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Factors associated with HIV infection in 6-8 week old infants in Swaziland

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FACTORS ASSOCIATED WITH HIV INFECTION IN 6-8 WEEK OLD INFANTS IN SWAZILAND.

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand,

In partial fulfilment of the requirements for the degree of MSc (Med) in the field of Child Health (Community Paediatrics)

March 2019

DECLARATION

I, Linda Mirira, declare the Research Report as being is my own unaided work. The work is being submitted for the Degree Master of Science in Medicine, Child Health (Community Paediatrics) at the University of the Witwatersrand. This is my original work except where I have mentioned otherwise and it has not been presented before for any examination or degree at any other University.



Signature

Signed on 6*TH MARCH, 2019*

DEDICATION

First and foremost, this excellent piece of work is entirely dedicated to my biological parents; Naison and Sarah who sacrificed all their resources from my infancy till today for me to realise this achievement.

To my husband, Munamato, my mentor, soulmate, role model and best friend, who stood by me through thick and thin to see this development to its end.

To my beloved children; Tawananyasha, Tanyaradzwa and Taropafadzwa who endured the pain of sharing their mother with her studies.

Last but not least, my siblings and in-laws who understood the vital role of education in a woman's emotional being and upkeep.

ABSTRACT

Background: Mother-to-child transmission of the Human Immunodeficiency Virus (HIV) is a major cause for increased child morbidity and mortality in sub-Saharan Africa. Prevention of Mother to Child Transmission (PMTCT) programmes have been linked with significant reductions in vertical HIV transmissions resulting in low morbidity and mortality proportions in infants. However, a number of barriers continue to pose significant programme challenges that hinder the eradication of mother-to-child transmission of HIV. Literature on factors which are associated with HIV PCR positivity in infants aged 6-8 weeks in Swaziland is limited. It is against this background that we undertook the study to determine the factors associated with Polymerase Chain Reaction (PCR) positivity in HIV exposed infants at 6-8 weeks in Swaziland.

Study Aim: To determine factors associated with PCR positivity in HIV exposed infants aged 6-8 weeks who were attending child welfare clinics in Swaziland.

Methodology: The study utilised secondary data analysis collected on mother-infant pairs during the period of 2011 and 2012 to assess the efficiency of the PMTCT programme in Swaziland by the Health Management Information System department under the Ministry of Health. Study sample consisted of 1699 HIV infected mothers and their 6-8 week old infants. The study outcome was HIV PCR positivity at 6-8 weeks of age. Factors associated with PCR positivity among infants who were exposed to HIV were determined using univariate and multivariable logistic regression methods.

Results: Of the 1699 exposed infants, only 1415 were evaluated since 284 had missing data on the PCR outcome. The results revealed that 31infants were HIV PCR positive at 6-8 weeks, reflecting a mother-to-child transmission rate of 2.2%. Maternal age, number of antenatal care visits, maternal antiretroviral regimen, place of delivery and birth weight were significantly associated with HIV PCR positivity at 6-8 weeks in the univariate model. However, number of antenatal care visits remained significantly associated with HIV PCR positivity in the multivariable regression model, after controlling for other factors. In particular, infants of mothers who had attended more than four visits were less likely to be PCR positive at 6-8 weeks as compared to infants whose mothers had less than four visits (OR = 0.83; 95% CI: 0.02, 0.44; p-value = 0.004).

Conclusion: Increased number of antenatal care visits attended by pregnant women is beneficial because it increases access to PMTCT services thereby decreasing the prospects of mother-to-child HIV transmission. Existing public health programmes that target the eradication of mother-to-child HIV transmission should improve access and strengthen antenatal care services so as to eliminate PCR positivity in infants exposed to HIV at 6-8weeks.

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NOMENCLATURE

ANC	Antenatal Care
ARV	Antiretroviral
ART	Antiretroviral Therapy
AZT	Zidovudine
BCG	Bacillus Calmette-Guirin
CD4	Cluster of Differentiation 4
CI	Confidence Interval
CSO	Central Statistics Office
DNA	Deoxyribonucleic Acid
ELISA	Enzyme Linked Immunosorbent Assay
HAART	Highly Active Antiretroviral Therapy
HIV	Human Immunodeficiency Virus
HMIS	Health Information Management System
NVP	Nevirapine
OR	Odds Ratio
PCR	Polymerase Chain Reaction test
PMTCT	Prevention of mother-to-child transmission
RNA	Ribonucleic Acid
WHO	World Health Organization

DEFINITION OF TERMS

HIV PCR Test: A virologic test which is used to detect HIV's genetic material called ribonucleic acid (RNA) in the blood to determine HIV infection and it has been seen to be more accurate in infants compared to the enzyme linked immunosorbent assay test (ELISA) which specifically identifies HIV antibodies (1). The ELISA test assesses the presence of HIV antibodies in the blood and can be used in infants above eighteen months since all exposed infants are likely to have the HIV antibodies passed from their HIV positive mothers and these would have disappeared by the age of eighteen months (1).

Infant: A child from birth to 12 months but for the purpose of this study, an infant is a baby aged 6-8 weeks.

HIV-exposed infant: An infant delivered by an HIV positive woman

PCR Positivity: Is an HIV DNA test which was positive upon testing at 6-8 weeks indicating that the infant is infected with HIV.

CHAPTER 1

1. INTRODUCTION

This chapter begins by providing an introduction and background to the study on factors associated with HIV PCR seropositivity in infants at 6-8 weeks in Swaziland. Thereafter, a brief summary of the Swaziland PMTCT programme is provided. A discussion on published literature on the factors associated with HIV seropositivity in infants is outlined. The chapter ends with a description of the aims and objectives of the study.

1.1. Background

Human Immunodeficiency Virus (HIV) is a key issue in public health which pose detrimental effects (2). One of the major related effects include mother-to-child HIV transmission to unborn infants which happens during pregnancy, delivery or can occur during breastfeeding (2). Prevention of mother-to-child transmission (PMTCT) of HIV has been a great intervention in the decline of mother-to-child HIV transmission (2). PCR testing is an effective test which is used to detect the HIV's genetic material in the blood to determine its presence and this test is more accurate to be used in HIV exposed infants who have the antibodies of HIV from their HIV positive mothers (1). PCR positivity is allied with increased morbidity and mortality in infants (2). Several factors which cause PCR positivity in infants have been identified in several studies and these include mixed feeding, not seeking antenatal care services, non-use of antiretroviral prophylaxis and non-adherence (3). Africa is affected the most by HIV with sub-Saharan Africa being greatly affected (4). Swaziland is one of those countries with a highest prevalence in HIV and is bearing the effects of mother-to-child HIV transmission resulting in PCR positivity in exposed infants (4).

Globally, mother-to-child HIV transmission remains one of the biggest challenges, with sub-Saharan Africa being greatly affected (3,5-8). The devastating effects of mother-to-child HIV transmission can be prevented if pregnant women and mothers have better access to health care services and are retained in care (7,9-11). Several studies have demonstrated that the risk of mother-to-child HIV transmission is lowest in women who are initiated on full highly active antiretroviral therapy (HAART) throughout pregnancy when compared to women who only take nevirapine as a single dose or the dual combination of zidovudine and nevirapine during the same period (3,7,11-14).

Swaziland is a small country which is landlocked, with an estimated population of 1.1 million people and has one of the highest HIV prevalence rates in the world (4,15). HIV prevalence rate among pregnant women in Swaziland is reported at 42% with a HIV PCR positive rate of 2.4% in exposed infants (16,17). The high HIV prevalence rate burdens the inadequate budget allocation and acquisition of critical resources for the management of programmes aimed at reducing HIV PCR positivity in infants (18). Regrettably, most of these programmes are set to achieve the national targets for HIV transmission rates in infants as an outcome of mother-to-child transmission (18). Swaziland had a set national target of 1% transmission rate by the year 2018 with zero percent targets in the near future (19). It has therefore become critical for public health practitioners and programme managers to have an improved understanding of the factors associated with infant HIV transmission as this helps in developing and implementing appropriate policies to alleviate the effects of mother-to-child transmission (18). There have been gradual changes in the prevention of mother-to-child HIV transmission since the introduction of single dose antiretroviral therapy to more comprehensive triple therapy regimen for the improvement of care of exposed children so as to lessen vertical transmission of HIV in Swaziland as recommended by the World Health Organization (WHO) (18).

Swaziland started with giving nevirapine as a single dose to mothers who were in labour and also to infants upon delivery in 2003 (18). This regimen was then changed in 2007 when more sites for PMTCT were identified and this led to introduction of zidovudine in pregnant women from 28 weeks gestation until delivery, with nevirapine as a single dose and lamivudine to provide triple therapy during labour plus an additional week of zidovudine and lamivudine to complete the prophylaxis period (18). During that period, infant prophylactic treatment for HIV exposed infants consisted of nevirapine syrup which was given as a single dose and zidovudine syrup which was given for a duration of a week after delivery (18). A profile of these advancement as from 2003 to date are summarised in table 1.1.

Table 1.1: Different PMTCT Regimens in Swaziland.

Period	Maternal	Infant
2003	Single dose NVP during labour	Single dose NVP at birth
2007	AZT *(from 28 weeks gestation)* + NVP + 3TC + AZT *(during labour)* + 3TC + AZT *(for 7days)*	Single dose NVP + AZT *(for 7 days)*
2010	Option 1: AZT *(from 14 weeks)* + NVP +3TC + AZT *(during labour)* + AZT + 3TC *(7 days)* Option 2: AZT + 3TC + NVP *(CD4 Count > 350 cells/mm^3)*	Option 1: NVP *(breastfeeding infant from birth to 1 week post-breastfeeding)* Option 2: AZT/NVP *(exclusive replacement feeding from birth to 4-6 weeks)*
2014	Option B$^+$ TDF +3TC + 3EFV ZT *(from 14 weeks gestation if (CD4 Count > 350 cells/mm^3)*	AZT/ NPV *(for 4 – 6 weeks irrespective of feeding method)*
2018	Test and Start Option B$^+$ TDF +3TC +DTG	AZT/ NPV *(for 6 weeks if not breastfeeding) AZT/NVP(FOR 6weeks if breastfeeding) + NVP (from 6 -14weeks)*

A number of studies from different countries like Malawi, Nigeria, Uganda, South Africa and Ethiopia examined associations between socio-demographic and clinical factors and the possibility of mother-to-child HIV transmission (6,9,10,12,13,20). However, information on factors connected with mother-to-child HIV transmission in Swaziland is poorly understood. It is against this background that the study sought to understand the factors that put mothers at risk of passing on the HIV infection to their infants. There is limited scientific evidence available on the determinants of PCR positivity among exposed infants in Swaziland. This study provided an opportunity to explore the possible factors that determine PCR positivity at 6-8 weeks. The outcomes of this study will be used to improve programming in an effort to reduce

mother-to-child HIV transmission and its related morbidity and mortality among infants and children in Swaziland.

