FOLLOW-UP CARE OF INFANTS BORN IN A PREVENTION OF MOTHER-TO-CHILD TRANSMISSION PROGRAMME IN AN URBAN HOSPITAL IN KWAZULU-NATAL, SOUTH AFRICA

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BY

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ABSTRACT

Introduction

The Human Immunodeficiency Virus (HIV) is the main contributor to rising child mortality in South Africa. Although prevention of mother-to-child transmission programmes have been implemented in the country, little is known about the clinical and loss to follow-up outcomes of infants born to HIV-infected women attending these programmes.

Purpose

The purpose of the study was to describe the clinical and loss to follow-up outcomes of HIV-exposed infants whose mothers had received antiretroviral therapy or prophylaxis during their pregnancy at the Prevention of Mother-to-Child Transmission programme at McCord Hospital. Furthermore, maternal socio-demographic characteristics associated with these outcomes were determined.

Methods

An observational retrospective cohort study design was used. The study population consisted of infants whose mothers had received antiretroviral prophylaxis or therapy at McCord Hospital, and were delivered at McCord Hospital, and/or were brought back to McCord Hospital, following delivery from 1 May 2008 to 31 May 2009.

Results

Data on 265 infants was analysed. Of the 220 infants who were tested, the HIV transmission risk was 2.7% (n=6; 95% CI: 1.0% to 5.8%) at 6 weeks of age. Overall, 40.4% of infants in the cohort were lost to follow-up (n=105, 95% CI: 34.4 to 46.6). In the multivariable model (n=253), late booking for first antenatal visit at or after 28 weeks of gestation (adjusted hazard ratio (AHR) 2.3; 95% CI: 1.0 to 5.1, p=0.044) was a risk factor for loss to follow-up. Compared to having an emergency caesarean section, having an elective caesarean section (AHR 1.9; 95% CI: 1.1 to 3.5) or normal vaginal delivery (AHR 2.5; 95% CI: 1.4 to 4.5) was significantly associated with loss to follow-up of infants.

Discussion

The substantial attrition of infants born to HIV-infected mothers in the Prevention of Mother-to-Child Transmission programme at McCord Hospital undermined the goals of the programme, and underestimated the effect of infectious disease morbidity, mortality and HIV transmission risk associated with these infants.

Recommendations

Counselling mothers on the health benefits to their HIV-exposed infants of attending the follow-up clinic and tracing of infants who have been lost to follow-up is vital to the operational effectiveness of the Prevention of Mother-to-Child Transmission programme at McCord Hospital.

DECLARATION

I, Terusha Chetty, declare that:

(i) The research reported in this dissertation, except where otherwise indicated, is my original research.

(ii) I conducted the descriptive and analytic statistics for the research study.

(iii) This dissertation has not been submitted for any degree or examination at any other university.

(iv) This dissertation does not contain other persons' data, pictures, graphs or other information, unless specifically acknowledged as being sourced from other persons.

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Student: Dr T Chetty: Signature: 

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ACRONYMS AND ABBREVIATIONS

AIDS	Acquired Immune Deficiency Syndrome
AHR	Adjusted hazards ratio
AOR	Adjusted odds ratio
ARTs	Antiretroviral therapy
AZT	Zidovudine
$CD4^{+}$	T-lymphocyte count
DBS	Dried blood spot
EFV	Efavirenz
HAART	Highly Active Antiretroviral Therapy
HIV	Human Immunodeficiency Virus
3TC	Lamivudine
MDGs	Millennium Development Goals
NVP	Nevirapine
PCR	Polymerase chain reaction
PMTCT	Prevention of mother-to-child transmission of HIV
sd-NVP	sd-Nevirapine
WHO	World Health Organisation

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1 CHAPTER I: INTRODUCTION

1.1 INTRODUCTION

Sub-Saharan Africa is severely affected by the Human Immunodeficiency Virus (HIV) epidemic. In South Africa, HIV contributes substantially to child morbidity and mortality. Although prevention of mother-to-child transmission (PMTCT) programmes has been implemented, there is little information available on the clinical outcomes of HIV-exposed infants in terms of morbidity, mortality and HIV transmission. Moreover, little was known about the follow-up outcomes of these infants.

1.2 BACKGROUND

1.2.1 Global overview of HIV in women and children

Unheard of 27 years ago, HIV is responsible for substantial mortality causing an estimated 25 million deaths worldwide [1, 2]. In 2007, approximately 33 million people (95% Confidence Interval (CI): 30 million to 36 million) were living with HIV [1]. Sub-Saharan Africa continues to be the most severely affected and is home to 67% of all people living with HIV [1].

Globally, children less than 15 years old accounted for approximately 2.0 million (95% CI: 1.9 million to 2.3 million) of those living with HIV with an estimated 370 000 (95% CI: 330 000 to 410 000) children less than 15 years newly infected in 2007 [1]. Almost 90% of these children infected with HIV live in sub-Saharan Africa [1].

In September 2000, the Millennium Declaration was adopted by 189 nations during the United Nations Millennium Summit [2]. Eradicating HIV/Acquired Immune Deficiency Syndrome (AIDS) forms goal six of the Millennium Development Goals (MDGs) [3].

Globally, there has been some progress towards achieving the MDGs [3]. The incidence of new HIV infection was reduced from 2.0 million in 2001 to 1.7 million in 2007 largely due to expansion of HIV prevention programmes [3]. Furthermore, annual HIV-related mortality decreased from 2.2 million in 2005 to 2.0 million in 2007 [3].

Reductions were also noted in the HIV antenatal sero-prevalence in some African countries. The prevalence of HIV in pregnant antenatal clinic attendees has fallen since

2000/2001 in 14 of the 17 countries most affected by the pandemic [3]. In Zimbabwe, the antenatal prevalence of HIV dropped from 26% to 18% from 2002 to 2006 respectively [1]. Similarly, Botswana showed a reduction in HIV prevalence in 15 to 19 year old pregnant women from 25% in 2001 to 18% in 2006 [1]. Behavioural modifications in Zambia and Malawi have also led to reduction in the antenatal prevalence of HIV in these countries [1].

In children globally, the incidence of HIV infections peaked around 2001, and the recent decline was most likely related to fewer HIV infections in women of childbearing ages and improved coverage of prevention of mother-to-child transmission programmes [1, 3]. In 2007, approximately 270 000 children less than 15 years (95% CI: 250 000 to 290 000) died from HIV-related causes with 90% of these deaths occurring in sub-Saharan Africa [1].

1.2.2 HIV in South Africa

In 2007, there were approximately 5.7 million (95% CI: 4.9 million to 6.6 million) people living with HIV/AIDS in South Africa [1]. Although the growth of the epidemic may be stabilizing, South Africa has the highest proportion of mother-to-child transmission of any country [1]. In 2008, the HIV prevalence among 15 to 49 year old antenatal clinic attendees was 29.3% (95% CI: 28.5% to 30.1%) [4]. KwaZulu-Natal remains the worst affected province with an antenatal HIV prevalence of 38.7% (95% CI: 37.2 to 40.1) [4]. In contrast the Western Cape has an HIV prevalence of 16.1% (95% CI:12.6% to 20.2%) amongst its antenatal clinic attendees [4].

In 2007, there were over 18.2 million children between zero and 18 years living in South Africa constituting 39% of the total population. KwaZulu-Natal is home to 22% of the children living in South Africa [5]. HIV affects the lives of these children substantially. In 2005, there were more than 129 000 children aged between two and four years, and 214 000 children aged five to nine years living with HIV [6]. In the under-five year age group the overall prevalence of HIV was estimated to be 3.4% [7].

Access to antiretroviral therapy (ART) for those living with HIV has improved considerably over the past eight years [8]. The proportion of newly infected children less than 15 years receiving antiretroviral therapy increased from 2.1% in 2002/2003 to 37% in 2007/2008 [8]. However, access to antiretroviral therapy varied between provinces, with only 31% of newly infected children in KwaZulu-Natal receiving treatment compared to 97% in Western Cape [8]. The reason for the high antiretroviral therapy coverage in Western Cape was due

to the success of prevention of mother-to-child transmission programmes in the province, which has successfully reduced the incidence of HIV in children. In addition, the rollout of antiretroviral therapy to children has been well implemented in the Western Cape [8].

1.2.3 HIV and Prevention of Mother-to-Child Transmission programme in South Africa

The annual under five (child) mortality rate in South Africa increased steadily from 56 per 1000 live births in 1990 to 67 per 1000 in 2008 [9], which highlighted the deteriorating health status of the children in South Africa. HIV was the main contributor to the rise in child mortality and was estimated to be responsible for 40% of the under-five mortality in 2000 [10].

In 2000, South Africa adopted the MDGs including reducing child mortality by two-thirds (MDG four), and combating HIV and AIDS by 2015 [3]. South Africa was one of 12 countries with an increase in the child mortality rate since the 1990 baseline for the MDGs [11] and it is unlikely, as a result, that MDG four will be achieved by 2015. The reasons for this failure are complex but HIV/AIDS and poor implementation of prevention of mother-to-child transmission interventions have contributed to increasing child mortality [11].

The South African National Prevention of Mother-to-Child Transmission programme aimed to alleviate some of the burden of HIV in South Africa [10, 12]. Prior to April 2008, the South African national policy for Prevention of Mother-to-Child Transmission advocated the use of a single dose of nevirapine to mothers at the onset of labour, and a single dose of nevirapine to the newborn baby within 72 hours of delivery [12]. The HIVNET 012 randomised trial reported the efficacy of the sd-nevirapine regimen. It reduced the risk of perinatal HIV transmission among breastfeeding women in Uganda by 47% at four months and by 41% at 18 months (n=645) [13].

In South Africa, poor leadership, the lack of a comprehensive policy framework, and ineffective implementation of the National Prevention of Mother-to-Child Transmission programme led to poor coverage and gaps in the programme [11]. These gaps included problems with uptake of HIV testing pregnant woman, inappropriate or no use of sd-nevirapine and limited follow-up care of mothers and their infants [11]. For instance, statistics showed that 94% of pregnant women in South Africa had at least one antenatal clinic visit in 1998 [14]. Of the 52 districts in South Africa, only seven tested more than 80%

of antenatal women for HIV and only 68% of pregnant women receiving antenatal care had an HIV test performed in 2005/2006 [15]. Sixty-one percent of HIV-infected women took sd-nevirapine during labour, but the proportion dropping out of care was large, with only 47% babies born to HIV-infected women receiving nevirapine after delivery [16].

In April 2008, a new protocol on prevention of mother-to-child transmission was adopted nationally, which better reflected World Health Organisation recommendations [12, 17]. The main change to the national protocol was the addition of a short course of zidovudine (AZT) to be given antenatally and to replace the single intrapartum dose of nevirapine for all pregnant women with $CD4^+$ counts above 200 cells/mm^3, from a gestational age of 28 weeks or more. These new South African guidelines did not include a World Health Organisation recommendation that mothers should receive an antiretroviral "tail" comprising zidovudine and lamivudine for seven days post partum [17]. The zidovudine dose administered to the infant depended on the duration of the zidovudine given to the mother during the antenatal period. If the mother received less than four weeks zidovudine antenatally, the infant was to be given four weeks of zidovudine postpartum. Alternatively, an infant born to a mother who received more than four weeks of zidovudine was given zidovudine for one week postpartum [12]. According to one modelling exercise, the lives of 37 200 children could be saved by 2015 by scaling up prevention of mother-to-child transmission that included dual therapy and improving infant feeding strategies[1] in South Africa [11].

In April 2010, the National Prevention of Mother-to-Child Transmission guidelines were again revised to be far more comprehensive [18]. These guidelines now include the provision of triple antiretroviral therapy for women with $CD4^+$ count less than or equal to 350 cells/mm^3 for life; or zidovudine from 14 weeks of pregnancy with sd-nevirapine and a tail for women with $CD4^+$ count greater than 350 cells/mm^3 [18]. The guideline on infant antiretroviral prophylaxis has also been revised to include nevirapine to the infant for 6 weeks in the non-breastfed infant or if the mother is receiving lifelong antiretroviral therapy [18]. In breastfed infants, oral nevirapine should be provided as long as the mother is breastfeeding for up to one year [18].

[1] Prevention of mother-to-child transmission of HIV by dual therapy at 95% coverage, exclusive breastfeeding at 50%, exclusive replacement feeding at 40%, and mixed feeding at 10%

1.2.4 Prevention of Mother-to-Child Transmission services at McCord Hospital

McCord is a state-aided hospital with substantial autonomy mostly due to funding received from the private sector as well as from many donor agencies. This autonomy put McCord Hospital in a unique position to diverge from national Prevention of Mother-to-Child Transmission policy where appropriate and respond more rapidly to reported evidence-based improvements in changing therapeutic regimens. The Prevention of Mother-to-Child Transmission guidelines implemented at McCord Hospital, before the state adopted the World Health Organisation recommendation of dual therapy, were based on evidence from international studies [19, 20]. Pregnant women with a CD4+ count greater than 200 cells/mm^3 were initiated on a prophylactic antiretroviral regimen. The regimen chosen depended on the mother's viral load and the gestational age at which she presented for antiretroviral treatment.[219, 20] Moreover, HIV-infected pregnant women were offered a choice of normal vaginal delivery or elective caesarean section (before labour and before rupture of membranes) based on their viral load at 36 weeks, and affordability of the surgical procedure to the mother. Newborn infants whose mothers received less than four weeks zidovudine antenatally were administered four weeks zidovudine postpartum. An infant whose mother received more than four weeks zidovudine antenatally was given zidovudine for one week post partum. These pregnant women also received intensive counselling regarding infant feeding.[3]

During 2004 to 2005 at McCord Hospital over 90% of mothers at McCord Hospital reported that they intended to exclusively formula feed their infants, a finding that reflected the message given to these women during counselling about the risks of HIV transmission

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[2] Option A. CD4 count ≤ 200: HAART for life: stavudine, lamivudine & nevirapine.

Option B. CD4 count >200: decision depends on the viral load (VL):

- VL <1500 copies/ml: zidovudine monotherapy from 28 weeks until birth and SD-nevirapine at birth and lamivudine and zidovudine tail for 7 days.
- VL ≥1500 copies/ml: Combivir (zidovudine/lamivudine) & efavirenz (EFV) from 28 weeks until birth and zidovudine/ lamivudine tail for 7 days.

Option C. Women who present late (after 38 weeks gestation / in labour): sd- nevirapine in labour with a lamivudine and zidovudine tail of 7 days.

[3] Giddy J, 2009. Personal communication, June 10 2009

through breastfeeding [21]. The effects of this policy and practice on infant morbidity and mortality has not been assessed.

The 2004/2005 cohort of pregnant mothers who received antiretroviral prophylaxis studied at McCord Hospital showed that the implementation of modified therapeutic regimens had reduced the transmission of HIV from mother-to-child to 2.9% (95% CI: 1.3 to 6.2) at six weeks [21]. The low level of HIV vertical transmission was in line with that reported in resource rich settings despite the fact that McCord Hospital serves a mixed but lower middle class population in a predominantly developing country [22-24].

1.3 STATEMENT OF THE PROBLEM

The reduction of mother-to-child transmission of HIV is one of the key priority areas of the National Strategic Plan for HIV in South Africa [25]. According to the plan, scaling up coverage and improving Prevention of Mother-to-Child Transmission programmes is one of the goals to reduce mother-to-child transmission to less than 5% [25]. Furthermore, a key objective of the plan is the expansion of Prevention of Mother-to-Child Transmission guidelines to provide care to mothers and infants beyond six weeks [25]. In line with the goals of National Strategic Plan, there was an opportunity at McCord Hospital to study the follow-up care of infants born to mothers who attended the Prevention of Mother-to-Child Transmission programme at McCord Hospital.

In May 2008, McCord Hospital established a new clinic to offer follow-up health care to HIV-infected mothers and their infants. Women who enrolled antenatally in the Prevention of Mother-to-Child Transmission programme and their infants were invited to attend the Well Mother and Baby Clinic (***Mamanengane)*** following delivery to receive care for themselves and their infants until the children reached 18 months of age. The clinic offered ongoing postnatal HIV-care for mothers and their infants. Services offered included antiretroviral treatment for the mother, primary health care, reproductive health services, psychosocial support, and health promotion services. Socio-demographic, behavioural, clinical and immunologic data on mothers and their infants were collected as part of the standard level of care.

Whilst the implementation of the Prevention of Mother-to-Child Transmission programme at McCord Hospital from 2005 to 2007 reduced the transmission of HIV from mother to child to between 1.3% to 6.2% at six weeks of age, data on the clinical outcomes and proportion of loss to follow-up of the infants beyond six weeks were not recorded. Furthermore, 39% of the mothers in the Prevention of Mother-to-Child Transmission programme who delivered at McCord Hospital did not return with their infants for follow-up care at six weeks of age[4]. Given this substantial proportion of mothers and infants lost to follow-up, the six-week HIV transmission risk at McCord Hospital may have been underestimated. The new postnatal service provided an opportunity to study the clinical outcomes of the infants born to mothers in the Prevention of Mother-to-Child Transmission

[4] Thrumbra M, McCord Hospital, 2009. Personal communication, 22 June 2009

programme and the socio-demographic characteristics associated with loss to follow-up of infants attending the clinic.

1.3.1 Research Questions

i. What are the clinical outcomes of infants born to HIV-infected women who follow-up at McCord Hospital for a minimum of six months?
ii. What are the maternal demographic, socioeconomic, clinical and immunologic characteristics associated with loss to follow-up of infants at McCord Hospital?

1.4 PURPOSE OF THE RESEARCH

The purpose of the study was to measure the clinical and loss to follow-up outcomes of infants, born to HIV-infected mothers who received antiretroviral prophylaxis and therapy in the McCord Hospital Prevention of Mother-to-Child Transmission programme, from 1 May 2008 to 31 May 2009[5]. Furthermore, the maternal demographic, socio-economic, clinical and immunological characteristics associated with these outcomes were examined.

1.5 SPECIFIC OBJECTIVES OF THE RESEARCH

The specific objectives were:

(1) To determine the morbidity, mortality and HIV transmission risk of infants presenting to McCord Hospital;
(2) To determine the loss to follow-up outcomes of these infants presenting to McCord Hospital; and
(3) To measure the association between infants who were lost to follow-up and maternal demographic, socio-economic, clinical and immunologic characteristics.

[5] All infants included in the study were born from 1 May 2008 to 31 May 2009, either at McCord Hospital or elsewhere. All HIV-infected women whose infants were included in the study received antiretroviral therapy or prophylaxis at McCord Hospital.

1.6 ASSUMPTION UNDERLYING THE STUDY

- The demographic, socio-economic (including employment status) and residence of the mothers remained unchanged for the duration of the study.
- Antiretroviral prophylaxis for prevention of mother-to-child transmission or antiretroviral therapy was received and taken by the women in the study and was adhered to for the duration of her pregnancy.
- The caregiver correctly reported maternal feeding practice.
- Infant caregivers remained the same throughout the duration of the study for infants not lost to follow-up.

1.7 OPERATIONAL DEFINITIONS USED IN THE STUDY

Maternal antiretroviral regimen:

The antiretroviral regimen prescribed to pregnant women according to clinical guidelines followed by McCord Hospital. The regimen was as follows:

Option A. $CD4^+$ count ≤ 200: antiretroviral therapy: stavudine, lamivudine and nevirapine
Option B. $CD4^+$ count >200: decision depended on the viral load (VL):
VL <1500 copies/ml: zidovudine from 28 weeks until birth and sd-nevirapine at birth, and lamivudine and zidovudine tail for seven days.
VL ≥1500 copies/ml: Combivir (zidovudine/ lamivudine) and efavirenz (EFV) from 28 weeks until birth, with zidovudine/ lamivudine tail for seven days.
Option C. Women who present late (after 38 weeks gestation / in labour): sd- nevirapine in labour with a tail of zidovudine/ lamivudine for seven days.

The **booking gestational age** was the gestational age of the foetus at the woman's first presentation for antenatal care at any health care facility determined by estimation of the date of the women's last known menstrual period or ultrasound estimation.

Baseline $CD4^+$ count were the $CD4^+$ count measure taken at the mother's first antenatal visit (McCord Hospital or other antenatal clinic).

Baseline viral load was the viral load measure taken at the mother's first antenatal visit to clinic (McCord Hospital or other antenatal clinic).

Any **illnesses during pregnancy** was any maternal illness requiring treatment during or prior to pregnancy excluding World Health Organisation stage IV conditions.

The **maternal baseline height** was the height measured in metres at the woman's first presentation to any facility offering antenatal services.

The **baseline maternal weight** was the weight measured in kilograms at the woman's first presentation to any facility offering antenatal services.

Infant heel stick samples were **tested for HIV-1 DNA** by using polymerase chain reaction (PCR) [26].

The timing of HIV testing of infants was at six weeks and 14 weeks of age.

Infants were **presumed HIV infected** if they tested HIV-infected at six or 14 weeks of age followed by a confirmatory DNA PCR assay.

An i**nfant was classified as HIV-infected** if one or more antibody tests were positive at or after 18 months.

An **infant was presumed HIV-1 uninfected** if they had two or more negative DNA polymerase chain reaction assays at McCord Hospital with one test performed at six weeks of age and the second test performed at 14 weeks of age. For breastfed infants, the DNA PCR assays were taken six weeks after cessation of breastfeeding.

A **child was classified as HIV-1 uninfected** if one or more antibody tests were negative at or after 18 months.

Definitive diagnosis of infection: In order for a diagnosis to be classified as definitive, the organism needed to be identified, or serologic, and/or antigenic evidence needed to be found in the majority of the cases. The diagnosis was also classified as definitive if the clinical picture was pathognomonic of the causative agent (for instance Koplik's spots on buccal mucosa in measles) [27].

Presumptive diagnosis of infection: If the above criteria were not met, the diagnosis of infection was classified as presumptive [27].

The infant morbidity for the purposes of the proposed study was defined as the following conditions and was based on a cohort study in Latin America [27].

Gastrointestinal	Acute or chronic gastroenteritis, presumed: cause not identified. Diarrhoea, presumed: Clinical diagnosis only.
Upper respiratory tract infection	Otitis externa Otitis media, acute, clinical: diagnosed through physical examination. Specific organism not identified. Otitis media with effusion: diagnosed through physical examination Tonsillitis/ pharyngitis, presumed, unknown cause Upper respiratory infection
Lower respiratory infection	Pneumonia, suspected Pneumonia, presumed Bronchiolitis, presumed. Specific cause unknown Bronchitis, presumed: cause not determined Asthma, presumed ***Pneumocystis jiroveci*** pneumonia: clinical diagnosis
Skin and mucous membranes	Conjunctivitis, presumed. Clinical diagnosis Dermatitis, other Candidiasis, oral, presumed Cellulitis Impetigo Lymphadenitis Tinea, presumed: infection suspected clinically but cause unproven Gingivitis Gingivostomatitis Scabies Pityriasis versicolor

Other Conditions not included in the above categories

The researcher assigned the **loss to follow-up status** of infants based on the date of the infant's next scheduled visit. Infants who missed a scheduled visit but subsequently presented for a visit (either scheduled or unscheduled) to McCord Hospital were not lost to follow-up. The initial follow-up periods were at one, six, ten and 14 weeks. If the infant did not return within two weeks of these scheduled visits, the infant was lost to follow-up in the study. Infants who were brought back to McCord Hospital outside of their appointment, but within the two-week period of their scheduled appointment were not considered lost to follow-up. Infants brought back to McCord Hospital outside this two-week period were classified as lost to follow-up, irrespective of the reason for the delayed visit.

The **later infant follow-up periods** were at six, nine, 12, 15 and 18 months. If the infant did not return within one month of these scheduled visits, the infant was lost to follow-up in the study. Infants who were referred to other clinics by clinicians or were discharged from the clinic at 18 months were not considered lost to follow-up.

Vaccination coverage: the numerator was the number of children that reached the specified time point who had received the specified vaccine(s), according to data from a Road-to-Health card or report by the mother. The denominator was the total number of children who reached the specified time point [28].

1.8 ORGANISATION OF THE REPORT

This dissertation is divided into six chapters. Chapter one provides an overview of HIV in the context of child health globally and locally. This chapter also outlines the research questions, main objectives and purpose of this study.

Chapter two outlines the body of knowledge related to consequences of HIV on infant and child health. Furthermore, literature on loss to follow of infants in operational prevention of mother-to-child transmission settings and characteristics of patients lost to follow-up is critically analysed.

Chapter three describes the methods undertaken in this research study. The study design, study population, data sources, sampling methods, variables and statistical

analysis applied by this study are further explored in this chapter. The reliability and validity of the study and handling of bias and limitations are also described.

