UNIVERSITY OF THE WITWATERSRAND

UNIVERSITY OF THE
WITWATERSRAND,
JOHANNESBURG

TITLE: THE EFFECT OF MATERNAL HIV INFECTION ON PREGNANCY AND INFANT SURVIVAL OUTCOMES IN AGINCOURT, RURAL NORTHEAST SOUTH AFRICA, 2015-2019.

Name: **Denny Mabetha**

Student Number: **1915798**

Supervisor:

Dr. Chodziwadziwa Whiteson Kabudula

November 2021

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 in Field Epidemiology

DECLARATION

I, Denny Mabetha declare that this is my own unaided work. It is being submitted in the fulfilment of the requirements for the degree of Master of Science in Field Epidemiology at the University of the Witwatersrand, Johannesburg. This research has not been submitted before for any degree or examination to any other university.

10November 2021

……

Signature

……

Date

DEDICATION

I dedicate this work to my God for his mercy and grace. To my children Kuvonga and Singita, thank you for being patient with me and for always giving me reasons to work even harder and to my parents and siblings for supporting me throughout my studies.

ABSTRACT

Background: HIV infection is an important cause of maternal and perinatal morbidity and mortality in Sub-Saharan Africa. HIV infected pregnant women have been found to have higher risks of having adverse outcomes such as stillbirth, congenital malformation, miscarriages and other birth-related complications. In addition, Infants born from HIV positive mothers have been found to be at high risk of dying as compared to infants born from HIV negative mothers.

Available evidence in the literature shows that the magnitude of the effect of maternal HIV infections on pregnancy and infant survival outcomes is vary across space and time. Therefore, there is an ongoing need to assess the effect of maternal HIV infections on pregnancy and infant survival outcomes in different settings with high prevalence levels of maternal HIV infections.

Aim: The study aims to assess the effect of maternal HIV infection on perinatal and infant survival outcomes in Agincourt, rural South Africa over the period 2015-2019.

Methods: Secondary data from two data sources, the routine Agincourt HDSS and the Agincourt HDSS-Clinic Link Study data collected from 2015-2019 among 10942 pregnancies were analyzed. A descriptive analysis was conducted to describe maternal characteristics of total sample and across HIV status, to describe the distribution of adverse perinatal outcome (abortion, low birth weight and preterm delivery). Binary logistic regression was used to model the unadjusted and adjusted association between adverse perinatal outcomes and maternal factors. Lasty Kaplan-Meier curves were used to describe the patterns of infant mortality and the Cox regression technique was used to obtain both the Crude hazard ratio (CHR) and adjusted hazard ratio by maternal factors. To compare the effect of maternal HIV infection, the above process was performed for the total sample of all women regardless of their HIV status and for observations from women with known HIV status.

Results: The total sample included 10942 pregnancies regardless of HIV status with 4661 pregnancies in the HIV negative subgroup. Prevalence of maternal HIV infections among women aged 13-49 years was 16.58%. Maternal HIV infections were associated with preterm delivery in the multivariate logistic regression (OR=2.12;95%CI: 1.28 – 3.51). There was no association between maternal HIV and low birth weight. The risk of abortion/stillbirths and preterm deliveries

was double for women who attended 3 or less antenatal care (ANC) visits in the adjusted model for both total sample and sample consisting of women with known HIV status. Attending 3 or less ANC visits was also a risk factor of infant mortality (OR: 1.96; 95% CI; 0.91 – 4.23).

Conclusion: There is no difference in risk of having adverse perinatal outcomes including infant mortality between HIV infected and non-infected mothers. The result from this suggests that introduction of ART to all pregnant women regardless their CD4 counts in the past 5 years made a huge impact in combatting adverse perinatal outcomes. There has been a decrease in cases of pregnancy loss, low birth weight (LBW), preterm delivery (PTD) and infant mortality over the years.

Keywords: Maternal HIV, outcomes, infants

ACKNOWLEDGEMENT

This work took a lot of the support of many individuals and without their support it would have not been possible to complete.

Firstly, I would like to acknowledge my supervisor Dr Chodziwadziwa Whiteson Kabudula for his continuous support, supervision, and his guidance in completing my research project. I extend my gratitude to the MRC/Wits Rural Public Health and Health Transitions Research Unit (Agincourt) for the financial support and for providing me with the data. A special thanks to my managers Dr Twine from the MRC/Wits Agincourt Unit and DR D'Ambruoso from the University of Aberdeen for their support.

I would also like to thank Innocentia Vukeya, Dr Ndlovu, Prof Levin and all the lecturers from school of Public Health at the University of the Witwatersrand for imparting their knowledge and their guidance through my studies.

Finally, I want to thank everyone who assisted me directly or indirectly through the whole process.

Table of contents

CHAPTER ONE: INTRODUCTION

This chapter gives an overview of global maternal HIV infections and how it affects perinatal outcomes and infant survival in the rural settings of South Africa. It discusses various adverse perinatal outcomes associated with maternal HIV infections, including infant mortality. It also defines key concepts around perinatal outcomes and identifies gap in the existing literature on the effects of maternal HIV infections on perinatal outcomes and infant mortality. The chapter ends with an adapted conceptual framework for this study.

1.1. Background

HIV infection is a significant cause of maternal and perinatal morbidity and mortality in Sub-Saharan Africa (Paulo, 2015; Dzanibe *et al.*, 2019). The main negative impact of maternal HIV infections are the potentially increased risk of negative pregnancy and fetal health (Joseph, Biodun and Michael, 2011). HIV infected pregnant women have been found to have higher risks of having adverse outcomes such as stillbirth, congenital malformation, miscarriages and other birth-related complications (González *et al.*, 2017). Maternal HIV infections and infant survival are also highly interrelated (Evans, Jones and Prendergast, 2016). Infants born from HIV positive mothers have been found to be at high risk of dying as compared to infants born from HIV negative mothers in Africa (Marinda *et al.*, 2007; Kurewa *et al.*, 2010). Maternal HIV infections contributes to infant mortality directly through mother-to-child HIV transmission (MTCT) or indirectly through maternal ill-health (Rao, Lopez and Hemed, 2006).

The rate of negative outcomes led to global consensus that pregnant women who are HIV positive should receive timely diagnosis and be provided with antiretroviral treatment to reduce the negative consequences of HIV (Joseph, Biodun and Michael, 2011). This is in addition to multi-nutrient supplementation and vitamin A supplementation which are given to pregnant women as other measures to improve pregnancy outcomes (Ikpim *et al.*, 2016).

Available evidence in the literature shows that the magnitude of the effect of maternal HIV infections on pregnancy and infant survival outcomes vary across space and time. Work done post Prevention of mother-to-child transmission (PMTCT) in China found HIV-infected women to be at risk of low birth weights and preterm delivery as compared to Non-HIV infected women (Xiao

et al., 2015) while González *et al.*(2017) reported that HIV infected women had double the risk of stillbirths while no differences in prematurity, birth weight and neonatal mortality between the HIV infected and non-infected women was noted in Mozambique. In addition, maternal HIV infections remain a contributing factor of adverse perinatal outcomes in different settings of South Africa (Naidoo, Sartorius and Tshimanga-Tshikala, 2016; Madhi *et al.*, 2019) . Thus, there is an ongoing need to assess the effect of maternal HIV infections on pregnancy and infant survival outcomes in different settings with high prevalence levels of maternal HIV infections. This is essential to guide the setting of locally relevant programs to address the negative consequences of maternal HIV infections on pregnancy and infant survival outcomes. Therefore, this research study investigates how maternal HIV infections have impacted pregnancy and infant survival outcomes in Agincourt, rural northeast South Africa over the period 2015-2019.

1.2.Problem statement

South Africa has the biggest HIV epidemic in the world, with about 7.1 million people living with HIV in 2017. The burden of the HIV epidemic is disproportionately higher among the black population and differs widely between provinces and local communities (Klaas, Thupayagale-Tshweneagae and Makua, 2018). The highest HIV prevalence is reported in the north-eastern parts of the country while western parts of the country have the lowest prevalence (Klaas, Thupayagale-Tshweneagae and Makua, 2018). Women have been found to have high prevalence of HIV infections compared to men.

Overall HIV prevalence among pregnant women aged 15 – 49 years exceed 30 % in Mpumalanga, KwaZulu-Natal and Eastern Cape provinces, while Free State, Gauteng, North West and Limpopo provinces are standing between 20% and 30% and below 20% in Western Cape and Northern Cape provinces (Babb and Pruett, 2019). South Africa is among the countries with largest public HIV treatment and care programme that provide a lifelong highly active antiretroviral therapy (HAART) for all eligible pregnant and breastfeeding women irrespective of their CD4 count (Van Der Merwe *et al.*, 2011; Malaba *et al.*, 2017).

Although there are interventions such as HAART in place, maternal HIV infections continues to have a detrimental effect on pregnancy and infant survival outcomes (González et al., 2017).

Therefore, there is ongoing need to assess the effect of maternal HIV infections on pregnancy and infant survival outcomes in different settings with high prevalence levels of maternal HIV infections. This work attempts to guide the setting of locally relevant programmes to adequately address the negative consequences of maternal HIV infections on perinatal and infant survival outcomes.

1.3.Justification of the study

Studies done globally have shown that maternal HIV infections are associated with unfavorable perinatal and infant survival outcomes (Kurewa *et al.*, 2010; Paulo, 2015; González *et al.*, 2017). Studies in South Africa also provide evidence that despite high ART coverage, good maternal health and very low vertical HIV transmission rate, maternal HIV infection continues to have detrimental effects on perinatal outcomes and in early infancy (Venkatesh *et al.*, 2011; Naidoo, Sartorius and Tshimanga-Tshikala, 2016; Santosa *et al.*, 2019). However, limited information exists that reflect on factors associated with adverse perinatal and infant survival outcomes in different South African settings, especially the north-eastern part where HIV is more prevalent.

The study proposed in here will attempt to address this problem by assessing the effect of maternal HIV infections on perinatal and infant survival outcomes in the rural setting of Agincourt in Bushbuckridge Municipality, Mpumalanga Province, South Africa. Findings in this study have a potential to contribute to the strengthening of public health systems to adequately address the negative consequences of maternal HIV infections on perinatal and infant survival outcomes in South African rural settings.

1.4.Research questions and aims

Research question: What is the association between maternal HIV infection and perinatal and infant survival outcomes in Agincourt rural North-East South Africa, 2015-2019?