In Swaziland, the PMTCT programme was introduced in 2003 and it started in only three pilot sites through the support of UNICEF and these sites were Siteki Public Health Unit, King Sobhuza II Clinic and Hlathikhulu Public Health Unit (17,18). This formed the basis for the expansion of the programme to cover an astounding 150 sites by the year 2010 (18). PMTCT started with the integration of HIV testing services with antenatal care services and nevirapine (NVP) was given as a single dose to mothers who were HIV positive as a prophylaxis to inhibit mother-to-child transmission (18). In 2007, the prophylaxis was modified to giving zidovudine (AZT) to HIV pregnant women from 28 weeks gestation, during labour, triple therapy doses would be given and these included, zidovudine, lamivudine and nevirapine with a continuation of zidovudine and lamivudine for a week during postnatal period to complete prophylaxis period as recommended by the WHO (18). Early infant diagnosis of HIV for infants at 6-8 weeks was established fully in Swaziland in 2009 and it was integrated with child welfare clinics who offer growth monitoring and immunisations to children below the age of 5 years and this has led to early identification of PCR positive infants leading to linkages for care and treatment thereby reducing infant morbidity and mortality (18,19).

1.2. Factors associated with PCR positivity

Factors associated with PCR positivity include late ANC presentation, low opportunistic infection screening, high viral load, mode of delivery, prematurity, mixed feeding, breast feeding, complimentary feeding, no prophylaxis or not taking ART amongst others (3,5,6,9,20). These factors have been categorised into maternal, viral, obstetrical, foetal, infant, treatment and programme as shown in Table 1.2.

It is estimated that approximately 35% of infants born to mothers who are HIV positive will acquire HIV infection in the absence of any intervention (10,21,22). The prevention of mother-to-child HIV transmission is previously applauded as one of the greatest successful HIV prevention measures to date (11,22,23). Nonetheless, regardless of some gains in the prevention of mother-to-child HIV transmission in sub-Saharan Africa, mother-to-child transmission rates are still significantly elevated (3,21). Studies from different parts of the world have demonstrated an association between infant HIV PCR positive status and certain clinical and socio-demographic factors, such as mixed feeding, not using prophylactic antiretroviral treatment and not attending antenatal care services (20,24-27).

In Kenya, scaling up PMTCT services is crucial to the elimination of mother-to-child HIV transmission, which is considered as one of its greatest health challenges and this also applies to Swaziland which has a high burden of HIV and is also aiming to eliminate HIV which is transmitted from the mother to the child during pregnancy or delivery (27). In a number of sub-Saharan countries, challenges faced are related to implementation of PMTCT guidelines, which presents significant barriers and bottlenecks to achieve optimal access, uptake of services and retention into care for HIV positive pregnant women (27). In an effort to lessen vertical transmission of HIV, a number of national programmes in Southern Africa have been revising their PMTCT guidelines on a regular basis in an effort to ensure that PMTCT services are equitably provided to both high and low income settings (6,27). However, timely implementation of guidelines in low income sites continues to be challenged as mothers present late to the health facilities during pregnancy, attend less than four ANC visits, have low opportunistic infections screening rates, and there is inadequate contraception counselling for the mothers (25,27). In addition, these challenges are more complicated by poor disclosure to partners leading to poor or non-adherence to treatment (3,27). Implementation of PMTCT services and its effective scale up requires that such programme challenges be acknowledged and they should be addressed appropriately within the local context (27).

Preventing mother-to-child HIV transmission has been a fundamental advancement in response to the HIV pandemic for the past decade (11,22). According to a Cameroonian study, HIV-exposed infants have greater morbidity as well as mortality rates when compared to infants not exposed to HIV (21,24). The causal mechanism of this variance is principally unknown. In the same study, prematurity, non-ART use, and mixed infant feed were predictors of mortality in infants (24). The same study demonstrated that even though mortality rates were considerably greater in the rural areas, the rural site itself was not found to be a possible factor for the infant mortality (24). A retrospective cohort study undertaken in Ethiopia demonstrated that mothers who were not frequently attending ANC visits; those practicing mixed feeding and those with WHO stage III and IV HIV disease were associated with infant HIV PCR positive results (20).

Several studies have demonstrated that infant antiretroviral prophylaxis also protects infants from acquiring HIV infection (3,5,7). Breastfeeding has been connected with an increased possibility of perinatal transmission (3,7,28). Triple antiretroviral treatment given throughout pregnancy has been linked with reduced risk of infant HIV transmission (3,20,24-26). Studies have also demonstrated that commencing full antiretroviral therapy before conception significantly protected infants from acquiring HIV (25).

Home deliveries have also been associated with higher perinatal transmission rates when compared to facility deliveries while caesarean section deliveries are associated with a low risk of HIV transmission (3,25). This finding is likely to be due to the fact that untrained birth attendants are likely to practice unsafe procedures at home, thereby placing infants at a greater possibility of acquiring HIV infection during the perinatal period (3,29).

A significant number of maternal elements have been recognised as risk factors perpetuating mother-to-child HIV transmission. Some of the identified maternal factors include: presenting late in the facilities when pregnant, fewer than four antenatal visits, limited contraception counselling, lower rates of screening for opportunistic infections, WHO stage III, WHO stage IV and a high viral load (20,26,27). Non-disclosure and lack of male involvement were also identified as factors that increased the risk of HIV transmission from the mother to the child (27). This is likely due to the fact that non-disclosure and lack of male involvement compromise condom use and other HIV preventive methods thereby exposing women to HIV infection.

Mixed or complimentary feeding was also found to be linked with an increased risk of HIV transmission from the mother to the child (7,20,24). The most plausible explanation for this connection is likely due to the amplified risk of infection, which happens when practicing mixed feeding. HIV exposed infants were observed to have higher morbidity and mortality if they were premature or received mixed feeding compared to the HIV non-exposed infants (20,24,28).

While a significant number of studies from different parts of the world have demonstrated links between a number of factors related to antenatal care attendance, staging of HIV disease, feeding practices, among others, there is limited evidence regarding such associations in the Swaziland context (3,20,24-27).

Table 1.2: Summary of factors associated with PCR positivity

Factor	Description
Viral	Viral resistance (10) and viral load (6,9)
Maternal	Maternal immunological status (6), maternal socio-economic status (6), maternal clinical status (6,20,30), behavioural factors (3,26)
Obstetrical	Mode of delivery (6), Home deliveries/unskilled births attendance (5,6,24)
Foetal	Prematurity (24)
Infant	Breast feeding (20,26), Infant prophylaxis (9), mixed feeding (5,9,20,24), complimentary feeding (20)
Treatment	No prophylaxis (20), No ANC attendance (20), No antiretroviral treatment (5,9,20,24), Limited contraception counselling and provision(30)
Programme	Challenges related to implementation of PMTCT (6,12,26), Lack of male involvement (6,30)

1.3. Study Aim and objectives

1.3.1. Aim

The aim of the study is to determine the factors associated with PCR positivity in HIV exposed infants aged 6-8 weeks in Swaziland.

1.3.2. Specific Objectives

1.3.2.1 To describe the characteristics of HIV positive mothers and their HIV exposed infants aged 6-8 weeks at different primary health care facilities in Swaziland.

1.3.2.2 To determine the incidence of PCR positivity among infants exposed to HIV seen at 6-8 weeks of age at primary health facilities in Swaziland.

1.3.2.3 To investigate the factors associated with HIV PCR positivity among HIV-exposed infants at 6-8 weeks of age.

CHAPTER 2

2. METHODOLOGY

This chapter outlines the study design and methods used in the study. The study population and selection of participants, as well as data collection and management are described. The chapter concludes with an outline of the data analysis and ethical considerations.

2.1. Study design

The study is based on a cross-sectional study design. This is a secondary data analysis, for a study which was conducted to assess the effectiveness of the national prevention of mother-to-child transmission of HIV programme at 6-8 weeks post-partum in the four regions of Swaziland during 2011-2012 period**.** Mother-infant pairs were chosen from a stratified random sample of child welfare clinics as these were convenient points of access to assess exposure and PCR status for effects of mother-to-child HIV transmission for the population. Fifty child welfare clinics were sampled for the study with 15 clinics from Hhohho region, 14 clinics from Manzini region, 11 clinics from Shiselweni region and 10 clinics from Lubombo region. In the 50 selected sites, 34 were in rural areas while 16 were in urban areas and these were a nationally representative sample. A representative sample of 3 592 mother-infant pairs who were either HIV positive or HIV negative were selected for the primary study to evaluate the effectiveness of the PMTCT programme.

2.2. Data Source

This study utilised data from the Swaziland Health Management Information System (HMIS) under the Ministry of Health for their study to evaluate the effectiveness of the national PMTCT programme in Swaziland.

2.3. Study Site

The study was a secondary data analysis which was conducted using secondary data which was collected by the Swaziland HMIS at different health facilities in the four regions which are Hhohho, Manzini, Shiselweni and Lubombo, for the Ministry of Health (Figure 2.1). The Swaziland Statistics Office (CSO) identified enumeration areas that ensured representativeness of different surveys that are undertaken in the country. The data used for this study was collected from child welfare clinics offering postnatal care services, immunisations, growth monitoring and these clinics had services for PCR testing which are routinely offered to HIV exposed

infants at 6-8 weeks in both rural and urban facilities. These child welfare clinics fall under these enumeration areas.

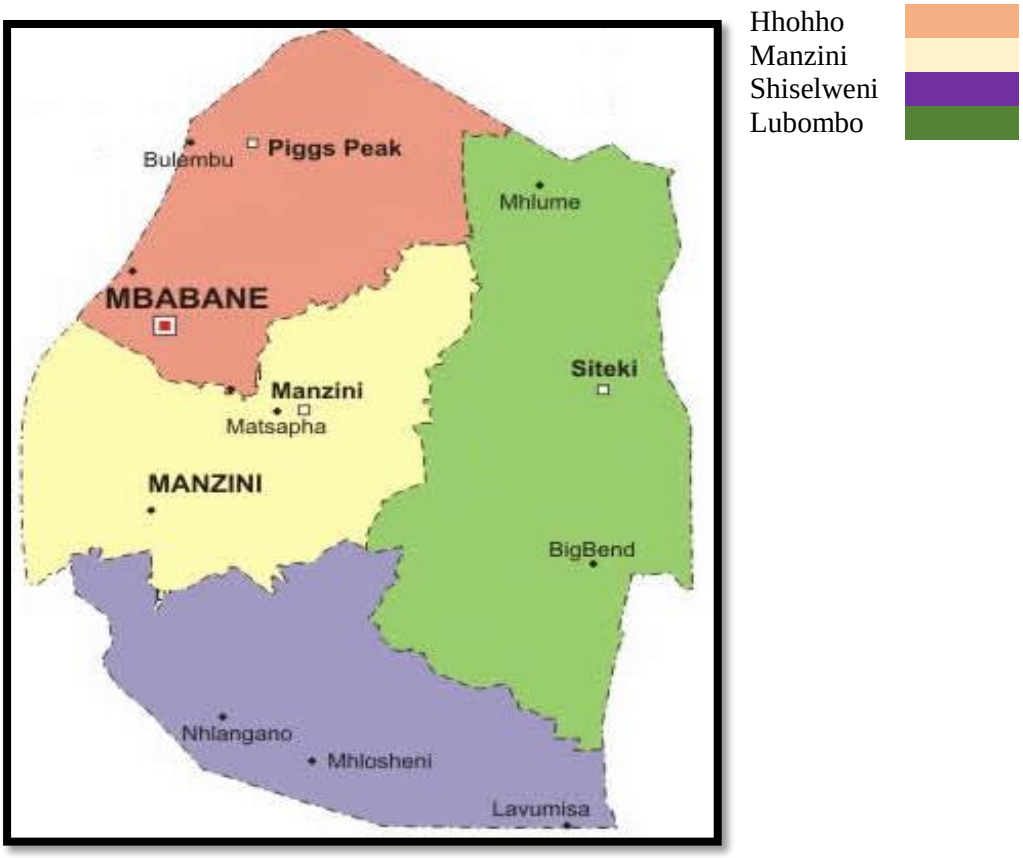


Figure 2.1: Map of Swaziland

Swaziland has four regions, Hhohho with Mbabane as the capital city of the country, Manzini region has the city of Manzini as the capital, while Shiselweni region has Nhlangano as the capital city and Lubombo region has Siteki as the capital city for the region. Hhohho had 15 sites selected and these were five urban facilities and 10 rural, Lubombo had a total of 10 facilities with three urban while seven were rural, Manzini had a total of 14 facilities with six being urban and eight rural facilities and Shiselweni region had a total of 11 facilities selected with two in urban areas and nine in rural areas.

