exposed infants who turn HIV- positive on paediatric HAART because these two factors threaten to reverse the gains made in control of paediatric HIV.

5.2. Conclusion

The PMTCT program in Embu District reduced mother-to-child transmission rate of HIV and improved the HIV-free survival of the HIV-exposed infants. However, it had a lot of challenges of late enrolment of the infants in follow-up care, missed opportunities in ARV prophylaxis for PMTCT, delays in conducting early infant diagnosis of HIV, poor uptake of paediatric HAART and a high loss-to-follow-up rate.

5.3.1 Recommendations from the study

Based on the findings of the study, the following are recommended:

- i) To ensure that early infant diagnosis through HIV DNA virologic testing is conducted by the sixth week of life, early enrolment into the PMTCT follow-up care should be encouraged and practised. The District Health Management Team and the Health Facility Management teams should establish an early and effective referral system in the health facilities for HIV-exposed infants from postnatal wards and maternal-child health clinics. Health education for HIV-positive pregnant women on importance of enrolling their infants at the earliest opportunity after delivery in the prevention of mother-to-child follow-up care should be intensified during antenatal visits in the health facilities.
- ii) The District Health Management Team should work towards eliminating the several missed opportunities in ARV prophylaxis for PMTCT for both the mother and infant. This should be done through concerted efforts with point of care health workers and other relevant stakeholders. Gaps that create opportunities for HIV positive mothers and HIV-exposed infants to miss ARV prophylaxis should be urgently identified and corrective measures implemented.
- ii) The District Health Management Team should task itself to eliminate MTCT of HIV (from 7.3%) by implementing a package of interventions that could also involve the community. These may include encouraging antenatal attendance, discouraging home deliveries etc. These will ensure that all HIV positive mothers are identified and enrolled for PMTCT earliest, thus further eliminating the missed opportunities in ARV prophylaxis.
- iv) The Hospital Management Teams should identify the impediments to antiretroviral provision to HIV positive infants and formulate practical strategies to overcome them. This may

include creation of referral linkages between the PMTCT clinic and the HIV comprehensive care clinics and setting of clear performance targets against which health workers involved in provision of paediatric HAART can be evaluated against. Integration of paediatric ART services in maternal-child health services should also be considered. This would stem possible challenges in delays of referring HIV-exposed and infected infants from the PMTCT care to HIV care clinics and improve enrolment rate into paediatric HAART.

) The National AIDS and STI Control Program (NASCO) should formulate a policy guideline on defaulter tracing for HIV-exposed infants who are lost-to-follow up. Vital details of guardians/parents of the infants like mobile telephone numbers and geographical location landmarks could be incorporated in the follow-up care register for the infants. This would make tracing and bringing back to care of HIV-exposed infants who default easier. Community health workers can also be utilized as volunteer defaulter tracers and funding provided to enable this activity.

5.3.2 Recommendations for further research

Further research is recommended to;

- i) Identify factors associated with the low uptake of highly active antiretroviral therapy among HIV-exposed and infected infants.
- ii) Identify factors associated with a high mortality among HIV-exposed but uninfected infants.
- iii) Identify constraints associated with loss to follow-up in HIV-exposed children enrolled in PMTCT follow-up care.
- iv) Assess the outcomes among HIV-exposed infants who default from PMTCT follow-up care.

REFERENCES

- Braitstein P, Katshcke A, Shen C, Sang E, Nyandiko W, Ochieng VO, Vreeman R, Yiannoutsos C, Wools-Kaloustian K, Ayaya S. (2010). Retention of HIV-infected and HIV-exposed children in a comprehensive HIV clinical care programme in Western Kenya. *Tropical Medicine and International Health*, Volume 15 (7), pages 833-41.
- Braun M, Kabue M, McCollum ED, Ahmed S, Kim M, Aertker L, Chirwa M, Eliya M, Mofolo I, Hoffman I, Kazembe P, van der Horst C, Kline MW, Hosseinipour M. (2011). Inadequate Coordination of Maternal and Infant HIV Services Detrimentally Affects Early Infant Diagnosis Outcomes in Lilongwe, Malawi. *Journal Acquired Immune Deficiency Syndrome*, Volume 241 (3), pages 456-463.
- Chetty T, Naidu K, Newell M. (2010). Systematic review of HIV-free survival by infant feeding practices from birth to 18 months. Kwa Zulu-Natal, South Africa.
- Chopra M. (2008). Operational research to reduce post-natal transmission and infant mortality. Uppsala university, Sweden, 2008.
- Fernandes R, Ribas G, Silva D, Gomes A, Medina-Acosta E. (2010). Persistent operational challenges lead to non-reduction in maternal-infant transmission of HIV. *Jornal de pediatria*, Volume 86 (6) pages, 503-8.
- Filteau S. (2009). The HIV-exposed, uninfected African child. *Tropical Medicine & International Health*, Volume 14 (3), pages 276-287.
- Hassan A, Sakwa E, Nabwera H, Taegtmeier M, Kimutai R, Sanders E, Awuondo K, Mutinda M, Molyneux C, Berkley J. (2011). Dynamics and Constraints of Early Infant Diagnosis of HIV Infection in Rural Kenya. *AIDS Behaviour*, Volume 56 (8), pages 231-234.
- Joint United Nations Programme on HIV/AIDS (UNAIDS). (2010). Global report on AIDS epidemic. New York, United States.