Aim: The study aims to assess the association between maternal HIV infection and perinatal and infant survival outcomes in Agincourt, rural South Africa over the period 2015-2019.

The objectives are:

1. To describe the social, demographic, and economic characteristics of HIV infected and non-infected women aged between 15 – 49 years in Agincourt from 2015 to 2019.
2. To describe the trends of perinatal and infant survival outcome amongst HIV infected and non-infected women in Agincourt, rural South Africa over the period of 2015 -2019.
3. To determine maternal factors associated with adverse perinatal outcomes and infant mortality amongst HIV infected and non-infected women in Agincourt over the period of 2015 to 2019.

1.5. Literature review

1.5.1. PMTCT and ART guidelines

Around 37.9 million people globally were estimated to be living with HIV in 2018, 1.7 million were newly infected. Around 6000 young women aged 15–24 years become infected with HIV every week (UNAIDS, 2019). There are approximately 2.1 million children below the age of 15 years living with HIV infections of which 90% occurred in a region with highest burden of infectious diseases, Sub-Saharan Africa (Dzanibe *et al.*, 2019). In South Africa, 4 200 000 women were known to be living with HIV in 2017 (UNAIDS, 2018)

The South African government rolled-out a national PMTCT program since 2002 as an intervention to reduce MTCT (Burton, Giddy and Stinson, 2015). In 2005 it joined other Sub-Saharan African countries in prioritizing the provision of antiretroviral therapy for HIV pregnant women (Moodley *et al.*, 2016) and later introduced lifelong HAART for all eligible pregnant and breastfeeding women irrespective of their CD4 count in 2015 (Burton, Giddy and Stinson, 2015). There has been a lot of interventions developed and improved to prevent MTCT over the years. Table 1 gives a summary of developed interventions.

Table 1: Changes in national PMTCT and ART guidelines from 2002-2015, South Africa.

Year	PMTCT guidelines
2002	A single dose of Nevirapine was introduced to mothers during labour and to the infants within the first 72 hours of life.
2004	A National roll-out of Antiretroviral programme, zidovudine was introduced to mothers classified under for WHO stage 4 disease from 28 weeks gestation. A single dose of Nevarapine was given to mothers during labor and to the infant within 72 hours of birth.
2008	Introduction of zidovudine to mother from 28 weeks gestation, single dose nevirapine to mother in labour and to infant within 72 hours of birth
2010	Introduction of zidovudine from 14 weeks gestation, a single dose of nevirapine and tenofovir/ 3TC in labour, infant prophylaxis with nevirapine for 6 weeks provided the mother is on HAART or formula feeding, or until the end of breastfeeding if mother not eligible for HAART.
2013	All pregnant women eligible for HAART, irrespective of CD4 count. Infant prophylaxis with nevirapine for 6 weeks. Women initiating HAART with CD4 count of less than 350 and no other indication for HAART, to stop treatment after all breastfeeding has ended.
2015	All pregnant and breastfeeding women eligible for lifelong HAART. Eligibility for HAART includes CD4 count of less than 500 cells/mm3

(Burton, Giddy and Stinson, 2015)

The rates MTCT were 30 – 40% prior implementation of antiretroviral treatment, however, have since been reduced to 1–3% following an adoption of these programs. MTCT rated have also dropped in resource-limited settings (Dzanibe *et al.*, 2019). The improvement of the PMTCT program over the years also came with decreasing numbers of HIV infected infants (Barron *et al.*, 2013).

1.5.2 HIV infections and adverse perinatal outcome

Untreated HIV infection in pregnancy is linked with increased risks of several adverse outcome as well as still births (Bailey, 2018). HIV infected women in their reproductive age are capable of

passing the infections to their fetus, (Ikpim *et al.*, 2016). Transmission mainly occur during fetal development in utero and perinatally during labor, delivery or postpartum during breastfeeding (Dzanibe *et al.*, 2019). These negative outcomes are due to immunological changes which are induced by fetal exposure to the maternal HIV infections (Dzanibe *et al.*, 2019).

The changes include increased proinflammatory responses of innate and adaptive immune cells which lead to negative impact on the maternal/fetal unit, resulting in an increase in spontaneous abortions, low birth weight, and increased susceptibility to infections also in HIV-uninfected but exposed infants (Pfeifer and Bunders, 2016).

Another possible mechanism describing how maternal HIV infection leads MTCT and adverse pregnancy outcomes is increased proinflammatory cytokine on maternal placental cells. As an indicator of immune response towards infections, this process interrupts the normal build-up of an infant's immune system interfering with a normal development of the fetus. In addition, women are immunocompromised during pregnancy which makes them susceptible to develop reproductive tract infections that is linked to adverse perinatal outcome (Yang *et al.*, 2019).

Studies including work conducted at Benin teaching hospital in Nigeria post introduction of PMTCT program, found that HIV positive women were significantly more likely than HIV negative women to have higher incidence of adverse perinatal outcomes such anemia during pregnancy, still birth, preterm labor and low birth weight (Olagbuji *et al.*, 2010; Macdonald *et al.*, 2015; Yang *et al.*, 2019). Evidence from these studies support the hypothesis that maternal HIV infections has negative impact pregnancy outcomes.

A metanalysis including 35 studies, 25 from Sub-Saharan Africa found maternal HIV infections to be significantly linked with preterm delivery, low birth weight and still birth. However, the evidence did not support an effect of maternal HIV infections on neonatal death, miscarriage and very low birthweight on preterm birth (Wedi *et al.*, 2016). In a recent similar study conducted in China, HIV positive women had increased risks of having adverse pregnancy outcomes as compared to non-infected however, high prevalence of these outcomes were observed in rural areas with limited resources and access to health services. These findings suggest that apart from HIV infections, there could be other contributing factors linked to adverse outcomes (Yang *et al.*, 2019)

1.5.2.1. Perinatal deaths

Maternal HIV infection and still birth and abortion

Abortion is defined as the ending of pregnancy and expulsion of an embryo or a fetus prior to completion of 20 weeks of gestation while still births is defined as a fetal death occurring after completion of 20 weeks of gestation (González *et al.*, 2017). These perinatal deaths have been reported to be highly associated with maternal HIV infections.

A study conducted in Mozambique found HIV infected women to be at a high risk of having still births as compared to uninfected women (González *et al.*, 2017). Similar results were also observed in South Africa. However, an improvement in the rate of stillbirths was also registered over the period 2011 and 2014 (Moodley *et al.*, 2016). Besides HIV, there are others contributing factors of pregnancy loss.

Factors such as the low maternal body mass index ,use of HAART in pregnancy, poor maternal nutritional status and presence of opportunistic infections have been found to be associated with still births and abortions (Olagbuji *et al.*, 2010; Santosa *et al.*, 2019).

1.5.2.2. Low birth weight

Low birth weight (LBW) is defined as a birth weight below 2500 g (Ndirangu *et al.*, 2012). Available evidence indicates that LBW infants or those born before gestational periods have increased rates of illnesses and mortality (Schulte *et al.*, 2015). Ikpin *et.al* (2016) have argued that it is an undeniable fact that LBW is the major contributing factor for neonatal and early infant mortality in all populations regardless of maternal HIV status. The prevalence of LBW are reportedly higher among certain risk groups, including women who use illegal drugs or have sexually transmitted diseases (Schulte *et al.*, 2015).

A study by (Kurewa *et al.*, 2010) reported LBW to be high in HIV infected mothers compared to non-infected mothers. Another cohort study conducted in the United States of America (USA) found similar results, LBW were higher among infants born to HIV-infected women compared with the general population with high concentration among mothers who were not taking antiretroviral drugs (ARVs).

Some studies found no significant association between LBW and HIV infection among mothers who are on ARVs. In these studies, LBW was associated with socio-demographic and medical

factors such as gravidity, maternal age, nutritional status, obstetrical history, medical risks and antenatal care. Other contributing risks of LBW included maternal drug use and symptomatic maternal HIV disease (Schulte *et al.*, 2015; González *et al.*, 2017).

Schulte *et al.* (2015) observed that between 1989 and 2004 the proportion of LBW infants declined from 35%in 1989 to 21%in 2004 and reached a lowest point of 19%in 2003. This decline is assumed to be due to evolving of highly potent HAART of therapy for maternal treatment and perinatal HIV prevention, rejecting the hypothesis that HIV positive mothers deliver LBW infants.

In a South African study by Moodley *et al.* (2016), HIV infection remained a significant risk factor for LBW. Like findings in other studies, this study also found that the risk was much higher in women who were not taking ARVs, supporting the hypothesis that maternal HIV infections contribute to LBW infants.

1.5.2.3. Preterm delivery

Preterm delivery (PTD) is defined as birth before 37 completed weeks of pregnancy (Van Der Merwe *et al.*, 2011). PTD is among the most crucial factor determining neonatal morbidity and mortality (Fuchs *et al.*, 2018). Delivery of infants before time can be caused by the presence of infections such as urinary tract infections, malaria, bacterial vaginosis, syphilis and HIV in pregnant women (Naidoo, Sartorius and Tshimanga-Tshikala, 2016). Although there is high prevalence of preterm birth among the HIV infected mothers especially in rural areas, PTD are found not to be associated with maternal HIV infection but dependent on maternal age, low maternal weight, symptomatic maternal HIV disease, poor socio economic status and maternal drug use among other factors (Olagbuji *et al.*, 2010; Van Der Merwe *et al.*, 2011; Rollins *et al.*, 2013). Findings from these studies suggest that there are factors contributing to PTD that need attention.

1.5.2.4. Infant mortality

The rise in interventions for eliminating pediatric HIV infections has shown to decrease number of infants infected with HIV. However, number of HIV exposed uninfected infants continue to increase (Evans, Jones and Prendergast, 2016; Dzanibe *et al.*, 2019). HIV-exposed uninfected infants have been found to have increased infectious morbidity, increased mortality rates and impaired growth compared with HIV-unexposed infants.

HIV exposed uninfected infants more likely suffer from severe infections such as lower respiratory tract and gastrointestinal infections in their first year of life compared to HIV unexposed infants. This is as a result of many contributing factors such as i) increased exposure to maternal viral and bacterial infections, ii) severity of maternal HIV infections whereby infants born to mothers with high HIV viral loads and low CD4+ lymphocyte count are more likely to die than unexposed infants, iii) poor feeding practices such as breastfeeding avoidance and mix feeding iv) malnutrition and por adherence to ARV treatment (Dzanibe *et al.*, 2019).