2.4. Study population

The study population comprised of 3 592 women and their infants who were seen during the 6-8 weeks visit during the period of 2011 and 2012 when the primary study was conducted. The women included in the primary study were either HIV negative (1893) or HIV positive (1699).

For this current study, the study population comprised of 1699 women who were HIV positive and their infants who were exposed to HIV only.

2.5. Study Sample

No sampling was done in the secondary data analysis. All mothers who were HIV positive and their infants who were exposed to HIV (1699) were included in this current study since the study only considered possible factors associated with HIV PCR positivity in exposed infants at 6-8 weeks of age.

2.6. Inclusion and Exclusion Criteria

The current study is a secondary data analysis with the following inclusion and exclusion criteria since it considered the women who were HIV positive and their HIV exposed infants only.

Inclusion Criteria

i. HIV positive women seeking postnatal services for their infants aged 6-8 weeks at different sites in the four regions of Swaziland.
ii. HIV exposed infants seeking child health services at 6-8weeks.

Exclusion Criteria

i. All women who tested negative for HIV seeking postnatal care services in the four regions of Swaziland.
ii. HIV non-exposed infants seeking child health services at intervals other than the 6-8 weeks visit.

2.7. Study Variables

2.7.1. Outcome Variable

The outcome variable was infant HIV PCR positivity at 6-8 weeks. The possible outcomes of HIV PCR infant status at 6-8 weeks of age were either positive or negative, thereby making the outcome variable a binary categorical variable.

2.7.2. Exposure Variables

The exposure variables were categorical variables and grouped as shown in Table 2.1.

Table 2.1 Exposure Variables

SOCIO-DEMOGRAPHIC VARIABLES		
Exposure variables	**Variable definitions**	**Categorisation and assigned coding**
Age	Age refers to maternal age at enrolment into the study	15-24 years = 1 25-34 years = 2 >35 years = 3
Region	Region refers to which region the mother and infant reside	Hhohho = 1 Lubombo = 2 Manzini = 3 Shiselweni = 4
Marital Status	It is the maternal marital status upon enrolment into the study	Not married = 1 Married = 2 Cohabiting = 3
Educational level	Educational level is the maternal educational status on enrolment into study	≤ Primary (Grade 7 and less = 1 Secondary (Form 3 and less) = 2 ≥ High (Form 4 and above) = 3
Residential status	Residential status is whether the mother and infant reside in a rural or urban setting	Rural = 1 Urban = 2
Employment status	Employment status refers to whether the mother was employed or not upon enrolment into study	Yes = 1 No = 2
ANTENATAL CARE VARIABLES		
Gestation at 1st ANC	It refers to the gestational age when the mother attended her first ANC visit	≤ 3 months = 1 4-6 months = 2 ≥ 7 months = 3
Number of ANC visits	It refers to the antenatal care visits attended by the mother during the pregnancy	≤ 2 = 1 3-4 = 2 > 4 = 3

Syphilis status	Syphilis status refers to whether the mother had Syphilis or not	Positive = 1 Negative = 2
CD4 count	CD4 count is the maternal CD4 count level during pregnancy	≤ 200 = 1 201-350 = 2 > 350 = 3
Maternal ARV regimen	ARV regimen refers to the treatment given to the mother during the pregnancy for prophylaxis	AZT = 1 NVP = 2 Infant prophylaxis = 3 ART = 4
Duration on ART	Duration on ART refers to the period the mother has been taking ART medications	≤ 12 months =1 > 12 months =2
Duration on AZT	Duration on AZT refers to the duration the mother took the AZT prophylaxis during the pregnancy	≤2 months = 1 3-5 months = 2 ≥6 months = 3
INTRA-PARTUM VARIABLES		
ARV's taken in labour	It refers to which ARV's were taken during labour	AZT = 1 NVP = 2
Place of delivery	This refers to whether the mother delivered her infant at health facility or at home	Hospital/clinic = 1 Home = 2
Mode of delivery	Mode of delivery refers to whether the mother delivered her infant normally or was assisted	Normal Vaginal delivery = 1 Caesarean Section = 2
POSTNATAL/INFANT VARIABLES		
Gestation at birth	This refers to the gestational age of the pregnancy when the infant was delivered	Full term = 1 Premature = 2

Birth weight	This refers to the weight of the infant at birth	<2.5 kg = 1 ≥2.5 kg = 2
Child welfare card	This refers to whether the infant had a child welfare card on enrolment into the study	Yes = 1 No = 2
BCG immunisation	This refers to whether the child received the BCG immunisation at birth	Yes = 1 No = 2
Infant NVP at birth	This refers to whether the infant NVP prophylaxis was given at birth	Yes = 1 No = 2
Infant feeding method	Infant feeding method refers to whether the infant was breastfed or given other feeds as provided by the mother at 6-8 weeks visit.	Breast milk only = 1 Other feeds = 2
Child still taking NVP	This referred to whether the infant was still taking NVP prophylaxis on enrolment into the study	Yes = 1 No = 2
Duration of missed infant NVP	This refers to the duration the infant had not received the NVP from birth to enrolment into the study	≤2 weeks = 1 >2 weeks = 2
Additional infant medicine Gripe Water Umutsiwenyoni (Antacid)	This refers to whether the child had received any other additional infant medicine other than the NVP	 Yes = 1 No = 2 Yes = 1 No = 2

2.8. Data management

The dataset was collected from the Swaziland HMIS department as a full data set and only HIV positive mothers and their exposed infants were selected and verified by the statistician for the purpose of relevance to this secondary data analysis. The data were cleaned and recoded to generate new variables to allow for appropriate analysis to meet the study objectives. The outcome variable, PCR status was coded "0" if negative and "1" if positive. Age was categorised into the following categories, <25years, 25-34 years and >35years. The following variables were dropped from the analysis; time of diagnosis because it was not answering the question anticipated by the researcher on whether time of HIV positive diagnosis was before or during the pregnancy while the responses on ANC attendance, syphilis treatment, adherence and duration on missed AZT/ART showed that 100% of the participants had attended ANC, received syphilis treatment, were adherent and had not missed their AZT/ART indicating no statistical variation.

2.9. Data Analysis

The data were analysed using STATA 12.0 (StataCorp, College Station, Texas, USA) statistical software package. Most of the data were previously categorical, with another category created for age for better interpretation of results. Data were summarised using descriptive statistics to summarise the baseline characteristics which were divided into four categories which were socio-demographic, ANC, intrapartum and postnatal characteristics. The categorical variables were region, age, marital status, maternal education, syphilis status, marital status, employment status, residential status, gestational age of pregnancy at first ANC visit, number of ANC visits, CD4 cell count results, ARV regimen, duration on AZT, duration on ART, ARV's taken in labour, place of delivery, mode of delivery, gestational age at birth, birthweight, child welfare card, BCG immunisation, infant NVP, infant feeding method, NVP for the child, child still taking NVP and additional infant medicine and these were summarised using frequencies, percentages and tables. CD4 cell count results of the mothers, ARV regimen during pregnancy, duration of taking AZT during pregnancy, region of origin, mother-to-child transmission rate were presented as graphs and pie chart as appropriate. For inferential analysis, univariate and multivariable logistic regression methods determined associations between exposure variables and infant HIV PCR positivity at 6-8 weeks.

The outcome is categorical, therefore, logistic regression was utilised to determine associations between the independent variables (exposure variables) and the outcome variable (infant PCR HIV status at the age of 6-8 weeks). Firstly, univariate logistic regression was undertaken to

determine whether there was any association between each of the exposure variables and the infant HIV PCR status. The exposure variables that were associated with the outcome variable at 5% significance level in the univariate analysis were included in the multivariable logistic regression model. For an exposure variable to be incorporated in the final regression model, it had to have a p-value < 0.05 or there had to be a plausible biological relationship or theoretical link between that variable and HIV PCR status. The multivariable logistic regression associations were conveyed as adjusted odds ratios (OR) with corresponding 95% Confidence Intervals (CI).

2.10. Ethical considerations

The primary study, "Evaluation of the effectiveness of the national prevention of mother-to-child transmission of HIV (PMTCT) programme at 6-8weeks post-partum in Swaziland" was awarded ethical clearance in 2011 by the Scientific and Ethics Committee of Swaziland (Clearance certificate number MH/599C) (Appendix 1). An ethical clearance certificate was attained from the Scientific and Ethics Committee of Swaziland for the current study (Appendix 2). Before commencement of this secondary analysis, permission was sought and attained from the Human Research Ethics Committee (Medical) at the University of the Witwatersrand (Clearance No. M170803) (Appendix 3). A letter granting permission for the use of the data for analysis was obtained from the Swaziland HMIS department (Appendix 4). Names of the patients were replaced with unique identifiers to respect their privacy and confidentiality. All results are presented using de-identified aggregate data.

CHAPTER 3

3. RESULTS

This chapter outlines the results of the research study which are presented by first describing how the study sample was obtained. The baseline characteristics of the study participants, mother-to-child transmission rate and the factors associated with PCR positivity are presented. Factors associated with HIV infection in 6-8 week old infants in Swaziland are investigated and presented. Out of 1699 exposed infants, 16% of the data sets were incomplete for PCR result and could not be analysed.

3.1. Study participants

A total of 3592 mother-infant pairs were included in the primary study to assess the effectiveness of the national PMTCT programme. For the purposes of this study, 1893 mothers and their infants were excluded as they were HIV negative. Thus, 1699 mothers who had HIV and their exposed infants were included in the secondary analysis (Figure 3.1). The primary study enrolled 3592 HIV positive and HIV negative mothers who had brought their infants for the Diphtheria/Tetanus/Pertussis (DPT) 1 immunisation visit at 6-8 weeks of age. The mother-infant pairs were seen at the different facilities in the four regions of Swaziland which are Hhohho, Manzini, Lubombo and Shiselweni, with participants from both rural and urban settings.