Kenya National Bureau of Statistics^a (KNBS^a). (2010). Kenya Demographic and Health survey 2008-09. Nairobi, Kenya.

Kenya National Bureau of Statistics^b (KNBS^b). (2010). Kenya Census 2009 Report. Nairobi, Kenya.

Khamadi S, Okoth V, Lihana R, Nabwera J, Hungu J, Okoth F, Lubano K, Mwau M. (2008). Rapid Identification of Infants for Antiretroviral Therapy in a Resource Poor Setting: The Kenya Experience. *Journal of Tropical Pediatrics*, Volume 54(6), pages 370–4.

Kiarie J, Gachuno O, Kinuthia J, Ongech J, Inwani I, Nguti R, Cherutich P, Mubuu K, Sirengo M, Mutsoso W, Nyunya B, Muraguri N, Koigi K. (2011). Evaluation of Utilization and Effectiveness of PMTCT Services in Kenya. Presented at the PMTCT Technical Working Group meeting at NASCOP boardroom, Nairobi, Kenya on 1-3-2011.

Konyangi A, Humphrey J, Ntozini R, Nathoo K, Moulton L, Iliff P, Mutasa K, Ruff A, Ward B. (2011). Morbidity Among Human Immunodeficiency Virus-exposed But Uninfected, Human Immunodeficiency Virus-infected, and Human Immunodeficiency Virus-unexposed Infants in Zimbabwe before Availability of Highly Active Antiretroviral Therapy. *Pediatric Infectious Disease Journal*, Volume 30(1), pages 45-51.

Kumwenda N, Hoover D, Mofenson L, Thigpen C, Kafulafula G, Qing L, Mipando L, Kondwani N, Mebraht T, Bulterys M, Fowler M, Taha E. (2008). Extended Antiretroviral Prophylaxis to Reduce Breast-Milk HIV-1 Transmission. *New England Journal of Medicine*, Volume 359, pages 119-129.

Lisa-Gaye E and Aracelis D. (2010). Clinical Care of the Exposed Infants of HIV-Infected Mothers. *Clinics of Perinatology*, Volume 24, pages 12-31.

Marinda E, Humphrey J, Iliff P, Mutasa K, Nathoo K, Piwoz EG, Moulton L, Salama P, Ward B. (2007). Child Mortality According to Maternal and Infant HIV Status in Zimbabwe. *Pediatric Infectious Disease Journal*, Volume 26, pages 519-526.

National AIDS/STI Control Programme (NAS COP). (2009). Guidelines for Prevention of Mother to Child Transmission (PMTCT) of HIV/AIDS in Kenya. Nairobi, Kenya.

National AIDS Control Council (NACC^a). (2010). Kenya National AIDS Strategic Plan III 2010-15. Nairobi, Kenya.

National AIDS Control Council (NACC^b). (2010). United Nations General Assembly Special Session on HIV and AIDS. Country Report – Kenya. Nairobi, Kenya.

National AIDS Control Council (NACC^c). (2009). Kenya HIV Prevention Response and Modes of Transmission Analysis. Nairobi, Kenya.

National AIDS/STI Control Programme Kenya (NAS COP). (2009). Kenya AIDS Indicator Survey: Final Report. Nairobi, Kenya.