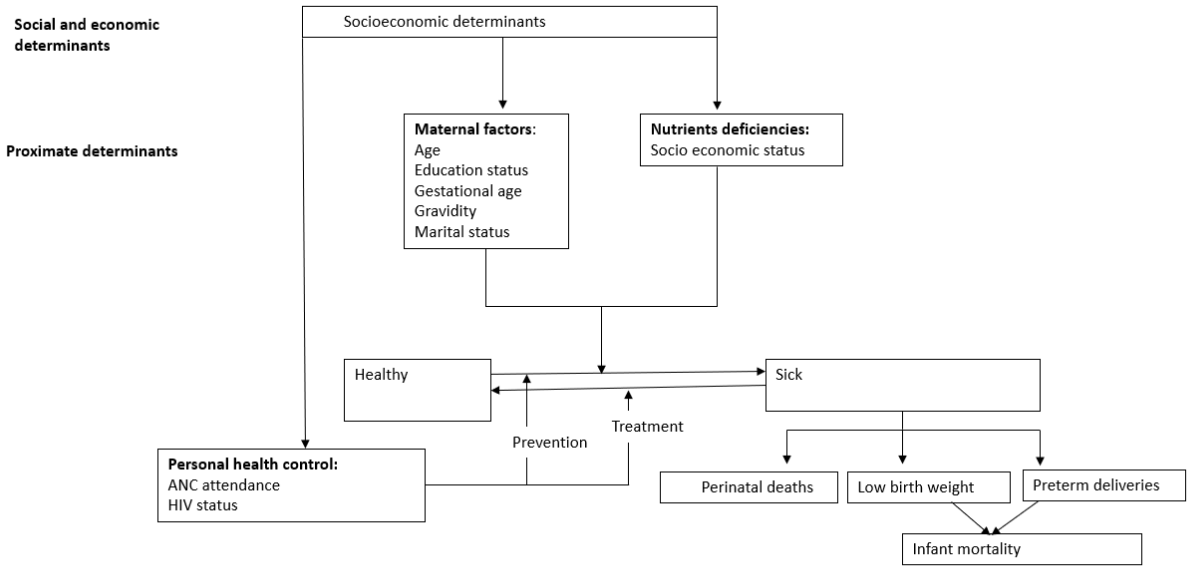
Several studies have found maternal HIV infections to be associated with infant mortality. A study conducted in Zimbabwe revealed that infants born to HIV-infected mothers were three times more likely to die as compared to those born to HIV-negative mothers (Kurewa *et al.*, 2010). (Marinda *et al.*, 2007) in a study with 14,110 mother–infant pairs found that the death rate among infants born to HIV-positive mothers was ten times higher compared to that in infants born to HIV-negative mothers. The study further found that among infants who survived to 6 months, those born to HIV-positive mothers were 16 times more likely to die in the second half of infancy compared to those born to HIV-negative mothers.

Another study in Rwanda found maternal HIV status to be associated with a 3.5 times increased risk of death among children under the age of two years (Mugwaneza *et al.*, 2011). Although they may be other factors that are associated to infant mortally, these results support the hypothesis that exposed infants have increased risk of dying than the non-exposed.

1.5.3. Conceptual framework

The study was guided by the conceptual framework adapted from Mosley and Chen's analytical framework of proximate determinants of health dynamic of a population. (Mosley and Chen, 1984). The conceptual backbone is that socioeconomic and cultural variables operate through a set of proximate determinants that directly influence perinatal and infant survival outcomes. Proximate determinants include categories such as maternal factors (age, education status, HIV status, gestational age), Nutrients deficiencies, socio economic status, and personal illness control (e.g. AHV status, ANC attendance). Following this framework, the proposed study will investigate background and proximate variables, and will incorporate two levels of observation (individual and household level).

Figure 1: Conceptual framework



Adapted from: (Mosley and Chen, 1984)

CHAPTER 2: METHODOLOGY

2.1. Introduction

This chapter describes the study design, study site and study population. It also provides justification for the chosen study site. Other sections of this chapter provide details of the data collection procedure and management, study variables, data analysis plan and ethical considerations.

2.2. Study design

A retrospective cohort study design was used to assess the effect of maternal HIV infection on perinatal and infant survival outcomes using secondary data collected from the Agincourt Health and Demographic Surveillance System (HDSS) 2015-2019.

2.3. Study site

The Agincourt HDSS study area is situated in Bushbuckridge sub-district of Mpumalanga Province, northeast South Africa and covers 31 villages spread over 450 square kilometres. The area is densely populated with about 118,000 individuals in 18,500 households. The population is largely Tsonga-speaking and almost a third are former Mozambican refugees who arrived in the area in the early to mid-1980s and their descendants (Kahn *et al.*, 2012).

Infrastructure and population density in the study area are heterogeneous ranging from fully serviced houses to isolated rural homesteads. There is little formal sanitation and electricity is universally available but affordable only to a minority. Unemployment is also high in the area. In addition, about 84% of the population live below the poverty line and a significant number of households rely on social grants for survival (Kahn *et al.*, 2012).

The Agincourt HDSS population has been under surveillance since 1992 by the MRC/Wits Rural Public Health and Health Transitions Research Unit (Agincourt). Over the years, the HDSS has evolved into a robust research infrastructure supporting advanced community-based research with studies ranging from the biomedical to the ethnographic designs(Kahn *et al.*, 2007, 2012).

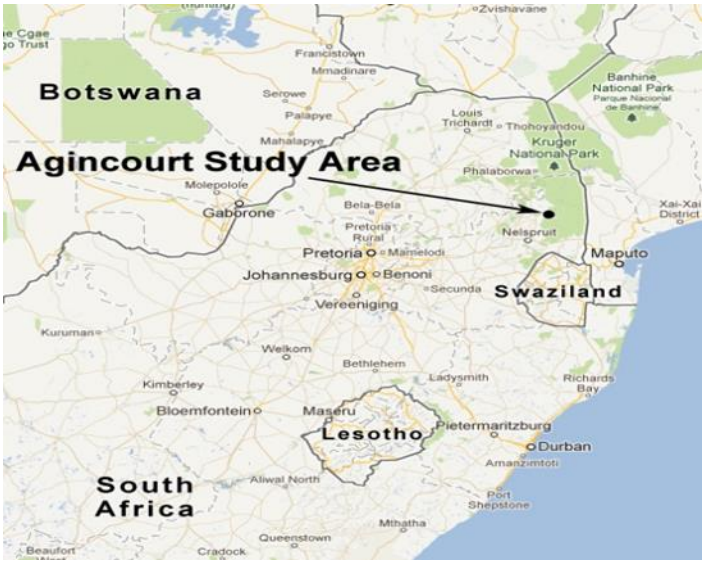


Figure 2: A map of Agincourt HDSS in Mpumalanga rural North East South Africa

Source: (Kahn *et al.*, 2007)

2.4. Study population

The study population included in the analysis comprised of all pregnant women who were part of the household census that is conducted routinely in the Agincourt HDSS and had attended at least one antenatal visit at any of the nine primary health care facilities within the Agincourt HDSS study area during the period of 2015 – 2019.

2.5. Study sample

No sampling technique was applied. All pregnancies that occurred during 2015-2019 and all infants aged one year or less who were born from the women who were pregnant during this period were included in the study. The study sample included 10962 pregnancies from 10962 women, 3 pregnancies were dropped because they had missing data on the outcome of interest and 17 because they were outside the desired age range. The total number of pregnancies that were included in the final analysis were 10942.

2.6. Data collection method

The dataset used in this study was collected from two sources obtained from the MRC/Wits Rural Public Health and Health Transition Research Unit (Agincourt) which runs the Agincourt HDSS and is conducting the Agincourt HDSS-Clinic Link study. The first data consisted of demographic, HIV counseling and testing and care and treatment data collected from pregnant women visiting

nine public health facilities in the Agincourt (HDSS) study area. The second dataset consisted of individual and household characteristics, pregnancy outcomes, and survival status collected from residents of the Agincourt HDSS.

The data from the public health facilities came from a large study on Record Linkage of Health registries within the Agincourt HDSS (Agincourt HDSS-Clinic Link study). In this study, whenever a new patient presented at a health facility, a data clerk first explained the study objectives and obtained written informed consent to collect medical data and to link that to the Agincourt HDSS population. The data clerk subsequently collected a set of identifiers that were used to search and match individuals to the Agincourt HDSS population database (Kabudula *et al.*, 2014). In addition to identifying the patient in the Agincourt HDSS database, the data clerk extracted information from the medical records, including the date of HIV positive diagnosis; CD4 count at HIV diagnosis; date of ART initiation; dates of follow-up care and treatment visits as well as follow-up CD4 counts and viral load results. The data that were collected at the clinic facilities and the population database were merged using the parent ID and relevant variables were included for the study. Only data from pregnant women and their infants was used in this study.

2.6.1. Study variables

For this study, perinatal and infant survival outcomes were the main outcomes of interest and HIV status of the pregnant women was the exposure variable. Both the exposure and outcome variables of interest are explained in detail below:

2.6.1.1. Outcomes:

The study investigated the following 'adverse outcomes':

- Stillbirths: defined as the death or loss of a baby before 36 weeks of gestation.
- Abortion: defined as the termination of pregnancy within first 28 weeks of pregnancy.
- Preterm delivery: defined as the delivery a live baby before 37 weeks of pregnancy are completed.
- Perinatal death: the sum of stillbirths and abortions
- Low birth weight: defined as infant birth weight of 2.5 kg or less.
- Infant death: defined as the death of an infant before the first birthday.