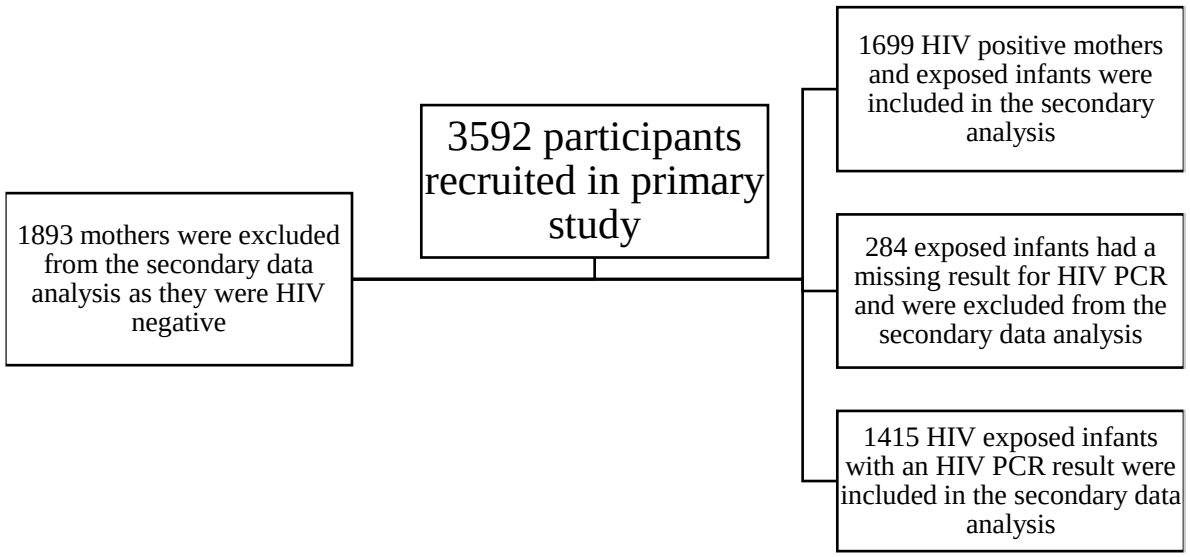


Figure 3.1: Flow chart showing selection of study participants

3.2. Socio-demographic factors

Region of origin

In the study, majority of the women resided in Manzini region 650 (38.2%), with the least amount of women from the Shiselweni region, 290 (17.1%), as shown in Figure 3.2.

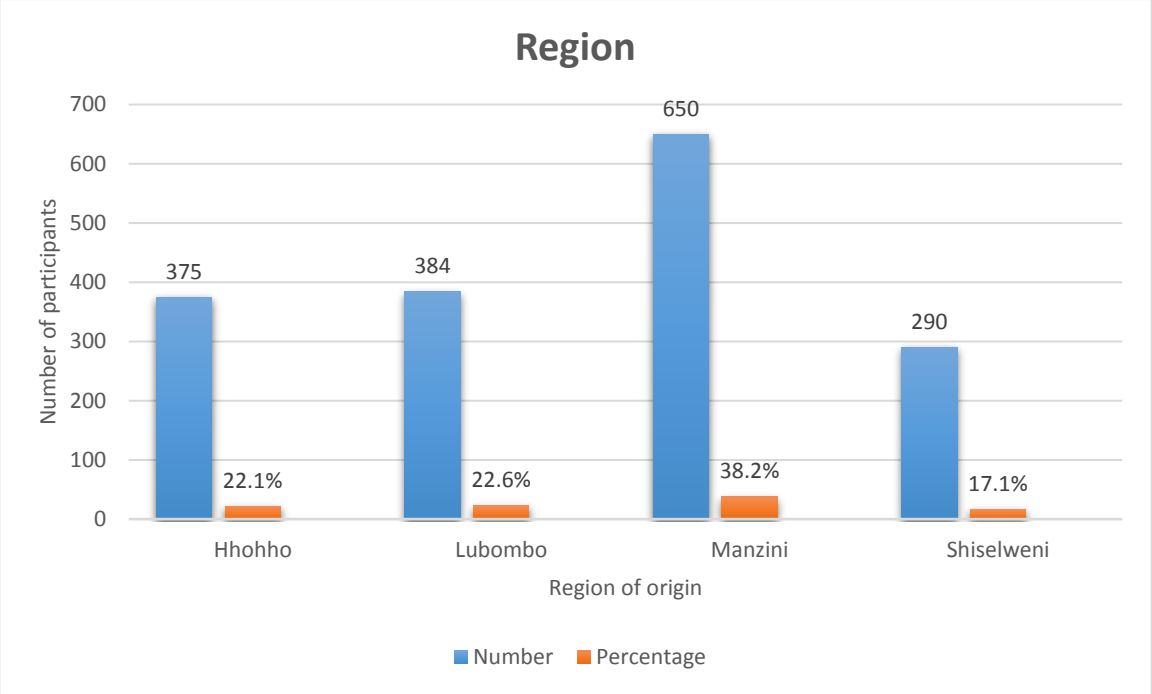


Figure 3.2: Region of origin

Baseline characteristics

The ages of the mothers participating in this study were ranging from 15 to 47 years giving a mean of 27 (SD 5.6) years. The majority of the mothers were in the 25-34 year age category 900 (52.9%), and the least number in the >35 year age category with 217 (12.8%). The majority of the mothers, 642 (40.7%) had secondary level education, 481 (30.4%) had primary level education or less and 456 (28.9%) had high school education or more. The majority 788 (46.6%) of mothers were not married and a small proportion 143 (8.5%) were cohabiting. Most of the women resided in a rural setting 1405 (83.7%) and 273 (16.3%) resided in an urban setting. Rural population refers to people living in rural areas as defined by the national statistics offices and Swaziland has a total of 78.68% of its population residing in the rural areas according to the 2016 World Bank collection of development indicators (29). Urban population refers to people living in the urban areas as defined by the national statistics offices and this gives 21.32% (29). The majority of the women 489 (62%) were not employed and only 304 (38%) of the women were employed.

The baseline characteristics compared by HIV PCR status are presented in Table 3.1 based on the negative or positive status. The findings revealed that in the maternal age category, the 15-24 year age category had the majority of HIV PCR positive infants, 18 (58%), the 25-34 year age category had 10 (32.3%) and the least were from >35 year age category with 3 (9.7%) of the HIV PCR positive infants. The category of the women who were not married had the highest number of HIV PCR positive infants, 21(67.7%) while the cohabiting women had the least number of 2 (6.5%). Most of the babies in the rural areas had a HIV PCR result, 26 (86.7%) with the least number in the urban areas 4 (13.3%). Lubombo region had the majority of the HIV PCR positive infants, 11 (35.5%) while Shiselweni had the least, 5 (16.1%).

The analysis was based on the whole data set of HIV positive mothers and their exposed infants giving a total of 1699. About 16% of the data sets on exposed infants were incomplete for PCR result and these were not analysed. The analysis was done on 1415 infants who had a HIV PCR result out of a sample size of 1699 since 284 exposed infants had missing data on the PCR result, hence these were excluded from the analysis . Worth noting is that there were different variations in the total number of participants analysed per category noted as a result of the missing data whose effect on the result could not be ascertained as the secondary data source was used.

Table 3.1: Baseline characteristics compared by HIV PCR status

Maternal characteristics	**N=1699**	**HIV PCR STATUS**	
		Negative n (%)	**Positive** n (%)
Age Category (years)	1415		
<25 years		477 (34.5)	18 (58.0)
25-34 years		728 (52.6)	10 (32.3)
≥35 years		179 (12.9)	3 (9.7)
Maternal education	1318		
Primary and less		386 (30)	12 (38.7)
Secondary		526 (40.9)	15 (48.4)
High school and above		375 (29.1)	4 (12.9)
Marital status	1409		
Not married		644 (46.7)	21 (67.7)
Married		624 (45.3)	8 (25.8)
Cohabiting		110 (8.0)	2 (6.5)

Employment status	669		
Yes		252 (38.5)	6 (42.9)
No		403 (61.5)	8 (57.1)
Residential status	1394		
Rural		1140 (83.6)	26 (86.7)
Urban		224 (16.4)	4 (13.3)
Region	1415		
Hhohho		287 (20.7)	6 (19.4)
Lubombo		343 (24.8)	11 (35.5)
Manzini		525 (37.9)	9 (29.0)
Shiselweni		229 (16.6)	5 (16.1)

***N** - Total number of participants; **n** - number of participants analysed per category with no missing data*

3.3. Antenatal care characteristics

3.3.1. CD4 Count Results

The majority, 263 (62.2%), of the mothers had a CD4 count of greater than 350cells while those with a count of 201-350 were 106 (25.0%) and those with a CD4 count of less than 200 were 54 (12.8%) as shown in figure 3.3. A consideration of the CD4 variable was critical under ANC characteristics because it has a huge effect on PCR positivity as it increases chances of mother-to-child transmission of HIV if the result is too low.

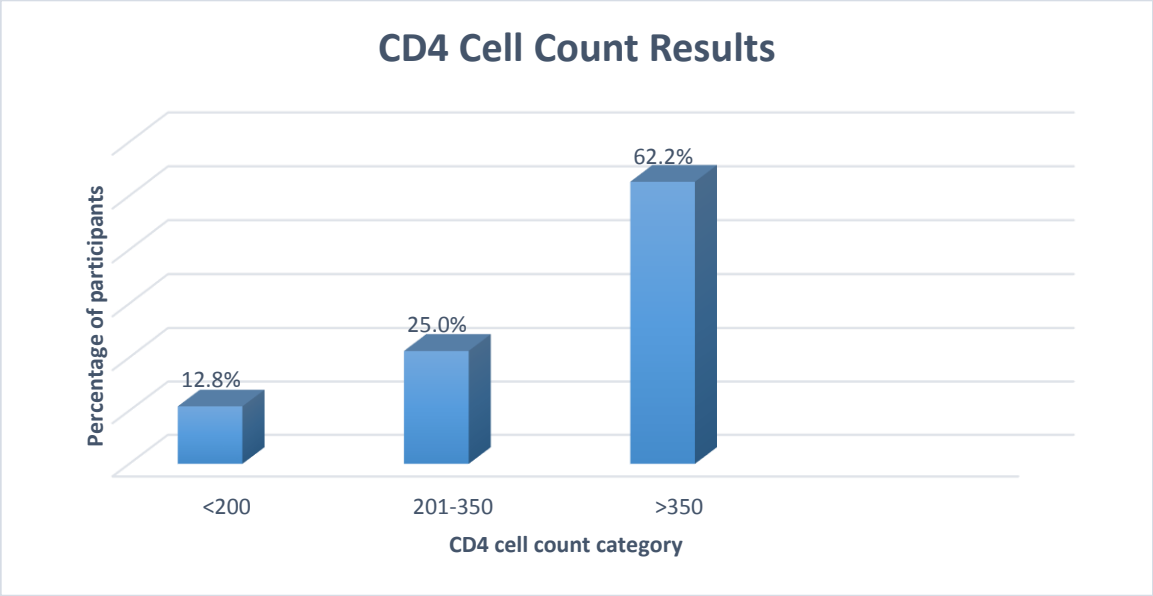


Figure 3.3: CD4 cell count results for mothers

3.3.2. ARV Regimen

The majority of the women, 1011 (61.6%) were on single dose NVP regimen, 469 (28.6%) of the women received AZT, 143 (8.7%) had received infant prophylaxis during pregnancy and 19 (1.2%) were taking ART as shown in figure 3.4