Chapter four focuses on the results of the research study. The overall study population is described and infant outcomes in terms of morbidity, mortality, HIV transmission, and loss to follow-up are outlined. Furthermore, risk factors associated with loss to follow-up of infants and predictors of upper respiratory tract infection are determined.

Chapter five outlines the finding of the study and discusses these results in relation to previous studies and importance of these results for South Africa.

Chapter six provides recommendations and conclusions based on the results of the study.

1.9 SUMMARY

HIV remains a leading cause of child mortality in South Africa. This chapter outlined both the global and local burden of disease and the extent and limitations of Prevention of Mother-to-Child Transmission programme in South Africa.

2 CHAPTER II: LITERATURE REVIEW

2.1 INTRODUCTION

The Prevention of Mother-to-Child Transmission programme at McCord Hospital has had success in reducing the mother-to-child transmission risk of HIV to less than 5%. This meant that the number of HIV-exposed, uninfected children born to HIV-infected women who attended the Prevention of Mother-to-Child Transmission programme at McCord Hospital exceeded the number of HIV-exposed but infected children born to these women. In a developing setting, HIV-exposed uninfected infants are vulnerable to acquiring infectious diseases. The clinical outcomes of this cohort of HIV-exposed, uninfected children at McCord Hospital were not previously studied. This study was therefore important in contributing to the body of knowledge regarding the clinical outcomes of HIV-exposed, uninfected children.

Children born to HIV-infected women were seldom identified as a potentially high-risk, vulnerable group who need ongoing health care after their mothers leave the Prevention of Mother-to-Child Transmission service. Losing these infants to follow-up care represented a missed opportunity for ongoing care and undermined the goals of the programme to reduce HIV-related incidence, morbidity and mortality. Thus, identifying the socio-demographic, clinical and immunological characteristics of the mother that were associated with high levels of attrition was necessary. The knowledge obtained enables health care workers to identify high-risk patients and implement measures to reduce loss to follow-up.

2.2 PURPOSE OF THE LITERATURE REVIEW

The purpose of the literature review was to examine the literature on infant feeding, morbidity and mortality particularly in HIV-exposed, uninfected infants, and loss to follow-up of infants in a prevention of mother-to-child transmission programme.

Studies examining the health outcomes of HIV-exposed, uninfected infants were critically reviewed to determine the risk factors associated with morbidity and mortality of these infants. Studies exploring the loss to follow-up children born to mothers in prevention of mother-to-child transmission programmes were also critically reviewed to determine the

risk factors associated with loss to follow-up from the facility where the child had been born.

2.3 SCOPE OF LITERATURE REVIEW

Literature assessing morbidity and mortality in HIV-infected and uninfected infants and loss to follow-up of infants in Prevention of Mother-to-Child Transmission programmes were reviewed. Moreover, predictors of morbidity and mortality and loss to follow-up of these infants were explored.

2.4 SOURCES OF LITERATURE REVIEWED

The ***Pubmed*** database was searched for studies between 1990 and 2010 pertaining to factors associated with loss to follow-up of infants in Prevention of Mother-to-Child Transmission programmes, and the morbidity of HIV-exposed, uninfected infants in terms of infectious and non-infectious disease. The following search terms were used to find citations related to morbidity of HIV-exposed infants: "respiratory tract infections", "diarrhoea", "infectious disease" "non-communicable disease", "infant morbidity" and "HIV-uninfected infants". The ***Pubmed*** database was also searched for citations related to loss to follow-up: "Prevention of Mother-to-Child Transmission", "follow-up", "drop-out", and "loss to follow-up".

2.5 LITERATURE REVIEWED

2.5.1 Modes of transmission of HIV from mother-to-child

Transmission of HIV can occur ***in utero*** (5%), during the intrapartum period (15%) and in the postpartum period during breastfeeding (15%) [29]. The combined risk of mother-to-child transmission of HIV without any interventions in non-breastfed populations is 15 to 30% [17]. The combined risk of transmission in the absence of interventions, in breastfed populations who practice prolonged breastfeeding is 35% [29].

Transmission of HIV can be reduced ***in utero*** and intrapartum from 20% to between 7 and 9% by implementing short course prophylactic antiretroviral therapeutic regimens administered to the mother during pregnancy and the infant immediately postpartum [30]. A combination of interventions, including antiretroviral therapy that optimally suppressed viral load, elective caesarean section and complete avoidance of breastfeeding can reduce

vertical transmission of HIV to infants to 1 to 2% in developed countries [22, 24, 31-34]. However, infants in the postpartum period are still particularly vulnerable to HIV due to risk imparted by prolonged breastfeeding. In parts of Africa, where prolonged breastfeeding for 18 to 24 months is still the norm, HIV transmission through breast milk imposes a further risk of approximately 10-15% [35-37].

In 2006, an estimated 39% of pregnant women attending antenatal clinics in KwaZulu-Natal were HIV-infected compared to the national average of 29% [38]. A prospective cohort study of mother–infant pairs who participated in the South African national Prevention of Mother-to-Child Transmission programme for the period 2002 to 2004 described the mother-to-child transmission of HIV as 11.8% (68 out of 585) at three to four weeks. The rate of early transmission of HIV to infants at three to four weeks of age ranged from 8.6% (95% CI: 4.5% to 14.5%) in Paarl, 11.9% (95% CI: 8.3% to 16.3%) in Umlazi to 13.7% (95% CI: 8.9% to 19.8%) in Rietvlei [39].

2.5.2 Predictors of mortality in infants born to HIV-infected mothers

Findings of several studies have highlighted the factors affecting mortality of HIV-exposed infected and uninfected infants [40-43].

Findings of the studies showed maternal death, advanced maternal HIV disease, and anaemia were significantly associated with infant mortality. A meta-analysis of 3468 infants in seven randomised intervention trials of mother-to-child transmission in sub-Saharan Africa showed that 35% of HIV-infected infants and 4.9% of HIV-uninfected infants were estimated to die by one year of age [41]. Infant mortality was associated with maternal death (adjusted odds ratio (AOR) 2.3; 95% CI: 1.6 to 3.2; $p < 0.001$), and maternal $CD4^+$ cell count less than 200 cells/mm^3 (AOR 1.91; 95% CI: 1.4 to 2.6; $p < 0.001$) [41]. Moreover, infant mortality was greater in infants whose mothers had advanced disease or died during follow-up, regardless of their HIV status. The effect of maternal death on infant mortality was considerable in the group of uninfected infants (AOR 3.6; 95% CI: 1.9 to 6.9; $p < 0.001$) [41].

Timing of HIV transmission risk may also affect infant mortality. Late (breastfeeding) transmission of HIV was significantly associated with lower infant mortality when compared to early (perinatal) transmission (AOR 0.52; 95% CI: 0.29 to 0.70; $p<0.0001$) [41]. The children included in this meta-analysis were part of research studies where health care

support was likely to be better than existed in the routine health care setting. The estimates of infant mortality were therefore lower than estimates of mortality in real-life settings.

The findings of a cohort study conducted in Lusaka, Zambia were in agreement with the meta-analysis described above. The cohort of 620 HIV-uninfected infants were recruited as part of a randomised controlled trial investigating early cessation of breastfeeding [40]. The study findings showed that infants born to mothers with $CD4^+$ cell count less than 350 cells/mm^3 were at greater risk for death (hazards ratio 2.9; 95% CI: 1.0 to 8.0) [40]. Cumulative mortality was 4.6% (26/620) (95% CI: 2.8% to 6.3%) by four months of age [40]. Causes of death was known in 20 infants, the most frequent of which was pneumonia (10/20) and sepsis (4/20) [40]. In multivariate analysis, maternal haemoglobin <10 g/dL (hazards ratio 2.37; 95% CI: 1.0 to 5.4), maternal death (hazards ratio 6.8; 95% CI: 2.7 to 17.7) and birth weight < 2500 g (hazards ratio 2.4; 95% CI: 1.1 to 5.7), was also significantly associated with mortality of the infant through four months of age [40]. A limitation of this study was that the cohort of uninfected infants born to uninfected mothers was followed until four months of age only, hence morbidity and mortality of these infants beyond this age remains unknown. Moreover, although infants had frequent heel-stick blood samples tested for HIV-1 DNA at birth, one week, and one, two, three and four months of age by polymerase chain reaction, unidentified HIV infection that contributed to morbidity and mortality in the cohort could not be ruled out [40].

Maternal HIV-infection may increase infant mortality regardless of the infants HIV status. The findings of a prospective cohort study in a rural Uganda showed that the two-year child mortality rate was 540 per 1000 HIV-infected children (n=69), 165 per 1000 children in HIV-uninfected infants born to HIV-infected mothers (n = 269) and 128 per 1000 children born to HIV negative mothers (n=3183) [43]. Relative to uninfected mothers, the hazard ratio of child mortality was 2.0 ($p < 0.001$) in HIV-exposed but uninfected infants, and 3.8 ($p < 0.001$) if the infant was infected [43]. A limitation of this study was the loss to follow-up of HIV-infected infants resulting in a small sample size in this group [43]. Similar findings were observed in a retrospective cohort analysis of 13 583 children under two years of age in rural, northern KwaZulu-Natal [44]. The data from this study showed that mortality of children under 2 years (n=848; 6.2%) was independently associated with maternal HIV status (adjusted hazards ratio (AHR) 4.3; 95% CI: 3.1 to 6.0) [44].

Infant receipt of cotrimoxazole prophylaxis may be a predictor of infant mortality. According to the findings of a randomised controlled trial comparing cotrimoxazole prophylaxis (n=265) to a placebo (n=269) in HIV-infected children in Zambia, cotrimoxazole prophylaxis was associated with lower mortality (cause-specific hazard ratio 0.6; 95% CI: 0.4 to 0.8; $p < 0.001$) [45]. Data from a clinic-based, multi-centre prospective cohort conducted in Puerto Rico, Texas, Illinois, Massachusetts and New York over an 11 year period showed that infant receipt of cotrimoxazole prophylaxis for ***Pneumocystis jiroveci*** pneumonia was associated with reduced risk of death (relative risk 0.04; 95% CI: 0.0 to 0.3; $p = 0.002$) [42].

2.5.3 Infant morbidity of HIV-exposed but uninfected infants

Infants born to HIV-infected women may be at greater risk for morbidity due to various factors. These HIV-exposed infants are vulnerable to losing one or both parents to HIV-related mortality [46]. In addition, HIV-infected mothers may not be able to provide appropriate childcare or may transfer infectious pathogens to their infants [41].

A two-year prospective cohort study in Latin America and the Caribbean countries described the clinical outcomes of HIV-exposed but uninfected infants born to HIV-infected women. The study outcome measure was infectious disease, either definitely or presumptively diagnosed, occurring at birth, six to 12 weeks, and six months of age [27].

The study population consisted of 462 HIV-exposed but uninfected infants [27]. None of the infants was breastfed. All except one of the infants were administered zidovudine prophylaxis. The remaining infant received nevirapine prophylaxis. The infections were classified according to age of diagnosis as early neonatal (zero to six days), late neonatal (seven to 27 days), and post-neonatal (greater than 28 days) [27]. Sixty one percent (283 of 462) of infants developed 522 infections (1.8 infections per infant). The cumulative incidence rate of infections was 4.5 infections per 100 child-weeks of observation [27].

Skin or mucous membrane infections were most common (1.9 cases per 100 child-weeks) followed by respiratory tract infections (1.7 cases per 100 child-weeks) [27]. Early neonatal sepsis occurred in 12 infants (26 cases per 1000 infants) [27]. Overall, hospitalisations occurred in 17% (81 of 462) of the infants with more admissions occurring in infants with lower respiratory tract infections (41%). Advanced maternal HIV disease (AOR 2.1; 95% CI: 0.9 to 4.5), infant anaemia (AOR 2.3; 95% CI: 1.4 to 3.8), tobacco smoking antenatally

(AOR 2.2; 95% CI: 1.3 to 3.8), and overcrowding (AOR 1.5; 95% CI: 0.9 to 2.4) were independently associated with more than one neonatal infection [27]. Post-neonatal infections were associated with the use of intrapartum antibiotics (AOR 1.7; 95% CI: 1.2 to 2.5) and lower maternal $CD4^+$ counts (AOR 1.7; 95% CI: 0.8 to 3.6) [27].

A limitations to the study was selection bias [27]. The mothers volunteered to enrol in the study and there was no control group of HIV-1 uninfected mothers. The strength of the research was its prospective study design and analysis where data were collected prospectively starting antenatally [27]. Presumptive and confirmed diagnoses of infections were included in the study to avoid underestimation of the occurrence of disease [27]. Early onset respiratory conditions without systemic signs or radiographic findings were not included to avoid differential misclassification bias [27].

An analysis of a cohort of infants (n=620) in a randomised trial of breastfeeding cessation in Lusaka, Zambia showed that HIV-uninfected infants had a greater risk of hospital admissions (hazards ratio 2.3; 95% CI: 1.2 to 4.4) if maternal $CD4^+$ count was less than 350 cells/mm^3, after adjusting for maternal death and low birth weight [40]. Cessation of breastfeeding before four months of age was also significantly associated with time to first hospital admission (hazard ratio 3.4; 95% CI: 1.0 to 11.5) in the adjusted analysis [40]. Thirty-nine infants were admitted to hospital between four days and four months of age [40]. The most common cause of admission was pneumonia and sepsis (31 of 39) [40].

A prospective cohort study of 808 children in a clinical setting in Blantyre, Malawi assessed the patterns of morbidity in HIV-infected and uninfected infants over 18-months of age [47]. HIV infected children (n=190) had more frequent events of age-adjusted recurrent fever, chronic diarrhoea, vomiting, ear infections, skin conditions, oral thrush and cough relative to HIV-uninfected children (n=499) ($p < 0.05$) [47]. However, there was no significant difference between illness events in HIV-exposed but uninfected children and children born to HIV-seronegative mothers (n=119) [47]. The strength of this study was the large number of infants followed up to 18 months of age [47]. However, a large proportion of children (n=184) (23%) were lost to follow-up over the 18 month period [47]. In addition, the number of maternal deaths in the HIV-uninfected infant group was small (n=23) and hence may not have shown an effect on the survival of these infants [47].

2.5.4 Loss to follow-up of mothers and infants in Prevention of Mother-to-Child Transmission interventions

HIV-infected children were rarely identified for ongoing health care after leaving the care of a prevention of mother-to-child transmission service. A 13-month retrospective record review (N = 1234) of HIV-infected women who attended the Prevention of Mother-to-Child Transmission programme was conducted at Coronation Women and Children's Hospital in Johannesburg in 2002 [48]. Of the 8221 deliveries at this hospital in the 13-month period, 1234 (15%) occurred in HIV-infected women [48]. The mother-to-child transmission risk of HIV was 8.7% at six weeks and 8.9% at three months of age [48]. By four months of age, more than 70% of infants were lost to follow-up in the routine Prevention of Mother-to-Child Transmission service [48].

From 2002 to 2003, a prospective cohort study was conducted of infants born to mothers in the Prevention of Mother-to-Child Transmission service at Coronation Women and Children's Hospital [49]. Three-hundred infants born to HIV-infected women in the Prevention of Mother-to-Child Transmission service at the hospital were followed up to 12 months of age [49]. Of the 300 infants, 233 (78%) remained in with study at 12 months of age [49]. At the 12-month visit, mothers who returned with their infants were asked questions about their socio-economic circumstances [49]. Cross-sectional data were collected from 176 (76%) of the 233 patients with a semi-structured interview [49]. Of the 176 mothers interviewed, 101 were unemployed (57%), 103 (58.5%) were living with the father of the infant at the time of the interview and 117 (67%) of women had disclosed their HIV-infection status to their partners [49]. The primary caregiver was the mother in 150 of the 176 infants (85.2%). Most of the mothers who returned to Coronation Women and Children's Hospital at the 12-month visit resided in Johannesburg (n=102, 58%), with 32 mothers (18.2%) residing in another province [49]. The major limitation to this study was that it evaluated the socio-demographic profile of women who returned to the hospital at 12 months and were therefore not representative of women who were lost to follow-up [49]. The authors of this study concluded that the results of the study were not generalisable to other situations. However, the findings of this study highlighted the socio-economic circumstances of HIV-infected women and their infants.[49]

A prospective cohort study conducted in 1994 examined the predictors of loss to follow-up of HIV-exposed infants in Malawi [50]. HIV infection status could not be determined for 797

infants (37%) of 2156 infants in the study as 653 of these 797 infants (30%) were not brought back for follow-up care [50]. Social and biological variables as predictors of loss to follow-up were assessed. Infants with lower birth weight (odds ratio (OR) 0.8; p=0.003) and singletons (OR 0.7; p=0.09) were less likely to receive follow-up care. Furthermore, the parents of infants lost to follow-up were less educated (OR 1.2; p<0.001) and were more likely to be farmers (OR 4.0; p < 0.001) [50].

A retrospective cohort study conducted from 2000 to 2005 examined the loss to follow-up proportion of mother-infant pairs (N=567) in the Prevention of Mother-to-Child Transmission programme in rural Uganda [51]. Maternal antenatal data, HIV diagnosis, antiretroviral history, delivery and follow-up of mother-infant pairs were retrospectively collected from medical records [51]. The study definition for loss to follow-up was "those with unknown infant HIV status at 18 months of age and who had missed their last scheduled appointment for greater than or equal to two months before the start of the study [51]." Mother-infant pairs who were lost to follow-up were actively traced, and a cross-sectional survey was then conducted to determine the reasons for loss to follow-up in the Prevention of Mother-to-Child Transmission programme [51].

Overall, loss to follow-up of mother-infant pairs was 54% (n=303) after a median duration of one month (interquartile range (IQR) 0-5) [51]. There were 197 mother-infant pairs successfully traced. Timing for loss to follow-up was as follows: 45 (23%) mother-infant pairs were lost to follow-up after Prevention of Mother-to-Child Transmission enrolment, 42 (22%) after delivery and 108 (55%) during follow-up [51].

The reasons for poor retention included poor maternal understanding of the importance of follow-up (n=59; 30%), infant death (n=54; 27%), lack of partner involvement (n=26; 13%) and change in residence (n=24; 12%) [51]. Fear of stigma (n=12; 6.1%) and maternal illness (n=6; 3.1%) accounted for a small proportion of the reasons for loss to follow-up [51]. In the multivariable model, incomplete antiretroviral prophylaxis in the mother or infant (AOR 1.9; 95% CI: 1.1 to 3.4); infants who were breastfed for greater than six months (AOR 4.4; 95% CI: 2.0 to 9.7); and infants less than six months at the start of weaning (AOR 2.6; 95% CI: 1.4 to 4.6) were significantly associated with loss to follow-up or death (p < 0.05) [51]. Record of acute illness in the infants was negatively associated with loss to follow-up or death (AOR 0.3; 95% CI: 0.2 to 0.6; p< 0.05) [51]. Maternal and infant predictors of loss to

follow-up factors in this study were limited by the cross-sectional nature of the data collection, as the data may have been subject to recall bias [51].

2.5.5 Benefits and Risks of Formula Feeding

Exclusive formula feeding eliminates the risk of postpartum transmission of HIV from mother to infant in the postpartum period. However, formula feeding can be negatively associated with infant morbidity and mortality, including increased risk of malnutrition and infectious diseases other than HIV [52-54].

A randomised controlled trial conducted in antenatal clinics in Kenya involving 401 mother-infant pairs showed that formula-fed infants, where mothers had access to potable water, had 40% less risk of HIV transmission compared to their breastfeeding counterparts [52]. However, the two-year mortality risk in those breastfeeding was 24% (95% CI: 8% to 31%) versus 20.0% (95% CI: 14.4% to 25.6%; p = 0.30) in the formula-fed group [52]. During the first three months of life, formula-fed infants had an increased risk of diarrhoea and upper respiratory tract infection. There were limitations to the comparability of the groups included the larger loss to follow-up in the formula group. Mortality in the formula fed group may have been missed. In addition, the analysis followed an intention to treat approach. Those patients who were initially assigned to the formula group may not have adhered to exclusive formula feeding and may actually have breastfed [52].

The paediatric diarrhoeal outbreak in Botswana in 2006 highlighted the importance of breastfeeding to child survival [55]. The morbidity and mortality in this outbreak occurred primarily in HIV-negative non-breastfeeding infants. The HIV prevalence at the time of the outbreak was 33% [55]. Of the 153 infants hospitalized with diarrhoea, 97% were less than two years old and 88% were not breastfeeding. Eighteen per cent of the children and 64% of the mothers were HIV-infected [55]. Only one breastfed infant under two years (1/16; 6%) died, compared to 24% (27/115) of children who were non-breastfed (relative risk 0.3; 95% CI: 0.1 to 1.9; p=0.19) [55]. The breastfeeding infant who died was also given formula milk and cow's milk [55].

A cohort study in Côte d'Ivoire found no significant difference between the formula feeding and exclusively breastfeeding groups in terms of rates of illness at 24 months [56]. Over the 2-year follow-up, 37% of infants in the formula-fed group and 34% of infants in the breastfed group were free from any adverse health outcomes (hospitalisation or death or

validated diarrhoea or acute respiratory infection) (AHR 1.1; 95% CI: 0.8 – 1.9; p=0.44) [56]. The study was conducted in an urban setting. Women who chose to breastfeed exclusively were counselled to practice early cessation at 4 months of age [56].

The benefits and risks of formula feeding should be contextualized by whether the living environment of mothers is supportive of her choice to formula feed [56-58]. According to the World Health Organisation in 2006, formula feeding should only be recommended as an alternative to breast milk to HIV-infected infants when it is affordable, feasible, acceptable, sustainable and safe (AFASS) [57, 58]. These criteria are rarely met in developing countries and mixed feeding is usually the practice. The consequences for the infants of being exposed to the high risk of HIV transmission associated with breastfeeding combined with the risks of formula feeding are large. The World Health Organisation recommendations on infant feeding in the context of HIV were revised in 2009 [59]. These guidelines reflect new evidence regarding breastfeeding in the presence of antiretroviral interventions [60-64]. The World Health Organisation now recommends that HIV-uninfected infants be exclusively breastfed for six months, followed by introduction of complementary foods and continued breastfeeding until one year of age [59]. The provision of breast milk should only be stopped once a nutritionally adequate, safe diet can be given to the infant [59].

2.5.6 Benefits and Risks of Exclusive Breastfeeding

Findings from the Breastfeeding and HIV International Transmission Study, a meta-analysis of nine clinical trials, showed that the risk of continued HIV transmission through breastfeeding was related to the duration of breastfeeding [37]. The study described the cumulative probability risk of transmission as 1.6% at three months (95% CI: 0.3 to 2.9), 4.2% at six months (95% CI: 1.8 to 6.7), 6.0% at nine months (95% CI: 3.3% to 8.6%), 7.0% at 12 months (95% CI: 4.7% to 9.3%) and 9.3% at 18 months (95% CI: 3.8% to 14.8%). This equates to about 1% risk of maternal to child transmission per month from exclusive breast-feeding [37].

The most important benefit of exclusive breastfeeding is a reduction in infant morbidity and mortality in developing countries. Babies who receive mixed feeds in their first month of life were more at risk of becoming infected with HIV than infants who were exclusively breastfed [65, 66].

A non-randomised intervention cohort study conducted in one urban, one semi-urban and seven rural antenatal clinics in KwaZulu-Natal determined the association between early infant feeding practices and the risk of HIV transmission and mortality at 18 months [66]. The cohort of 1193 infants born between October 2001 and April 2005 to HIV-infected women was followed up until they were 18 months of age. One hundred and forty-seven children died, of which 113 (77%) children were HIV-infected. HIV-infection was diagnosed in 237 children. The probability of death at 18 months for infants who were HIV-uninfected was 0.04 (95% CI: 0.03 to 0.06) and for HIV-infected 0.53 (95% CI: 0.46 to 0.60). The overall estimated HIV transmission risk exposure for breastfeeding during the 18 months was 9.1 cases per 100 child-years of breastfeeding (95% CI: 5.8 to 12.5) [66]. Furthermore, the study determined the association between infant feeding practices conducted at birth and the 18-month probability of death or acquiring HIV-infection [66]. An estimated 25% of exclusively breastfed infants born to women who were HIV-infected would have acquired HIV or died by 18 months compared to 20% of infants who were never breastfed (p=0.005) [66]. Infants who were breastfed beyond six months were 2.7 times (95% CI: 1.2 to 6.0, p = 0.01) more likely to acquire HIV or die between seven and 18 months compared to the groups who were either replacement fed, exclusively breastfed up to six months, or ceased all breastfeeding at any time point before six months [66]. The overall 18-month probability of survival for HIV-uninfected infants was not significantly different between the breastfed (n=800) and the replacement fed group (n=128). Socio-economic differences were described between mothers who breastfed for less than six months (n=136) with access to piped water inside their homes compared to mothers who continued to breastfeed beyond six months (n=688) (9.5% versus 7.7%, p=0.25). The difference was not significant [66].