2.6.1.2. Exposure variable and other explanatory variables

The main exposure variable of the study was maternal HIV status which was classified as either HIV positive or HIV negative. The following explanatory variables were included in the analysis:

- Maternal age: refers to the age category of the woman at the time of pregnancy and was categorised into the following: 13 – 19 years, 20 – 29 years, 30 - 39 years and 40 – 49 years.
- Residential status: refers to residential status of the woman at the time of pregnancy with the following categories, permanent and temporary/other residence.
- Education status: refers to level of education of the woman at the time of pregnancy categorised as "primary school level", "secondary school" and "complete secondary and/or higher school level".
- Marital status: refers to marital status at the time of pregnancy categorized as "single", "married/ cohabiting" and "widowed/ divorced/separated".
- Socioeconomic status: refers to the household wealth of the woman's household at the time of pregnancy measured using household assets and categorised into "Quintile 1", "Quintile 2", "Quintile 3", "Quintile 4" and "Quintile 5".
- Gravidity: refers to the number of times that a woman has been pregnant including the current pregnancy and categorised into 1, 2, 3 and 4 or more pregnancies.
- Number of ANC visits attended: refers to the number of antenatal care visits attended by the woman during the pregnancy categorised into "3 or less visits" and "4 or more visits".
- Delivery attendant: refers to the person who assisted or attended to the woman during delivery categorised into "Health care professional" (Midwife, doctor, nurse) and "Other" (family member, community member).

2.6.2. Data cleaning and quality check

STATA 15 was used to merge the data from the two sources as well as cleaning and analysis. Data cleaning was initially done by dropping all variables that were not relevant for the study such as the village name and household relation. The cleaning process was followed by data checking and reduction process which included checking for missing and miscoded data. Frequency tables were computed for categorical variables to investigate if all the observations were fitted within the

allowed categories. For example, an outcome value was indicated as a live birth instead of multiple liveborn in case of delivery of twins. Normal probability plots were used to check for the distribution of continuous variables (for example, all women outside the 13 – 49 years old range were removed from the analysis).

Variables with missing values on the explanatory variables were further investigated and computed using appropriate procedure. For example, some observations had missing values on the marital status, to address this a simple imputation process was done assuming that the woman's marital status from the previous year remained the same for the following year.

Variables were further labelled to make analysis and interpretation of results easy. The data reduction process included deriving categorical variables from continuous variables. For example, recoding the discrete variable, year of education into 5 levels of education categories. This step was conducted to create an ordinal outcome to fulfil objective 3 of the study. Noting the variation in responses for certain answers of education status, for example there were only 4.70 percent of women with tertiary education and more than 80 percent with higher secondary education level therefor further recategorization was done to reduce into 3 ordinal categories of education level.

For the purpose of this analysis, other variables were recategorized for example, relationship status was recategorized by collapsing 5 categories into 3 categories that best fit the study. Some new variables were generated using other variables. For example, age at death of infant was generated using delivery and date of death of an infant.

After the data checking process, data was re-examined to investigate errors and to get an understanding of the study population characteristics. The initial sample size of 10962 observations which was reduced to 10942 after the data management process. The multiple outcome variable was investigated and categorized accordingly. There were 70 twin deliveries (n=140) and 1 set of triples (n=3). So, the total number of pregnancy outcomes was 11082. Table 2 demonstrate in detail the data management process for each variable for the study.

Table 2: Data management process

Variable	Initial variable type	Procedure	Categories in analysis
Outcome variable			
Outcome	A categorical variable with 6 categories: Abortion Livebirths Multiple live births Stillbirth Multiple stillbirths Unknown	The outcome variable was collapsed into 2 perinatal outcome variables Still births and abortion ('Stillbirth, Multiple stillbirths, abortion') and Live births ('multiple livebirths, live births')	0 Live births 1 fetal death (in utero)
Birth weight	A numeric variable – birth weight in kg	A summary statistic was used to investigate outliers, observations with missing values and those outside 0.5 – 6 kg were dropped. Birth weights were further categorised into 2 groups, low birth weight (< 2.5kg) and normal birth weight (>=2.5 kg)	0 Normal birth weight 1 Low birth weight
Pregnancy duration	Numeric variable – duration of pregnancy in weeks	Pregnancy duration was categorized into 2 groups, preterm delivery (<36 weeks) and term delivery (>=37 weeks)	0 term delivery 1 preterm delivery
Infant survival/death	Derived	Derived from a subset of the main dataset on 'live births'. Censoring was done to generate survived and dead infants by first birthday.	0 survived 1 Dead
Explanatory variables			
Maternal age	Numeric variable – maternal age in years	A histogram was used to investigate outliers. Women outside 13 – 49 years old were dropped. Maternal age category was categorised into 6 age groups.	0 13 – 19 years 1 20 – 29 years 2 30 - 39years 3 40 – 49 years

Pregnancy variable	Derived	Generated from number of outcomes of each pregnancy and categorised into 3 groups (one group for single delivery and two groups for multiple deliveries).	0 Singletons 1 Twins deliveries 2 Triplets deliveries
Education categories	Numeric variable – years of education standards level	Generated from education level standards in years and categorised into 3 levels.	0 No education or primary level 1 Secondary level 2 Completed secondary education and more
Residential status	Categorical variable with 8 categories (permanent, education, migrants, visitor and other categories)	Generated from recategorizing 8 categories into a binary residential status variable	0 Permanent residence 1 Temporary residence
Relationship status	Categorical variable with 5 categories	Generated from recategorising the marital status variable into 3 categories	0 single 1 Married/cohabiting 2 widowed/ divorced
Socio economic status (SES)	Number of asset items owned by each household.	Information from a number of asset items (livestocks, source of water, housing material, household items including electronic appliances) was used to compute a household wealth index using principal component analysis (PCA). The PCA derived household wealth index was used to generate 5 SES quintiles ranging from poorer to rich quintile	0 Q1 1 Q2 2 Q3 3 Q4 4 Q5

Gravidity	Numeric variable – number of times a woman has fallen pregnant including the current pregnancy	Generated by collapsing the numeric variables into 3 categorical variables	0 0nce 1 twice 2 thrice 3 4 and more pregnancies
Number of ANC visits	Numeric variable – number of ANC clinic visits	Generated by collapsing the numeric number of visits into binary variable	0 3 or less ANC visits 1 4 or more clinic visits
Delivery attendant	Categoric variables with 7 categories that include nurse, family member, doctor and community member	The attendant variable was collapsed into a binary variable with the following levels: healthcare professional and other	0 Healthcare professionals 1 Other

2.7. Data analysis

2.7.1. Analysis methods for perinatal outcome

2.7.1.1. Descriptive analysis:

A bivariate descriptive analysis was conducted for categorical variables to describe the distribution of adverse perinatal outcomes (perinatal death, LBW and PTD).

Objective 1: To describe the sociodemographic characteristics of HIV infected and non-infected women aged between 13 – 49 years in Agincourt from 2015 to 2019.

The data to address this objective consisted of 5 maternal demographic categorical variables (age, marital status, residential status, education, and socio-economic status). Cross tabulations were computed to understand the characteristics of the study population. Chi-square test was also used to compare the association of the characteristics and HIV status. This was also done for the total sample to compare if there are differences.

Inferential analysis:

To identify factors associated with adverse perinatal outcomes, a binomial logistic regression was built using maternal factors that include HIV status, age, residence status, education status, marital status, socio economic status, gravidity, number of ANC visit and attendance personnel during delivery. The variables were first checked for independent association to each outcome variable. The adjusted model was then fitted with all variables. The results will be interpreted using the odds ratios and the level of statistical significance set at p =0.05 and marginally significant at p<0.05-1.00. Separate models were run for the total sample of women and for the sample with known HIV status.

Objective 2: To describe trends in perinatal outcomes amongst HIV infected and non-infected women in Agincourt, rural South Africa over the period of 2015-2019.

The trends of the outcomes were investigated using percentages and visually presented using stacked bar graphs to show changes over the period of 2015 – 2019.

Objective 3: To determine maternal factors associated with perinatal outcomes amongst HIV infected and non-infected women in Agincourt over the period of 2015 to 2019.

Outcome variables for this objective include perinatal deaths , low birth weight and preterm delivery. Exposure/explanatory variables include HIV status, maternal age, residential status, education status, relationship status, socio economic status, gravidity, number of ANC visits, and delivery attendant.

Pearson chi-square test was performed to check for association of each exposure variable with perinatal outcomes. To identify factors associated with each outcome, a binomial logistic regression model was built using all exposure variables stated above. First, a univariate analysis using simple logistic regression was employed to determine association between individual exposure variables and the outcome variables. This was followed by multivariable logistic regression which was applied to investigate factors associated with the outcome variables. The Pearson chi-square goodness test was performed to assess whether the model was a good fit. The p-value of <0.05 was set to be statistically significant while p>0.05 -1.00 was marginally significant. This process was performed for the 3 outcome variables and results are presented in Table 3.

To compare the effect of maternal HIV infections on the outcomes, the above process was executed for the total sample of all women regardless of their HIV status and for observations from women with known HIV status (HIV positive and HIV negative status)

2.7.2. Analysis methods for Infant survival:

2.7.2.1.Descriptive analysis:

A bivariate descriptive analysis was conducted for categorical variables to describe the distribution of infant survival status, alive or dead.

Objective 1: To describe the sociodemographic characteristics of HIV infected and non-infected women aged between 13 – 49 years in Agincourt from 2015 to 2019.

The distribution of maternal characteristics was also computed for infant survival which is a subset of the outcome variable “live births”. The results of descriptive analysis are presented in Table 2.

2.7.2.2. Inferential analysis:

The outcome variable was infant survival measured as survival from birth to first birthday and exposure/explanatory variables include HIV status, maternal age, residential status, education

status, relationship status, socio economic status, gravidity, number of ANC visits and pregnancy term. Pearson chi-square test was performed to check for association of each exposure variable with infant survival. Kaplan-Meier curves were used to describe the patterns of infant mortality. A Log rank test was used to compare patterns of mortality between the HIV positive and HIV negative groups.

Objective 2: To describe trends in infant survival outcome amongst HIV infected and non-infected women in Agincourt, rural South Africa over the period of 2015-2019.

The trends of the outcomes were investigated using percentages and visually presented using stacked bar graphs to show changes over the period of 2015 – 2019.

Objective 3: To determine maternal factors associated with infant survival amongst HIV infected and non-infected women in Agincourt over the period of 2015 to 2019.

We used the Cox regression technique to obtain both the Crude hazard ratio (CHR) and adjusted hazard ratio (AHR) together with the corresponding 95% confidence interval and P-value to assess the strength and significance of association between exposure variables and infant survival. In the Cox regression analysis, p-values <0.05 were considered as statistically significant. Kaplan-Meier survival analysis technique was used to assess differences in survival time.