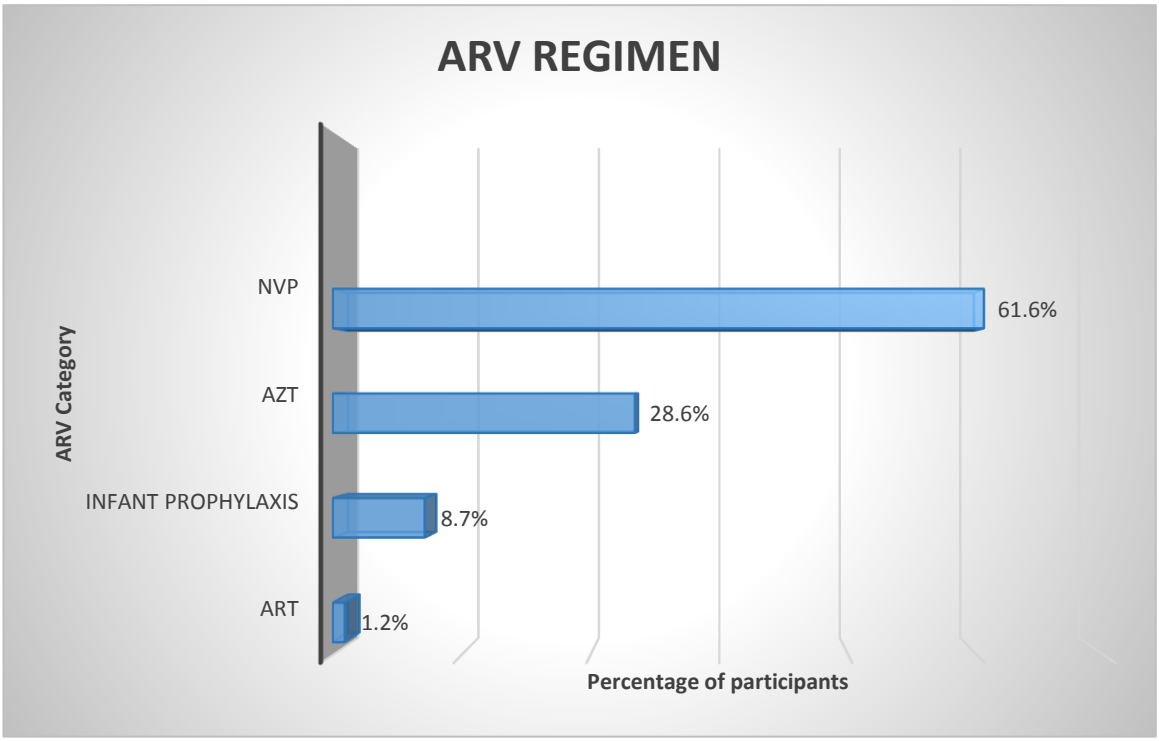


Figure 3.4: ARV regimen given to mothers during pregnancy

3.3.3. Antenatal baseline characteristics

The majority, 1085 (65.2%), of the women attended their first ANC visit at 4-6 months gestation and fifty percent of the women attended 3-4 ANC visits. The majority of the women, 1317 (93%), tested negative for syphilis. Nearly sixty percent of women, 345 (59%), had been on ART for more than 12 months, while 237 (41%) had taken ART for less than 12 months. The baseline characteristics compared by HIV PCR status and the findings revealed that the women who had their first ANC visit before 3 months gestation had the least number of HIV PCR positive infants, 3 (10%) when compared to those who had their first ANC attendance after 4 months gestation age who had the majority, 27 (90%) of the HIV PCR positive infants. The women who attended more than 4 ANC visits had fewer HIV PCR positive infants, 5 (16.1%) when compared to those who had attended less than four visits who had the most HIV PCR positive infants, 26 (83.9%). The women who were on the triple therapy ART regimen had the least HIV PCR positive infants, 2 (6.5%) when compared to those on single prophylactic medications whose total was 28 (89.8%). The findings of the antenatal baseline characteristics when compared by HIV PCR status are presented in Table 3.2.

Table 3.2 Antenatal baseline characteristics compared by HIV PCR status

Antenatal Characteristics	N=1699	HIV PCR STATUS	
		Negative n (%)	Positive n (%)
Gestational age at 1st ANC visit	1372		
<3 months		203 (15.1)	3 (10.0)
4-6 months		880 (65.6)	16 (53.3)
>7 months		259 (19.3)	11 (36.7)
Number of ANC visits	1406		
< 2		179 (13.0)	11 (35.5)
3-4		691 (50.3)	15 (48.4)
> 4		505 (36.7)	5 (16.1)
Syphilis status	1178		
Positive		79 (6.9)	2 (7.7)
Negative		1073 (93.1)	24 (92.3)
CD4 cell count	365		
≤ 200cells/mm^3		44 (12.2)	1 (20.0)
200-350cells/mm^3		90 (25.0)	2 (40.0)
≥350cells/mm^3		226 (62.8)	2 (40.0)
Maternal ARV regimen	1376		
AZT		383 (28.5)	3 (9.7)
NVP		820 (60.9)	25 (80.1)
Infant prophylaxis		130 (9.7)	1 (3.2)
ART		12 (0.9)	2 (6.5)
Duration on AZT	985		
<2 months		256 (26.7)	12 (46.2)
3-5 months		554 (57.8)	12 (46.2)
>6 months		149 (15.5)	2 (7.6)
Duration on ART	488		
<12 months		196 (40.6)	3 (60.0)
≥12 months		287 (59.4)	2 (40.0)

***N** - Total number of participants; **n** - number of participants analysed per category with no missing data; **ANC** – Antenatal Care; **AZT** – zidovudine; **NVP** – nevirapine; **ARV** – Antiretroviral; **ART** – Antiretroviral Therapy*

3.3.4. Duration on AZT

The majority of the women, 691 (59.2%), had taken AZT for 3-5 months, 303 (26%) had taken AZT prophylaxis for less than 2 months and 173 (14.8%) took it for more than 6 months duration as shown in figure 3.5

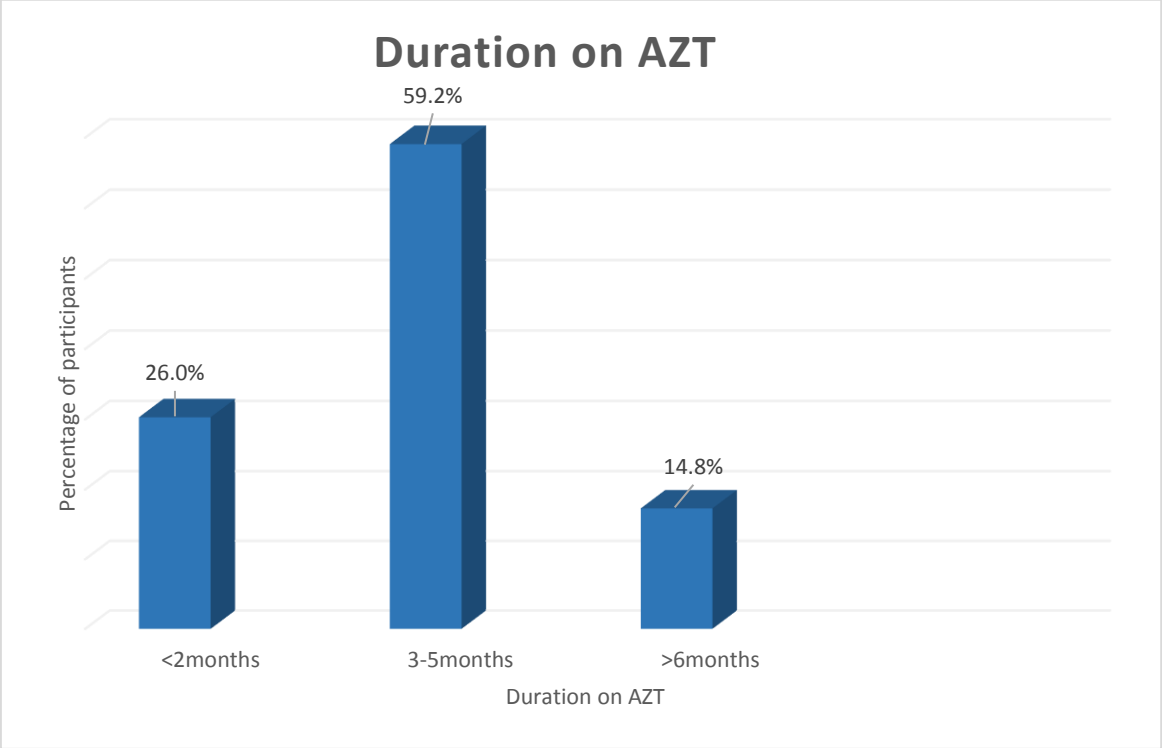


Figure 3.5: Duration of time mothers were on AZT

3.4. Intra-Partum characteristics

The majority of women, 1470 (87%), delivered their infants at the hospital or clinic while 224 (13%) delivered their infants at home. The majority of the women, 1513 (90%) delivered their infants through normal vaginal delivery while 170 (10%) delivered through caesarean section. Most women, 841 (94%), took AZT during labour while 54 (6%) took NVP prophylaxis during the intrapartum stage. The baseline characteristics were compared by HIV PCR status and the findings revealed that the majority of the HIV PCR positive infants, 19 (86.4%) were from the mothers who had taken AZT during labour while the least, 3 (13.6%) were from those who had taken NVP regimen. Most of the babies who were delivered through NVD, 29 (93.6%) had a positive HIV PCR result when compared to 2 (6.4%) delivered through caesarean section. The intrapartum baseline characteristics compared by HIV PCR status are presented in Table 3.3.

Table 3.3 Intrapartum baseline characteristics compared by HIV PCR status

INTRAPARTUM CARE CHARACTERISTICS	N=1699	HIV PCR STATUS	
		Negative n (%)	**Positive** n (%)
ARVs taken in labour	751		
AZT		682 (93.6)	19 (86.4)
NVP		47 (6.4)	3 (13.6)
Place of delivery	1410		
Hospital/clinic		1199 (86.9)	23 (74.2)
Home		180 (13.1)	8 (25.8)
Mode of delivery	1400		
NVD		1229 (89.8)	29 (93.6)
Caesarean section		140 (10.2)	2 (6.4)

N *- Total number of participants;* ***n*** *- number of participants analysed per category with no missing data;* ***AZT*** *– zidovudine;* ***NVP*** *– nevirapine;* ***NVD*** *– Normal Vaginal Delivery*

3.5. Postnatal /infant characteristics

Most of the infants, 1646 (97.3%), were delivered at full term gestation and only 45 (2.7%) were delivered prematurely. Of the delivered infants, 1454 (99.3%) received infant NVP at birth, while only 10 (0.7%) of the infants did not receive it. The majority of the infants, 1451 (88.3%) were still taking NVP during the study period and only 193 (11.7%) had stopped taking it. The majority of the infants, 1388(84%) weighed more than 2.5kg and only 258 (16%) weighed less than 2.5kg of the infants seen during the study, 1674 (98.8%) had a child welfare card and only 20 (1.2%) did not have one. The majority of infants 1637 (96.7%), had received BCG immunisation and only 56 (3.3%) had not been immunised. The greater proportion of infants, 1413 (84%) were fed on breast milk only while 277 (16%) received other feeds. A few infants received additional medicines, with only 156 (9.2%) having been given gripe water. The majority of the infants were not given any additional infant medicine. The mothers indicated that 144 (65%) of the infants had missed taking the NVP prophylaxis for less than 2 weeks, while 78 (35%) had missed taking it for a duration of more than 2 weeks. Worth noting is that primary data source did not indicate whether they were any twin deliveries participating in the study even though the effect of such remains unknown.