Nuwagaba-Biribonwoha H, Werq-Semo B, Abdallah A, Cunningham A, Gamaliel J, Mtunga S, Nankabirwa V, Malisa I, Gonzalez F, Massambu C, Nash D, Justman J, Abrams E. (2010). Introducing a multi-site program for early diagnosis of HIV infection among HIV-exposed infants in Tanzania. *Bio Med Central Pediatric*, Volume 10(4) pages 7-10.

Namukwaya Z, Mudiope P, Kekitiinwa A, Musoke P, Matovu J, Kayma S, Salmond W, Bitarakwate E, Mubiru M, Maganda A, Galla M, Byamugisha J, Fowler M. (2011). The impact of maternal highly active antiretroviral therapy and short-course combination antiretrovirals for prevention of mother-to-child transmission on early infant infection rates at the Mulago national referral hospital in Kampala, Uganda, January 2007 to May 2009. *Journal of Acquired Immune Deficiency Syndrome*, Volume 56 (1), pages 69-75.

Nyandiko W, Otieno-Nyunya B, Akhaabi P, Musick B, Bucher-Yiannoutsos S, Lane K, Yiannoutsos C, Wools-Kaloustian K . (2010). Outcomes of HIV-exposed children in western Kenya: efficacy of prevention of mother to child transmission in a resource-constrained setting. *Journal of Acquired Immune Deficiency Syndrome*, Volume 54 (1), pages 42-50.

Nyandiko W, Ayaya S, Nabakwe E, Tenge C, Sidle J, Yiannoutsos C, Musick B, Wools-Kaloustian K, Tierney W. (2008). Outcomes of HIV-infected orphaned and non-orphaned children on antiretroviral therapy in Western Kenya. *Journal of Acquired Immune Deficiency Syndrome*, Volume 43 (4), pages 418-25.

Palombi L, Nielsen-Saines K, Giuliano M, Marazzi M. (2010). Easier Said than Done: World Health Organization Recommendations for Prevention of Mother-to-Child-Transmission of HIV: Areas of Concern. *AIDS Research and Human Retroviruses*, Volume 49, pages 1039-47.

Sauvageot D, Schaefer M, Olson D, Pujades-Rodriguez M, O'Brien P. (2010). Antiretroviral therapy outcomes in resource-limited settings for HIV-infected children <5 years of age. *Pediatrics*, Volume 125(5), pages 1039-47.

Shapiro R, Lockman S. (2010). Mortality among HIV-exposed infants: the first and final frontier. *Clinical Infectious Diseases*, Volume 50(3), pages 445-7.

Stringer E, Benjamin H, Namwinga C, Creek L, Ekouevi K, Coetzee D, Tih P, Boulle A, Dabis F, Shaffer N, Wilfert M, Stringer J. (2008). Monitoring effectiveness of programmes to prevent mother-to-child HIV transmission in lower-income countries. *Bulletin of World Health Organization*. Volume 86. pages 57-62.

Songok E, Tukei P, Kiptoo M, Fujiyama Y, Tukei P, Vulule M, Adungo N, Kakimoto K, Kobayashi N, Genga I, Mpoke S, Ichimura H. (2006). The use of short-course zidovudine to prevent perinatal transmission of human immunodeficiency virus in rural Kenya. *American Journal of Tropical Medicine and Hygiene*, Volume 69(1), pages 8-13.

Sturt A, Dokubo E, Sint T. (2010). Antiretroviral therapy (ART) for treating HIV infection in ART-eligible pregnant women. *Cochrane Database Systematic Reviews*. 3:CD008440.

Sutcliffe C, Bolton-Moore C, van Dijk H, Cotham M, Tambatamba B, Moss W. (2010). Secular trends in pediatric antiretroviral treatment programs in rural and urban Zambia: a retrospective cohort study. *Bio-Med Central Pediatrics*, Volume 54, pages 1471-1486.

The PEARL Study Group. (2010). Only half of HIV-exposed infants in Africa receive HIV prophylaxis. Presented at the 18th International AIDS Conference on July 19, 2010. Vienna, Austria.

The Kesho Bora Study Group. (2010). Impact of triple ARV prophylaxis during pregnancy and breastfeeding compared with short-ARV prophylaxis for MTCT prevention on maternal disease progression. Oral abstract ThLBB105. Presented at the 18th International AIDS Conference, 18–23 July 2010, Vienna, Austria.

Tonwe-Gold B, Ekouevi D, Viho I, Amani-Bosse C, Toure S, Coffie P, Rouet F, Becquet R, Leroy V, El-Sadr W, Abrams EJ, Dabis F. (2010). Antiretroviral treatment and prevention of peripartum and postnatal HIV transmission in West Africa: evaluation of a two-tiered approach. *Journal Acquired Immune Deficiency Syndrome*, Volume 54(4), pages 415-22.