To compare the effect of maternal HIV infection on infant survival, the above process was performed for the total sample of all women regardless of their HIV status and for observations from women with known HIV status (HIV positive and HIV negative status)

2.8. Ethical consideration

The primary studies that collected the data that was used for this study were approved by the Human Research Ethics Committee (Medical) of the University of Witwatersrand, Johannesburg (clearance numbers M090232, M960720 and M110138) and M071141) and the Department of Health in Mpumalanga province. For the secondary analysis in the present study, permission was sought and obtained from the Human Research Ethics Committee (Medical) at the University of the Witwatersrand (Clearance No. M2001013). A letter granting permission for the use of the data for was also obtained from the MRC/Wits Rural Public Health and Health Transition Research Unit (Agincourt). To maintain confidentiality and privacy of information from participants, data

access was restricted to the researchers and participants were de-identified through the use of participants ids.

CHAPTER 3: RESULTS

This chapter presents results of the effect of maternal HIV infections on perinatal and infant survival outcomes. First, the chapter presents descriptive statistics of maternal characteristics and their association with perinatal outcomes. Next, the chapter presents the results from univariate and multivariable logistic regression analysis of factors associated with perinatal outcomes. Presented last are univariate and multivariable cox regression analysis results of factors associated with infant survival.

3.1. Study flow diagram

Figure 3 presents a flow diagram of the study. A total of 10962 pregnancies recorded in the Agincourt HDSS during the period 2015 to 2019 were included in the study. However, 20 pregnancies were excluded because 17 were from women outside the required age range of 13 -49 years and 3 had missing data on outcome variables. As a result, the analysis was restricted to 10942 pregnancies with 11085 outcomes. The difference between the number of pregnancies and outcomes was due some pregnancies having multiple outcomes. There were 70 sets of twins and 1 set of triplets. As a result, there were more outcomes recorded compared to pregnancies.

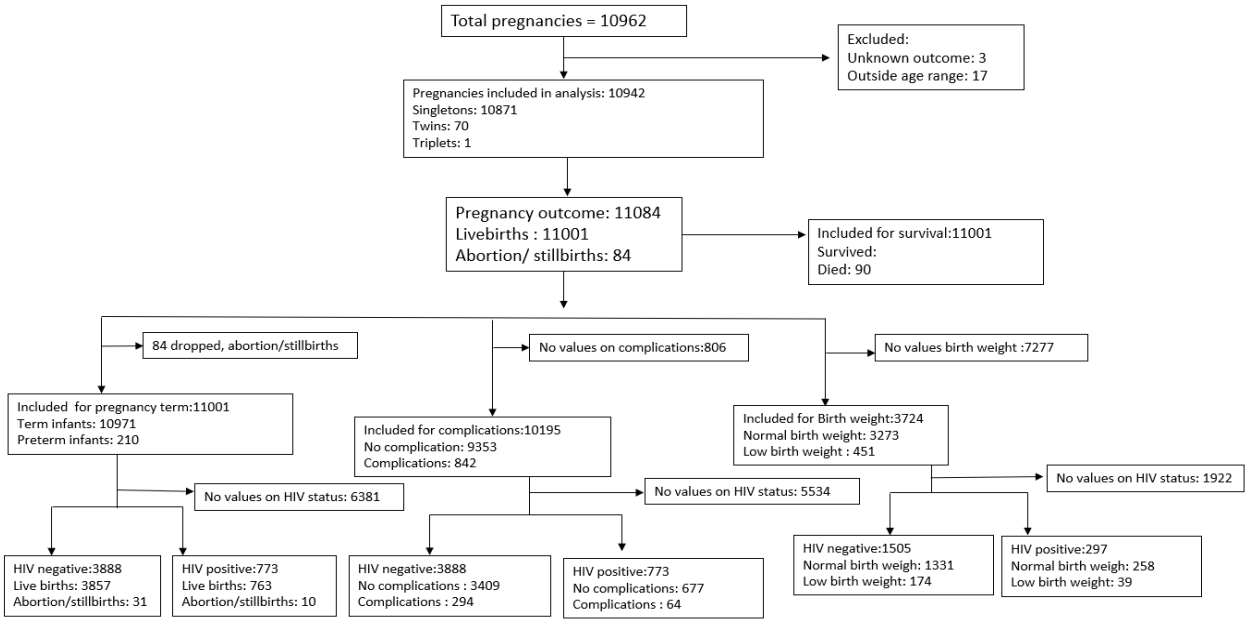


Figure 3: Flow diagram showing number of records and outcomes included in the study.

3.2. Objective 1: To describe the social and economic characteristics of HIV infected and non-infected women aged between 13 – 49 years in Agincourt from 2015 to 2019.

Table 3presents the distribution of characteristics of the overall sample and across HIV status. Maternal characteristics were firstly presented for the overall sample and across HIV status. Of the total pregnancy outcomes of 11085, more than 50% were carried by women with unknown HIV status, 3888 pregnancy outcomes by HIV-negative women, and 773 by HIV-positive women.

Analysis of the overall sample shows that majority of the outcomes were distributed among women aged 20-24 years and 25-29 years, contributing 25.76% and 25.30% of the outcomes, respectively. The least was distributed among women aged between 40 – 49 years (4.18%). The distribution of pregnancy outcomes by residence status showed that more than 80 % were permanent residents. More than 45% of pregnancy outcomes were distributed among women who completed secondary school or more education, while less than 10 % were reported among women who had primary school or less education.

Considering pregnancy outcomes by marital status, the majority of the outcomes (64%) were from single women whereas less than 3% of the outcomes were from widowed/divorced/separated women. There was no difference in the distribution regarding household socioeconomic status (SES) in the total sample. The distribution ranged between 18% and 21% across the 5 quintiles. SES status was generated based on the number of assets such as furniture, livestock, etc., that each household possesses.

The comparison of maternal characteristics by HIV status is also presented in table. The distribution of pregnancy outcomes show that the majority of the HIV positive women were within the 25-29 age group (31.91%), while for the HIV-negative women, the majority were within the 20-25 years age group (26.91%). More than 85% of the HIV positive women were permanent residents and a similar trend observed among HIV-negative women. The proportion of pregnancy outcomes was higher (67.40 %) among HIV-positive women who were single and similar results were observed among single HIV-negative women, whereby 70% of the pregnancies were among permanent residents.

Around 10% of the pregnancy outcomes were reported among HIV positive women who only attained primary education level and around 7% among HIV negative women. Results also show that many HIV positive women were poor compared to HIV negative women. A high proportion of pregnancy outcomes were reported among HIV positive women in quintile 1 & 2 while among HIV negative women, the majority of the outcomes were observed in quintile 4 & 5.

Table 3: This table describes the maternal characteristics of all women and by HIV status.

	Total sample 11085	**Known HIV status sample, n= 4661**	
Characteristics	**Pregnancies N=11084 n (%)**	**HIV-Negative pregnancies N= 3888, n (%)**	**HIV- Positive pregnancies N= 773, n (%)**
Age			
13 – 19 years	1758 (15.86)	845 (21.99)	33 (4.27)
20-24 years	2855 (25.76)	1220 (31.38)	143 (18.50)
25 - 29 years	2804 (25.30)	871 (22.40)	208 (26.91)
30 - 34 years	2011 (18.14)	491 (12.63)	197 (25.49)
35 – 39 year	1194 (10.77)	325 (8.36)	138 (17.85)
40 - 49 years	463 (4.18)	126 (3.24)	54 (6.99)
Residential status			
Permanent	9019 (81.36)	3360 (86.42)	706 (91.33)
Temporary	2066 (18.64)	528 (13.58)	67 (8.67)
Education status			
Primary or less education	974 (8.79)	259 (6.66)	83 (10.74)
Secondary education	4657 (42.01)	1793 (46.12)	336 (43.47)
Complete secondary or more	5453 (49.20)	1836 (47.22)	354(45.80)
Relationship status			
Single	7126 (64.29)	2752 (70.78)	521 (67.40)
Married/cohabiting	3648 (32.91)	1073 (27.60)	208 (26.91)
Widowed/divorced/separated	311 (2.81)	63 (1.62)	44 (5.69)
Socio-economic status			
Q1	1986 (17.92)	623 (16.02)	151 (19.53)
Q2	2316 (20.89)	815 (20.96)	179 (23.16)
Q3	2207 (19.91)	806 (20.73)	144 (18.63)
Q4	2276 (20.53)	840 (21.60)	172 (22.25)
Q5	2300 (20.75)	804 (20.68)	127 (16.43)

3.3. Objective 2: To describe trends in perinatal outcomes outcome amongst HIV infected and non-infected women in Agincourt, rural South Africa over the period of 2015 -2019.

3.3.1. Low birth weight

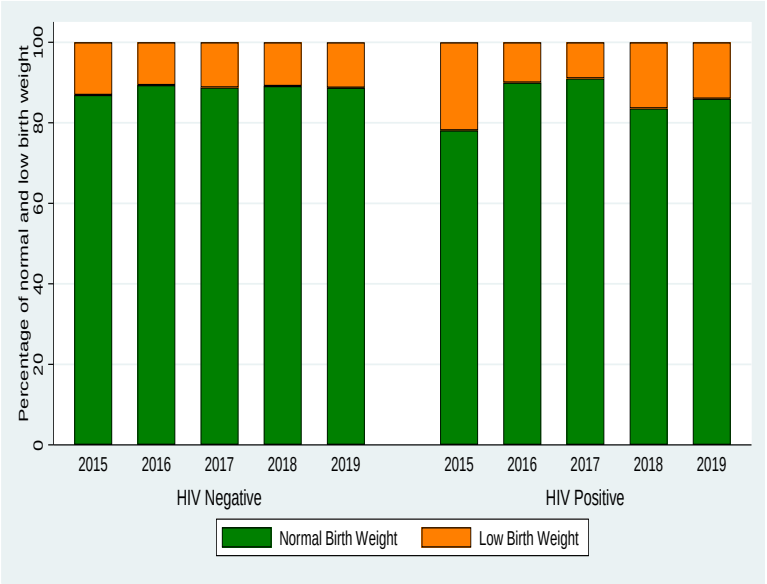


Figure 4: Trends in LBW by HIV status

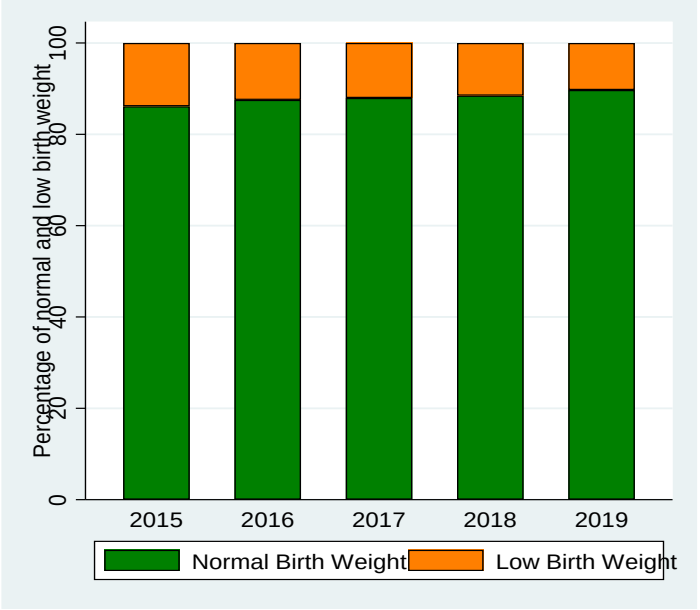


Figure 5: Trends in LBW among all women

As shown in Figure 4, there were no observed differences in the occurrence of LBW in the total sample from 2015- 2019. However, among HIV positive women in Figure 5, LBW was high in 2015, dropped and remained constant in 2016-2017 then went up in 2018 followed by a drop in 2019.