Although the study showed similar 18-monthly mortality rate in breastfed and replacement fed HIV-uninfected infants, the results of the study should be placed into context of the environment in which the study was conducted [66]. Mothers were supported in both their choice and practice of infant feeding and received extensive counselling beyond the antenatal period [66]. Furthermore, women who chose to exclusively replacement feed were in a higher socio-economic class and could afford to do so hence the minimal mortality risk difference when compared to the exclusively breast fed group [66].

A non-randomised intervention cohort study conducted in KwaZulu-Natal, South Africa showed an increased HIV-1 transmission risk associated with a maternal $CD4^+$ count less

than 200 cells per mm^3 (AOR 3.6; 95% CI: 2.0 to 6.4, $p < 0.001$) and birth weight less than 2500 grams [54]. Most women given appropriate counselling chose to breastfeed (83%). Forty per cent of these women exclusively breastfed for six months [54]. Results from the Mashi Study in Botswana showed that although breastfeeding combined with zidovudine did not result in less vertical HIV transmission compared with formula feeding, the infant mortality at seven months was lower (9.3% versus 4.9%; p=0.003) [65]. The Mashi Study involved an intent-to-treat analysis and those patients initially assigned formula groups may have breastfed [65].

Recent evidence from randomised controlled studies demonstrated that the use of (lifelong) antiretroviral therapy or antiretroviral prophylaxis provided to the mother or infant during breastfeeding reduces the risk of mother-to-child transmission [60-64]. Although these interventions have demonstrated HIV risk reduction in clinical trial settings, the effectiveness of these interventions were not assessed throughout the entire duration of breastfeeding or in operational settings.

Breast milk contains immune factors that confer protection against infections and contain all the nutrient requirements the infant needs during the first six months of life. A World Health Organisation meta-analysis of studies in developing countries showed that when diarrhoea and acute respiratory infection were the most common cause of death in infants, breastfeeding during the first six months of life provided measurable protection against these infections [67]. Breastfeeding also benefited the mother by suppressing ovulation thereby acting as an important method of contraception in developing countries.

2.6 SUMMARY

The literature reviewed in this chapter revealed that information related to the morbidity, mortality and loss to follow-up of HIV-exposed infants was lacking, particularly from study settings in South Africa. The factors related to infant morbidity, mortality and loss to follow-up were described.

3 CHAPTER III: METHODS

3.1 INTRODUCTION

Whilst the level of prevention of mother-to-child transmission of HIV at McCord Hospital was comparable to developed countries, there was a paucity of data regarding the clinical outcomes of HIV-exposed infants in terms of morbidity, mortality, growth, and also about the number lost to follow-up care at the hospital. This study explored the maternal demographic, socioeconomic, clinical and immunologic characteristics associated with loss to follow-up of infants in order to determine which mother-infant pairs were more likely to be lost to follow-up. In this chapter, the type of research carried out and the study design applied is outlined. In addition, the study population, sampling methods, data sources, statistical analysis, and bias and limitations of the study are described.

3.2 TYPE OF RESEARCH

This study was an epidemiological research study.

3.3 STUDY DESIGN

An observational, analytical retrospective cohort study design was used.

3.4 STUDY SETTING

The study was conducted at McCord Hospital, KwaZulu-Natal, South Africa.

3.5 TARGET POPULATION

The results of this study could be generalised to infants born to HIV-infected women who received antiretroviral prophylaxis and therapy during pregnancy in prevention of mother-to-child transmission programmes in semi-private, urban settings in South Africa.

3.6 STUDY POPULATION

Inclusion criteria[6]: HIV-infected women who received antiretroviral prophylaxis or therapy in the McCord Prevention of Mother-to-Child Transmission programme and either:

1) Delivered their infants at McCord Hospital between 1 May 2008 and 31 May 2009; and/or

2) Presented their infants for care to McCord Hospital, following delivery elsewhere, between 1 May 2008 and 31 May 2009.

Exclusion criteria: HIV-infected pregnant women who received antiretroviral prophylaxis or therapy from McCord Hospital Prevention of Mother-to-Child Transmission programme and who had stillbirth deliveries.

3.7 SAMPLING

3.7.1 Sampling method

The period for inclusion in the study was 13 months[7]. This allowed a minimum follow-up time of six months for infants born in May 2009 at the time of data abstraction. Convenience sampling was used[8]. The records of a consecutive sample of all HIV-infected women who received antiretroviral prophylaxis and treatment in the McCord

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[6] The inclusion criteria for this study were narrow. All HIV-infected mothers included in the study received either antiretroviral prophylaxis for prevention of mother-to-child transmission or antiretroviral therapy at McCord Hospital. All infants included in the study were born from 1 May 2008 to 31 May 2009 at either McCord Hospital or elsewhere. If mothers met the study definition, but their infants were delivered elsewhere and were not brought back to McCord Hospital, these mother-infant pairs were not included in the study.

[7] The study period was extended from 10 months to 13 months to ensure an adequate small sample size.

[8] The follow-up clinic at McCord Hospital was established at the beginning of May 2008. Prior to the inception of this clinic, follow-up data on HIV-exposed infants whose mothers received PMTCT or lifelong antiretroviral therapy was not available. Given these limitations, and the narrow inclusion criteria for the study, the records of all mother-infant pairs meeting the inclusion criteria were selected from the Well Mother and Baby clinic database for the study.

Prevention of Mother-to-Child Transmission programme, and who delivered at McCord Hospital and/or presented their infants for care following delivery between 1 May 2008 and 31 May 2009, were included in the study.

3.7.2 Size of sample

A biostatistician at the University of KwaZulu-Natal was consulted[9]. The sample size was calculated based on the estimated prevalence of loss to follow-up of infants born to mothers in a Prevention of Mother-to-Child Transmission programme at McCord Hospital. A sample size of 256 infants with 95% confidence intervals was sufficient to provide precision of 6% based on the population estimate of loss to follow-up of 40%. For the Cox proportional hazards model, at a 5% level of significance with power of 80% and withdrawal of 40%, the minimum number of events to for each category was 38.

3.8 DATA SOURCES

3.8.1 Measurement instruments/Data collection techniques

The routine follow-up visits for infants born to HIV-infected women who attended the Prevention of Mother-to-Child Transmission programme at McCord Hospital were scheduled at one, six, ten, and 14 weeks, and thereafter at six, nine, 12, 15 and 18 months.

<u>One-week visit</u>

The one-week visit was an enrolment visit to the Well Mother and Baby Clinic. At this visit, mothers reported their method of feeding and the nurses weighed the infants and recorded their weight. The head circumferences and lengths of the infants were not measured at the one-week visit.

<u>Follow-up visits</u>

At the follow-up visits, mothers reported their method of feeding and any illness episodes prior to the infant being brought to McCord Hospital. Nurses at the Well Mother and Baby Clinic measured the weights, lengths and head circumferences of all infants. A nurse or a

[9] Ms Tonya Esterhuizen, biostatistician for the College of Health Sciences, University of KwaZulu-Natal

family practitioner conducted the general physical examination on infants. This examination included an assessment of developmental milestones and growth of the infants.

Laboratory tests

Infants who tested HIV-infected at six or 14 weeks of age were confirmed with a repeat DNA polymerase chain reaction assay. All infants who tested negative for HIV-infection were tested for HIV at 18 months using two HIV Elisa antibody tests. All infants who were confirmed as HIV-infected at six weeks, 14 weeks or 18 months of age were referred to a paediatrician at McCord Hospital.

3.8.1.1 Data abstraction

Study data were abstracted from paper and electronic sources. The primary source of data were paper records. The sources are described below:

i. Paper sources

Maternal data

Routine data on antenatal history, care, treatment and delivery were collected from maternal records recorded by clinicians, usually family practitioners. The following variables were collected:

- maternal socio-demographic details;
- maternal diagnosis of HIV;
- enrolment in the Prevention of Mother-to-Child Transmission programme;
- antiretroviral prophylaxis or treatment taken during pregnancy;
- antenatal enrolment: height, weight, parity, previous pregnancies, prior complications in pregnancy and delivery, and pre-existing conditions;
- antenatal illness episodes;
- date, mode and complications during delivery , and
- infant antiretroviral prophylaxis.

Infant data

Clinical data on infants were collected from the infants' clinical record files. Nurses or family practitioners recorded all clinical data on infants. These standard custom-developed clinical record forms were developed by the researcher and were implemented at the inception of the Well Mother and Baby Clinic at McCord Hospital in May 2008 (Appendix B). The following data were collected from the infant charts:

- illness events prior to attendance at McCord Hospital;
- feeding history;
- immunization history;
- current illness events; and
- physical examination of the infant (Appendix B).

ii Electronic source

Maternal data

Prevention of Mother-to-Child Transmission programme staff also routinely entered clinical and personal data about HIV-infected mothers into an electronic database (Trakcare)[10]. The following data were entered into the database:

- diagnosis of maternal HIV;
- laboratory results including $CD4^+$ per cent and $CD4^+$ count, plasma RNA viral load,
- maternal antiretroviral regimen dispensed to women during their pregnancy and previous antiretroviral regimen prescribed if any;
- follow-up: illnesses during pregnancy,
- date and mode of delivery and complications

[10] Certain cadres of nurses and counsellors and all clinicians (general and specialists) in the Prevention of Mother-to-Child Transmission programme and the Obstetric and Gynaecology department at McCord Hospital routinely entered clinical data about pregnant women into Trakcare. Demographic data on pregnant women was entered into Trakcare by clerical staff at McCord Hospital.

Infant data

The routine capturing of data on infants were not well established, and limited data on infants were available from this electronic source. The electronic database was primarily used for the following purposes:

- verify dates of the infant visits to McCord Hospital;
- verify infant HIV-test results (six-weeks, ten-weeks, 14-weeks and 18-months); and
- track the location of infant files.

3.8.1.2 Data handling

Data for the study, accessed from various sources, were extracted to a specific study data-collation form by the researcher, a trained research assistant and a medical student (Appendix C). The data was then single-entered into a database (Microsoft Access 2007) by one data capturer. Data was cleaned and processed (descriptive and analytic statistics) by the researcher alone under the guidance of a biostatistician. The researcher exported data on illness events from the Access database to Microsoft Excel 2007. The researcher assigned each type of illness event a unique code, the events were filtered and sorted based on their codes and the dates of the events. The researcher then cleaned the illness events to ensure that there were no overlapping events. Preceding illness events overlapping or within a few days of the current illness events were excluded. Each type of illness event was exported to Stata/IC version 11 (Statacorp, College Station, Texas) and assigned as failure variables to derive incidence rates.

3.9 VARIABLES

Exposure variables were as follows:

- Maternal age;
- Marital status;
- Race;
- Employment status;
- Maternal exposure to smoking, alcohol or illicit drugs;
- Parity;

- Maternal anthropometry: weight (kg) and height (cm);
- Maternal illness antenatally;
- Maternal $CD4^+$ count and viral load;
- Maternal antiretroviral regimen;
- Mode of delivery;
- Parity;
- Infant antiretroviral prophylaxis;
- Infant cotrimoxazole prophylaxis; and
- Infant birth weight.

The infant clinical outcome variables included:

- Upper respiratory tract infections;
- Lower respiratory tract infections;
- Skin and mucous membrane infections;
- Gastrointestinal infections;
- Hospital admissions;
- Other (infections not meeting the criteria for the above categories);
- Loss to follow-up of infants following delivery; and
- Feeding practice (exclusive breastfeeding, exclusive formula feeding, mixed feeding).

3.9.1 Reliability and Validity of Data Source

The principal investigator spent seven months at McCord Hospital from December 2007 until June 2008. During that time, data collection techniques were implemented for routine clinical care. There were regular reviews of all maternal and infant records with all relevant staff during the first six months of the inception of the Well Mother and Baby Clinic at McCord Hospital to ensure that the records were complete in terms of history, investigation and clinical data. A monitoring and evaluation officer at McCord Hospital verified that the clinical information captured on the patient records and Trakcare database at the Well Mother and Baby Clinic was accurate.

Data on the antiretroviral therapy prescribed to women in the Prevention of Mother-to-Child Transmission programme were extracted from the peri-partum maternal record and

were verified from pharmacy records on the Trakcare database. Similarly, maternal antenatal baseline $CD4^+$ cell counts and viral loads were collected from records of laboratory results in the mothers' files and verified from laboratory records on Trakcare.

The clinician estimated the gestational age of the foetus at the mothers' first antenatal booking visit. In some instances, gestational age was verified by an early ultrasound scan.

A research assistant and a medical student were recruited to assist with data collection. The researcher trained the data capturers to conduct data entry. Both the research assistant and the medical student were familiar with the variables collected for the study. Data collection were initially conducted in the presence of the researcher in order to clarify definitions, the data collection tool and the data collection process. The researcher undertook the majority of the data collection. It was not possible to validate the clinical diagnoses recorded in the patient records and may have resulted in non-differential misclassification bias.

Prior to data abstraction, a code book with specific definitions for all data elements was prepared as part of the operational guidelines. The Microsoft Access database had built-in checks and validation rules, hence only accept legal values were accepted during data entry. Once data entry were completed, the researcher conducted descriptive statistics to detect outliers. The researcher checked missing or erroneous data against patient records. The researcher also clarified any discrepancies in data with clinic staff. Due to logistic and time constraints, the researcher did not conduct double entry of data, which would have increased the validity of the study.

3.10 BIAS AND LIMITATIONS

3.10.1 Selection bias

The potential for selection bias was minimised by using charts of all mothers and infants enrolled at McCord Hospital during the study period.

3.10.2 Information bias

The variation[11] in the quality and consistency of data may result from differences in the human resources at McCord Hospital since 2008. However, the potential for information bias is minimal as data collection practices were standardised since the opening of the Well Mother and Baby Clinic in May 2008. The researcher-collected data on clinical outcomes of infants based on the availability of routine data, and may have resulted in misclassification information bias. Loss to follow-up forms was included in charts of infants who did not return to the clinic. Clinic staff attempted to contact caregivers to determine the reason for loss to follow-up. However, in most instances the reason for loss to follow-up was not determined and contributed to the information bias in the study. Data were not double entered and could have introduced information bias. The researcher cleaned the data and verified missing data by inspecting patient files. Exploratory data analysis were used to assess the study for outlying data and these errors were verified and corrected. The database was developed using validation rules to ensure the plausibility of data entered.

3.10.3 External generalisability

McCord Hospital is semi-private. The hospital is state-aided but funding is subsidised by private donors and patient fees. The socio-demographic characteristics of the population might differ from that of the general public and the results of the research may not be generalisable to the public HIV-infected antenatal population of South Africa.

3.10.4 Confounders

Each independent variable may act as a confounder when assessing the effect of each independent variable on the dependent variable in the bivariate analysis. These confounders were adjusted for by using multivariable analysis to control for confounding effects. No interactions were considered in the analysis of loss to follow-up of infants or upper respiratory illness. There may be confounding effects due to variables not assessed in the study. These variables may include maternal area of residence, maternal education level, maternal disclosure of HIV status, the number of persons living in the household,

[11] Both general medical practitioners and nurses examined infants at the McCord Hospital Well Mother and Baby Clinic. There may be variation in history taking, physical examination and clinical diagnoses of the infants.

infant anaemia and paternal factors such as living in the household, occupational status and level of education.

3.11 STATISTICAL ANALYSIS

3.11.1 Descriptive methods

Data were abstracted to Microsoft Access 2007 database, and thereafter imported into Microsoft Excel and SPSS version 15.0 (SPSS, Chicago, Illinois) for cleaning and basic frequency measures.

The characteristics of the study population, and outcomes in terms of morbidity, mortality, infant feeding and loss to follow-up of infants were measured using descriptive statistics. Frequencies and proportions were calculated to describe the data, and then presented in the form of frequency distribution tables. Ninety-five per cent confidence intervals (95% CI) were calculated using the exact binomial method.

3.11.2 Analytical methods

Morbidity events, HIV transmission, child deaths and loss to follow-up of infants were treated as time-to-event variables and were analyzed with Kaplan-Meier methods [68]. Frequencies of infections (excluding HIV) were calculated according to the age at the initial diagnosis; early neonatal (zero to six days), late neonatal (seven to 27 days), or post neonatal (greater or equal to 28 days). In addition, the cumulative rate of infections were calculated using Poisson regression to count outcomes [68].

Predictors of initial diagnosis of infant upper respiratory illness were explored as slightly more than half of the infants had experienced at least one upper respiratory event. Furthermore, most cases of upper respiratory infection were likely to be incident events. Although skin and mucous membrane infections were also common, this outcome was not considered further, as some cases of skin infections were likely to be chronic. It was therefore not possible to separate incident and prevalent cases of skin and mucous membrane infections.

In addition, predictors of loss to follow-up of infants were examined. Socio-demographic, clinical, immunological and biological (maternal, obstetric, perinatal and infant) factors were assessed to determine their association with loss to follow-up of infants.

Similar analyses were conducted to determine predictors of infant upper respiratory illness and loss to follow-up of infants. The proportional hazards-assumption of the Cox regression model was assessed with the Nelson-Aalen estimate in exposed and unexposed groups [68]. Associations between categorical variables with upper respiratory tract infections were evaluated by using the Pearson's chi square tests [68]. Cox proportional hazards regression analysis were used to retrieve baseline survival function and to model multivariate survival data [68]. The likelihood ratio test was used to assess the fit of the model [68]. For multiple regressions, a backward elimination procedure used log-likelihood criteria with $p > 0.1$ for removing variables and $p < 0.05$ for entering variables [68].

The researcher performed all descriptive and analytic statistics. All analyses were performed in SPSS version 15 (Chicago, Illinois) and Stata/IC version 11 (Statacorp, College Station, Texas).

3.12 ETHICS

Ethical approval for this study was obtained from University of KwaZulu-Natal Biomedical Research Ethics Committee (BE160/08) (Appendix A) as well as McCord Hospital Research Ethics Committee (Appendix A).

Individuals were not consented for participation in this retrospective chart review study. The reasons for this were as follows: (i) no patient identifiers were collected in this study; (ii) no patient contact was necessary; (iii) data used for the study included only data collected as per standard care at McCord Hospital. It should also be noted that women who enrolled to the Prevention of Mother-to-Child Transmission programme gave their consent for their and their child's data to be used for programmatic evaluation purposes.

3.12.1 Permissions

Permission to use the routine data collected for the secondary analysis was obtained from the Superintendent of McCord Hospital, Dr H. Holst. The study was registered as a research project (PGR008/08) (Appendix A) for the Master of Medicine (Public Health Medicine) with the Postgraduate Education Committee of the Nelson R. Mandela School of Medicine, University of KwaZulu-Natal.

3.13 SUMMARY

This epidemiological study used a retrospective cohort design. The purpose of the study was to measure the clinical and loss to follow-up outcomes of infants, born to HIV-infected women who attended the Prevention of Mother-to-Child Transmission programme at McCord Hospital, and assessed predictors of loss to follow-up of infants. In this chapter the study population, study sampling methods, data sources and biases and limitations were described.

4 CHAPTER IV: RESULTS

4.1 INTRODUCTION

The purpose of this retrospective cohort study was to measure the clinical, loss to follow-up and feeding outcomes of HIV-exposed infants at McCord Hospital. Furthermore, the study aimed to assess maternal demographic, socio-economic, clinical and immunological characteristics associated with loss to follow-up of infants. The study population comprised of infants, born to HIV-infected mothers who received antiretroviral prophylaxis and treatment in the McCord Prevention of Mother-to-Child Transmission programme, and who delivered at McCord Hospital and/ or presented their infants to McCord Hospital for care following delivery between 1 May 2008 and 31 May 2009.

4.2 STUDY SAMPLE

In total, 272 mothers presented to McCord Hospital for care between 1 May 2008 and 31 May 2009. Fourteen infants were excluded from the study for reasons that included records not being found, infants not meeting the inclusion criteria and stillbirths (Figure 1). There were 258 deliveries resulting in 265 infants (252 singletons, five sets of twins and one set of triplets).

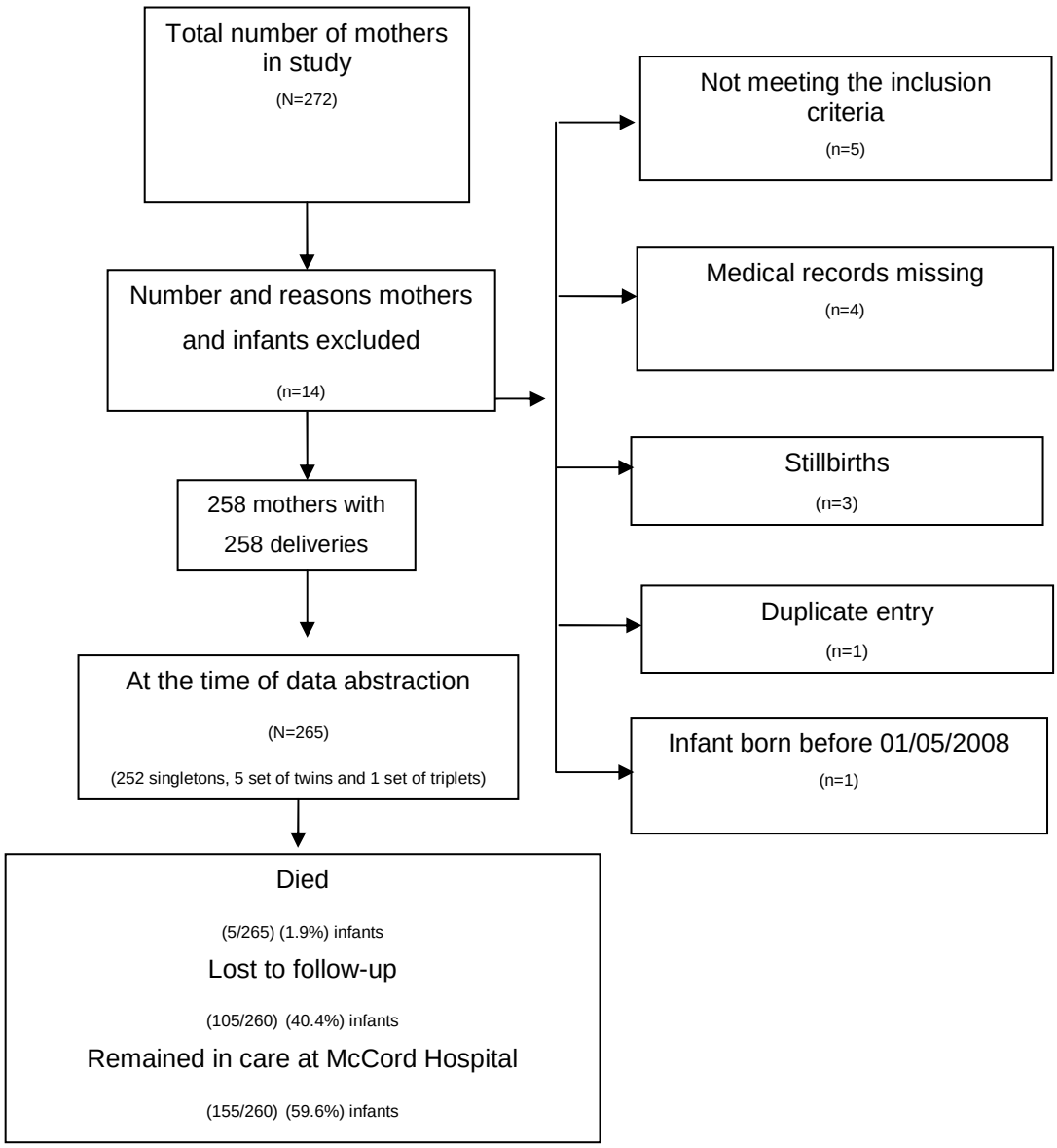

Figure 1: Study sample of infants born to HIV-infected mothers in the Prevention of Mother-to-Child Transmission programme at McCord Hospital, 1 May 2008 to 31 May 2009

4.3 PRESENTATION OF DATA

4.3.1 Characteristics of the study population at McCord Hospital

Socio-economic, demographic and other characteristics of the infected mothers was summarised (Table 1). The median maternal age was 28.0 years (IQR: 15.0 to 45.0 years). The race of only 125 (48.4%) mothers was recorded [12]. The majority (n=119, 95.2%) of women were Black (South Africans). Most (n= 214, 84.9%) mothers attending McCord Hospital were single and almost two-thirds (n=165, 65.7%) were employed.