The baseline characteristics were compared by HIV PCR status and they revealed that the majority of the HIV PCR positive infants, 30 (96.8%) had been delivered at full gestational term, 21 (67.7%) were born with a weight less than 2.5kg, 26 (96.3%) had received the infant prophylaxis of single dose NVP at birth, had been breastfed from birth 28 (90.3%). The findings

also showed that most HIV PCR positive infants had not taken any additional infant medications. The postnatal/infant baseline characteristics compared by HIV PCR status are presented in Table 3.4.

Table 3.4 Postnatal/infant baseline characteristics compared by HIV PCR status

POSTNATAL/INFANT CHARACTERISTICS	N=1699	HIV PCR STATUS	
		NEGATIVE n (%)	POSITIVE n (%)
Gestation at birth	1409		
Full term		1341 (97.3)	30 (96.8)
Premature		37 (2.7)	1 (3.2)
Birth Weight	1372		
<2.5kgs		182 (13.6)	10 (32.3)
≥2.5kgs		1159 (86.4)	21 (67.7)
Child welfare card	1413		
Yes		1367 (98.9)	29 (93.6)
No		15 (1.1)	2 (3.2)
BCG immunisation	1412		
Yes		1332 (96.5)	30 (96.8)
No		49 (3.5)	1 (3.2)
Infant NVP at birth	1226		
Yes		1193 (99.5)	26 (96.3)
No		6 (0.5)	1 (3.7)
Infant feeding method	1408		
Breast milk only		1148 (83.4)	28 (90.3)
Other feeds		229 (16.6)	3 (9.7)
Child still taking NVP	1377		
Yes		1180 (87.7)	26 (83.9)
No		166 (12.3)	5 (16.1)
Duration of missed infant NVP	190		
<2 weeks		127 (68.3)	3 (75)
≥2 weeks		59 (31.7)	1 (25)

Additional infant medicine			
Gripe-water	1412		
Yes		127 (8.8)	2 (6.4)
No		1254 (90.8)	29 (93.6)
Umutsiwenyoni	1413		
Yes		122 (8.8)	1 (3.2)
No		1260 (91.2)	30 (96.8)

N- Total number of participants; ***n****- number of participants analysed per category with no missing data;* ***NVP*** *– nevirapine;* ***BCG*** *– Bacillus Calmette Guirin. Umutsiwenyoni is an antacid which contains calcium carbonate 87mg, magnesium carbonate 87mg, sodium bicarbonate 87mg, sodium citrate 62mg, alcohol 3.739% per 5ml and is used by most mothers for the relief of colic pain and discomfort.*

3.6. Mother-to-child transmission rate

The HIV DNA PCR test was used to test the infants who were exposed to HIV at 6-8 weeks, postpartum. Out of 1415 exposed children who were tested for HIV, thirty-one, (2.2%) tested HIV positive and 1384 (97.8%) tested HIV negative (Figure 3.6).

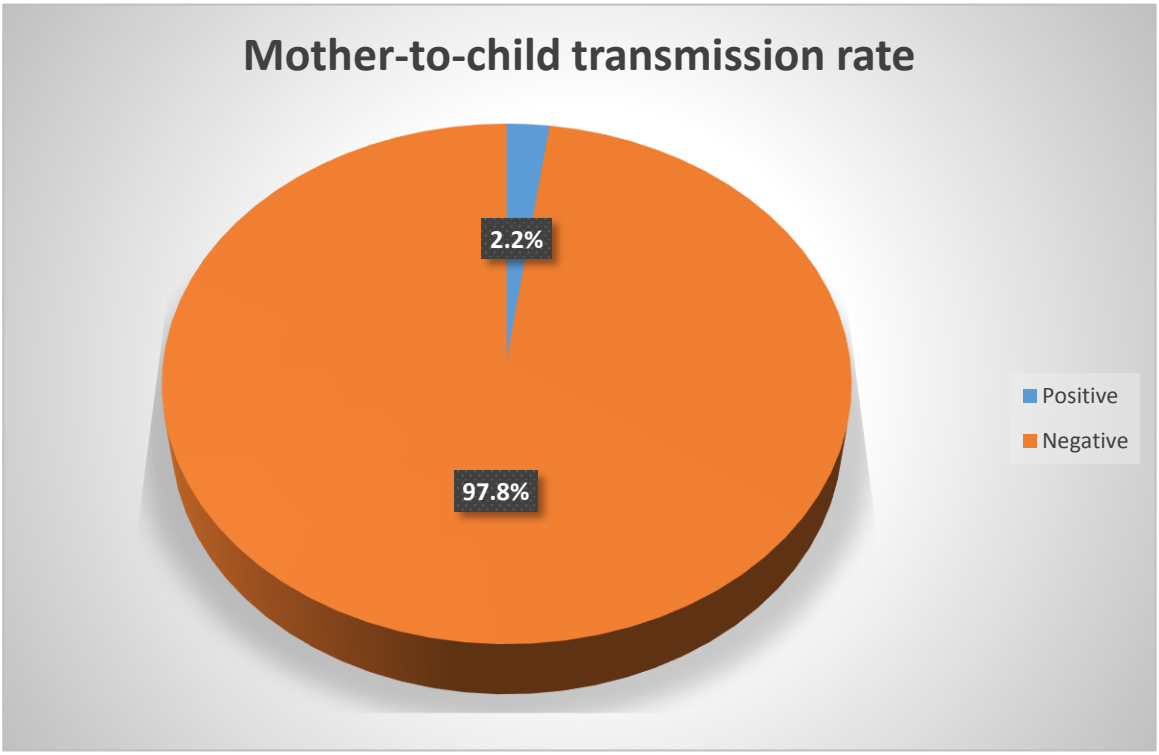


Figure 3.6: Mother-to-child transmission rate

3.7. Factors associated with infant PCR positivity at 6-8 weeks of age

Univariate logistic regression analysis identified maternal age, marital status, number of ANC visits and birth weight to be significantly associated with PCR positivity status at 6-8 weeks of age (Table 3.5).

Infants born to mothers aged 25-34 years were 64% less likely to be HIV PCR positive when equated to those in the <25 year age category (OR = 0.36; 95% CI: 0.17-0.8). Infants born to mothers aged >35 years were 56% less likely to be PCR positive when equated to those in the <25 age category (OR=0.44; 95% CI: 0.13-1.5). The married mothers, were 60 % less probable to have infants with a positive PCR positive when compared to those that were never married (OR=0.40; 95% CI: 0.17-0.89). The women who were cohabiting, were 44% less probable to have an HIV PCR positive infant when equated to those that were never married (OR=0.56; 95% CI: 0.13-2.41).

Women who attended 3-4 ANC visits, were 65% less likely to have an infant with an HIV PCR positive result when compared to women who had attended less than 2 ANC visits. Women who attended more than 4 ANC visits, were 84% less likely to have infants with a HIV PCR positive result when compared to mothers attending less than 2 ANC visits (OR=0.16; 95% CI: 0.06-0.47). The infants with a birth weight above 2.5 kg were 67% less likely to be PCR positive when compared to the infants weighing less than 2.5 kg (OR=0.33; 95% CI: 0.15-0.71).

Table 3.5: Factors associated with infant PCR positivity at 6-8 weeks

CHARACTERISTICS	**N**	**Unadjusted OR (95% CI)**	**p-value**
SOCIO-DEMOGRAPHIC CHARACTERISTICS			
Maternal age (years)	1415		
<25 years		1.00	
25-34 years		0.36 (0.17-0.80)	**0.011****
≥35 years		0.44 (0.13-1.50)	0.197
Maternal education	1318		
Primary and less		1.00	
Secondary		0.92 (0.42-1.98)	0.826
High school and above		0.34 (0.11-1.07)	0.066
Marital status	1409		
Not married		1.00	
Married		0.40 (0.17-0.89)	**0.026***
Cohabiting		0.56 (0.13-2.41)	0.434
Employment status	669		
Yes		1.00	

No		0.83 (0.29-2.43)	0.739
Residential status	1394		
Rural		1.00	
Urban		0.78 (0.27-2.27)	0.652
Region	1415		
Hhohho		1.00	
Lubombo		1.50 (0.56 – 4.20)	0.405
Manzini		0.80 (0.29 -2.33)	0.709
Shiselweni		1.00 (0.31 – 3.47)	0.943
ANTENATAL CARE CHARACTERISTICS			
Gestational age at 1st ANC visit	1372		
<3 months		1.00	
4-6 months		1.23 (0.36-4.26)	0.744
>7 months		2.87 (0.79-10.44)	0.109
Number of ANC visits	1406		
< 2		1.00	
3-4		0.35 (0.16-0.78)	**0.010****
> 4		0.16 (0.06-0.47)	**0.001*****
Syphilis status	1178		
Positive		1.00	
Negative		0.88 (0.21-3.81)	0.868
CD4 cell count	365		
>= 200 cells/mm^3		1.00	
200 -350 cells/mm^3		0.98 (0.09-11.08)	0.986
<350 cells/mm^3		0.39 (0.03-4.40)	0.445
Maternal ARV regimen	1376		
AZT		1.00	
NVP		3.89 (1.17-12.97)	**0.027***
Infant prophylaxis		0.98 (0.10-9.52)	0.988
ART		21.28 (3.25-139.33)	**0.001*****
Duration on AZT	985		
<2 months		1.00	
3-5 months		0.46 (0.20-1.04)	0.063

>6 months		0.29 (0.63-1.29)	0.105
Duration on ART	488		
<12 months		1.00	
≥12 months		0.46 (0.75-2.75)	0.391
INTRA-PARTUM CHARACTERISTICS			
ARVs taken in labour	751		
AZT		1.00	
NVP		2.29 (0.65-8.02)	0.195
Place of delivery	1410		
Hospital/clinic		1.00	
Home		2.32 (1.02-5.26)	**0.045***
Mode of delivery	1400		
NVD		1.00	
Caesarean section		0.61 (0.14-2.56)	0.496
POSTNATAL/INFANT CHARACTERISTICS			
Gestation at birth	1409		
Full term		1.00	
Premature		1.21 (0.16-9.10)	0.854
Birth Weight	1372		
<2.5kgs		1.00	
≥2.5kgs		0.33 (0.15-0.71)	**0.005****
Child welfare card	1413		
Yes		1.00	
No		6.29 (1.37-28.75)	0.018
BCG immunisation	1412		
Yes		1.00	
No		0.91 (0.12-6.78)	0.924
Infant NVP at birth	1226		
Yes		1.00	
No		7.65 (0.89-65.81)	0.064
Infant feeding method	1408		
Breast milk only		1.00	
Other feeds		0.54 (0.16-1.78)	0.310
Child still taking NVP	1377		

Yes		1.00	
No		1.37 (0.52-3.60)	0.528
Duration of missed infant NVP	190		
<2 weeks		1.00	
≥2 weeks		0.72 (0.73-7.04)	0.776
Additional infant medicine			
Gripe-water	1412		
Yes		1.00	
No		1.47 (0.35-6.23)	0.602
Umutsiwenyoni	1413		
Yes		1.00	
No		2.90 (0.39-21.50)	0.296

N- *Total number of participants;* ***n***- *number of participants per each category;* ***ANC*** *– Antenatal Care;* ***AZT*** *– zidovudine;* ***NVP*** *– nevirapine;* ***ARV*** *– Antiretroviral;* ***NVD*** *–Normal Vaginal Delivery;* ***BCG*** *– Bacillus Calmette Guirin.* *******$p<0.05$; **$p<0.01$, ***$p<0.001$*

3.8: Multivariable Analysis

The duration on AZT category was chosen upfront to be incorporated in the multivariable analysis based on the biological plausibility. In addition, factors which were significantly associated with PCR positivity in the univariate analysis, i.e. age, marital status, birth weight and number of ANC visits were also incorporated in the multivariable logistic regression model (Table 3.6).