3.3.2. Preterm delivery

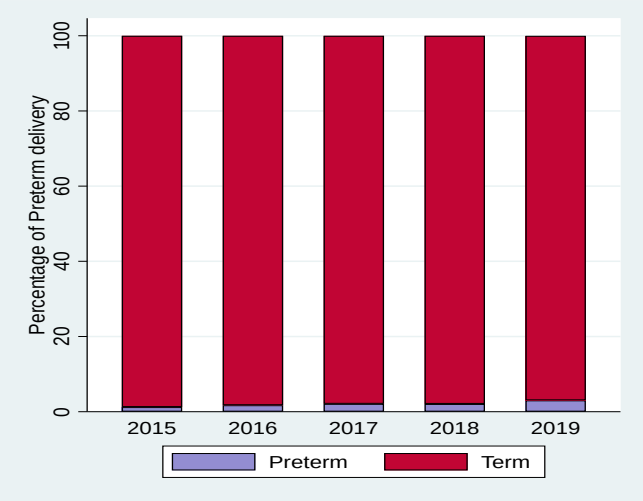


Figure 6: Trends in preterm delivery among all women

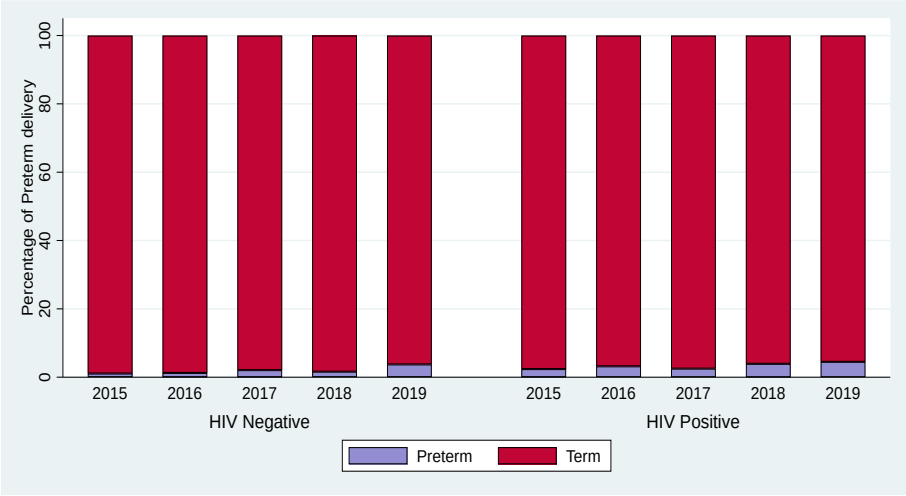


Figure 7: Trends in preterm delivery by maternal HIV status

The prevalence of preterm delivery increased gradually over the period 2015 – 2019 in the total sample. However, in the HIV positive subgroup, there was a gradual increase from 2015 to 2016, followed by a drop in 2017 and constant prevalence in the period 2018-2019.

3.3.3. Abortions/stillbirths

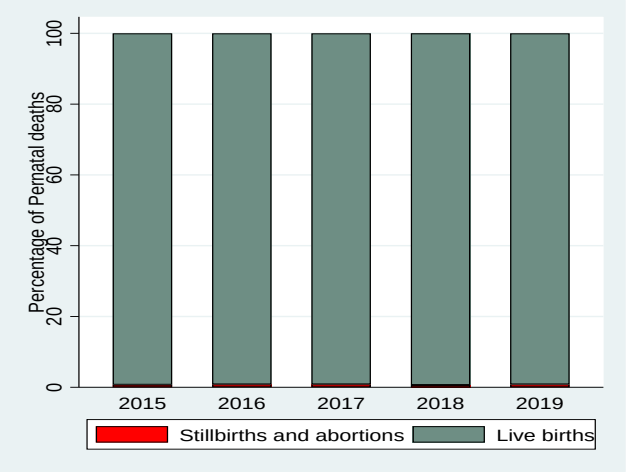


Figure 8: Trends in abortion/stillbirths among all pregnancies

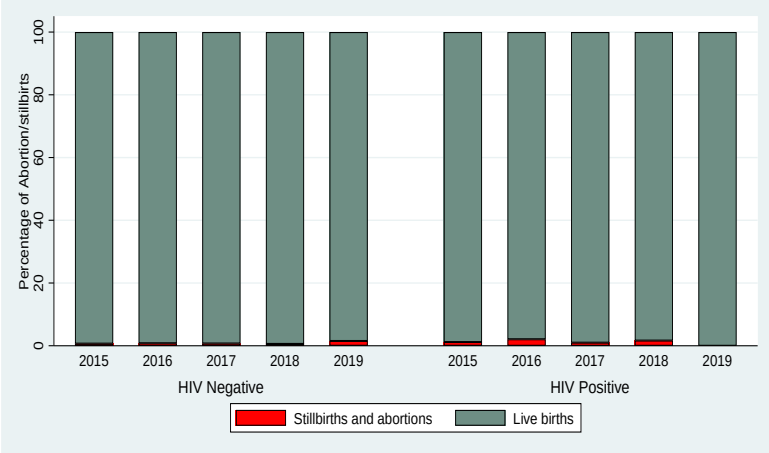


Figure 9: Trends in abortion/stillbirths by maternal HIV status

As shown in Figure 8, in the total sample, the prevalence of abortion/stillbirths remained constant around 1% during the period 2015 – 2019. However, in the HIV positive subgroup, Figure 9 shows that there was a gradual increase from 2015 to 2016 followed by a drop in 2017. There was also a sharp increase among the HIV positive women in 2018 followed by an abrupt drop in 2019.

3.4. Objective 3a: To determine maternal factors associated with perinatal outcomes amongst HIV infected and non-infected women in Agincourt over the period of 2015 to 2019.

Presented first are results of the factors associated with stillbirths and abortion compared to livebirths. A subset of livebirth was further analyzed for factors associated with PTD, LBW and infant survival. Observation with missing data on the outcome variables were dropped. As a result, the analysis was limited to records with data available on each outcome.

3.4.1 **Maternal factors associated with stillbirths and abortion**

Table 4 shows the prevalence and maternal factors associated with stillbirths and abortion. Statistical significance of the results was assessed using Pearson chi-square analysis. A total of 11085 outcomes were reported among all women and 0.76% (n=84) of the outcomes were stillbirths and abortion.

Results showed that maternal education and number of ANC visits were significantly associated with abortion/stillbirths (p=<0.05). The proportion of abortion/stillbirths was significantly higher among women with secondary school education level (44.05%) than those with primary school education level (21.43%). Among women whose pregnancies ended in abortions and still births 79.9% attended 4 or more ANC visits while among women whose pregnancies ended in live births 91.4% attended 4 or more ANC visits.

The analysis was also conducted for a subset of women with known HIV status (n=4661). The results were consistent with those observed from the total sample in that education status was significantly associated with abortion and stillbirth (p=0.022). More than 50% of pregnancies from women who achieved only secondary school education ended I abortion/still birth followed by 31.71% of pregnancies of women who completed secondary education level. A higher pregnancy loss prevalence of 80.49% was reported among women who had attended 4 or more ANC visits, the results were slightly lower compared to results of the total sample.

There was a marginal association between gravidity and abortion/stillbirth (p=0.074). Majority of abortions and stillbirths were observed in women who were pregnant for the first time (34.15%) and few among women who were pregnant for the third time, 19.51%.

There was no significant difference in the proportions of pregnancy loss by maternal age (p=0.333), residence status (p=0.304), relationship status (p=0.284), SES (p=0.394 and delivery attendant (p=0.147). These findings were similar for both total sample and sample of women with known HIV status. In addition, HIV status was not significantly associated with abortions and stillbirths (p=0.177).