Smoking, alcohol consumption and illicit drug use by the mothers was reported to be uncommon during pregnancy. The mean maternal parity prior to this pregnancy was 1.0 live births (IQR: 0 to 5). Most infants (n=163, 64.1%) were delivered by caesarean section. An obstetric emergency was given as the reason for the delivery requiring surgical intervention in 74 (29.1%) women with the rest being elective caesarean sections. Of the 89 elective caesarean sections, 57.3% (n=51) were indicated for maternal HIV to prevent mother-to-child transmission. Only 11.8% (n=29) of pregnant women presented for their first antenatal visit early, (before 12 weeks of gestation), and 25.2% (n=62) of patients booked late in their third trimester.

The clinical, immunological, and virologic disease characteristics were collected at the first antenatal visit. The baseline median maternal $CD4^+$ cell count was 308 cells/mm^3 (IQR: 17 to 962 cells/mm^3) and median viral load 4320 copies/ml (IQR: 25 to 1 810 000 copies/ml). Only 27 (10.5%) women had the WHO staging of their disease recorded at baseline.

Approximately half (n=127, 51.4%) of the mothers reported an illness event during the antenatal period. Approximately 12 mothers (9.4%) had pulmonary tuberculosis and were receiving anti-tuberculosis treatment. There was only one maternal death (0.4%) during the study period. The cause of the maternal death was reported as disseminated Kaposi's Sarcoma.

Less than half (n=123, 47.7%) of women were already on antiretroviral therapy at their first pregnancy visit. Of these 123 women, 36 (29.3%) women were commenced on

[12] Race was not routinely collected during the first six months at the McCord Hospital Well Mother and Baby clinic

antiretroviral therapy prior to their pregnancies, and 68 women (55.3%) were initiated on triple antiretroviral therapy in their current pregnancies. Approximately 15.4% (n=19) of women were commenced on triple antiretroviral therapy for prevention of mother-to-child transmission as their viral loads were greater than 1500 copies/ml[13] and were included in the category HAART for life.. There were 52.3% (n=135) of women on antiretroviral prophylaxis for prevention of mother-to-child transmission.

[13] Women who had $CD4^+$ counts >200 cells/mm^3 but viral loads > 1500 copies/ml were prescribed triple antiretroviral therapy for prevention of mother-to-child transmission. These regimens were discontinued after delivery of their infants; thereafter the women were initiated on seven days of zidovudine and lamivudine to prevent the development of resistance to antiretroviral drugs.

Table 1: Characteristics of HIV-infected women who attended the Prevention of Mother-to-Child Transmission programme at McCord Hospital, and whose infants were born from 1 May 2008 to 31 May 2009

Maternal characteristics	N*	n*	%	95% Confidence Intervals
Maternal age, yrs				
Mean (median)	255	28.5 (28.0)		27.8 – 29.2
≥ 30		107	42.0	35.8 - 48.3
< 30		148	58.0	51.7 - 64.2
Race	125			
Black (South African)		119	95.2	89.8 - 98.2
Asian		4	3.2	0.9 - 8.0
White		1	0.8	0.0 - 4.4
Black (other African)		1	0.8	0.0 - 4.4
Employed	251			
Yes		165	65.7	59.5 - 71.6
No		86	34.3	28.4 - 40.5
Marital status	252			
Single		214	84.9	79.9 - 89.1
Married		38	15.1	10.9 - 20.1
Parity	247			
Primiparity		86	34.8	28.9 - 41.1
Multiparity		161	65.2	58.9 - 71.1
Maternal $CD4^+$ count ($cells/mm^3$)	250			
< 200		68	27.2	21.8 - 33.2
200 – 499		147	58.8	52.4 - 65.0
≥ 500		35	14	9.9 - 18.9
Maternal viral load (copies/ml)	224			
<1000		70	31.2	25.2 - 37.8
1000 - 9999		77	34.4	28.2 - 41.0
≥ 10 000		77	34.4	28.2 - 41.0
Maternal antiretroviral regimen	258			
HAART for life		123	47.7	41.4 - 54.0
AZT+3TC from 28 weeks		76	29.5	24.0 - 35.4
AZT from 28 weeks		38	14.7	10.6 - 19.7
NVP only		7	2.7	1.1 - 5.5
Other		14	5.4	3.0 - 8.9

Table 1 (contd.)

Maternal characteristics	N*	n	%	95% Confidence Interval
Booking gestational age, weeks	246			
0-12		29	11.8	8.0 - 16.5
13-27		155	63.0	56.6 - 69.1
≥ 28		62	25.2	19.9 - 31.1
Any illness during pregnancy	247			
Yes		127	51.4	45.0 – 57.8
No		120	48.6	42.2 – 55.0
Pulmonary tuberculosis	127	12	9.4	5.0 -15.9
Mode of delivery	254			
Emergency C/S		74	29.1	23.6 - 35.1
Booked C/S		89	35.0	29.2 - 41.3
NVD		91	35.8	29.9 - 42.1
Maternal mortality	256			
No		255	99.6	97.8 – 100
Yes		1	0.4	0.0 - 2.2

N* the number of mothers across categories of maternal characteristics may not add up to 258 due to missing data.

The median length of infant follow-up at McCord Hospital in this study was 9.1 months (absolute range: 1 day to 21 months) (Table 2). Median birth weight was 3080 grams (IQR: 980 to 4500) and 32 (12.8%; 95% CI: 8.9% to 17.6%) infants were of low birth weight (<2.500 grams). The median gestational age at birth was 38 weeks (IQR: 30 to 42) and 189 infants were born at term at or after 37 weeks (89.2%, 95% CI: 84.2% to 93.0%) (Table 2). Approximately 223 (98.7%, 95% CI: 96.2% to 99.7%) infants received nevirapine and zidovudine as antiretroviral prophylaxis following delivery (Table 2). Of the 265 infants in the cohort, 13 (4.9%) were followed-up for 18 months and were discharged from the clinic[14]. Vaccination coverage for Bacillus Calmette Guérin (BCG) and oral polio

[14] The Well Mother and Baby Clinic at McCord Hospital routinely follow-up until infants from birth to 18 months of age, after which the infants were referred to clinics closer to their homes for follow-up care.

vaccine (OPV) was 83.0% (95% CI: 77.9% to 87.3%) at birth (Table 2). By six weeks of age, vaccine coverage for diphtheria, pertussis and tetanus (DPT), and Haemophilus influenzae type B (HiB) vaccine fell to 79.2% (Table 2). Vaccine coverage for Hepatitis B at six weeks was 76.2% (Table 2), as the vaccination was out of stock and some infants were not vaccinated with Hepatitis B at this visit. By nine months of age, only 53.5% of infants requiring measles were vaccinated at McCord Hospital and measles coverage diminished further to 27.1% (95% CI: 15.3 to 41.8) by 18 months of age.[15]

[15] Pneumococcal and rotavirus vaccination commenced in November 2008 at McCord Hospital. Data on these vaccinations were inconsistently recorded in infant medical records and was therefore not described in this study.

Table 2: Characteristics of infants born to HIV-infected women in the Prevention of Mother-to-Child Transmission programme at McCord Hospital, from 1 May 2008 to 31 May 2009.

Infant characteristics	N*	n*	%	95% Confidence Interval
Observed length of follow-up				
Mean (median), months		7.9 (9.1)		7.2 – 8.6
Sex	**252**			
Male		122	48.4	42.1 - 54.8
Female		130	51.6	45.2 - 57.9
ARV prophylaxis at birth	**226**			
Nevirapine and zidovudine		223	98.7	96.2 - 99.7
Gestational age at delivery, weeks	**212**			
Mean (median)		38.2 (38.0)		37.8 – 38.2
< 37		23	10.8	7.0 - 15.8
≥ 37		189	89.2	84.2 - 93.0

Table 2 cont

Infant characteristics	N*	n*	%	95% Confidence Interval
Vaccination coverage				
Birth	**265**			
BCG		220	83.0	77.9 – 87.3
OPV		220	83.0	77.9 – 87.3
6 week	**265**			
DPT and HiB		210	79.2	73.9 – 84.0
OPV		210	79.2	73.9 – 84.0
Hepatitis B		202	76.2	70.6 – 81.2
10 week	**265**			
DPT and HiB		189	71.3	65.5 – 76.7
OPV		189	71.3	65.5 – 76.7
Hepatitis B		180	67.9	61.9 – 73.5
14 week	**265**			
DPT and HiB		181	63.8	62.3 – 73.9
OPV		181	63.8	62.3 – 73.9
Hepatitis B		167	63.0	56.9 – 68.8
9 month	**245**			
Measles		131	53.5	47.0 – 59.8
18 months	**48**			
Measles, OPV and DPT		13	27.1	15.3 – 41.8
Birth weight, g				
Mean (median)	**250**	3052.3 (3080)		3000.3 – 3139.7
< 2500		32	12.8	8.9 – 17.6
≥ 2500		218	87.2	82.4 – 91.1

N* the number of infants across each category of characteristics do not add up to 265 due to missing data

4.3.2 Proportion of infants by feeding category at birth

The majority of the 265 infants in the study were reported to be exclusively formula-fed at birth (97.5%; 95% CI: 94.7% to 99.1%) (Table 3). The median duration of exclusive breastfeeding was 18.5 weeks, slightly longer than the median duration of exclusive formula feeding at 13.0 weeks.

Table 3: Type and length of exclusive infant feeding methods reported by HIV-infected women in the Prevention of Mother-to-Child Transmission programme at McCord Hospital, following delivery of their infants from 1 May 2008 to 31 May 2009

Feeding category	n*	(%)	95 % Confidence Intervals	Median duration of feeding (weeks)
Exclusive formula feeding	235	97.5	94.7 - 99.1	13.0
Exclusive breast feeding	6	2.5	0.9 - 5.3	18.5

n* does not add up to 265 due to missing data on reported feeding methods

4.3.3 Clinical outcomes of infants

4.3.3.1 Types of infections

Overall, 177 infants (N=265, 66.7%) were reported to have suffered 542 infections from birth to 18 months (3.3 infections per infant). The most frequent infections involved the upper respiratory tract (51.2%) and skin and mucous membrane infections (30.9%) (Table 4). Two hundred and eighty infections of the upper respiratory tract occurred in 136 of 265 (51.3%) infants. Cumulatively, the incidence rate of upper respiratory infections was 0.44 cases per 100 child-weeks of follow-up (95% CI: 0.39 to 0.49). More than one-third (n=98, 37.0%) of infants had skin and mucous membrane infections. Infections of the gastrointestinal tract were less common with only 50 infants (18.9%) acquiring an infection. Other infrequent infections were of the lower respiratory tract (n=18, 6.8%).

In terms of lower respiratory tract infection, one infant was presumed HIV-infected. Two infants were diagnosed with pulmonary tuberculosis (0.8%) at approximately three months of age. The mothers of both these infants were diagnosed with pulmonary tuberculosis in

their pregnancies. The receipt of isoniazid prophylaxis[16] was inconsistently recorded in the study and it was unclear if these infants received prophylaxis.

Table 4: Number and types of infections in infants born to HIV-infected women who attended the Prevention of Mother-to-Child Transmission programme at McCord Hospital, from 1 May 2008 to 31 May 2009

Diagnostic category	n (%) of infants	Number (%) of infections
Upper respiratory tract	136 (51.3)	280 (51.2)
Gastrointestinal	50 (18.9)	67 (12.2)
Skin, mucous membrane	98 (37.0)	169 (30.9)
Lower respiratory tract	18 (6.8)	22 (4.2)
Other**	4 (1.5)	4 (0.7)

N = 265 infants

Other** infections comprised two cases of chicken pox, one case of febrile seizures, and one case of urinary tract infection.

4.3.3.2 Age at initial diagnosis of infection

The types of infection and the time to first diagnosis to each infection were recorded (Table 5). The initial diagnosis of upper respiratory (n=48, 35.3%), lower respiratory (n=7, 38.9%), and skin and mucous membrane infections (n=37; 37.8%) was most common from 61 to 120 days.

The incidence rate of upper respiratory tract infections was 2.5 cases per 100 child-weeks (95% CI: 2.1 to 2.9 infections per 100 child-weeks) (Table 5). The proportion of upper respiratory tract infections decreased after 240 days with 26 (19.1%) cases occurring during this period.

Unexpectedly, gastrointestinal infections were infrequent with an incidence rate of 0.6 cases per 100 child-weeks (95% CI: 0.5 to 0.8 per 100 child-weeks) (Table 5). In contrast to skin and mucous membrane and upper respiratory tract infections, the majority of gastrointestinal infections occurred after 240 days (n=33, 66.0%).

[16] Twelve HIV-infected pregnant women were diagnosed with pulmonary tuberculosis and received anti-tuberculosis medication – two infants were recorded as receiving isoniazid prophylaxis.

Lower respiratory tract infections were least common with an incidence rate of 0.2 cases per 100 child-weeks of observation (95% CI: 0.1 to 0.3 cases per 100 child-weeks) (Table 5).

Table 5: Number and percent of types of infections, age of onset to first infection, and incidence rate of infections for infants born to HIV-infected women attending the Prevention of Mother-to-Child Transmission programme at McCord Hospital, 1 May 2008 to 31 May 2009

	n (%) of infants with infections							
Diagnostic category	**Early neonatal (0-6 d)**	**Late neonatal (7-27 d)**	**28 – 60 days**	**61 – 120 days**	**121 – 240 d**	**>240 d**	**n**	**Incidence rate of infections per 100 child-weeks at risk (95% CI**
Upper respiratory tract	0 (0)	7 (5.1)	23 (16.9)	48 (35.3)	32 (23.5)	26 (19.1)	136	2.5 (2.1 - 2.9)
Skin, mucous membrane	2 (2.0)	1(1.0)	31 (31.6)	37 (37.8)	15 (15.3)	12 (12.2)	98	1.6 (1.3 - 1.9)
Gastrointestinal	2 (4.0)	1(2.0)	4 (8.0)	2 (4.0)	8 (16.0)	33 (66.0)	50	0.6 (0.5 - 0.8)
Lower respiratory tract	1 (5.6)	0 (0.0)	1(5.6)	7 (38.9)	4 (22.2)	5 (27.8)	18	0.2 (0.1 - 0.3)

N = 265 infants

4.3.3.3 Factors associated with URTI

Cox proportional hazards regression analysis was conducted to quantify any associations between the maternal and infant exposures and first upper respiratory tract event in infants[17] (Table 6). Only first-born infants[18] from multiple births were included in the analysis (n=7). Exposure variables from the unadjusted analyses were included in the multivariable analyses if the test for heterogeneity showed that the risk factor was significant[19].

Maternal socio-demographic, clinical, immunologic, virologic and infant exposure variables were explored to determine their association with upper respiratory events in infants. In the adjusted analyses, infants born to mothers younger than 30 years old at the time of delivery had a 10% greater risk of their infant experiencing an upper respiratory event relative to infants with older mothers but the association was not statistically significant (AHR 1.1; 95% CI: 0.7 to 1.8; p = 0.655). Infants of single mothers had a 50% increased risk of illness compared to married mothers, but this was also not statistically significant (AHR 1.5; 95% CI: 0.9 to 2.8; p = 0.136).

There was no significant association between maternal illness during pregnancy and infantile upper respiratory infection (AHR 1.3; 95% CI: 0.9 to 2.0; p = 0.167). The use of zidovudine (AHR 0.5; 95% CI: 0.0 to 4.7; p= 0.506), zidovudine and lamivudine (AHR 1.2; 95% CI: 0.1 to 11.1; p = 0.902) and triple antiretroviral therapy (AHR 1.3; 95% CI: 0.1 to

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[17] The Cox proportional hazards regression analysis was conducted by myself after consultation with Ms Tonya Esterhuizen, a biostatistician, who taught me how to conduct the analysis.

[18] Only first-born infants were included in the analyses as a population-based study showed that second born twins were at greater risk for neonatal morbidity and mortality (Shinwell 2004). The inclusion of second-born and third born infants of multiple births may have overestimated the association between exposure variables and first upper respiratory tract event.

[19] Cox proportional hazards regression analysis was used to retrieve baseline survival function and to model multivariate survival data. The log-likelihood ratio was used to determine the fit of the model. For multiple regressions, a backward elimination procedure used log-likelihood criteria with $P > 0.1$ for removing variables and $P < 0.05$ for entering variables.

12.8; p = 0.81) during pregnancy was not found to be statistically significant in the development of upper respiratory tract illness in infants.

With respect to maternal immunologic and virologic characteristics, only maternal viral load predicted infantile upper respiratory infection. Maternal $CD4^+$ counts between 200 to 499 cells/mm^3 (AHR 1.6; 95% CI: 0.9 to 2.6; p = 0.085) and ≥ 500 cells mm^3 (AHR 2.1; 95% CI: 0.9 to 4.5; 95% CI: 0.069) were associated with infant upper respiratory illness in both the crude models. This finding of increased risk of infantile upper respiratory illness and high maternal $CD4^+$ count may be due to random error and was not found to be significant in the adjusted model. An association was observed between maternal viral load and infant upper respiratory infection. In the adjusted model, infants of mothers with viral load from 1000 to less than 10 000 copies/ml had a 40% greater risk of an upper respiratory event (95% CI: 0.8 to 2.4; p = 0.280) compared to mothers with low viral loads but the association was not significant. The risk of infection increased as viral load increased to 10 000 copies/ml and above and was shown to be statistically significant (95% CI: 1.0 to 3.3; p = 0.039).

Other significant risk factors for infantile upper respiratory illness were the gestational age at delivery and the use of infant cotrimoxazole prophylaxis[20]. In the adjusted analysis, compared to infants born at term (≥ 37 weeks), infants who were less than 37 weeks of gestation at birth (n=22) were 2.7 times more likely to experience an upper respiratory illness event (95% CI: 1.4 to 5.3, p= 0.002). Infants who were prescribed cotrimoxazole prophylaxis at six weeks of age were 2.2 times more likely to experience an upper respiratory event (95% CI: 1.2 to 3.9; p = 0.011) compared to infants who were not on prophylaxis.

Maternal parity was found to be a risk factor for infantile upper respiratory illness but this association was not statistically significant after adjustment for confounders (AHR 1.2; 95 CI: 0.7 to 1.9; p = 0.497). Compared to emergency caesarean section, elective caesarean delivery (AHR 1.3; 95% CI: 0.8 to 2.2; p = 0.217) and normal vaginal delivery (AHR 1.3; 95% CI: 0.8 to 2.1, p= 0.234) increased the risk of infantile upper respiratory illness but the association was also not statistically significant

[20] Infants were prescribed cotrimoxazole prophylaxis from six weeks of age until DNA polymerase chain reaction assays diagnosed the infants as HIV-uninfected.

Infant exposures that were not significant risk factors for upper respiratory illness were the sex of infants (AHR 0.7; 95% CI: 0.5 to 1.1; p = 0.131), weight at birth (AHR 1.3; 95% CI: 0.7 – 2.5; p = 0.359), and loss to follow-up of infants (AHR 1.2; 95% CI: 0.7 to 2.0; p = 0.496). These exposure variables remained in the model as potential confounders.

Table 6: Cox regression analysis of risk factors associated with first onset of upper respiratory tract infection in infants born to mothers in a Prevention of Mother-to-Child Transmission programme at McCord Hospital, 1 May 2008 to 31 May 2009

Characteristic	N*	n	%	Unadjusted hazard ratio (95% CI)	p value	Adjusted hazard ratio (95% CI)	p value
Maternal age							
≥30 years	107	54	50.5	1.0		1.0	
< 30 years	148	76	51.4	1.3	0.175	1.1	0.655
				(0.9 – 1.8)		(0.7 – 1.8)	
Marital status							
Married	38	16	42.1	1.0		1.0	
Single	214	114	53.3	1.6	0.069	1.5	0.136
				(1.0 - 2.7)		(0.9– 2.8)	
Alcohol use							
No	249	126	50.6	1.0		1.0	
Yes	2	1	50	1.1	0.909	0.9	0.951
				(0.2 – 8.0)		(0.1 – 7.4)	
Any antenatal maternal illness							
No	120	55	45.8	1.0		1.0	
Yes	127	73	57.5	6.4	1.00	1.3	0.167
				(0.9 – 1.9)		(0.9 – 2.0)	

N* 258 infants were included in the Cox regression model after exclusion of second does add up to 258 due to missing data

Table 6 (contd.)

Characteristic	N	n	%	Unadjusted hazards ratio (95% CI)	p-value	Adjusted hazards ratio (95% CI)	p-value
Maternal $CD4^+$ count, cells/mm^3							
< 200	68	39	57.4	1.0		1.0	
200 – 499	147	75	51.0	1.0	0.852	1.6	0.085
				(0.7 – 1.5)		(0.9 - 2.6)	
≥ 500	35	17	48.6	1.1	0.743	2.1	0.069
				(0.6 – 2.0)		(0.9 – 4.5)	
Viral load, copies/ml[21]							
< 1000	70	36	51.4	1.0		1.0	
1000 - < 10 000	77	37	48.1	1.1	0.66	1.4	0.28
				(0.7 – 1.8)		(0.8 – 2.4)	
≥ 10 000	77	43	55.8	1.4	0.142	1.9	0.039
				(0.9 – 2.2)		(1.0 – 3.3)	
Maternal antiretroviral regimen							
Nevirapine only	6	1	16.7	1.0		1.0	
Zidovudine from 28 weeks	38	17	44.7	2.3	0.428	0.5	0.506
				(0.3 – 17.1)		(0.0 – 4.7)	
Zidovudine/ lamivudine from 28 weeks	76	37	48.7	4.3	0.149	1.2	0.902
				(0.6 – 31.7)		(0.1 – 11.1)	
Triple antiretroviral therapy	122	71	58.2	4	0.172	1.3	0.81
				(0.5 – 28.7)		(0.1 – 12.8)	
Other	16	6	37.5	2.4	0.415	0.6	0.644
				(0.3 – 20.2)		(0.1 – 6.4)	

[21] Indicates maternal viral load at the antenatal baseline visit. When the 3 categories of viral load were collapsed into 2 groups, greater than 100 000 copies/ml (n=25) and less than 100 000 copies/ml (n=201) , the association between maternal viral load and infant upper respiratory illness was no longer significant, P> 0.05

Table 6 (contd.)

Characteristic	N	n	%	Unadjusted hazards ratio (95% CI)	p-value	Adjusted hazard ratio (95% CI)	p-value
Parity							
Primiparity	86	43	50.0	1.0		1.0	
Multiparity	161	83	51.6	0.9	0.458	1.2	0.497
				(0.6 – 1.3)		(0.7 – 1.9)	
Mode of delivery							
Emergency C/S	74	43	58.1	1.0		1.0	
Elective C/S	89	45	50.6	0.9	0.691	1.3	0.217
				(0.6 – 1.4)		(0.8 – 2.2)	
NVD	91	44	48.4	1.0	0.664	1.3	0.234
				(0.7 – 1.7)		(0.8 – 2.1)	
Sex of infant							
Male	120	63	52.5	1.0		1.0	
Female	125	63	50.4	0.7	0.14	0.7	0.131
				(0.5 – 1.1)		(0.5 – 1.1)	
Gestational age at delivery							
≥ 37 weeks	187	93	49.7	1.0		1.0	
< 37 weeks	22	16	72.7	1.5	0.118	2.7	0.002
				(0.9 – 2.6)		(1.4 – 5.3)	
LTFU of infant							
Not LTFU	154	109	70.8	1.0		1.0	
LTFU	104	23	22.2	1.0	0.881	1.2	
				(0.7 – 1.6)		(0.7 – 2.0)	0.496

Table 6 (contd.)

Characteristic	N	n	%	Unadjusted hazard ratio (95% CI)	p-value	Adjusted hazard ratio (95% CI)	p-value
Infant birth weight, g							
< 2500	27	14	51.9	1.0		1.0	
≥ 2500	215	112	52.1	1.1	0.65	1.3	0.359
				(0.7 – 2.0)		(0.7 – 2.5)	
Infant cotrimoxazole prophylaxis							
No	80	19	23.8	1.0		1.0	
Yes	178	113	64.5	1.7	0.043	2.2	
				(1.0 - 2.7)		(1.2 – 3.9)	
							0.011

Number of subjects = 258

Number of failures = 132

Time at risk = 5349 child-weeks

Number of observations = 258

Log likelihood = - 582.30718

Logistic regression chi square (30df) = 58.22

Prob > chi square = 0.0015

The original models considered all the biological and socio-economic variables listed in table 1.

Log likelihood criteria p > 0.1 for the following exposure variables; hence eliminated from the final model:

Maternal race; maternal employment status; maternal death; smoking; illicit drug use; gestational age of foetus at first antenatal visit; preterm labour; obstetric sepsis; feeding method at birth reported by mother; HIV-infection status of the infant; sex of infant; and number of visits to McCord Hospital

4.3.3.4 Hospital admissions

Overall, 21 of 265 (7.9%) children had one hospital admission (Table 7) at an incidence rate of 0.3 admissions per 100 child-weeks (95% CI: 0.2 to 0.4 admissions per 100 child-weeks).