Torpey K, Kaonde P, Kabaso M, Weaver M, Bryan G, Mukonka V, Bweupe M, Zimba C, Mwale F, Colebunders R. (2010). Reducing pediatric HIV infection: estimating mother-to-child transmission rates in a program setting in Zambia. *Journal Acquired Immune Deficiency Syndrome*, pages Volume 54(4), pages 415-22.

Unpublished (2010). District Medical Officer of Health (DMOH), Embu. Embu District Annual Health Report for 2009. Embu, Kenya.

Violari A, Cotton M, Gibb D, Babiker A, Steyn J, Madhi S, Jean-Philippe P, McIntyre J. (2007). Early Antiretroviral Therapy and Mortality among HIV-Infected Infants. Presented at the Fourth International AIDS Conference. Sydney, Australia.

Wamalwa D, Obimbo E, Farquhar E, Richardson B, Mbori-Ngacha D, Inwani I, Benki-Nugent S, John-Stewart G. (2010). Predictors of mortality in HIV-1 infected children on antiretroviral therapy in Kenya: a prospective cohort. *Biomed Central Pediatrics*, Volume 10, pages 471-483.

World Health Organization (WHO^a). (2010). Rapid advice: use of anti retroviral drugs for treating pregnant women and preventing HIV infection in infants. Geneva, Switzerland.

World Health Organization (WHO^b). (2010). Antiretroviral drugs for treating pregnant women and preventing HIV infection in infants: towards universal access .Recommendations for a public health approach (2010 version). Geneva, Switzerland.

World Health Organization (WHO^c). (2010). New guidance on prevention of mother-to-child transmission of HIV and infant feeding in the context of HIV. Geneva, Switzerland.

World Health Organization (WHO^d). (2010). Prevention of mother-to-child transmission Strategic Vision 2010-2015, preventing mother-to-child transmission of HIV to reach the UNGASS and MDGS, Geneva, Switzerland.

12) Type of health facility:

Government hospital

Faith based hospital

Government health centre

13) Sex:

Male

Female

14) Registered

15) Age in weeks when child was enrolled in PMTCT follow-up care

16) What was the outcome of the child at the end of follow-up?

Alive	<input type="checkbox"/>
Deceased	<input type="checkbox"/>
Stillborn (N=22)	<input type="checkbox"/>
Not known	<input type="checkbox"/>

APPENDIX I: DATA EXTRACTION TOOL

1. Patient code:

2. Type of health facility:

Government hospital	<input type="text"/>
Faith based hospital	<input type="text"/>
Government health centre	<input type="text"/>

3. Infant's gender

Male

Female

Not recorded

4. Age in weeks when child was enrolled in PMTCT follow-up care

5 a) What was the outcome of the child at the end of follow-up?

Alive	<input type="text"/>
Died	<input type="text"/>
Lost-to-follow-up	<input type="text"/>
Not recorded	<input type="text"/>

b) If death is recorded as an outcome, at what age in weeks did it occur?

6. a) Was a dried blood sample taken for the HIV DNA polymerase chain reaction test?

Yes	
No	
Not recorded	

b) If yes, at what age in weeks was it taken?

7. What was the HIV status at first HIV DNA polymerase chain reaction test for early infant diagnosis?

Negative	
Positive	
Indeterminate	
Not recorded	

8. What is the HIV status at end of 18-month follow-up ?

Negative	
Positive	
Indeterminate	
Not recorded	

9. Did the infant receive antiretroviral drugs for prevention mother -to-child transmission of HIV?

Yes	
No	
Not recorded	

10. If YES, what kind?

Single dose nevirapine	
Short course double ARVs regimen(Zidovudine + Nevirapine)	
Zidovudine	
Not recorded	

11. Did the child's mother receive antiretrovirals for prevention of mother-to-child HIV transmission?

Yes	
No	
Not recorded	

12. If yes, what kind?

Single dose nevirapine	
Short course double ARVs regimen (zidovudine and nevirapine)	
ARVs for HIV-infected pregnant women eligible for treatment (HAART)	
Not recorded	

13. If the infant was diagnosed to be HIV positive, what care was he/she enrolled in?

Cotrimaxazole	
Pediatric HAART	
Not on care	
Not recorded	

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