Table 4: Factors associated with abortion/ stillbirths

Characteristics	Total outcome, regardless of HIV status: n= 11085			Outcomes with known HIV status: 4661		
	Stillbirths, and abortions (84)	Live births (11001)	P - value	Stillbirths and abortions (41)	Live births (4620)	P - value
Maternal HIV status						
HIV negative				31 (75.61)	3857 (83.48)	0.177
HIV positive				10 (24.39)	763 (16.52)	
Age						
13 – 19 years	12 (14 .29)	1746 (15.87)		5 (12 .20)	883 (19 .11)	
20-24 years	15 (17.86)	2840 (25.82)		10 (24.39)	1353 (29.29)	
25 - 29 years	27 (32.14)	2777 (25.24)	0.333	14 (34.15)	1065 (23.05)	0.406
30 - 34 years	14 (16.67)	1997 (18.15)		6 (14.63)	682 (14.76)	
35 – 39 year	10 (11.90)	1184 (10.76)		3 (7.32)	460 (9.96)	
40 - 49 years	6 (7.14)	457 (4.15)		3 (7.32)	177 (3.83)	
Residential status						
Permanent	72 (85.71)	8947 (81.33)	0.304	37 (90.24)	4029 (87.21)	0.562
Temporary	12 (14.29)	2054 (18.67)		4 (9.76)	591 (12.79)	
Education status						
Primary or less education	18 (21.43)	956 (8.69)		7 (17.07)	335 (7.25)	
Secondary education	37 (44.05)	4620 (42.00)	<0.001	21 (51.22)	2108 (45.63)	0.022
Complete secondary or more	29 (34.52)	5425 (49.31)		13 (31.71)	2177 (47.12)	
Relationship status						
Single	48 (57.14)	7078 (64.34)		25 (60.98)	3248 (70.30)	
Married/cohabiting	32 (38.10)	3616 (32.87)	0.284	14 (34.15)	1267 (27.42)	0.305

Widowed/divorced	4 (4.76)	307 (2.79)		2 (4.88)	105 (2.27)	
Socio-economic status						
Q1	14 (16.67)	1972 (17.93)		7 (17.07)	767 (16.60)	
Q2	23 (27.38)	2293 (20.84)		11 (26.83)	983 (21.28)	
Q3	15 (17.86)	2192 (19.93)	0.392	10 (24.39)	940 (20.35)	
Q4	20 (23.81)	2256 (20.51)		8 (19.51)	1004 (21.73)	0.687
Q5	12 (14.29)	2288 (20.80)		5 (12.20)	926 (20.04)	
Gravidity						
1	35 (41.67)	4891 (44.44)		14 (34.15)	2062(44.63)	
2	18 (21.43)	3140 (28.54)	0.110	9 (21.95)	1301 (28.16)	
3	15 (17.86)	1705 (15.50)		8 (19.51)	689 (14.91)	0.074
4+	16(19.05)	1265 (11.50)		10 (24.39)	568 (12.29)	
Number of ANC visits						
3 and less	17 (20.24)	952 (8.65)	<0.001	8 (19.51)	371 (8.03)	0.007
4 or more	67 (79.76)	10049 (91.35)		33 (80.49)	4249 (91.97)	
Delivery attendant						
Healthcare professional	72 (85.71)	9945 (90.40)	0.147	38 (92.68)	4325 (93.61)	
Others	12 (14.29)	1056 (9.60)		3 (7.32)	295 (6.39)	0.808

3.4.2. Univariate and multivariate logistic regression analysis of factors associated with abortions and stillbirths (perinatal death)

The univariate and multivariable logistic regression models were used to determine factors associated with perinatal deaths. The results in table 5 shows the unadjusted odds ratio and confidence intervals of the association of each factor with perinatal deaths for total sample.

Unadjusted model – univariate analysis

Education status, number of ANC visits were independently associated with perinatal death (p=<0.05). Gravidity (women who had 4 and/ more pregnancies) was marginally associated with perinatal deaths , (p=<0.1). The odds of losing a pregnancy through abortion, miscarriage, or stillbirth declined with attainment of high education status. The highest risk was among women with primary/less school education (OR=0.43. 95% CI=0.24 – 0.75). Similarly, women who attended 3 or less ANC visits were 3 times more likely to have their pregnancies terminated by abortion or stillbirths compared to those that attended 4 or more ANC visits (OR= 2,73; 95% CI=1.57 – 4.58).

Women who had been pregnant 4 times or more were 77% more likely to have abortion/stillbirths as compared to women who were pregnant for the first time (OR=1.77; 95% 0.99 -3.20). Increase in age was associated with increased risk of perinatal deaths. However, the association was not significant for all age groups (p> 0.05). Being a temporary residence was protective against having abortion/stillbirth although the relationship was not significant (p=0.306). Similarly, we found no association between perinatal deaths and marital status, socio economic status and delivery attendant.

Table 5 also shows results of unadjusted odds ratios and confidence intervals of the risk factors associated with adverse outcome among women with known HIV status (n=4661). Compared to the total sample, univariate analysis shows that education status, gravidity and number of ANC visits were significantly associated with perinatal deaths.

Education status was found to be a protective factor, risks of having perinatal deaths reduced with increase in education level. The odds of having adverse perinatal outcome among women who had secondary education and those that completed secondary education and higher were 0.48 and 0.29, respectively.

Compared to women who attended 4 or more ANC visits, women who attended 3 or less were almost 3 times likely to have abortion/stillbirths (OR=2.78; CI=1.27 – 6.05). Similarly, the risks of having perinatal deaths increased with the number of pregnancies a woman has had in her life, although the results were not significant in all gravidity categories. Women who had four or more pregnancies were 2.59 most likely to have perinatal deaths (P=0.022) as compared to women who had fewer than four pregnancies.

In addition, there was no relationship between HIV status and perinatal deaths (p=0.408). Similar to the univariate analysis of the total sample, maternal age, residence status, SES, and delivery attendance were not significantly associated with adverse perinatal outcomes.

Adjusted regression models – multivariable analysis

Multivariable logistic regression analysis was used to assess the effects of multiple independent variables on a single binary dependent variable. Column 4 & 8 in table 5 shows results of adjusted odds ratios and confidence intervals for both total sample and women with known HIV status, respectively. This model showed that 3 factors for the overall sample (maternal age, education status and number of ANC) and 2 factors for known HIV sample (education status and number of ANC status) were significantly associated with the risk of perinatal deaths at 95% confidence level and a p-value <0.05.

In the overall sample analysis, the odds of having perinatal deaths increases with maternal age, however the association was not significant for all age groups. Woman aged 25-29 were 1.95 more likely to experience adverse outcomes (OR=1.95; 95% CI=0.88- 4.30).

Women who had attained secondary education level were 52% less likely to have perinatal deaths (OR=0.46; 95%CI= 0.26 – 0.84) compared to women who attained primary/less education This showed that education status was a protective factor as those with completed secondary school or higher had 72% less risk of having perinatal deaths (p=0.008). The positive association of number of ANC visits attended by the woman during pregnancy observed in the unadjusted model remained in the adjusted model.

Analysis among women with known HIV status showed that only ANC visits were significantly associated with perinatal deaths (p=0.012). Woman who attended 3 or less ANC visits were 2.77 likely to have perinatal deaths compared to those attended 4 or more ANC visits. In contrast to the

results from unadjusted analysis, maternal education was marginally associated with adverse outcome. Women who completed secondary education had 78% risk of having adverse outcome compared to those that attained primary education level (OR=1.78; 95% CI= 0.13- 1.04).

Table 5: Univariate and multivariate analysis of factors associated with stillbirths/abortions (Perinatal deaths)

	Total sample				**Known HIV status**			
Variable	**Univariate**		**Multivariable**		**Univariate**		**Multivariable**	
	Unadj OR (95% CI)	**P-value**	**Adj OR (95% CI**	**P-value**	**Unadj OR (95% CI)**	**P-value**	**Adj OR (95% CI**	**P-value**
HIV status								
HIV positive								
HIV negative					1.63 (0.80-3.34)	0.181	1.39(0.64- 3.02)	0.408
Age								
13 – 19 years	Ref							
20-24 years	0.77 (0.36 – 1.65)	0.498	1.03 (0.46 -2.29)	0.938	1.31 (0.44 – 3.83)	0.628	1.69 (0.53-5.39)	0.372
25 - 29 years	1.41 (0.71 – 2.80)	0.319	1.95 (0.88 -4.30)	0.099	2.32 (0.83 – 6.47)	0.107	2.52 (0.70- 9.02)	0.156
30 - 34 years	1.02 (0.47 -2.21)	0.960	1.22 (0.48 – 3.09)	0.673	1.55 (0.47 – 5.11)	0.468	1.03 (0.22-4.91)	0.969
35 – 39 year	1.23 (0.53 – 2.85)	0.632	1.27 (0.45 – 3.61)	0.651	1.15 (0.27 – 4.84)	0.847	0.55 (0.09-3.56)	0.532
40 - 49 years	1.91 (0.71 – 5.12)	0.198	1.71 (0.50 -5.77)	0.390	2.99 (0.71- 12.64)	0.136	1.05 (0.16 – 7.16)	0.957
Residential status								
Permanent	Ref							
Temporary	0.73 (0.39 – 1.34)	0.306	0.77 (0.41 -1.45)	0.418	0.74 (0.26 – 2.08)	0.563	0.88 (0.30 - 2.60)	0.823
Education status								
Primary/ less education	Ref							
Secondary education	0.43 (0.24 – 0.75)	0.003	0.46 (0.26 – 0.84)	0.011	0.48 (0.20 -1.13)	0.093	0.61(0.24 – 1.55)	0.302
Complete secondary or more	0.28 (0.16 – 0.51)	<0.001	0.32 (17 – 0.61)	0.001	0.29 (0.11 – 0.72)	0.008	1.78 (0.13 -1.04)	0.058
Marital status								
Single	Ref							
Married/cohabiting	1.30 (0.83 – 2.04)	0.245	1.11 (0.68 – 1.80)	0.678	1.44 (0.74 – 2.77)	0.281	1.42 (0.49 -2.35)	0.856

Widowed/divorced	1.92 (0.69 – 5.36)	0.212	1.39 (0.48 – 4.05)	0.549	2.47 (0.58– 10.58)	0.222	1.78 (0.37 - 8.48)	0.471
Socio-economic status								
Q1	Ref							
Q2	1.41 (0.73 – 2.75)	0.310	1.64 (0.84 – 3.22)	0.149	1.23 (0.47 – 3.18)	0.675	1.42 (0.54 – 3.72)	0.497
Q3	0.96 (0.46- 2.00)	0.921	1.16 (0.56 – 2.44)	0.688	1.17 (0.44 – 3.08)	0.757	1.43 (0.53 – 3.83)	0.481
Q4	1.25 (0.63 – 2.48)	0.525	1.55 (0.77 3.11)	0.221	0.87 (0.32- 2.42)	0.794	1.11 (0.39 – 3.13)	0.848
Q5	0.74 (0.34 – 1.60)	0.443	1.01 (0.46 – 2.23)	0.984	0.59 (0.19 – 1.87)	0.372	0.87 (0.27 – 2.84)	0.815
Gravidity								
1	Ref							
2	0.80 (0.45 – 1.42)	0.446	0.69 (0.37 – 1.28)	0.244	1.02 (0.45 – 3.36)	0.965	0.83 (0.32 – 2.13)	0.699
3	1.23 (0.67 – 2.26)	0.505	0.95 (0.47 – 1.93)	0.888	1.71 (0.71 – 4.09)	0.228	1.44 (0.48 – 4.32)	0.513
4+	1.77 (0.99 - 3.20)	0.061	1.06 (0.47- 2.41)	0.882	2.59 (1.15 - 5.87)	0.022	2.61 (0.73 - 9.41)	0.141
Number of ANC visits								
4 or more	Ref							
3 and less	2.73 (1.57 - 4.58)	< 0.001	2.73 (1.59 – 4.70)	<0.001	2.78 (1.27 – 6.05)	0.010	2.77 (1.25 – 6.11)	0.012
Delivery attendant								
Healthcare professional	Cons							
Others	1.57 (0.85 – 2.90)	0.150	1.41 (0.76 -2.62)	0.280	1.16 (0.36 – 3.77)	0.808	0.97(0.29 –3.22)	0.963

3.5. **Maternal factors associated with preterm delivery:**

Table 6 shows the prevalence of preterm delivery and results from Pearson chi-square analysis which was used to determine the association between individual maternal factors and preterm birth for overall sample and known HIV status sample.