Table 7: Timing of hospitalisation of infants born to HIV-infected women who attended the Prevention of Mother-to-Child Transmission programme at McCord Hospital, from 1 May 2008 to 31 May 2009

Timing of hospitalisation	Number (%) of infants hospitalized	Incidence rate per 100 person-weeks at risk	95% CI Hospitalisations per 100 person-weeks at risk
Early neonatal (0-6 day	4 (1.5)	1.7	0.6 - 4.5
Late neonatal (7-28 day	0 (0)	0	-
Post neonatal (> 28 day	17(6.4)	0.2	0.1 - 0.3
	21 (7.9)	0.3	0.2 - 0.4

N = 265 infants

The reason for hospital admission was unknown in 15 (71.4%) infants (Table 8). Two children were admitted with lower respiratory tract infection (9.5%). One child was admitted with acute gastroenteritis (4.8%), and three children (14.3%) were admitted with diagnoses classified as “other” (one with burn injuries, one with cellulitis and one child for prematurity). Only one of the admitted children was presumed HIV-infected.

Table 8: Cause of hospital admissions in infants born to HIV-infected women who attended the Prevention of Mother-to-Child Transmission programme at McCord Hospital, from 1 May 2008 to 31 May 2009

Cause of hospitalisation	N *	%
Unknown	15	71.4
Lower respiratory tract	2	9.5
Acute gastroenteritis	1	4.8
*Other	3	14.3
	21	100

N = 265 *Three admitted infants were classified as "other" – one with cellulitis, one with burns, and one infant was premature

4.3.3.5 HIV transmission

Overall, the HIV transmission risk was 2.7% (n=6; 95% CI: 1.0% to 5.8%) in the 220 (83.0%) infants who had a DNA polymerase chain reaction assay taken at 6 weeks. The HIV status was therefore unknown in 45 infants (17.0%) at 6 weeks of age. None of the 13 infants who were followed-up until 18 months of age were diagnosed as HIV-infected.

4.3.3.6 Mortality of infants from birth to five months

Among 231 infants in the cohort, the perinatal mortality rate was 13.0 per 1000 live births (95% CI: 2.7 to 37.4 per 1000 live births) (Table 9). After exclusion of stillborns (n=3) and infants lost to follow-up by 5 months (n=84), the neonatal mortality rate was 3.8 per 1000 live births (n=1; 95% CI: 0.0 to 21.0 per 1000 live births) and 27.6 per 1000 live births (95% CI: 9.0 to 63.3 per 1000 live births) cumulatively by five months (five deaths). There were no deaths from birth to seven days (Table 9). The HIV-infection status was unknown for five of the infants that died. One infant that died was presumed HIV-uninfected.

Table 9: Mortality rate of infants born to HIV-infected women in a Prevention of Mother-to-Child Transmission programme at McCord Hospital, from 1 May 2008 to 31 May 2009

Timing of mortality	n	Mortality rate per 1000 live births	95% Confidence Interval
Stillborn*	3	13.0*	2.7 – 37.4
Birth to 28 days**	1	4.4*	1.0 – 23.9
Birth to five months**	5	27.6**	9.0 – 63.3

*After exclusion of 34 infants LTFU in the first week, N =231 ** After exclusion of 84 infants LTFU, N=181

4.3.4 LTFU

Of the 265 live births, five infants died. Of the remaining 260 infants, 105 infants (40.4%; 95% CI: 34.4% to 46.6%) were lost to follow-up compared to the 155 infants (59.6%; 95% CI: 53.4% to 65.6%) still in care at McCord Hospital (Table 10).

Table 10: Proportion lost to follow of infants born to HIV-infected women who attended a Prevention of Mother-to-Child Transmission programme at McCord Hospital, from 1 May 2008 to 31 May 2009

Variable	n	%	95% Confidence Interval
LTFU	105	40.4	34.4 - 46.6
Not LTFU	155	59.6	53.4 - 65.6

N = 260 infants

Thirty-four infants were lost to follow-up in the first week of life (Table 11). The incidence rate of loss to follow-up of infants during this period was 14.5 per 100 child-weeks (95% CI: 10.3 to 20.3 per 100 child-weeks) (Table 11).The incidence rate of loss to follow-up declined steadily after the first week of life. From one week to ten weeks, the incidence rate of attrition was 1.8 per 100 child-weeks (95% CI: 1.3 to 2.5 per 100 child-weeks). Sixteen infants were lost to follow-up between 11 and 19 weeks (incidence rate 1.0; 95% CI: 0.6 to 1.6 per 100 child-weeks). The incidence rate of loss to follow-up of infants between the time periods 20 to 28 weeks and more than 28 weeks halved from 0.6 per 100 child-weeks (95% CI: 0.3 to 1.2 per 100 child-weeks) to 0.3 per 100 child-weeks (95% CI: 1.0 to 1.4 per 100 child-weeks) respectively.

Table 11: Timing of loss to follow-up of infants born to HIV-infected women in a Prevention of Mother-to-Child Transmission programme at McCord Hospital, from 1 May 2008 to 31 May 2009

Timing of loss to follow-up, weeks	n	Incidence rate (per 100 child-weeks)	95% Confidence Interval
0 <1	34	14.5	10.3 - 20.3
1- 10	34	1.8	1.3- 2.5
11-19	16	1.0	0.6 - 1.6
20-28	10	0.6	0.3 - 1.2
> 28	11	0.3	1.0 - 1.4

N = 260 infants

4.3.4.1 Maternal socio-demographic, clinical and immunologic factors associated with loss to follow-up of infants

Cox regression analysis was conducted to determine the predictors of loss to follow-up of infants at McCord Hospital[22] (Table 12). After exclusion of second and third infants of multiple births and infant deaths, 104 infants were lost to follow and 149 infants remained in care at McCord Hospital.

In terms of demographic and socio-economic characteristics, in the multivariable analyses, maternal age less than 30 years (n=68; AHR 1.3; 95% CI: 0.8 to 2.1) and being single (n=89; AHR 1.2; 95% CI: 0.6 to 2.4) increased the risk of being lost to follow-up but the association was not statistically significant. Compared to infants born to mothers whose race was unknown, infants whose mothers were classified as Black South Africans were 40% less likely to be lost to follow-up (n=37; AHR 0.6; 95% CI: 0.4 to 1.0; p= 0.035). Unemployment was not a risk factor for attrition of infants at McCord Hospital (n=34; AHR 0.9; 95% CI: 0.6 to 1.4; p = 0.636).

Clinically, maternal disease staging was absent from 89.5% of patients' charts and could not be used as a predictor of loss to follow-up of infants. Maternal $CD4^+$ count was used as a marker of immunological status. In both the crude and adjusted model, maternal $CD4^+$ count equal to or greater than 500 cells/mm^3 (n=18; AHR 1.9; 95% CI: 1.0 to 3.7; p = 0.041) was associated with loss to follow-up infants but the association did not remain

[22] The Cox proportional hazards regression analysis was conducted by myself after consultation with Ms Tonya Esterhuizen, a biostatistician, who taught me how to conduct the analysis.

statistically significant after adjustment for confounders (AHR 1.6; 95% CI: 0.9 to 3.1; p = 0.142).

Biological variables were included in the multivariable analysis of loss to follow-up. Infants born to mothers who had their first antenatal visit at or after 28 weeks were 2.3 times more likely to be lost to follow-up, relative to infants whose mothers booked in their first trimester. The association was statistically significant (n=31; 95% CI: 1.0 to 5.1; p = 0.044). In addition, mode of delivery was independently significantly associated with loss to follow-up. Infants whose mothers had a normal vaginal delivery (n=41; AHR 2.5; 95% CI: 1.4 to 4.5; p = 0.002) or an elective caesarean section (n= 39; AHR 1.9; 95% CI: 1.1 to 3.5; p = 0.028) were more likely to be lost to follow-up. Maternal parity (primiparous) was a risk factor for loss to follow-up of infants but the association did not reach statistical significance (n=41; AHR 1.4; 95% CI: 0.8 to 2.2; p = 0.212).

Table 12: Cox regression analysis of maternal socio-demographic, clinical and immunologic factors associated with loss to follow-up of infants born women in a PMTCT programme at McCord Hospital, from 1 May 2008 to 31 May 2009

Characteristics	Number	n	%	Unadjusted Hazards Ratio (95% CI)	p-value	Adjusted Hazards Ratio (95% CI)	p-value
Maternal age							
≥ 30 years	107	36	33.6	1.0		1.0	
< 30 years	144	68	47.2	1.5	0.061	1.3	0.28
				(1.0 – 2.2)		(0.8 – 2.1)	
Marital status							
Married	37	12	32.4	1.0		1.0	
Single	210	89	42.4	1.4	0.254	1.2	0.526
				(0.8 – 2.6)		(0.6 – 2.4)	
Race							
Unknown	130	65	50.0	1.0		1.0	
Black (South African)	117	37	31.6	0.6	0.007	0.6	0.035
				(0.4 – 0.9)		(0.4 – 1.0)	
Employed							
Yes	162	65	40.1	1.0		1.0	
No	84	34	40.5	1.0	0.948	0.9	0.636
				(0.7 – 1.5)		(0.6 – 1.4)	
Gestational age at booking							
0 – 12 weeks	29	8	27.6	1.0		1.0	
13 - 27 weeks	151	58	38.4	1.4	0.343	1.6	0.246
				(0.7 – 3.0)		(0.7 – 3.4)	
≥ 28 week	61	31	50.8	2.0		2.3	
				(0.9 – 4.4)	0.079	(1.0 – 5.1)	0.044

Table 12 (contd.)

Characteristics	N	n	%	Unadjusted Hazards Ratio (95% CI)	p-value	Adjusted Hazard Ratio (95% CI)	p-value
$CD4^+$ count (cells/mm^3)							
< 200	66	20	30.3	1.0		1.0	
200 - 499	144	59	41	1.5	0.132	1.5	0.118
				(0.9 – 2.5)		(0.9 – 2.6)	
≥ 500	35	18	51.4	1.9	0.041	1.6	0.142
				(1.0 – 3.7)		(0.9 – 3.1)	
Parity							
Multiparity	158	60	38	1.0		1.0	
Primiparity	84	41	48.8	1.4	0.121	1.4	0.212
				(0.9 – 2.0)		(0.8 – 2.2)	
Mode of delivery							
Emergency C/S	73	20	27.4	1.0		1.0	
Elective C/S	89	39	43.8	1.7	0.047	1.9	0.028
				(1.0 – 3.0)		(1.1 – 3.5)	
NVD	87	41	47.1	2.0	0.012	2.5	0.002
				(1.2 – 3.4)		(1.4 – 4.5)	

Number of subjects = 253

Number of observations = 253

Number of failures = 104

Time at risk = = 61 163

Logistic regression chi square (19 df) = 54.78

Log likelihood = -517. 76801

Prob > chi square = 0.0000

The original models considered all the biological and socio-economic variables listed in table 1.

Log likelihood criteria p >0.1 for the following exposure variables; hence eliminated from the final model

Maternal death; smoking; illicit drug use; maternal baseline viral load (taken at the first antenatal visit); maternal illness during pregnancy, maternal antiretroviral regimen during pregnancy; preterm labour; obstetric sepsis; maternal mortality; feeding method at birth reported by mother; sex of infant; and infant birth weight

4.3.4.2 Reasons for attrition of infants at McCord Hospital

The reasons for attrition of infants at McCord Hospital are shown in Table 13. The reason for loss to follow-up of infants was missing in the majority of cases (n=83; 79.8%). Maternal employment (n=1; 1.0%) infant residing with someone else (n=6, 5.8%), and attending a clinic closer to home (n=6, 5.8%) were reported by mothers as reasons for attrition. "Other" reasons were reported for nine infants lost to follow-up at McCord Hospital. These reasons included financial problems (n=4), transport issues (n=3), adoption (n=1), and maternal death (n=1)

Table 13: Reasons reported by mothers for loss to follow-up of infants born in a Prevention of Mother-to-Child Transmission programme at McCord Hospital, from 1 May 2008 to 31 May 2009

Reasons for loss to follow-up of infants	n	%
Mother working	1	1.0
Infant living with someone else	6	5.8
Attending a clinic closer to home	6	5.8
Other reasons*	9	8.7
Reason for loss to follow-up missing	83	79.8

N = 105 infants lost to follow-up (includes infants of multiple births)

*Four mothers reported financial issues, three mothers had problems with transport, one infant was adopted, and one mother died

4.4 SUMMARY

The majority of HIV-infected mothers attending the Prevention of Mother-to-Child Transmission programme at McCord Hospital were single, employed, South African Black women and were less than 30 years old. Infants in the cohort were predominantly formula-fed at birth and were HIV-uninfected. Infections of the upper respiratory tract were most frequent in infants. In the multivariable analysis, there was a significant association between gestational age of delivery, high maternal viral load and the use of infant cotrimoxazole prophylaxis and first upper respiratory illness in infants. An estimated forty per cent of infants were lost to follow-up after delivery. Maternal race, gestational age of the foetus at the first antenatal visit and mode of delivery were significantly associated with loss to follow-up of these infants.

5 CHAPTER V: DISCUSSION

5.1 INTRODUCTION

In chapter five, the clinical and loss to follow-up outcomes of infants born to HIV-infected women who received antiretroviral prophylaxis or therapy at McCord Hospital are discussed. The significance of the risk factors associated with upper respiratory illness and loss to follow-up of infants are explored in view of the biological plausibility of these associations and the findings of other studies are analysed. The findings of this study are also considered in light of the possible biases and limitations of the study design, the data collection process and results obtained in the study. The generalisability of the study to the antenatal HIV-infected population South Africa is also discussed.

5.2 FINDINGS

The format of the discussion is similar to the results.

5.2.1 Socio-demographic characteristics of HIV-infected women and their infants attending the Prevention of Mother-to-Child Transmission programme at McCord Hospital

The socio-demographic characteristics of this study population differ somewhat from other observational studies documenting the follow-up characteristics of infants born to HIV-infected women who received antiretroviral prophylaxis or therapy antenatally [27, 47]. The majority of the women at McCord Hospital were employed (n=165, 65.7%) compared to one prospective study in Latin America and Caribbean countries where only 23.6% (N=462) of women in the study were employed. The median maternal age of HIV-infected women in this study was 28.0 years, which is older than HIV-infected women who received antiretroviral prophylaxis or therapy in a cohort study in three Prevention of Mother-to-Child Transmission pilot sites[23] in South Africa [39] and a cohort study in Malawi[24] (mean maternal age 24.1 years) [47]. The median maternal age of women in this study was comparable to the median maternal age of women in a cohort study conducted in eight European countries [69]. The antiretroviral regimen prescribed to women at McCord Hospital differed from the national guidelines and almost 48% of women were on triple

[23] Mean maternal age 25.8 years in Paarl, 26.1 years in Umlazi and 24.1 years in Rietvlei

[24] Group 2: socio-demographic characteristics of HIV-uninfected children born to HIV-infected mothers

therapy. Whilst this may seem like a substantial proportion of women in the prevention of mother-to-child transmission programme on lifelong antiretroviral therapy, 84.6% (n=104) was indicated due to low $CD4^+$ count either in the current or prior pregnancy.

The birth weight of infants in this study was slightly greater than the birth weights of infants in the cohort study at three Prevention of Mother-to-Child Transmission sites in South Africa [39] and comparable to a non-randomised cohort study in antenatal clinics KwaZulu-Natal [54]. The gestational age at birth of infants in this study was comparable to the three South African sites [39].

One of the objectives of the Well Mother and Baby Clinic at McCord Hospital was to improve the post-natal care of infants receiving peri-natal antiretroviral therapy. The proportion of infants receiving BCG and polio vaccines at birth should have been 100% and the low coverage of 83% was worse than coverage of infants born to HIV-infected women in a rural district in KwaZulu-Natal [72]. The proportion of infants having received their third dose of oral polio vaccine was 71.3%, which is still below the 80% target set by the World Health Organisation to achieve polio eradication [70]. The coverage of measles vaccine was far less than the 90% benchmark recommended by South Africa in 2003 [71]. Overall, the vaccination coverage achieved by McCord Hospital was worse than the coverage of infants born to HIV-infected women in a rural district in northern KwaZulu-Natal [72]. The implementation of the rotavirus and pneumococcal vaccine[25] at McCord Hospital was not evaluated in this study. The reasons for the low coverage of BCG and polio and birth were unclear and of concern. Factors affecting childhood vaccination status include maternal age [73], maternal education [74-77], maternal HIV status , distance to health care facilities [78-81], and household wealth [82, 83]. Studies have shown that children born into wealthier households have a higher probability of having their vaccination status checked and receiving missed doses of vaccines than children in poorer households. Given that the socio-economic profile of the women attending McCord Hospital was presumed to be better than that of the general population, the low vaccination coverage is unlikely to be related to socio-economic factors and may reflect the quality of care provided at the infant follow-up clinic at McCord Hospital.

[25] Rotavirus and pneumococcal vaccines were implemented at McCord Hospital in November 2008 and this data was inconsistently collected.

5.2.2 Types of infections

In this cohort of predominantly non-breastfed, HIV-exposed, uninfected infants at McCord Hospital, approximately two-thirds of the infants experienced infectious disease morbidity from birth to 18 months. This study found an incidence rate of upper respiratory infection greater than that of cohort studies in both developing (0.89 cases per 100 child-weeks in Latin America) [27, 84] and developed settings (2.0 cases per 100 child-weeks in United States [85].

Conversely, the observed rate of lower respiratory tract infections in this study was less than half that observed in a Latin American cohort study (0.9 cases per 100 child-weeks) [27], a randomised trial of formula-fed uninfected infants in Kenya (7.1 per 100 person-weeks) [86], and a multicentre cohort study in the United States (2.8 cases per 100 child-weeks) [85]. Only two infants in the study were admitted with lower respiratory tract infection (9.5%) compared to 40.7% of infants who were admitted with lower respiratory tract infection in a Latin American study [27]. The proportion of infants diagnosed with pulmonary tuberculosis by three months of age in this study (n=2; 0.8%) was lower than that of infants with culture confirmed cases of pulmonary tuberculosis at the same age in a prospective cohort study (33/596; 5.5%) in two hospitals in Cape Town, South in 2005 [87].

The study findings of 169 skin and mucous membrane infections (30.9%) was higher than that detected in a Brazilian cohort study in urban slums (5.9%) [84]. However, the incidence rate of skin infections was comparable to that observed in the Latin-American study (1.9 cases per 100 child-weeks) [27]. The diagnosis of upper respiratory tract infection was dependent on both parental recall and the clinical diagnosis of illness during a scheduled or unscheduled visit. Although, there is a possibility of overestimation of upper respiratory infections, this was less likely for skin and mucous membrane infections as the clinical diagnosis was less subjective.

The incidence rate of gastrointestinal infections was two-fold higher than that observed in the Latin-American study (0.3 per 100 child-weeks). However, the proportion of gastrointestinal infections was much lower than that found in infants (35.1%) in the Brazilian cohort [84], in two hospitals (30.6%) (King Edward VIII and McCord Hospital) in South Africa from 1995 to 1998, and in formula feeding uninfected infants in Kenya (21.4 per 100 person-weeks) [86, 88]. It is difficult to comment on the effect of infant feeding on the incidence of infections as the feeding methods reported by the mother were not validated. Whilst the incidence of skin and upper respiratory tract infections were higher or

comparable to other developing countries, the lower incidence of gastrointestinal and lower respiratory tract infections may be reflective of the better socio-economic profile of the HIV-infected women attending McCord Hospital. The implementation of rotavirus and pneumococcal vaccine may have reduced the incidence of lower respiratory tract and gastrointestinal infections but this intervention was not assessed.

The reason for upper and lower respiratory and skin infections occurring from 61 to 120 days of age compared to gastrointestinal infections which occurred after 240 days in this study was unclear. HIV-infected women who did not breastfeed may have exposed their infants to dietary pathogens and hence increased the risk of morbidity from non-HIV related infectious diseases [54, 67, 89, 90]. The higher incidence of gastrointestinal infections after 240 days may be related to weaning and introduction of solid foods [55, 91, 92]. However, further research at McCord Hospital on the association between feeding practice and infant morbidity is required to answer these questions.

5.2.3 Factors associated with upper respiratory tract infection

The lack of association between maternal demographic risk factors and infant upper respiratory events in the multivariable model was surprising but may be indicative of the better socio-economic profile of the mother. Factors that were associated with neonatal and post neonatal infections but not measured in this study were maternal use of intrapartum antibiotics, maternal $CD4^+$ count at hospital discharge, tobacco smoking during pregnancy, number of persons living in the household, indoor air pollution and infant anaemia [27, 93].

The factors associated with upper respiratory illness in HIV-exposed infants in this study included maternal viral load antenatally, the infant's gestational age at delivery and the use of infant cotrimoxazole prophylaxis.

This study demonstrated that maternal viral load above 10 000 copies/ml at the baseline antenatal visit was significantly associated with upper respiratory illness in the infant. In HIV-infected patients, plasma viral load is a predictor of the rate of decline in $CD4^+$ count and progression to AIDS and death [94]. In a multicentre cohort study of 1604 patients, 55.2% of patients with viral loads between 10 000 copies/ml and 30 000 copies/ml progressed to AIDS within six years of follow-up [94]. If the maternal viral load at baseline is taken as an indicator of maternal progression to AIDS, then it might be possible to explain the association between the higher maternal viral load and infant upper respiratory illness. Several studies have shown the association between stage of maternal disease and infant

morbidity and mortality [27, 40]. The exact link between stage of maternal disease and infant morbidity is still uncertain and a few theories have been postulated. The first is the reduced level of maternal antibody titres to common pathogens with inadequate trans-placental transfer of maternal antibodies [95]. Secondly, in-utero exposure and failure of maternal immune system secondary to HIV may result in inadequate immune functioning in the infant. Subsequently the infant is unable to resist common infections. These changes may persist over time [96, 97]. Other abnormalities in cytokine production have been shown in HIV-exposed, uninfected infants but the association between specific abnormalities and infant morbidity or mortality is not established [98, 99]. Lastly, deteriorating health in the mother due to HIV-infection could lead to increased morbidity in the infant [47].

Preterm delivery at less than 37 weeks of gestation was shown to be a risk factor for the infant experiencing an upper respiratory event. This association may be explained by predisposition of preterm infants to infections due to immaturity of the immune system and longer periods of hospitalisations, which may increase the risk acquiring nosocomial infections [100]. Preterm infants also have inadequate functioning of the alternate and complement pathways required for complement- mediated opsonisation, that is, the alteration of antigens for phagocytosis and destruction by immune cells [100]. Moreover, the process of phagocytic migration to the site of infection is dampened in preterm infants further predisposing them to infections from common pathogens [100]. Immune mechanisms against viral pathogens in the preterm infant may also be lacking due to the absence of antibody-dependent, cell-mediated immunity by natural killer lymphocytes [100]. The sample of infants who were born preterm was small (n=22) and this may have overestimated the effect found. In addition, the association between upper respiratory illness and preterm infants may be subject to recall bias with mothers of preterm infants more likely to recall an upper respiratory episode in their infants relative to women whose infants were born at term.

The observation that the prophylactic use of cotrimoxazole in infants is a predictor for upper respiratory events is contradictory to what might be expected. Previous studies have shown cotrimoxazole prophylaxis has improved survival and changed the pattern of respiratory infections of HIV-infected children [101-103]. In addition to preventing infection with ***Pneumocytis jiroveci***, cotrimoxazole prophylaxis may also prevent illness secondary to other bacterial infections and malaria [104]. These benefits also extend to HIV-uninfected infants [104]. A previous cohort study in South Africa demonstrated an increase in diarrhoeal disease in infants to whom cotrimoxazole prophylaxis was administered [88]. However, the study was subject to loss to follow-up bias. The findings of this study of

cotrimoxazole prophylaxis as a risk factor for upper respiratory illness in infants may be due to random error.

5.2.4 HIV transmission

Similar to the previous cohort study at McCord Hospital [21], the proportion of infants who were presumed HIV-infected at six weeks was small (2.7%; 95% CI: 1.0% to 5.8%). Findings from a one-year HIV surveillance study of primary health care clinics offering prevention of mother-to-child transmission services showed that the mother-to-child transmission risk of HIV in the general population was much higher than at McCord Hospital [105]. According to the data in this study the vertical transmission was 20.2% (n=188; 95% CI: 17.7% to 24.2%) among all HIV-exposed infants (n=931) at 4 to 8 weeks of age and 15.0% (95% CI: 11.9% to 18.6%) in infants whose mothers reported the use of sd-nevirapine [105].