Number of ANC visits was the only factor which remained significantly associated with PCR positivity in the multivariable logistic regression analysis model after adjusting for all other factors. Women who attended more than four antenatal care visits were less likely to have a HIV PCR positive infant at 6-8 weeks (OR =0.83; 95% CI: 0.02-0.44; p-value = 0.004) as compared to those attending less than four visits. This indicated a statistically significant association between the number of ANC visits a woman attended and the PCR positivity status of their baby at 6-8 weeks. Age, marital status and birth weight were not significantly associated with PCR positivity.

Table 3.6: Multivariable Analysis

CHARACTERISTICS	N	ADJUSTED OR (95%CI)	P-VALUE
Maternal age (years)	794		
<25 years		1.00	
25-34 years		0.61 (0.23-1.65)	0.331
≥35 years		0.69 (0.14-3.49)	0.652
Marital status	794		
Not married		1.00	
Married		0.94 (0.33-2.64)	0.905
Cohabiting		1.31 (0.27-6.26)	0.737
Syphilis status	794		
Positive		1.00	
Negative		0.71 (0.15-3.35)	0.667
Number of ANC visits	794		
< 2		1.00	
3-4		0.35 (0.12-1.02)	0.055
> 4		0.83 (0.02-0.44)	**0.004***
Duration on AZT	794		
<2 months		1.00	
3-5 months		1.03 (0.35-3.03)	0.958
>6 months		1.04 (0.20-5.50)	0.959
Birth Weight	794		
<2.5kgs		1.00	
≥2.5kgs		0.55 (0.19-1.60)	0.271

N- *Total number of participants;* ***ANC*** *– Antenatal Care;* ***AZT*** *– zidovudine;* *******$p<0.05$

CHAPTER 4

4. DISCUSSION AND CONCLUSION

The chapter begins by discussing the study findings which are divided into factors associated with HIV PCR and the HIV transmission rate from the mother to the infant. In addition, strengths and limitations of the study are also highlighted. The chapter ends by providing concluding remarks and recommendations.

4.1. Introduction

The aim of the current study was to determine factors associated with PCR positivity among HIV exposed infants at 6-8 weeks in Swaziland. Mothers who attended more than four visits were less likely to have an HIV PCR positive infant. These results are consistent with findings from studies conducted in Brazil, Nigeria and other developing countries especially in sub-Saharan Africa, which revealed that low ANC uptake leads to poor access to PMTCT thereby increasing the HIV transmission risk from the mother to the infant (31-34). The study findings were compared with existing evidence and the differences and similarities with other studies which were conducted before will be highlighted.

4.2. Discussion of study findings

This was a secondary data analysis with a sample size of 1699 mothers who were HIV positive and their HIV exposed infants even though 1415 were analysed for PCR positivity since 284 had missing data. However, the data source excluded the viral load count as the country lacked suitable resources to conduct the test even though its effect on PCR positivity is known to be highly significant.

The study's main aim was to determine the PCR positivity rate at 6 weeks and the factors associated with PCR positivity amongst HIV exposed infants at 6-8 weeks in Swaziland. This study found that maternal age, marital status, infant birth weight and the number of ANC visits were associated with infant PCR positivity at 6-8 weeks in the unadjusted analysis. The study findings revealed that number of ANC visits was the single factor that continued to be significantly associated with PCR positivity in the adjusted analysis. This is consistent with findings in sub-Saharan Africa (6,9,10,12).

In terms of characteristics there is a huge difference evident between developing and developed countries which might be attributable to scarcity of resources in low income settings (35,36). In developed countries there are efficient ANC models for care whilst in developed countries there are still challenges with late or no ANC attendances which are a platform for access to PMTCT services which are contributory to reduction of maternal viral load (36-38).

By the time this study was done, developed countries had constant access to ARVs, CD4 count tests and viral load monitoring as opposed a low-income setting of Swaziland (36,37). In high-income resource settings, HIV positive mothers had a privilege of delivering the infants through caesarean section method with a choice of not breastfeeding at all to reduce mother-to-child transmission of HIV (36,38) whereas in low-income settings, caesarean section deliveries were for emergency situations and non-breastfeeding is challenged by the lack of resources (35,37,39). However, with the assistance of development partners, there has been some major strides noticeable in provision and access of ARVs, CD4 count testing and viral load monitoring since 2014 in Swaziland (19,29).

PCR positivity among infants exposed to HIV is a substantial challenge resulting from HIV transmission from the mother to their infant, particularly in sub-Saharan Africa (2). It is a common basis of morbidity and mortality in children (40,41). Globally, prevention of mother-to-child transmission of HIV remains one of the most effective HIV preventive measures even though PCR positivity rates are still significantly high in sub-Saharan Africa (42,43). Conversely, there is sparse literature on the factors associated with PCR positivity of HIV at 6-8 weeks of age in Swaziland even though the benefits of PMTCT have significantly reduced HIV transmission from the mother to their infant globally (44).

Number of ANC visits was the single factor that continued to be independently associated with PCR positivity after adjusting for age, marital status, duration on AZT, syphilis status and birthweight. An increased number of ANC visits was a protective factor for infant PCR seropositivity at 6-8 weeks. The mothers who attended more than four ANC visits, were significantly less likely to have children who were PCR positive as compared to mothers who had attended fewer ANC visits. This result is consistent with other findings from studies which demonstrated improved perinatal outcomes with increased number of ANC visits (45-47).

The importance of antenatal care in public health cannot be emphasized enough and has been hailed as one of the greatest cost effective interventions for improving maternal and infant

outcomes (48). Women attending less than four antenatal care visits are also at greatest risk of transmitting HIV to their infants since they have lack of access to prophylactic antiretroviral medications, thereby increasing seropositivity (33,49). The World Health Organization (WHO) recommends and places emphasis on the significance of four antenatal visits in order to advance the health outcomes of the mother, prevent complications, safe childbirth and creation of health seeking behaviours and this has now been increased to eight visits in the 2016 WHO ANC model (34,37).

The WHO ANC model recommends eight antenatal care visits for much improved pregnancy experiences and better maternal and neonatal outcomes (37). Antenatal care remains the entry point for HIV services and is key to the reduction of seropositivity in infants since it allows for early intervention through the provision of ART prophylaxis (32,50). Antenatal care provides a solid base for PMTCT interventions to be initiated and utilised so as to reduce HIV transmission from the mother to their unborn child (33,37). Throughout ANC, the women who are pregnant are given an opportunity to test and know their HIV status, viral load testing, syphilis testing and treatment, initiation of ART, screening for opportunistic infections and counselling on adherence and infant feeding practices (35,37). ANC encourages health seeking behaviour for skilled birth care, infant ARV prophylaxis, maintenance of adherence on ART and early infant diagnosis through HIV PCR tests for early identification of seropositivity and linkage to HIV care and treatment (22,37,38).

The joint United Nations report also emphasised the importance of antenatal care through decentralisation of services to rural areas and poor communities so as to increase access and uptake in low-middle income countries and this will decrease mother-to-child transmission of HIV thereby reducing seropositivity (11,51). Studies in high income countries have shown that there are different models of ANC which may be more effective since they have more human and financial resources when compared to low-middle income countries, which have limited resources (36,37,52).

While maternal age was significantly associated with HIV PCR positivity in the unadjusted model, this variable was not statistically associated with the outcome of interest in the adjusted model. Some studies have shown maternal age as an important factor, which may show that as the women get older, they are bound to make wiser choices with issues pertaining to their health with improved health seeking behaviours and better adherence to their treatment leading to a reduction in PCR positivity for their infants as opposed to the younger generation that may be

more experimental and less knowledgeable with limited resources (51,53). In addition, younger women have also been associated with poor adherence to PMTCT interventions, causing higher viral loads and an increased risk of transmitting HIV to their infants (47).

Maternal syphilis status was chosen upfront to be included in the multivariate analysis based on biological plausibility. The outcomes of this study discovered that there is no association amongst syphilis status and HIV PCR positivity. These findings are contrary to other studies which were conducted in Malawi and Maryland, which demonstrated an association between syphilis and the transmission of HIV from the mother to their infant (54,55). The lack of association between syphilis status and PCR positivity in this study could have been due to other unmeasured confounding factors. While the results did not demonstrate any association, it is important for PMTCT programmes to improve the integration of the management of sexually transmitted infections within PMTCT programmes.

The infants who weighed above 2.5 kg at birth were less likely to be PCR positive. Previous studies demonstrated that premature and low birth weight infants were more probable to be HIV positive when equated to term and normal weight infants while low birth weight and prematurity were significantly associated with increased risk of HIV transmission from the mother to their infant (24,55-57). Infants with a birth weight above 2.5 kg were less probable to be PCR positive when equated to those weighing below 2.5 kg in the unadjusted model but this association was no longer significant in the adjusted model.

The duration on AZT category was chosen upfront to be incorporated in the multivariate analysis based on the biological plausibility. The findings of this study revealed that there was no association between the duration on AZT and HIV PCR positivity. These findings were contrary to the results of other studies, which demonstrated that women who had taken antiretroviral prophylaxis for a longer duration during pregnancy were at lesser risk of passing on the HIV to their unborn infants (58). Other study findings also concurred and revealed that the use of antiretroviral prophylactic medication are significantly associated with reduction of HIV transmission from the mother to the infant (59,60).

4.3. Mother-to-child transmission rate

Transmission of HIV from the mother-to-child has been an area of concern especially in sub-Saharan Africa which bears the burden of the pandemic (2). Mother-to-child transmission rates have lessened from 20% to 2% in the United Kingdom and Ireland as a result of effective use

of highly effective life-long ART treatment, avoidance of breastfeeding and planned caesarean section deliveries in women who are HIV positive (36). There has been improved PMTCT services in Africa which also led to reductions in mother-to-child transmission rates from 28% in 2009 to 18% in 2013, while the pregnant women who are HIV positive and are initiated on ART have also increased from 33% in 2009 to 63% in 2013 (35). The use of skilled birth care, different regimens of ART prophylaxis and treatment, have contributed immensely to the reduction of mother-to-child HIV transmission rates globally (35,38,39).

This study found a transmission rate of 2.2%, which is comparable to the current mother-to-child transmission rate of 2.0% when using Swaziland programme data (19). In addition, the HIV transmission rate from the study is also consistent with the rates seen in neighbouring South Africa where the intrauterine transmission rate is at 1.6% and 1% in developed countries (36,43,61). The low rates in developed countries are attributed to efficient ANC models and appropriate management of deliveries owing to availability of resources (36,37). These low HIV transmission rates are consistent with the continuously improving PMTCT ART regimens that southern African countries have adopted following the WHO recommendations (44).