However, given the large proportion of infants who were lost to follow-up in the first ten weeks following delivery in this study, and were not tested for HIV-infection, it is likely that there was an underestimation of the HIV transmission risk at McCord Hospital. If the infants who died (n=5) in the study were assumed to be HIV-infected, and proportionally the same number of infants whose HIV status was unknown (1/45; 2.7%) were assumed to be infected as those whose HIV status was known at 6 weeks, then the HIV transmission risk in this study increased to 4.5%[26] at 6 weeks.

A small proportion of infants (4.9%) reached the 18-month follow-up period at McCord Hospital and were confirmed HIV-uninfected. Infants who were presumed[27] HIV-uninfected at six and 14 weeks require further testing at 18 months in order to confirm the low HIV transmission risk at McCord Hospital.

5.2.5 Mortality of infants

The five-month mortality of infants in this study (27.6 per 1000 live births) was higher than the six-month mortality of infants in a cohort study in Latin American and Caribbean countries (n=462) (12.3 per 1000 live births) [27]..The neonatal mortality rate shown in this study was four times less than the 2004 South African estimate (17 per 1000 live births) [9]

[26] 6 infants known HIV infected + 5 infants died assumed infected + 1 infant with unknown status assumed infected out of 265 infants in the cohort

[27] An infant was presumed HIV-1 uninfected if they had ≥ two negative DNA polymerase chain reaction assays at McCord Hospital with the first test performed at six weeks of age and the second test performed at 14 weeks of age.

which may be related to the socio-demographic characteristics of the study population. The cause of the five infant deaths was unknown. It was not possible to do statistical analyses to determine the predictors of mortality as the number of deaths in the infant cohort was small. As with HIV transmission risk, it is possible that mortality in this infant cohort was underestimated, due to the poor retention of infants in the study.

5.2.6 Factors associated with loss to follow-up of infants

The proportion of attrition of infants in this study was higher than a prospective study in Malawi (n=653; 30.3%) [50] and a cohort study in Johannesburg (22.3%) [48], but 10% less than a programmatic study in rural Uganda (n=303; 53%) [51]. The incidence rate of loss to follow-up of infants in the study was highest in the week following delivery and diminished as the infants grew older. The reason for loss to follow-up of infants was missing in the majority of cases. The antiretroviral regimens provided by McCord Hospital differ from the public sector. Women attending the Prevention of Mother-to-Child Transmission programme at McCord Hospital may do so to ensure better care for their infants. After delivery, women may seek care at their regular clinics or hospitals. Financial and transport issues may determine the retention of infants at the hospital.

In the multivariable Cox proportional hazards model, although maternal age less than 30 years and being single was a risk factor for loss to follow-up of infants in this study, the association did not remain significant after adjustment. Unemployment was not a significant predictor of loss to follow-up of infants, unlike the cohort study in Malawi [50], but the socio-demographic characteristics of these study populations are not comparable. The lack of association between recorded maternal demographic characteristics with attrition of infants is probably indicative of the higher socio-economic profile of this group. However, this finding could not be confirmed, as maternal socio-economic measures, such as income and type of housing, were not routinely collected by McCord Hospital. Mothers who were categorised as Black South Africans in this study were less likely to be lost to follow-up relative to women whose race was unknown. When race of unknown women in the cohort was assumed to be Black South Africans in the multivariable model of this study, the association between maternal race and loss to follow-up did not remain significant (AHR 0.8; 95% CI: 0.2 – 3.8; p=0.839).

This study demonstrated that relative to infants of HIV-infected women with $CD4^+$ counts equal to or less than 200 cells/mm^3, infants born to mothers with $CD4^+$ counts above 200 cells/mm^3 were more likely to be lost to follow-up, but the finding was not statistically significant. Maternal well-being may be a risk factor for poor retention at McCord Hospital

as mothers do not perceive themselves or their infants to be at risk for disease and are hence less likely to seek health care. A similar correlation between infant wellbeing and loss to follow-up was shown in a study in rural Uganda, where infant illness was a protective against loss to follow-up in the Prevention of Mother-to-Child Transmission programme [51].

The Ugandan study showed that incomplete or absent antiretroviral prophylaxis taken by the mother or the infant was a risk factor for loss to follow-up [51]. However, when maternal and infant antiretroviral regimen and baseline viral load[28] was initially included in the multivariable model in this study, no correlation was found with loss to follow-up. These variables were subsequently removed from the model ($p > 0.1$)

Infants of HIV-infected women who presented at or after 28 weeks of gestation for their first antenatal visit were more likely to be lost to follow-up relative to infants whose mothers presented early for care. This finding suggests that late presentation for antenatal care was related to poor maternal health seeking behaviours and therefore increases the likelihood that the infant is lost to follow-up. An alternate explanation may be that these women have differing demographic or socio-economic profiles compared to women who present early in their pregnancy for antenatal care that have not been measured (for instance education level, income status, or distance from the hospital).

In the multivariable model, having an elective caesarean section or normal vaginal delivery relative to an emergency caesarean section was shown to be a predictor of loss to follow-up of infants in this study. A possible explanation for this finding is that women who have emergency deliveries were more concerned for the wellbeing of their infants, following the indication for the emergency surgery, and hence more likely to seek care for their infants.

5.3 VALIDITY

This section discusses the internal validity of the study, which refers to whether the outcomes of this study are a function of the variables measured. The generalisability of the study findings to the population was also considered under external validity.

[28] Baseline maternal viral load and maternal antiretroviral regimen taken during pregnancy was initially included in the model of risk factors associated with loss to follow-up of infants but was not statistically significant ($p > 0.1$) and was eliminated from the model

5.3.1 Internal validity

Two main data sources were used to extract maternal and infant exposure and outcome variables.

Some exposure variables were missing from patient files. Routine maternal demographic data on race were absent from patient charts for the early period of the study from May 2008 to November 2009. Thereafter, the counsellors at McCord Hospital began collecting routine demographic and psychosocial data from all mothers attending the Well Mother and Baby Clinic at McCord Hospital. Data on World Health Organisation staging of HIV disease on enrolment of women in the Prevention of Mother-to-Child Transmission programme at McCord Hospital were not recorded in 90% of maternal records.

Maternal anthropometric data were collected when mothers were at different gestational ages as it was recorded when they presented for their booking antenatal visit. The consequence is that the anthropometric data were probably not comparable. In addition, baseline data on height (20.9%) and weight (15.9%) were absent from patient files and could not be used as an exposure variable.

Maternal antenatal illnesses were diagnosed and recorded by clinical staff (general and specialist practitioners) in the maternal records and could not be verified. These maternal diagnoses ranged from minor to major illnesses. In some instances of serious illness events, laboratory or radiological evidence were available to confirm the diagnosis. Maternal illness events during the pregnancy were extracted from maternal records. If the clinician in the presence of symptoms or signs of illness recorded no clinical diagnosis, the illness event was not captured for this study.

With respect to infant illness events, presumptive diagnoses of infection were made by nurses, or family practitioners at McCord Hospital, and recorded in the infants' records. The researcher could not verify these diagnoses. Data were collected on infant feeding at birth and follow-up visits. However, this data were based on maternal or caregiver report and was not validated.

Infant anthropometric measurements were taken at birth and follow-up visits by the clinical staff at McCord Hospital. These measurements were not standardized.

Assignment of infant HIV-infection status was based on two or more HIV-1 DNA polymerase chain reaction assays at six and 14 weeks and two HIV Elisa antibody tests at 18 months. Data on loss to follow-up of infants were based on the date of the last visit

and date of the next expected visit to McCord Hospital. The researcher assigned loss to follow-up status of infants. Staff at McCord Hospital was aware of patients who had missed the scheduled visits. These patients were contacted telephonically to verify their intent to return to the hospital or their reason for missing the scheduled visit.

Infant mortality was based on caregiver report and could not be verified. The date and cause of death was also not confirmed.

5.3.2 External validity

McCord Hospital is a semi-private institution. HIV-infected women at McCord Hospital are subsidised by donor funding or pay user fees to attend the Prevention of Mother-to-Child Transmission programme. Although, no user fees were charged to infants born to these women to attend the Well Mother and Baby Clinic and receive routine care, the results of this study are not generalisable to the HIV-exposed infant population in South Africa. The results of this study can be generalised to infants born to HIV-infected women who attend Prevention of Mother-to-Child Transmission services in urban, semi-private settings.

5.4 BIAS AND LIMITATIONS

The bias and limitations of this study are discussed with regards to its design, data collection and the findings of the study.

The major limitation to this study was the retrospective nature of the cohort design. Although data were prospectively collected, it was not possible to assess the potential effect of other risk factors that may have contributed to loss to follow-up or infant illness from routinely collected clinical records. Risk factors such as maternal education, income level, number of people living in the household, paternal factors, number of siblings and infant anaemia were variables that were not routinely collected so could not be assessed. Clinic staff routinely collected data on the reasons infants were lost to follow-up by telephoning the caregivers. However, in the majority of instances the reason for lost to follow-up was missing and was a limitation of the study. In particular, the contribution of infant feeding practices to the clinical outcomes of the infants could not be determined, as this exposure variable was not validated by administration of a feeding questionnaire to the mothers or observation of feeding practice practiced by the mothers. Data on infant feeding practice were instead based on maternal report.

Another limitation of this study was the selection of the study population. According to the selection criteria[29], infants not delivered at McCord Hospital or were not brought back to the hospital for follow-up care were excluded from the study. This constitutes a selection bias. Furthermore, the study did not include a comparison group of infants born to HIV-uninfected women from McCord Hospital, which would have made it possible to determine the background risk of HIV-exposed uninfected infants in terms of infectious disease morbidity and loss to follow-up.

McCord Hospital is a semi-private institution. Women were either charged a user-fee or subsidised by donor funding to attend the Prevention of Mother-to-Child Transmission programme. The socio-economic profiles of women who paid for care may be different from women whose user fees were subsidised and represents a selection bias, which may have biased the effect observed in terms of loss to follow-up, morbidity and mortality towards the null

In terms of the clinical outcomes of morbidity, mortality and HIV transmission risk, the high proportion of infants lost to follow-up would also result in a selection bias, and underestimate the effect observed.

Information bias in the study may be attributed to the following:

i. The skill levels of nurses and practitioners attending to HIV-infected mothers and infants differed in the Prevention of Mother-to-Child Transmission programme. This was likely to have resulted in a non-differential misclassification of clinical diagnoses of mothers and infants.

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[29] Inclusion criteria: HIV-infected women who received antiretroviral prophylaxis or therapy in the McCord Prevention of Mother-to-Child Transmission Programme and either:

1) Delivered their infants at McCord Hospital between 1 May 2008 and 31 May 2009; and/or

2) Presented their infants for care to McCord Hospital, following delivery elsewhere, between 1 May 2008 and 31 May 2009.

Exclusion criteria: HIV-infected pregnant women who received antiretroviral prophylaxis or therapy from McCord Hospital Prevention of Mother-to-Child Transmission Programme and who had stillbirth deliveries.

ii. Illness events may have been overestimated due to recall bias by the caregiver resulting in bias away from the null.
iii. Estimation of illness in infants attending the clinic represented a cohort of infants who were well and subject to survival bias.
iv. The loss to follow-up status of the infants was assigned by the researcher and may have resulted in an overestimation of the effect seen due to ascertainment bias.
v. The researcher, a trained research assistant and a medical student conducted the data collection. Data collection by the researcher may have resulted in an overestimation of the study outcomes away from the null.
vi. Study data were entered only once into the study database by a single data capturer.

A further limitation of the findings of this study was that growth of infants still needs to be determined as a further objective and was not assessed in this study due to insufficient time available to the researcher. In terms of incidence of infectious diseases, infants who were HIV-exposed infected and uninfected infants were combined into one group due to the small sample size of HIV-infected infants. When infants who were HIV-infected were excluded from the Cox proportional hazards model of risk factors associated with upper respiratory tract infection, there was no difference in the significance of the findings.

The statistical analyses of this study were conducted by the researcher under supervision by a biostatistician at the University of KwaZulu-Natal.

5.5 SUMMARY

This study demonstrated clinical and loss to follow-up outcomes of predominantly HIV-exposed, uninfected infants whose mothers received care at the McCord Hospital Prevention of Mother-to-Child Transmission programme. The risks associated with upper respiratory illness and losses to follow-up of these infants were explored. The study demonstrated that women with higher viral loads and preterm infants were more likely to experience an upper respiratory event. Predictors for loss to follow-up of these infants were maternal factors such as the late presentation of women for first antenatal visit and having an elective caesarean section or normal vaginal delivery. The periods of greatest risk in terms of infectious diseases and loss to follow-up was also described. Knowledge of the timing and risk factors associated with infectious disease morbidity and loss to follow-up can facilitate the development of appropriate clinical interventions to improve the health outcomes of HIV-exposed infected and uninfected infants attending McCord Hospital.

6 CHAPTER VI: RECOMMENDATIONS AND CONCLUSIONS

6.1 INTRODUCTION

This study observed high proportions of common infectious diseases and loss to follow-up of infants whose mothers attended the Prevention of Mother-to-Child Transmission programme at McCord Hospital. The problem of poor follow-up presented a barrier to the effectiveness of the Prevention of Mother-to-Child Transmission programme at the hospital. Increased proportions of dropout of infants were observed in HIV-infected women who presented late for their first antenatal visit and women who had normal vaginal deliveries or elective caesarean section. Knowledge of risk factors associated with infectious disease morbidity and attrition of infants at McCord Hospital will facilitate the implementation of appropriate clinical interventions to reduce the frequency of common illnesses and loss to follow-up among these infants.

6.2 CONCLUSIONS

The Prevention of Mother-to-Child Transmission programme at McCord Hospital has been successful in reducing the HIV transmission risk of infants to less than 5% at 14 weeks of age, despite servicing a low to middle class population in a developing country. The low vertical transmission was in line with that reported in resource-rich settings [22-24]. Nonetheless, the five- month mortality of infants in this study was comparable to a cohort of infants in Latin America and Caribbean countries [27]. Although the burden of disease of infants in terms of pulmonary tuberculosis, lower respiratory and gastrointestinal infections were remarkably low, the incidence of upper respiratory and skin and mucous membrane illnesses was concerning, and exceeded that in other developing countries [27, 84]. Preterm delivery and high maternal viral load predisposed infants to upper respiratory events and the greatest risk of illness occurred from two to four months. Moreover, the low vaccination coverage at McCord Hospital, particularly the BCG and polio at birth, was concerning and falls short of national and international benchmarks. While the low vaccination coverage may be a function of the attrition, the poor coverage of BCG and polio at birth indicate health system issues at facility level and further investigation is warranted.

The proportion of infants lost to follow-up at McCord Hospital was greater than other Prevention of Mother-to-Child Transmission programmes in public settings in Africa [48, 50] and was comparable to one other developing country [51]. The proportion of infants lost to follow-up was greatest in the week following delivery and represents a missed opportunity

to improve the health outcomes of HIV-exposed infants born to women in this Prevention of Mother-to-Child Transmission programme.

6.3 RECOMMENDATIONS

Recommendations are made to improve the loss to follow-up and morbidity outcomes of HIV-exposed infants born to women attending the Prevention of Mother-to-Child Transmission programme at McCord Hospital. As McCord Hospital is a semi-private institution, these recommendations are implementable at facility level.

The prevention of mother-to-child transmission and infant feeding guidelines in South Africa have undergone major transformation. These changes are outlined below.

At a policy level, the South African Department of Health implemented the new prevention of mother-to-child transmission guidelines on the 1 April 2010 [18]. According to these guidelines, all pregnant women with $CD4^+$ counts less than or equal to 350 cells/mm^3 or World Health Organisation stage three or four are eligible for antiretroviral therapy and should be commenced on tenofovir, nevirapine and either lamivudine or emtracitabine depending on availability [18]. Pregnant women with $CD4^+$ counts above 350 cells/mm^3 or World Health Organisation stage one or two are eligible for antiretroviral prophylaxis with antenatal zidovudine commencing at 14 weeks, intrapartum single-dose nevirapine, three-hourly zidovudine and a postpartum single-dose of tenofovir and emtracitabine [18]. HIV-infected pregnant women with tuberculosis are regarded as having stage three disease and should be started on antiretroviral therapy [18].

The infant guidelines on antiretroviral prophylaxis have also been revised [18]. The duration of nevirapine prophylaxis to the infant depends on the method of infant feeding and if the mother is on antiretroviral prophylaxis or therapy [18]. Criteria for six weeks administration of infant nevirapine prophylaxis are (i) infants who are exclusively formula fed, (ii) infants who are exclusively breastfed and the mother is on antiretroviral therapy, (iii) infants who are HIV-infected. Infants who are exclusively breastfed and whose mothers are not on antiretroviral therapy should be provided with nevirapine until complete cessation of breastfeeding. According to these guidelines all breastfeeding should be stopped at one year of age [18].

The World Health Organisation set new recommendations on infant feeding in the context of HIV in November 2009. The WHO rapid advice guidelines recommended that all HIV-uninfected infant be exclusively breastfed for six months, with the introduction of

complementary foods thereafter and continued breastfeeding until 12 months of age [59]. The provision of breast milk should only be stopped once a nutritionally adequate, safe diet can be given to the infant. The provision of commercial formula milk to the HIV-uninfected infants should only be considered in a setting where formula feeding is affordable, feasible, acceptable, sustainable and safe [58, 59].

In light of these changes, McCord Hospital should consider revising their Prevention of Mother-to-Child Transmission protocol in line with new Prevention of Mother-to-Child Transmission guidelines released by the South African National Department of Health.

McCord Hospital should focus their efforts on improving the morbidity outcomes of preterm infants and infants born to women with baseline antenatal viral loads at or greater than 10 000 copies/ml. These infants should be identified as high risk cases that require careful monitoring and active follow-up to ensure their continued well-being. According to the new national prevention of mother-to-child transmission guidelines, all HIV-exposed infants should have weekly follow-up visits in the first month of life and monthly visits until one year of age [18]. However, these recommendations may be logistically impractical to implement.

The low vaccination coverage at McCord Hospital warrants further investigation. The issues surrounding poor coverage of BCG and polio at birth should be determined. Furthermore, health system issues, particularly in the period following delivery, should be resolved. This may include, for instance, assigning responsibility for administration of the vaccines following delivery to a specific ward, checking the neonates' vaccination statuses before discharge, and ensuring missed doses of vaccine are received if the infants' return for follow-up care. The following interventions to improving vaccination coverage should be considered [106]:

(i) Parental reminders of the dates of scheduled vaccinations – a bulk short message service to parents' cellular phones should be considered;
(ii) Nurse or clinician reminders of the vaccinations required during the visit using charts on the wall, or patient stickers on individual files;
(iii) Regular monitoring and evaluation of the coverage of vaccinations to ensure implementation of the immunization programme; and
(iv) Improve access to vaccination services provided at McCord Hospital to include the casualty and general paediatric outpatient departments. In addition, all visits by

caregivers to McCord Hospital should be considered opportunities to vaccinate the infant if present at the time of the visit.

The attrition rates of infants at McCord Hospital can be improved by sending caregivers' reminders of the date of the scheduled visits – again, bulk short message services could facilitate this process. Mothers of infants who are known to be at high risk for loss to follow-up should be intensively counselled on the value of remaining in care for their own health and that of the infant. All infants who are lost to follow-up should be active traced and educated to remain in care.

6.4 RECOMMENDATION FOR FURTHER STUDY

Although the study observed high rates of attrition and infectious disease morbidity of infants born to mothers in the Prevention of Mother-to-Child Transmission programme at McCord Hospital, the reasons for poor retention and morbidity were incompletely assessed. In addition, the infant morbidity, mortality and HIV transmission risk may have been underestimated due to the high proportion of loss to follow-up in the study. A key area to consider further is the impact of infant feeding practices and maternal nutrition on infant morbidity and mortality. The reasons for high incidence of infant infections at two to four months should be studied further. Maternal socio-economic characteristics and paternal factors associated with poor retention should also be explored. A prospective cohort study design is recommended to answer these questions

6.5 SUMMARY

McCord Hospital is a good model for integrated maternal and child health services for HIV-infected women and their infants. However, the attrition of these infants represented a missed opportunity to improve the health outcomes and the effectiveness of the Prevention of Mother-to-Child Transmission programme at McCord Hospital. Improved counselling of women on the health benefits of attending follow-up care for themselves and their infants should be emphasised.

7 REFERENCES

1. UNAIDS. Report on the global HIV/AIDS epidemic 2008: executive summary. UNAIDS; 2008 [updated 2008; cited 2009 Aug 24]; Available from: http://data.unaids.org/pub/GlobalReport/2008/JC1511_GR08_ExecutiveSummary_en.pdf

2. Declaration of commitment on HIV/AIDS. United Nations General Assembly Special Session on HIV/AIDS 25-27 June 2001 [database on the Internet]. UNAIDS. 2001 [cited 2010 March 22]. Available from: http://data.unaids.org/publications/irc-pub03/aidsdeclaration_en.pdf.

3. The Millennium Development Goals Report 2008 [database on the Internet]. United Nations Development Programme. 2008 [cited 2010 March 22]. Available from: http://www.undp.org/mdg/basics.shtml.

4. South African National Department of Health. 2008 National Antenatal Sentinel HIV & Syphilis Prevalence Survey. 2009.

5. Statistics South Africa. General Household Survey 2007 Metadata. Cape Town, Pretoria: Statistics South Africa; 2008.

6. Statistics South Africa. General Household Survey 2004. Cape Town: Statistics South Africa; 2005.

7. Actuarial Society of South Africa. ASSA2002 AIDS and demographic model. Actuarial Society of South Africa; 2004 [updated 2004; cited 2009 Jun 6]; Available from: http://www.assa.org.za.

8. Johnson L. HIV and health - children starting ART [database on the Internet]. Children Count. 2008 [cited 2010 March 31]. Available from: http://www.childrencount.ci.org.za/uploads/factsheet_20.pdf.

9. UNICEF. Statistics South Africa [database on the Internet]. 2010 [cited 2010 April 24]. Available from: http://www.unicef.org/infobycountry/southafrica_statistics.html.

10. Bradshaw D, Bourne D, Nannan N. What are the leading causes of death among South African Children? MRC Policy Brief No 3. 2003.

11. Chopra M, Daviaud E, Pattinson R, Fonn S, Lawn JE. Health in South Africa. Saving the lives of South Africa's mothers, babies, and children: can the health system deliver? Lancet. 2009:29-40.

12. National Department of Health. Policy and guidelines for the implementation of the PMTCT programme. Government of South Africa; 2008.

13. Jackson JB, Musoke P, Fleming T, Guay LA, Bagenda D, Allen M, et al. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomised trial. Lancet 1999;354(9181):795-802.

14. National Department of Health, Medical Research Council. Measure DHS, 1998 South Africa Demographic and Health survey. 2002.
15. Barron P, Day C, Fonticelli F, et al. The district health barometer 2005/06. Durban: Health Systems Trust; 2006 Contract No.
16. South Africa Every Death Counts Writing Group. Every death counts: use of mortality audit data for decision making to save the lives of mothers, babies, and children in South Africa. Lancet. 2008;371:1294-304.
17. World Health Organisation. Antiretroviral drugs for treating pregnant women and preventing HIV infection in infants: towards universal access. Recommendations for public health approach. Geneva: World Health Organisation; 2006.
18. National Department of Health South Africa. Clinical guidelines: Prevention of mother-to -child transmission [database on the Internet]. South African National AIDS Council. 2010 [cited April]. Available from: http://www.hiv911.org.za/wp-content/uploads/2010/04/2010-PMTCT-Guidelines.pdf.
19. Wade NA, Birkhead GS, Warren BL, Charbonneau TT, French PT, Wang L, et al. Abbreviated regimens of zidovudine prophylaxis and perinatal transmission of the human immunodeficiency virus. N Engl J Med. 1998;339:1409-14.
20. Lallemant M, Jourdain G, Le Coeur S, et al. Single dose perinatal Nevirapine plus standard Zidovudine to prevent mother-to-child transmission of HIV-1 in Thailand. N Engl J Med. 2004;351:217-28.
21. Geddes R, Knight S, Reid S, Giddy J, Esterhuizen T, Roberts C. Prevention of mother-to-child transmission of HIV programme: Low vertical transmission in KwaZulu-Natal, South Africa. SAMJ. 2008 Jun;98(6):458-62.
22. The European Collaborative Study. HIV-infected pregnant women and vertical transmission in Europe since 1986. AIDS. 2001;15(6):761-70.
23. Dorenbaum A, Cunningham CK, Gelber RD, Culnane M, Mofenson L, Britto P, et al. Two-dose intrapartum/newborn nevirapine and standard antiretroviral therapy to reduce perinatal HIV transmission: a randomised trial. JAMA. 2002;288(2):189-98.
24. Cooper E, Charurat M, Mofenson L, et al. Combination antiretroviral strategies for the treatment of pregnant HIV-1-infected women and prevention of perinatal HIV-1 transmission. J Acquir Immune Defic Syndr 2002;29(5):484-94.
25. South African National AIDS Council (SANAC). HIV and AIDS and STI national strategic plan 2007-2011. Department of Health. Pretoria; 2006.
26. Ghosh MK, Kuhn L, West J, et al. Quantitation of human immunodeficiency virus in breast milk. J Clin Microbiol. 2003;41:2465-70.

27. Mussi-Pinhata M, Korelilitz J, Pinto J, Cruz M, Losso M, Freimanis L, et al. Infectious disease morbidity among young HIV-1 exposed but uninfected infants in Latin America and the Carribean countries: the National Institute of Child Health and Development International Site Development Initiative Perinatal Study. Paediatrics 2007;119:e694-e704.
28. Demographic and Health Surveys [database on the Internet]. Macro International Inc. 2008 [cited 2010 May 21]. Available from: http://www.measuredhs.com.
29. De Cock K, Fowler M, Mercier E. Prevention of mother-to-child HIV transmission in resource-poor countries - Translating research into policy and practice. JAMA. 2000;283(9):1175-82.
30. Farley T, Buyse D, Gaillard P, Perriens J. Efficacy of antiretroviral regimens for prevention of mother to child transmission of HIV and some programmatic issues. Background paper prepared for technical consultation on new data on the prevention of mother to child transmission of HIV and their policy implications. 2000; Geneva. World Health Organisation; 2000.
31. European Collaborative Study. Mother-to-child transmission of HIV infection in the era of highly active antiretroviral therapy. Clin Infect Dis. 2005;40(458-65).
32. Townsend CL, Cortina-Borja M, Peckham CS, de Ruiter A, Lyallc H, Tookey PA. Low rates of mother-to-child transmission of HIV following effective pregnancy interventions in the United Kingdom and Ireland, 2000-2006. AIDS. 2008;22(8):973-81.
33. The International Perinatal HIV Group. The mode of delivery and the risk of vertical transmission of human immunodeficiency virus type 1 - a meta-analysis of 15 prospective cohort studies. N Engl J Med. 1999;340(13):977-87.
34. Read JS, Newell ML. Efficacy and safety of caesarean delivery for prevention of mother-to-child transmission of HIV-1. Cochrane Database Syst Rev. 2005 Oct 19(4).
35. Miotti PG, Taha ET, Kumwenda NI, Broadhead R, Mtimavalye LAR, Van der Hoeven L, et al. HIV transmission through breastfeeding: a study in Malawi. JAMA. 1999 Aug 25;282(8):744-49.
36. Fawzi W, Msamanga G, Spiegelman D, et al. Transmission of HIV-1 through breastfeeding among women in Dar es Salaam, Tanzania. J Acquir Immune Defic Syndr. 2002;31:331-38.
37. Read JS, Newell ML, Leroy V, Dabis F, Fazwi W, for the Breastfeeding and HIV International Transmission Study Group. Late postnatal transmission of HIV in breastfed children: an individual patient data meta-analysis. J Infect Dis. 2004;189:2154-66.
38. National Department of Health. National HIV and Syphilis Prevalence Survey in South Africa: National Department of Health; 2006.

39. Jackson D, Chopra M, Doherty T, Colvin M, Levin J, Willumsen J, et al. Operational effectiveness and 36 week HIV-free survival in the South African programme to prevent mother-to-child transmission of HIV. AIDS. 2007;21(4):509-16.
40. Kuhn L, Kasonde P, Sinkala M, Kankasa C, Semrau K, Scott N, et al. Does severity of HIV disease in HIV-infected mothers affect mortality and morbidity among their uninfected infants? Clin Infect Dis. 2005;41:1654-61.
41. Newell M, Coovadia H, Cortina-Borja M, Rollins N, Gaillard P, Dabis F. Mortality of infected and uninfected infants born to HIV-infected mothers in Africa: a pooled analysis. Lancet. 2004 October 2;364:1236-43.
42. The Women and Infants Transmission Study. Morbidity and mortality during the first two years of life among HIV-uninfected children born to Human Immunodeficiency Virus Type 1-Infected Women. Pediatr Infect Dis J. 2005;24(1):46-56.
43. Brahmbhatt H, Kigozi G, Wabwire-Mangen F, Serwadda D, Lutalo T, Nalugoda F, et al. Mortality of HIV-infected and uninfected children of HIV-infected and uninfected mothers in rural Uganda. JAIDS. 2006;41:504-8.
44. Ndirangu J, Newell ML, Tanser F, Herbst AJ, Bland R. Decline in early life mortality in a high HIV prevalence rural area of South Africa: evidence of HIV prevention or treatment impact? AIDS. Feb 20;24(4):593-602.
45. Mulenga V, Ford D, Walker AS, Mwenya D, Mwansa J, Sinyinza F, et al. Effect of cotrimoxazole on causes of death, hospital admissions and antibiotic use in HIV-infected children. AIDS. 2007 Jan 2; 21(1):77-84.
46. Crampin AC, Floyd S, Glynn JR, et al. The long-term impact of HIV and orphanhood on the mortality and physical well-being of children in rural Malawi. AIDS. 2003;17:389-97.
47. Taha TE, Graham SM, Kumwenda NI, Broadhead RL, Hoover DR, Markakis D, et al. Morbidity among Human Immunodeficiency Virus-1-infected and -uninfected African children. J Pediatr. 2000 Dec;106(6):e77.
48. Sherman G, Jones S, Coovadia A, Urban M, Bolton K. PMTCT from research to reality-results from a routine service. S Afr Med J. 2004;94(4):289-92.
49. Jones S, Sherman G, Varga C. Exploring socio-economic conditions and poor follow-up rates of HIV-exposed infants in Johannesburg, South Africa. AIDS Care. 2005;17(4):466-70.
50. Ioannidis JP, Taha TE, Kumwenda N, Broadhead R, Mtimavalye L, Miotti P, et al. Predictors and impact of losses to follow-up in an HIV-1 perinatal transmission cohort in Malawi. Int J Epidemiol. 1999 August 1;28(4):769-75.

51. Ahoua L, Ayikoru H, Gnauck K, Odaru G, Odar E, Ondoa-Onama C, et al. Evaluation of a 5-year programme to prevent mother-to-child transmission of HIV infection in Northern Uganda. J Trop Pediatr. 2009 Feb;56(1):43-52.
52. Nduati R, John G, Mbori-Ngacha D, Richardson B, Overbaugh J, Mwatha A, et al. Effects of breastfeeding and formula feeding on transmission of HIV-1. JAMA. 2000 March 1;283(9):1167-75.
53. Fowler M, Newell M. Breast-Feeding and HIV-1 Transmission in Resource-Limited Settings. JAIDS. 2002;30(2):230-9.
54. Coovadia H, Rollins N, Bland RM, Little K, Coutsoudis A, Bennish ML, et al. Mother-to-child transmission of HIV-1 infection during exclusive breastfeeding in the first 6 months of life: an intervention cohort study Lancet. 2007;369(9567):1107-16.
55. Creek T, Kim A, Lu L, Bowen A, Masunge J, Arvelo W, et al. Hospitalisation and mortality among primarily non-breastfed children during a large outbreak of diarrhoea and malnutrition in Botswana, 2006. J Acquir Immune Defic Syndr. 2010;53(1):14-9.
56. Becquet R, Bequet L, Ekouevi DK, Viho I, Sakarovitch C, Fassinou P, et al. Two-year morbidity–mortality and alternatives to prolonged breast-feeding among children born to HIV-infected mothers in Côte d'Ivoire. PLoS Med. 2007;4(17).
57. WHO/UNICEF/UNAIDS. HIV and Infant Feeding: guidelines for decision makers [database on the Internet]. 1998 [cited 2008 Dec]. Available from: http://www.unaids.org/publications/documents/mtct/infantpolicy.pdf
58. World Health Organisation. Consensus Statement. WHO HIV and infant feeding technical consultation held on behalf of the Inter-Agency Task Team (IATT) on prevention of HIV infections in pregnant women, mothers and their infants; 2006 Oct 25-27; Geneva.
59. World Health Organisation. Rapid advice: revised World Health Organisation principles and recommendations on infant feeding in the context of HIV [database on the Internet]. 2009 [cited 2010 May 10]. Available from: http://www.who.int/hiv/pub/paediatric/advice/en/.
60. Bedri A, Gudetta B, Isehak A, Kumbi S, Lulseged S, Mengistu Y, et al. Extended-dose nevirapine to 6 weeks of age for infants to prevent HIV transmission via breastfeeding in Ethiopia, India, and Uganda: an analysis of three randomised controlled trials. Lancet. 2008 Jul 26;372(9635):300-13.
61. Chasela C, Hudgens M, Jamieson D, Kayira D, Hosseinipour M, Ahmed Y, et al. Both maternal HAART and daily infant nevirapine (NVP) are effective in reducing HIV-1 transmission during breastfeeding in a randomised trial in Malawi: 28 week results of the Breastfeeding, Antiretroviral and Nutrition (BAN) Study 5th IAS Conference on HIV

Pathogenesis, Treatment and Prevention; 2009 Jul 19-22; Cape Town, South Africa. 2009.

62. Shapiro R, Hughes M, Ogwu A, Kitch D, Lockman S, Moffat C, et al. A randomised trial comparing highly active antiretroviral therapy regimens for virologic efficacy and the prevention of mother-to-child HIV transmission among breastfeeding women in Botswana (The Mma Bana Study) 5th IAS Conference on HIV Pathogenesis, Treatment and Prevention; 2009 Jul 19-22; Cape Town, South Africa.

63. de Vincenzi I, Kesho Bora Study Group. Triple-antiretroviral (ARV) prophylaxis during pregnancy and breastfeeding compared to short-ARV prophylaxis to prevent mother-to-child transmission of HIV-1 (MTCT): the Kesho Bora randomised controlled clinical trial in five sites in Burkina Faso, Kenya and South Africa. 5th International Aids Society Conference on HIV Pathogenesis, Treatment and Prevention; 2009; Cape Town, South Africa. 2009.

64. Kumwenda NI, Hoover DR, Mofenson LM, Thigpen MC, Kafulafula G, Li Q, et al. Extended antiretroviral prophylaxis to reduce breast-milk HIV-1 transmission. N Engl J Med. 2008 Jul 10;359(2):119-29.

65. Thior I, Lockman S, Smeaton LM, Shapiro RL, Wester C, Heymann SJ, et al. Breastfeeding plus infant zidovudine prophylaxis for 6 months versus formula feeding plus infant zidovudine for 1 month to reduce mother-to-child HIV transmission in Botswana: a randomised trial: The Mashi Study. JAMA. 2006 August 16;296(7):794-805.

66. Rollins NC, Becquet R, Bland RM, Coutsoudis A, Coovadia HM, Newell M-L. Infant feeding, HIV transmission and mortality at 18 months: the need for appropriate choices by mothers and prioritization within programmes. AIDS. 2008;22:2349–57.

67. WHO Collaborative Study on the role of breastfeeding on the prevention of infant mortality. Effect of breastfeeding on infant and child mortality due to infectious diseases in less developed countries: a pooled analysis. Lancet. 2000;355:451-5.

68. Kirkwood BR, Sterne JAC, eds. Essential Medical Statistics. Second ed. Massachusetts: Blackwell Science; 1988.

69. Hankin C, Thorne C, Peckham C, Newell ML. The health and social environment of uninfected infants born to HIV-infected women. AIDS care. 2004 April;16(3):293 - 303.

70. WHO/AFRO. Polio eradication [database on the Internet]. 2003 [cited 2010 May 20]. Available from: http://www/afro.who.int/polio/overview.html.

71. Department of Health. Goals, objectives and indicators, 2001 - 2005 [database on the Internet]. National Department of Health. 2005 [cited 2010 May 20].

72. Ndirangu J, Bärnighausen T, Tanser F, Tint K, Newell M-L. Levels of childhood vaccination coverage and the impact of maternal HIV status on child vaccination status in rural KwaZulu-Natal, South Africa. Trop Med Int Health. 2009 November;14(11):1383-93.
73. Breiman RF, Streatfield PK, Phelan M, et al. Effect of infant immunisation on childhood mortality in rural Bangladesh: analysis of health and demographic surveillance data. Lancet. 2004;364:2204-11.
74. Streatfield K, Singarimbun M, Diamond I. Maternal education and child immunisation. Demography. 1990;27:447-55.
75. Madise NJ, Matthews Z. Heterogeneity of child nutritional status between households: a comparison of six Sub-Saharan countries. Population Studies. 1999;53:331-43.
76. Anand S, Barnighausen T. Health workers and vaccination coverage in developing countries: an econometric analysis. Lancet. 2007;369:1277-85.
77. Munthali AC. Determinants of vaccination coverage in Malawi. Evidence from health and demographic surveys. Malawi Medical Journal. 2007;19:79-82.
78. Guerin N. Assessing immunisation coverage: how and why? Vaccine. 1998;16(Suppl):S81-3.
79. Reichler RM, Darwish A, Stroh G, et al. Cluster survey evaluation of coverage and risk factors for failure to be immunized during the 1995 National Immunisation Days in Egypt. Int J Epidemiol. 1998;27:1083-9.
80. Buor D. Analysing the primacy of distance in the utilisation of health services in the Ahafo-Ano South district, Ghana. International Journal of Health Planning and Management. 2003;18:293-311.
81. Ndiritu M, Cowgill KD, Ismail A, et al. Immunisation coverage and risk factors for failure to immunise within the Expanded Programme of Immunisation in Kenya after the introduction of haemophilus influenza type b and hepatitis b virus antigens. BMC Public Health. 2006;6:132.
82. Defo BK. Areal and socioeconomic differentials in infant and child mortality in Cameroon. Soc Sci Med. 1996;42:399-420.
83. INDEPTH NETWORK. Measuring health equity in small areas: findings from demographic surveillance system. Health inequalities in Kassena-Nankana District in Northern Ghana. Ashgate, England; 2005. p. 45-65.
84. Castro MX, Soares AM, Fonsêca WR, Luís C, Guerrant RL, Lima AAM. Common infectious diseases and skin test anergy in children from an urban slum in Northeast Brazil. Braz J Infect Dis. 2003;7(6):387-94.

85. Kattan M, Platzker A, Mellins RB, Schluchter MD, Chen XC, Peavy H, et al. Respiratory diseases in the first year of life in children born to HIV-1-infected women. Pediatr Pulmonol. 2001 Apr;31(4):267-76.
86. Mbori-Ngacha D, Nduati R, John G, Reilly M, Richardson B, Mwatha A, et al. Morbidity and mortality in breastfed and formula-fed infants of HIV-1 infected women: a randomised clinical trial. JAMA. 2001;286(19):2413-20.
87. Schaaf HS, Marais B, Whitelaw A, Hesseling A, Eley B, Hussey G, et al. Culture-confirmed childhood tuberculosis in Cape Town, South Africa: a review of 596 cases. BMC Infectious Diseases. 2007;7(1):140.
88. Coutsoudis A, Pillay K, Spooner E, Coovadia HM, Pembrey L, Newell ML. Routinely avaialble cotrimoxazole prophylaxis and occurrence of respiratory and diarrhoeal morbidity in infants born to HIV-infected mothers in South Africa. S Afr Med J. 2005;95(5):339-45.
89. Coutsoudis A, Pillay K, Kuhn L, Spooner E, Tsai WY, Coovadia HM. Method of feeding and transmission of HIV-1 from mothers to children by 15 months of age: prospective cohort study from Durban, South Africa. AIDS. 2001 Feb 16;15(3):379-87.
90. Bahl R, Frost C, Kirkwood BR, Edmond K, Martines J, Bhandari N, et al. Infant feeding patterns and risks of death and hospitalisation in the first half of infancy: multicentre cohort study. Bull World Health Organ. 2005 Jun;83(6):418-26.
91. Kafulafula G, Hoover DR, Taha TE, Thigpen M, Li Q, Fowler MG, et al. Frequency of gastroenteritis and gastroenteritis-associated mortality with early weaning in HIV-1-uninfected children born to HIV-infected women in Malawi. J Acquir Immune Defic Syndr. Jan 1;53(1):6-13.
92. Onyango-Makumbi C, Bagenda D, Mwatha A, Omer SB, Musoke P, Mmiro F, et al. Early Weaning of HIV-Exposed Uninfected Infants and Risk of Serious Gastroenteritis: Findings from Two Perinatal HIV Prevention Trials in Kampala, Uganda. J Acquir Immune Defic Syndr. 2009 Sep 25;25:25.
93. Misra V. Indoor air pollution from biomass combustion and acute respiratory illness in preschool age children in Zimbabwe. Int J Epidemiol. 2003;2003(32):847-53.
94. Mellors JW, Munoz A, Giorgi JV, Margolick JB, Tassoni CJ, Gupta P, et al. Plasma viral load and CD4+ lymphocytes as prognostic markers of HIV-1 infection. Ann Intern Med. 1997 Jun 15;126(12):946-54.
95. de Moraes-Pinto MI, Verhoeff F, Chimsuku L, Milligan PJ, Wesumperuma L, Broadhead RL, et al. Placental antibody transfer: influence of maternal HIV infection and placental malaria. Arch Dis Child Foetal Neonatal Ed. 1998 Nov;79(3):F202-5.

96. Chougnet CA, Kovacs A, Baker R, Mueller BU, Luban NL, Liewehr DJ, et al. Influence of human immunodeficiency virus-infected maternal environment on development of infant interleukin-12 production. J Infect Dis. 2000;181:1590-7.
97. Clerici M, Saresella M, Colombo F, Fossati S, Sala N, Bricalli D, et al. T-lymphocyte maturation abnormalities in uninfected newborns and children with vertical exposure to HIV. Blood. 2000 Dec 1;96(12):3866-71.
98. Rich KC, Siegel JN, Jennings C, Rydman RJ, Landay AL. Function and phenotype of immature CD4+ lymphocytes in healthy infants and early lymphocyte activation in uninfected infants of human immunodeficiency virus-infected mothers. Clin Diagn Lab Immunol. 1997 May;4(3):358-61.
99. Kuhn L, Coutsoudis A, Moodley D, Mngqundaniso N, Trabattoni D, Shearer GM, et al. Interferon-gamma and interleukin-10 production among HIV-1-infected and uninfected infants of HIV-1-infected mothers. Pediatr Res. 2001 Sep;50(3):412-6.
100. Behrman RE, Kliegman RM, eds. Nelson Essentials of Paediatrics. Fourth ed. Philadelphia: Saunders; 2002.
101. Graham SM, Gibb DM. HIV disease and respiratory infection in children. Brit Med Bull. 2002;61:131-50.
102. Perez MS, Van Dyke RB. Pulmonary infections in children with HIV infection. Semin Respir Infect 2002;17:33-46.
103. Graham SM. Prophylaxis against Pneumocystis carinii pneumonia for HIV-exposed infants in Africa. Lancet. 2002;360:1966-8.
104. Graham SM. Cotrimoxazole prophylaxis for infants exposed to HIV infection. Bull World Health Organ. 2004;82(4):297-8.
105. Rollins N, Little K, Mzolo S, Horwood C, Newell M. Surveillance of mother-to-child transmission prevention programmes at immunization clinics: the case for universal screening. AIDS. 2007;21(10):1341-7.
106. Committee on Community Health Services and Committee on Practice Ambulatory Medicine. Increasing Immunization Coverage. Paediatrics. 2003 October 1, 2003;112(4):993-6.

8 APPENDIX

APPENDIX A

University of KwaZulu-Natal Biomedical Research Ethics Approval

UNIVERSITY OF
KWAZULU-NATAL

BIOMEDICAL RESEARCH ETHICS ADMINISTRATION
Research Office, Westville Campus
Govan Mbeki Building
Private Bag X 54001
Durban
4000
KwaZulu-Natal, SOUTH AFRICA
Tel: 27 31 2604769 Fax: 27 31 2604609
Email: BREC@ukzn.ac.za
Website: http://research.ukzn.ac.za/Research/Ethics/BiomedicalEthics.aspx

23 January 2010

Dr Terusha Chetty
Dept of Public Health Medicine
Howard College Campus
Francois Road, Suite 3
George Campbell Bldg, 2nd floor
UKZN

Dear Dr Chetty

PROTOCOL: Follow up care of infants born in a Prevention of Mother to Child Transmission Programme in an urban Hospital in KwaZulu-Natal, South Africa. Dr Terusha Chetty, Department of Public Health. Ref No: BE160/08.

We wish to advise you that your letter received by BREC on 19 January 2010 requesting Amendments, i.e. an extension of study period to 31 May 2009, has been noted and approved by the sub-committee of the Biomedical Research Ethics Committee.

Yours sincerely

Prof D. Wassenaar
Chair: Biomedical Research Ethics Committee
DW/pn

University of KwaZulu-Natal Postgraduate Education Committee Approval

UNIVERSITY OF KWAZULU-NATAL

COLLEGE OF HEALTH SCIENCES

NELSON R MANDELA SCHOOL OF MEDICINE

M E M O R A N D U M

TO:	FROM:
Dr S Knight Department of Public Health NRMSM	Professor SR Thomson Assistant Dean: Postgraduate Administration Nelson R Mandela School of Medicine 08 April 2009

Dear Dr Knight

PROTOCOL: Follow up care of infants born in a Prevention of Mother to Child Transmission programme in KwaZulu-Natal, South Africa

Chetty T, Student No. : 983177133, MMed, Public Health

The Postgraduate Education Committee ratified the approval of the abovementioned study on 07 April 2009.

Please note :

- the Postgraduate Education Committee must review any changes made to this study.
- the study may not begin without the approval of the Bioethics Research Ethics Committee.

May I take this opportunity to wish the student every success with the study.

Yours sincerely,

Professor SR Thomson
Assistant Dean: Postgraduate Administration.

cc: Dr T Chetty, Department of Public Health, NRMSM

McCord Hospital Research Ethics Committee Approval

McCORD HOSPITAL

McCord Research Ethics Committee

12 October 2009

Dear Dr Chetty

Re: Follow up care of infants born in a Prevention of Mother to Child Transmission Programme in an urban hospital in KwaZulu-Natal, South Africa

This study was reviewed by the McCord Research Ethics Committee (MREC) on the 31st July 2009.

I have the pleasure in informing you that this study now has full approval.

Attached please find the Committee Clearance Certificate, with the MREC study number.

Please also complete and sign the document acknowledging the terms and conditions for undertaking research at McCord Hospital. The signed document should be returned to the Research Administrator.

May we wish you every success in your research.

Sincerely

Dr H Holst
Acting Chair: McCord Research Ethics Committee

APPENDIX B
Clinical record forms in infant files at McCord Hospital
Paediatric enrolment form

Sticker	FORM 6: PMTCT Programme **PAEDIATRIC ENROLMENT FORM**

Date:

Details of Mother and Child		
Mother	Child	
Name:	Name:	
ID Number:	Sex: [ ]M [ ]F	Date of Birth: dd/ mm / yyyy
Place of residence:	**Age:**	

Delivery Information			
Gestational age at delivery [ ] weeks	Birth weight: [ ]kg	Length [ ]cm	Head circumference [ ]cm
Mode of delivery: [ ]Vaginal delivery [ ]C/Section			
Delivery complications and Interventions:			
Apgar score: 1 minute [ ]/10 5 minute[ ]/10			
Multiple births: [ ] Y [ ] N	Comment:		
ARV prophylaxis at birth:	[ ]None [ ]NVP only [ ]NVP and AZT [ ] Other		
Comment:			

Reason for attending clinic today
Appointment type: [ ] Scheduled [ ]Off schedule How is child today? [ ] Well [ ] Unwell Comment:

History of Recent Illnesses including OIs (check clinic card)

Clinic visits or hospital admissions for any illnesses since birth? Indicate clinic/hosp/trad healer/GP/admission

Date	Admission: Y/N	Place	Diagnosis	Comment(including medication)

Infant mortality: [ ]Y [ ]N	Date of death:	**Cause:**

Is child on co-trimoxazole prophylaxis: [ ]Y [ ]N	Start /stop date: dd/ mm / yyyy

1/2

Paediatric enrolment form (contd.)