4.4. Strengths and Limitations

The main strength of this study was that it was conducted at study sites in the four regions of Swaziland providing a nationally representative sample for the study. While the Swaziland census enumeration areas were used as the sampling frame, the results should be inferred with some cautiousness considering a number of limitations. The study only limited the analysis to infants aged 6-8 weeks and there is a possibility that some infants who were not in the age category could have been missed and this could affect the transmission rate, resulting in a possible underestimation. With the study being a cross-sectional study, it was impossible to establish whether the independent variables preceded the outcome and thus cause-effect relationships were not explored. There was also an issue of recall bias since the participants had to recall events that happened during pregnancy and delivery.

The outcomes of this study revealed that there was no association between maternal CD4 count and HIV PCR positivity in the unadjusted model. A Zimbabwean study revealed that a maternal CD4 count which was less than 200cells/mm^3 and high viral load was associated with increased risk of HIV transmission from the mother to their unborn child (59). Unfortunately, when the secondary data analysed for this study was collected, viral load monitoring was not offered routinely to pregnant women. It would have been helpful to measure the viral load for the study

participants by age groups since some studies have previously demonstrated a positive relationship between viral load and risk of mother-to-child-transmission (20,26,62,63). The viral load measurement would have been a better marker of adherence and compliance to PMTCT interventions.

This study presents data from government and mission clinics. While the sample was large, there is a possibility of different characteristics in individuals in this study to those who were seeking services from the private clinics and were not included in this study, even though they are few. Those from the private sector may have different socio-demographic, antenatal, intrapartum and postnatal/infant factors or characteristics different from those in the study thereby limiting the generalisability of results.

4.5. Conclusion

The study successfully determined the factors associated with HIV infection in 6-8 week old infants in Swaziland. It revealed a transmission rate of 2.2%, which is comparable to the current mother-to-child transmission rate of 2.0% when using Swaziland programme data. ANC attendance of more than four visits was associated with a reduced risk of mother-to-child transmission thereby reducing seropositivity. Out of 1699 exposed infants, 16% of the data sets were incomplete for PCR result and could not be analysed. Of the 1415 HIV exposed infants, 31 were HIV PCR positive at 6-8 weeks.

Further, the study noted that increased number of antenatal care visits attended by pregnant women is beneficial in Swaziland because it increases access to PMTCT services thereby decreasing the prospects of mother-to-child HIV transmission.

In conclusion with notable and consistent improvements with maternal and infant ARV regimen, there is a greater possibility for achievement of total elimination of mother-to-child transmission of HIV target in line with His Majesty, King Mswati III vision 2022 of elimination of paediatric HIV infection.

4.6. Recommendations

a. Policy

Current policy emphasises attendance of four focused ANC visits. However, there is a new recommendation to increase the ANC visits to eight by the WHO. It is recommended that the Government of Swaziland should adopt the newly recommended WHO ANC guidelines as this increases access to PMTCT services thereby reducing mother-to-child transmission of HIV.

Also, existing policy on early infant diagnosis upholds that all HIV exposed infants should be tested for HIV using the DNA PCR test at 6 weeks at their first immunisation visit. Also, the policy maintains that the results should be released and made available on consecutive visits for immunisations which is at 10 weeks from date of birth. The efficiency of implementation of the policy is sustained if the infant stays in the same vicinity to access their 10 week immunisation at the same facility. It is highly recommended for the Government to consider implementation of an electronic centralised data management system to enable and support the dissemination of HIV/PCR results even when the mother and the baby have moved to a different location from where they initially conducted the test. The Government of Swaziland is also advised to consider point of care testing as critical to enable availability of HIV/PCR results on the day the test is conducted to avoid loss to follow-up.

The early infant diagnosis does not take into account infants who could have been infected whilst in utero and those that might not make it to the 6 week visit. Therefore, it is recommended that Swaziland consider the adoption and implementation of point of care birth testing to enable availability of HIV/PCR results on the day of birth.

There is need for a policy geared towards implementation and improvement of community health activities which include training and employment of community health workers who are skilled in educating the community on the importance of frequent ANC visits during pregnancy so as to reduce mother-to-child transmission of HIV.

b. Practice

The existing policy emphasises that all developmental partners willing to assist the Ministry of Health to strengthen their health care system should collaborate with Swaziland National Aids Programme (SNAP) for appraisal and approval of their programme implementation so as to avoid duplication of work activities. Government adopted this approach to ensure that resources

are equitably distributed throughout the country to maintain uniformity and compliance to recommended guidelines. Currently, the developmental partners are the core funders of the HIV programme in Swaziland which includes the testing and acquisition of ARVs and Government maintains the regulatory role. Therefore, it is highly recommended that Government should participate in the development and fully direct the programmes. This can be achieved if budget allocation towards HIV programmes and health services could be increased to allow sustainability and decrease financial reliance on developmental partners whose funding is periodical. This is likely to be achievable as technical staff is being trained on a continuous basis by the partners which reduces the budget Government should allocate towards the sustainability of the initiatives.

c. Research

In line with the study findings, future research should include viral load testing which is an important marker for mother-to-child transmission of HIV to improve the reliability of the results of this study. Also, there is need to conduct more primary studies to improve the quality and reliability of data to be analysed. More comparative studies should be conducted to determine factors associated with HIV infection in infants at different age groups in the local and regional communities.

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APPENDICES

APPENDIX 1: Primary Study Ethical Clearance Certificate

Telegrams:
Telex:
Telephone: (+268 404 2431)
Fax: (+268 404 2092

MINISTRY OF HEALTH
P.O. BOX 5
MBABANE
SWAZILAND

THE KINGDOM OF SWAZILAND

FROM: The Chairman
Scientific and Ethics Committee
P. O. Box 5
Mbabane

TO: Ms Sibongile Mndzebele
Ministry of Health M&E
Mbabane.

DATE: 21st April, 2011

REF: MH/599C

RE: EVALUATION OF THE EFFECTIVENESS OF THE NATIONAL PREVENTION OF MOTHER TO CHILD TRANSMISSION OF HIV (PMTCT) PROGRAMME AT 6-8 WEEKS POST – PARTUM IN SWAZILAND

The committee thanks you for addressing the issues raised by the committee on the 01st of April. In view of the changes incorporated and the fact that the study is in accordance with ethical and scientific standards, the committee therefore grants you authority to conduct the study in Swaziland. You are requested to adhere to the specific topic and inform the committee through the chairperson of any changes that might occur in the duration of the study which are not in this present arrangement.

The committee wishes you the best and is eagerly awaiting findings of the study to inform proper planning and programming.

Yours Sincerely,

DIRECTOR OF HEALTH SERVICES
MINISTRY OF HEALTH
21 APR 2011
P.O. BOX 5, MBABANE
SWAZILAND

DR S.ZWANE
For: Chairperson Scientific and Ethics Committee
cc: Sec Members

APPENDIX 2: Swaziland Ethical Clearance Certificate

Research Protocol clearance certificate

Type of review	Expedited	X		Full Board			
Name of Organization	STUDENT						
Title of study	FACTORS ASSOCIATED WITH PCR POSITIVITY IN HIV EXPOSED INFANTS AT 6-8WEEKS IN SWAZILAND						
Protocol version	V 5.0						
Nature of protocol	New	X		Amendment			
List of study sites	HMIS UNITS IN HHOHHO, LUBOMBO, SHISELWENI, AND MANZINI REGIONS						
Name of Principal Investigator	LINDA MIRIRA						
Names of Co- Investigators	N/A						
Names of steering committee members in the case of clinical trials	N/A						
Names of Data and Safety Committee members in the case of clinical trials	N/A						
Level of risk (Tick appropriate box)	Minimal				High		
	X						
Clearance status (Tick appropriate box)	Approved	X			Disapproved		
Clearance validity period	Start date	01/06/2017		End date	01/06/2018		
Signature of Chairperson							
Date of signing	02/06/2017						
Secretariat Contact Details	Name of contact officers			Ms Simangele Masilela			
	Email address		kaluamasi@gmail.com				
	Telephone no.		(00268) 24040865/24044905				

MINISTRY OF HEALTH
06 JUN 2017
HEALTH RESEARCH REVIEW BOARD
SWAZILAND

APPROVAL CONDITIONS

Ref.	Conditions	Indication of conditions (tick appropriate box)				
1	Implementation of approved version of protocol	✓				
2	Reporting of adverse events within 5 days of occurrence	✓				
3	Submission of progress reporting for multi-year studies	Yr 1	Yr 2	Yr 3	Yr 4	Yr 5
		N/A	N/A	N/A	N/A	N/A
4	Submission of end of project report (Hard copy)	✓				
5	Submission of end of project report (Soft copy)	✓				
6	Submission of data sets	✓				

List of reviewed documents

Ref.	Documents	Reviewed documents (tick appropriate box)
1	Completed application form	✓
2	Cover letter	✓
3	Evidence of administrative permission to conduct the research by involved institutions/sites (where applicable)	✓
4	Detailed current resume or curriculum vitae of Principal Investigator/s including Principal investigators declaration	✓
5	Summary resume or biography for other investigator(s)	✓
6	Evidence of approval/rejection by other Ethics Committees, including comments and requested alterations to the protocol, where appropriate.	
7	Research protocol (see outline in Annex 1)	✓
8	Questionnaires and interview guides (with back-translated versions where applicable)	✓
9	Case report forms (CRFs), abstraction forms and other data collection tools	✓
10	Participant/subjects Information Statement(s) (where applicable)	✓
11	Informed consent form(s) including photographic and electronic media consent statements.	✓
12	Advertisements relevant to the study (where applicable)	
13	Source of funding and detailed budget breakdown including material and incentives to participants if applicable	
14	Notification form for adverse effects/events.	
15	Proof of payment	✓
16	Proof of insurance cover for research subjects in clinical trials or where applicable	
17	Any other special requirements should be stated, if applicable	None

APPENDIX 3: University of Witswaterand HREC Ethics Clearance Certificate

R14/49 Ms Linda Mirira

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M170803

NAME: (Principal Investigator)	Ms Linda Mirira
DEPARTMENT:	Peadiatrics and Child Health, Division of Community Paediatrics Mbabane, Swaziland
PROJECT TITLE:	Factors Associated with PCR Positivity in HIV Infants at 6-8 Weeks in Swaziland
DATE CONSIDERED:	25/08/2017
DECISION:	Approved unconditionally
CONDITIONS:	South African Human Research Ethics Committees (HRECs) have no standing outside South Africa.
SUPERVISOR:	W. Slemming and O. Tagutanazvo
APPROVED BY:	C B Penny 1/9/2017 Professor C. Penny, Co-Chairperson, HREC (Medical)
DATE OF APPROVAL:	31/08/2017

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 301, Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in August and will therefore be due in the month of August each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature _____ Date _____

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX 4: Letter for permission to access data

Telegrams:
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Fax: (+268 404 2092

MINISTRY OF HEALTH
P.O. BOX 5
MBABANE
SWAZILAND

THE KINGDOM OF SWAZILAND

4th July 2017

Permission to access data for secondary analysis

This serves as a confirmation that permission is granted to **Linda Mirira** to access data for the study "**Factors associated with PCR Positivity in HIV exposed infants at 6-8 weeks in Swaziland"**. Permission to access this database is subject to final approval by the relevant academic institution.

MINISTRY OF HEALTH P.O. BOX 5 MBABANE TEL (+268) 404 2431 14 JUL 2017 MONITORING EVALUATION UNIT GOVERNMENT OF SW...

Sebentile Myeni
Senior M&E Officer
04th July 2017