Social Situation	
Who is the child's primary caregiver?	[ ]Mother [ ] Father [ ] Maternal grandmother [ ]Paternal grandmother [ ] Sibling [ ] Foster/Adoption [ ] Other Comment:
Is the child's mother/caregiver:	[ ]Well [ ]Sick [ ]Dead [ ]Unknown

Infant Feeding	
Current feeding method:	[ ] Exclusive breastfeeding [ ] Mixed feeding (BF and other) [ ] Exclusive formula feeding [ ]Formula and other foods [ ] Other: Comment_____
Age of breastfeeding cessation if breastfed: [ ]mths	
Age of initiation of solids: [ ]mths	Comment:

TB History		
Current household TB contact: [ ]Y [ ] N		If yes, child on prophylaxis [ ] Y [ ]N
Child investigated for TB: [ ]Y [ ] N		If yes, which test/s:
Current TB treatment: [ ]Y [ ] N		Start date: dd/ mm / yyyy
Type of TB:	[ ]Pulmonary [ ] Extrapulmonary Specify:	
Previous TB treatment	Date/s: dd/ mm / yyyy	Type:

Examination findings
Nutritional: weight ____kg length ____cm HC ____cm **Chart on RTHC** **Developmental**: Use chart and comment if problem Congenital abnormalities: [ ]Y [ ] N **Relevant findings**:

Overall Assessment		
Clinical	[ ]Normal [ ]Problem	Specify:
Nutritional:	[ ]Normal [ ]Problem	Specify:
Developmental:	[ ]Normal [ ]Problem	Specify:
Immunizations:	[ ]Up to date [ ]Incomplete	Specify missed: [ ]Birth [ ]6 weeks [ ]10 weeks [ ]14 weeks [ ] 9 months [ ]18 months

Plan:
Date for next visit:___/___/_____ **Name and sign:_____**

2/2 Version: 10/10/08

Paediatric follow-up form

Sticker

FORM 7: PMTCT Programme

PAEDIATRIC FOLLOW UP FORM

Date:

Details of Mother and Child		
Mother	Child	
Name:	Name:	
ID Number:	Sex: [ ]M [ ]F	Date of Birth: dd/ mm / yyyy
Place of residence:	Age:	

Reason for attending clinic today
Appointment type: [ ] Scheduled [ ]Off schedule How is child today? [ ] Well [ ] Unwell Comment:

History of Recent Illnesses including OIs (check clinic card)

Clinic visits or hospital admissions for any illnesses since birth? Indicate clinic/hosp/trad healer/GP/admission

Date	Admission: Y/N	Place	Diagnosis	Comment(including medication)

Is child on co-trimoxazole prophylaxis: [ ]Y [ ]N	Start /stop date: dd/ mm / yyyy

Social Situation	
Who is the child's primary caregiver?	[ ]Mother [ ] Father [ ] Maternal grandmother [ ]Paternal grandmother [ ] Sibling [ ] Foster/Adoption [ ] Other Comment:
Is the child's mother/caregiver:	[ ]Well [ ]Sick [ ]Dead [ ]Unknown

Infant Feeding	
Current feeding method:	[ ] Exclusive breastfeeding [ ] Mixed feeding (BF and other) [ ] Exclusive formula feeding [ ]Formula and other foods [ ] Other: Comment_____
Age of breastfeeding cessation if breastfed: [ ]mths	
Age of initiation of solids: [ ]mths	Comment:

TB History	
Current household TB contact: [ ]Y [ ] N	If yes, child on prophylaxis [ ] Y [ ]N
Child investigated for TB: [ ]Y [ ] N	If yes, which test/s:

1/2

Paediatric follow-up form (contd.)

Current TB treatment: [ ]Y [ ] N		Start date: dd/ mm / yyyy
Type of TB:	[ ]Pulmonary [ ] Extrapulmonary Specify:	
Previous TB treatment	Date/s: dd/ mm / yyyy	Type:
Comment:		

Examination findings
Nutritional: weight ____kg length ____cm HC ____cm **Chart on RTHC** **Developmental**: Use chart and comment if problem Congenital abnormalities: [ ]Y [ ] N **Relevant findings**:

Overall Assessment		
Clinical	[ ]Normal [ ]Problem	Specify:
Nutritional:	[ ]Normal [ ]Problem	Specify:
Developmental:	[ ]Normal [ ]Problem	Specify:
Immunizations:	[ ]Up to date [ ]Incomplete	Specify missed: [ ]Birth [ ]6 weeks [ ]10 weeks [ ]14 weeks [ ] 9 months [ ]18 months

Plan:

Date for next visit:___/___/_____

Name and sign:_____

2/2 **Version: 10/10/08**

Summary of routine care and assessment

Sticker

FORM 8: PMTCT Programme

SUMMARY OF ROUTINE CARE AND ASSESSEMENT

IMMUNISATION SCHEDULE

Age:	Date:			
Birth		[ ]BCG	[ ]OPV	
6 weeks		[ ]DPT + HIB	[ ]OPV	[ ]Hep B
10 weeks		[ ]DPT + HIB	[ ]OPV	[ ]Hep B
14 weeks		[ ]DPT + HIB	[ ]OPV	[ ]Hep B
9 months		[ ]Measles		
18 months		[ ]Measles	[ ]OPV	[ ]DPT

DEVELOPMENTAL ASSESSMENT ☑ if achieved ☒ if not achieved within specified time frame

AGE	GROSS MOTOR	FINE MOTOR	LANGUAGE	SOCIAL
6 – 10 weeks	[ ]Head held level with body	[ ]Hands held open some of the time	[ ]Makes vowel sounds	[ ]Smiles [ ]Regards face
14 -18 weeks	[ ]Head held above level of body	[ ]Holds objects placed into hand	[ ]Laughs/squeals	[ ]Regards hand
3 – 6 months	[ ]Pull to sit: no head lag [ ]Supports body on extended arms [ ]Moro reflex lost	[ ]Follows an arc of 180 [ ]Reaches for and grasps object [ ]Transfers objects to other hand	[ ]Turns head to sound	
9 – 12 months	[ ]Sits without support [ ]Stands holding on	[ ]Holds an object in each hand simultaneously [ ]Pincer grip	[ ]Babbling sounds [ ]Follows sound	[ ]Holds and eats biscuits [ ]Waves
15 -18 months	[ ]Stands alone [ ]Walks well		[ ]2 – 3 recognisable sounds	[ ]Feeds self from cup
21 – 24 months	[ ]Runs		[ ]Short phrases	

HIV TESTING

HIV test	Date	Result	Comment
PCR (6/52)			
DBS PCR (14/52)			
If breastfed: PCR post cessation			
18 month rapid test			

POSITIVE BABIES: **Confirmatory PCR done:** [ ]Y [ ]N **Date:**

Baseline CD4: % **Viral Load:** **WHO stage:** 1 2 3 4

ARV start date: **ARV regimen:**

1/1

Version: 10/10/08

APPENDIX C

Follow Up Care of Infants Born in a Prevention of Mother to Child Transmission Programme in an Urban Hospital in KwaZulu-Natal, South Africa					
DATA ABSTRACTION FORM					
A. MOTHER AND INFANT INFORMATION					
A.1	MOTHER STUDY ID ___ ___ ___ ___		A.2	INFANT STUDY ID ___ ___ ___ ___	
A.3	Date Of Data Abstraction	__ __/__ __ __/__ __ __ __ dd/ mmm/ yyyy	A.4	Initials of Data Abstractor ___ ___ ___	
A.5	Date of Delivery	__ __/__ __ __/__ __ __ __ dd/ mmm/ yyyy	A.6	Date of 1st Postnatal Visit	__ __/__ __ __/__ __ __ __ dd/ mmm/ yyyy
PART 1: MATERNAL INFORMATION					
B. SOCIAL/DEMOGRAPHIC INFORMATION					
B.1	Date of birth	__ __/__ __ __/__ __ __ __ dd/ mmm/ yyyy	[ ] Missing		
B.2	Race	[ ] Black (South African) [ ] Black (other African) [ ] Coloured [ ] White	[ ] Asian [ ] Other _____ [ ] Missing		
B.3	Currently employed	[ ] Yes	[ ] No		
B.4	How was the clinic/hospital visit paid for?	[ ] Cash [ ] Medical aid [ ] Missing	[ ] Cohen fund [ ] Other, Specify_____		
C. ANTENATAL VISIT INFORMATION					
C.1	First ANC booking date	__ __/__ __ __/__ __ __ __ dd/ mmm/ yyyy	[ ] Missing		
C.2	Gestational age at booking	_____weeks	[ ] Missing		

D. MATERNAL HIV CARE HISTORY				
D.1	Date of first HIV antibody test	__ __/__ __ __/__ __ __ __ dd/ mmm/ yyyy		[ ] Missing
D.2	Use of ART prior to pregnancy?	[ ]Yes	[ ]No – go to D.4	[ ]Missing
D.2.1	If yes, regimen:			
	NRTI 1	[ ] D4T/ Stavudine [ ] 3TC/ Lamivudine [ ] AZT/ Zidovudine [ ] COM/AZT/3TC [ ] DDI/Didanosine	[ ] ABC/ Abacavir [ ] TDF/ Tenofovir [ ] FTC/ Emtricitabine [ ] Truvada/ TDF/ FTC	
	NRTI 2	[ ] D4T/ Stavudine [ ] 3TC/ Lamivudine [ ] AZT/ Zidovudine [ ] COM/AZT/3TC [ ] DDI/Didanosine	[ ] ABC/ Abacavir [ ] TDF/ Tenofovir [ ] FTC/ Emtricitabine [ ] Truvada/ TDF/ FTC	
	NNRTI	[ ] EFV/ Efavirenz	[ ] NVP/ Nevirapine	
	PI 1	[ ] Kaletra [ ] Indinavir	[ ] Saquinivir [ ] Ritonivir	
	PI 2	[ ] Kaletra [ ] Indinavir	[ ] Saquinivir [ ] Ritonivir	
D.2.2	Date regimen above started/stopped	Date started __ __/__ __ __/__ __ __ __ dd/ mmm/ yyyy	Date stopped __ __/__ __ __/__ __ __ __ dd/ mmm/ yyyy [ ] Still using regimen	
D.3	Fell pregnant on Efavirenz	[ ]Yes [ ]Missing		
D.4	Date of starting maternal ART regimen	__ __/__ __ __/__ __ __ __ dd/ mmm/ yyyy		[ ] Missing
D.5	Maternal antiretroviral regimen	[ ] HAART for life [ ] AZT monotherapy from 28 wks + SD-NVP at birth + 3TC/AZT tail [ ] AZT/3TC from 28 wks + EFV + 3TC/AZT tail		[ ] NVP only Comment:_____ [ ] Missing
D.6	Gestational age at ART initiation	__ __ weeks	[ ] Already on ART at time of pregnancy	[ ] Missing
D.7	WHO Stage at PMTCT Enrolment	[ ] Stage I [ ] Stage II	[ ] Stage III [ ] Stage IV	[ ] Missing

E. ANTENATAL MEDICAL HISTORY				
E.1	Baseline weight	__ __ kg	[ ] Missing	
E.2	Baseline height	__ __m	[ ] Missing	
E.3.1	Any illnesses during pregnancy	[ ]Yes	[ ] No	[ ] Missing
E.3.1a	If yes, give details [illness1]	_____ _____		Date of 1st diagnosis in pregnancy __ __/__ __ __/__ __ __ __ dd/ mmm/ yyyy
E.3.1b	If yes, give details [illness2]	_____ _____		Date of 1st diagnosis in pregnancy __ __/__ __ __/__ __ __ __ dd/ mmm/ yyyy
E.3.1c	If yes, give details [illness3]	_____ _____		Date of 1st diagnosis in pregnancy __ __/__ __ __/__ __ __ __ dd/ mmm/ yyyy
E.4	Smoking during pregnancy	[ ]Yes	[ ] No	[ ] Missing
E.5	Any alcohol use during pregnancy	[ ]Yes	[ ] No	[ ] Missing
E.6	Any illicit drug use	[ ] Yes	[ ] No	[ ]Missing

F. OPPORTUNISTIC INFECTIONS [MATERNAL]				
F.1.1	Any WHO stage IV condition	[ ] Yes	[ ] No	[ ] Missing
F.1.2	If yes, specify condition	_____		Date of 1st diagnosis in pregnancy __ __/__ __ __/__ __ __ __ dd/ mmm/ yyyy

x

G.LABORATORY				
G.1	CD4 count at screening for PMTCT	cells/mm^3	__ __/__ __ __/__ __ __ __ dd/ mmm/ yyyy	[ ] Missing
G.2.1	Viral load at screening for PMTCT	__ ,__ __ __,__ __ __ Copies/ml	__ __/__ __ __/__ __ __ __ dd/ mmm/ yyyy	[ ] Missing

G.2.2	36 week viral load	__ ,__ __ __,__ __ __ Copies/ml	__ __/__ __ __/__ __ __ __ dd/ mmm/ yyyy	[ ] Missing

H.PREGNANCY HISTORY				
H.1	Parity	Para _____		[ ] Missing
H.2	Gravidity	Gravida _____		[ ] Missing
H.3	Preterm labour	[ ]Yes	[ ] No	[ ] Missing
H.4	Obstetric sepsis	[ ]Yes	[ ] No	[ ] Missing
H.5	Mode of delivery	[ ] NVD [ ] Booked C/S (obstetric) [ ] Booked C/S (PMTCT)		[ ] Emergency C/S [ ] Instrument delivery [ ] Missing
H.6	No of infants delivered [ ] Single [ ] Multiple	If multiple pregnancy, Specify_____		

I.MATERNAL MORTALITY Note maternal mortality refers to mothers who die at time of delivery or after first postnatal visit			
I.1	[ ] Not applicable		
I.2	Date of death	__ __/__ __ __/__ __ __ __ dd/ mmm/ yyyy	[ ] Missing
I.3	Cause of death	_____	[ ] Missing

J. INFANT INFORMATION					
J.1	Date of birth		__ __/__ __ __/__ __ __ __ dd/ mmm/ yyyy		[ ] Missing
J.2	Sex of infant		[ ] Male	[ ] Female	[ ] Missing
J.3	Immunisation				Date
J.3.1	Birth	[ ] BCG	[ ] OPV		__ __/__ __ __/__ __ __ __ dd/ mmm/ yyyy
J.3.2	6 week	[ ] DPT+HIB	[ ] OPV	[ ] HEP B	__ __/__ __ __/__ __ __ __ dd/ mmm/ yyyy

J.3.3	10 week	[ ] DPT+HIB	[ ] OPV	[ ] HEP B	__ __/__ __ __/__ __ __ __ dd/ mmm/ yyyy
J.3.4	14 week	[ ] DPT+HIB	[ ] OPV	[ ] HEP B	__ __/__ __ __/__ __ __ __ dd/ mmm/ yyyy
J.3.5	9 month	[ ] MEASLES			__ __/__ __ __/__ __ __ __ dd/ mmm/ yyyy
J.3.6	18 month	[ ] MEASLES	[ ] OPV	[ ] DPT	__ __/__ __ __/__ __ __ __ dd/ mmm/ yyyy
J.4	ARV prophylaxis at birth	[ ]None [ ]NVP only [ ] NVP and AZT	[ ] Other _____ [ ] Missing		
J.5	HIV TEST (complete for all tests documented)				

	Date	Result			Diagnostic Method		
J.5.1	__ __/__ __ __/__ __ __ __ dd/ mmm/ yyyy	Positive [ ]	Negative [ ]	Indeterminate [ ]	DNA PCR [ ]	DBS [ ]	Missing [ ]
J.5.2	__ __/__ __ __/__ __ __ __ dd/ mmm/ yyyy	Positive [ ]	Negative [ ]	Indeterminate [ ]	DNA PCR [ ]	DBS [ ]	Missing [ ]
J.5.3	__ __/__ __ __/__ __ __ __ dd/ mmm/ yyyy	Positive [ ]	Negative [ ]	Indeterminate [ ]	DNA PCR [ ]	DBS [ ]	Missing [ ]
J.5.4	__ __/__ __ __/__ __ __ __ dd/ mmm/ yyyy	Positive [ ]	Negative [ ]	Indeterminate [ ]	DNA PCR [ ]	DBS [ ]	Missing [ ]

K. INFANT FEEDING PRACTICE			
Visit No	K.1 Date Assessed	K.2 Feeding Method	
1	__/__ __/__ __ __ __ dd/ mmm/ yyyy	[ ] Breastfeeding [ ] Formula feeding	If breastfeeding, exclusive breastfeeding Yes [ ] No [ ] If formula feeding, exclusive formula feeding Yes [ ] No [ ]
2	__/__ __/__ __ __ __ dd/ mmm/ yyyy	Change in practice since last visit? [ ] Yes [ ] No	If yes, specify [ ] Mixed feeding [ ] Formula + solids [ ] Solids only [ ] Other [ ] Missing
3	__/__ __/__ __ __ __ dd/ mmm/ yyyy	Change in practice since last visit? [ ] Yes [ ] No	If yes, specify [ ] Mixed feeding [ ] Formula + solids [ ] Solids only [ ] Other [ ] Missing
4	__/__ __/__ __ __ __ dd/ mmm/ yyyy	Change in practice since last visit? [ ] Yes [ ] No	If yes, specify [ ] Mixed feeding [ ] Formula + solids [ ] Solids only [ ] Other [ ] Missing
5	__/__ __/__ __ __ __ dd/ mmm/ yyyy	Change in practice since last visit? [ ] Yes [ ] No	If yes, specify [ ] Mixed feeding [ ] Formula + solids [ ] Solids only [ ] Other [ ] Missing
6	__/__ __/__ __ __ __ dd/ mmm/ yyyy	Change in practice since last visit? [ ] Yes [ ] No	If yes, specify [ ] Mixed feeding [ ] Formula + solids [ ] Solids only [ ] Other [ ] Missing

L. GROWTH				
Visit No	L.1 Date	L.2 Weight	L.3 Length	L.4 Head circumference
1	__/__ __/__ __ __ __ dd/ mmm/ yyyy	___ g Missing [ ]	__ cm Missing [ ]	__ cm Missing [ ]
2	__/__ __/__ __ __ __ dd/ mmm/ yyyy	___ g Missing [ ]	__ cm Missing [ ]	__ cm Missing [ ]
3	__/__ __/__ __ __ __ dd/ mmm/ yyyy	___ g Missing [ ]	__ cm Missing [ ]	__ cm Missing [ ]
4	__/__ __/__ __ __ __ dd/ mmm/ yyyy	___ g Missing [ ]	__ cm Missing [ ]	__ cm Missing [ ]
5	__/__ __/__ __ __ __ dd/ mmm/ yyyy	___ g Missing [ ]	__ cm Missing [ ]	__ cm Missing [ ]
6	__/__ __/__ __ __ __ dd/ mmm/ yyyy	___ g Missing [ ]	__ cm Missing [ ]	__ cm Missing [ ]
7	__/__ __/__ __ __ __ dd/ mmm/ yyyy	___ g Missing [ ]	__ cm Missing [ ]	__ cm Missing [ ]
8	__/__ __/__ __ __ __ dd/ mmm/ yyyy	___ g Missing [ ]	__ cm Missing [ ]	__ cm Missing [ ]
9	__/__ __/__ __ __ __ dd/ mmm/ yyyy	___ g Missing [ ]	__ cm Missing [ ]	__ cm Missing [ ]

M. MEDICAL HISTORY							
No	Event	1 Date	2 Date	3 Date	4 Date	5 Date	6 Date
M.1	Bactrim prophylaxis	__/___/____ dd/mmm/yyyy	__/___/____ dd/mmm/yyyy	__/___/____ dd/mmm/yyyy	__/___/____ dd/mmm/yyyy	__/___/____ dd/mmm/yyyy	__/___/____ dd/mmm/yyyy
M.2	Acute gastroenteritis	__/___/____ dd/mmm/yyyy	__/___/____ dd/mmm/yyyy	__/___/____ dd/mmm/yyyy	__/___/____ dd/mmm/yyyy	__/___/____ dd/mmm/yyyy	__/___/____ dd/mmm/yyyy
M.3	Upper respiratory tract infection	__/___/____ dd/mmm/yyyy	__/___/____ dd/mmm/yyyy	__/___/____ dd/mmm/yyyy	__/___/____ dd/mmm/yyyy	__/___/____ dd/mmm/yyyy	__/___/____ dd/mmm/yyyy
M.4	Lower respiratory tract infection	__/___/____ dd/mmm/yyyy	__/___/____ dd/mmm/yyyy	__/___/____ dd/mmm/yyyy	__/___/____ dd/mmm/yyyy	__/___/____ dd/mmm/yyyy	__/___/____ dd/mmm/yyyy
M.5	Chronic otitis media	__/___/____ dd/mmm/yyyy	__/___/____ dd/mmm/yyyy	__/___/____ dd/mmm/yyyy	__/___/____ dd/mmm/yyyy	__/___/____ dd/mmm/yyyy	__/___/____ dd/mmm/yyyy
M.6	Tuberculosis	Type [ ] Pulmonary [ ] Extrapulmonary		Date started __/___/____ dd/mm/yyyy		Date stopped __/___/____ dd/mm/yyyy	
M.7	Skin problem	__/___/____ dd/mmm/yyyy	__/___/____ dd/mmm/yyyy	__/___/____ dd/mmm/yyyy	__/___/____ dd/mmm/yyyy	__/___/____ dd/mmm/yyyy	__/___/____ dd/mmm/yyyy
M.8	Hospital admission	__/___/____ dd/mmm/yyyy	__/___/____ dd/mmm/yyyy	__/___/____ dd/mmm/yyyy	__/___/____ dd/mmm/yyyy	__/___/____ dd/mmm/yyyy	__/___/____ dd/mmm/yyyy

N. HIV-INFECTED INFANTS				
N.1	[ ] Not applicable			
N.2	ARV Regimen if HIV positive	[ ] D4T/3TC/Kaletra	[ ] ZDV/ ddI/Stocrin	
		[ ] D4T/3TC/Stocrin	[ ] Missing	
		[ ] ZDV/ddI/Kaletra		
N.2.1	Date when ARV regimen initiated	__/___/____ dd/mmm/yyyy	[ ] Missing	
N.3	WHO Stage at time of ART initiation	[ ] Stage I	[ ] Unknown status	
		[ ] Stage II		
		[ ] Stage III		
		[ ] Stage IV		
		[ ] Missing		
N.4	CD4% *(complete for all available from 1st test date)*			
N.4.1	CD4 % date	__/___/____ dd/mmm/yyyy	CD4 %	__ __%
N.4.2	CD4 % date	__/___/____ dd/mmm/yyyy	CD4 %	__ __%
N.4.3	CD4 % date	__/___/____ dd/mmm/yyyy	CD4 %	__ __%
N.4.4	CD4 % date	__/___/____ dd/mmm/yyyy	CD4 %	__ __%
N.5	Viral Load *(complete for all available from 1st test date)*			
N.5.1	Viral load date	__/___/____ dd/mmm/yyyy	Viral load	__,__ __ __, __ __ __copies
N.5.2	Viral load date	__/___/____ dd/mmm/yyyy	Viral load	__,__ __ __, __ __ __copies
N.5.3	Viral load date	__/___/____ dd/mmm/yyyy	Viral load	__,__ __ __, __ __ __copies
N.5.4	Viral load date	__/___/____ dd/mmm/yyyy	Viral load	__,__ __ __, __ __ __copies

O. Opportunistic Infections					
No	Event	1 Date	2. Date	3 Date	4 Date
O.1	Cryptococcal meningitis	__/___/____ dd/mmm/yyyy	__/___/____ dd/mmm/yyyy	__/___/____ dd/mmm/yyyy	__/___/____ dd/mmm/yyyy
O.2	Chronic gastroeneteritis	__/___/____ dd/mmm/yyyy	__/___/____ dd/mmm/yyyy	__/___/____ dd/mmm/yyyy	__/___/____ dd/mmm/yyyy
O.3	*Pneumocystis jiroveci pneumoniae*	__/___/____ dd/mmm/yyyy	__/___/____ dd/mmm/yyyy	__/___/____ dd/mmm/yyyy	__/___/____ dd/mmm/yyyy
O.4	IRIS TB	__/___/____ dd/mmm/yyyy	__/___/____ dd/mmm/yyyy	__/___/____ dd/mmm/yyyy	__/___/____ dd/mmm/yyyy

P. LOSS TO FOLLOW UP OF INFANT		
P.1	Date of expected visit	__/___/____ dd/mmm/yyyy
P.2	Date of last visit	__/___/____ dd/mmm/yyyy
P.3	Reason for loss to follow up	1. [ ] Mother working 2. [ ] Baby living with someone else 4. [ ] No transport 5. [ ] Attending a clinic closer to home 6. [ ] Baby ill 7. [ ] Baby has died 7. [ ] Dissatisfaction with level of care 8. [ ] Other *Specify*_____ 9. [ ] Missing

	Q. INFANT MORTALITY		
Q.1	[ ] Not applicable		
Q.2	Date of death	__/___/____ dd/mmm/yyyy	[ ] Missing
Q.3	Cause of death	_____	[ ] Missing

END