A total of 11001 infants were included and the overall prevalence of preterm births was 1.90% from 2015 - 2019. The results from the bivariate analysis revealed that among all maternal variables included in the analysis only the number of ANC visits was significantly associated with preterm birth (p=0.003). Among women who had preterm deliveries, 85.71% attended 4 or more ANC visits while 91.46% attended 4 or more ANC visits among women who had full term births.

In an analysis of infants delivered by a sample of women with known HIV status (n=4620), prevalence of preterm births was 1.99% which was higher than in the overall sample. Maternal HIV status and number of ANC visits were reported to be significantly associated with preterm deliveries. Less than 30% of preterm infants were delivered by HIV positive women. Like in the overall sample analysis, among women who had preterm deliveries 81.52% attended 4 or more ANC visits while 92.18% attended 4 or more ANC visits among women who had full term births.

Table 6: Factors associated with preterm delivery.

Characteristics	**Total outcome, regardless of HIV status: n= 11001**			**Outcomes with known HIV status: 4622**		
	Preterm delivery (210)	**Term delivery (10791)**	**P - value**	**Preterm delivery (92)**	**Term delivery (4528)**	**P - value**
Maternal HIV status						
HIV negative				67 (72.83)	3790 (83.70)	0.005
HIV positive				25 (27.17)	738 (16.30)	
Age						
13 – 19 years	27 (12 .86)	1719 (15.93)		14 (15.22)	869 (19 .19)	
20-24 years	62 (29.52)	2778 (25.74)		28 (30.43)	1325 (29.26)	
25 - 29 years	49 (23.33)	2728 (25.28)	0.732	22 (23.91)	1043 (23.03)	0.505
30 - 34 years	39 (18.57)	1958 (18.14)		14 (15.22)	668 (14.75)	
35 – 39 year	24 (11.43)	1160 (10.75)		13 (14.13)	447 (9.87)	
40 - 49 years	9 (4.29)	448 (4.15)		1 (1.09)	176 (3.89)	
Residential status						
Permanent	170 (80.95)	8777 (81.34)	0.888	79 (85.87)	3950 (87.23)	0.698
Temporary	40 (19.05)	2014 (18.66)		13 (14.13)	578 (12.77)	
Education status						
Primary or less education	16 (7.62)	940 (8.71)		6 (6.52)	329 (7.27)	
Secondary education	80 (38.10)	4540 (42.07)	0.344	35 (38.04)	2073 (4578)	0.269
Complete secondary or more	114 (54.29)	5311 (49.22)		51 (55.43)	2126 (46.95)	

Relationship status						
Single	136 (64.76)	6942 (64.33)		61 (66.30)	3187 (70.38)	
Married/cohabiting	69 (32.86)	3547 (32.87)	0.935	28 (30.43)	1239 (27.36)	0.629
Widowed/divorced	5 (2.38)	302 (2.80)		3 (3.26)	102 (2.25)	
Socio-economic status						
Q1	36 (17.14)	1936 (17.94)		18 (19.57)	749 (16.54)	
Q2	35 (16.67)	2258 (20.92)		14 (15.22)	969 (21.40)	
Q3	53 (25.24)	2139 (19.82)	0.295	23 (25.00)	917 (20.25)	
Q4	42 (20.00)	2214 (20.52)		19 (20.65)	985 (21.75)	0.529
Q5	44(20.95)	2244 (20.80)		18 (19.57)	908 (20.05)	
Gravidity						
1	89 (42.38)	4802 (44.50)		39 (42.39)	2023 (44.68)	
2	69 (32.86)	3071 (28.46)	0.552	30 (32.61)	1271 (28.07)	
3	31 (14.76)	1674 (15.51)		14 (15.22)	675 (14.91)	0.740
4+	21 (10.00)	1244 (11.53)		9 (9.78)	559 (12.35)	
Number of ANC visits						
3 and less	30 (14.29)	922 (8.54)	0.003	17 (18.48)	354 (7.82)	<0.001
4 or more	180 (85.71)	9869 (91.46)		75 (81.52)	4249 (92.18)	
Delivery attendant						
Healthcare professional	188 (89.52)	9757 (90.42)	0.663	86 (93.48)	4239 (93.62)	
Others	22 (10.48)	1034 (9.58)		6 (6.52)	289 (6.38)	0.957

3.5.1. Univariate and multivariate logistic regression analysis of factors associated with preterm delivery

Unadjusted model: Univariate analysis

The results in table 7 shows the unadjusted odds ratios and confidence intervals of the risk factors associated with preterm delivery for overall sample included in the analysis (n=11001). Results shows that among maternal factors included in the univariate analysis, only number of ANC visits was found to be significantly associated with preterm delivery (p=0.004). Compared to women who attended 4 or more ANC visits, women who attended 3 or less ANC visits had 78% more risk of giving birth to preterm infants (OR=1.78; 95% CI=1.21 – 2.64).

In the sample of women with known HIV status,4622 as results presented in table 7, maternal HIV status was marginally associated with preterm delivery (p=006) and number of ANC visits were significantly associated with preterm delivery (P<0.05). HIV positive women were 2 times more likely to deliver preterm infants compared to HIV negative women (OR=1. 92; 95% CI= 1.20 – 3.05). The odds of delivering preterm infants among women who attended 3 or less ANC visits were 2.67 higher than women who attended 4 or more ANC visits.

Adjusted model: Multivariate analysis

In multivariable logistic regression analysis for factors associated with preterm delivery for the total sample included in the analysis, the relationship between number of ANC visits and preterm delivery remained unchanged. Women who attended less than 4 visits had 82% more chance of delivering preterm infants compared to women who attended 4 or more ANC visits (OR=1.82; 95% CI=1.22 -2.70).

Results for adjusted model for the sample of women with known HIV status were consistent with the univariate results. HIV status and number of ANC visits were still significantly associated with preterm delivery. HIV positive women were more likely to deliver preterm infants as compared to HIV negative women (OR = 2.12; 95% CI: 1.28 – 3.51). The odds of giving birth to a preterm infant among women who attended 3 or less ANC visits were 7% more than the odds of having a preterm delivery among women who attended 4 or more ANC visits.

Table 7: Univariate and multivariate analysis of factors associated with preterm deliveries

	Total sample				**Known HIV status**			
Variable	**Univariate**		**Multivariable**		**Univariate**		**Multivariable**	
	Unadj OR (95% CI)	**P-value**	**Adj OR (95% CI**	**P-value**	**Unadj OR (95%CI)**	**P-value**	**Adj OR (95%CI**	**P-value**
HIV status								
HIV positive								
HIV negative					1.92 (1.20 -3.05)	0.006	2.12 (1.28 - 3.51)	0.003
Age								
13 – 19 years	Ref							
20-24 years	1.42 (0.90 – 2.24)	0.131	1.32 (0.81 -2.14)	0.258	1.31 (0.69 – 2.51)	0.411	1.05 (0.52 - 2.14)	0.893
25 - 29 years	1.14 (0.71 – 1.84)	0.579	1.07 (0.62 - 1.83)	0.818	1.31 (0.67 – 2.57)	0.435	2.52 (0.70- 9.02)	0.948
30 - 34 years	1.27 (0.77 -2.08)	0.347	1.23 (0.68 – 2.21)	0.491	1.30 (0.62 – 2.75)	0.490	1.03 (0.22-4.91)	0.923
35 – 39 year	1.32 (0.76 – 2.29)	0.330	1.40 (0.72 – 2.73)	0.327	1.80 (0.84 – 3.87)	0.129	0.55 (0.09-3.56)	0.438
40 - 49 years	1.29 (0.60– 2.74)	0.526	1.45 (0.60 - 3.51	0.411	0.35 (0.05- 2.70)	0.316	1.05 (0.16 – 7.16)	0.285
Residential status								
Permanent	Ref							
Temporary	1.03 (0.72 – 1.45)	0.888	0.91 (0.63 -1.31)	0.608	1.12 (0.62 – 2.03)	0.698	1.07 (0.57 - 1.99)	0.839
Education status								
Primary/ less education	Ref							
Secondary education	1.04 (0.60 – 1.77)	0.900	1.00 (0.26 – 0.84)	0.996	0.93 (0.39 - 2.22)	0.863	0.92 (0.38 – 2.00)	0.875
Complete secondary or more	1.26 (0.74 – 2.14)	0.389	1.18 (17 – 0.61)	0.550	1.32 (0.56 – 3.09)	0.529	1.35 (0.54 -3.35)	0.518
Relationship status								
Single	Ref							
Married/cohabiting	0.99 (0.74 – 1.33)	0.962	0.99 (0.72 – 1.35)	0.935	1.80 (0.75 – 1.86)	0.472	1.47 (0.86 -2.49)	0.155

Widowed/divorced	0.85 (0.34 – 2.08)	0.714	1.18 (0.33 – 2.11)	0.708	1.54 (0.47– 4.98)	0.474	1.66 (0.47 - 5.82)	0.428
Socio-economic status								
Q1	Ref							
Q2	0.83 (0.52 – 1.33)	0.447	0.82 (0.51 – 1.32)	0.417	0.60 (0.30 – 1.22)	0.157	0.56 (0.28 – 1.14)	0.112
Q3	1.33 (0.87- 2.04)	0.188	1.30 (0.85 – 2.00)	0.231	1.04 (0.56 – 1.95)	0.893	1.00 (0.53 – 1.89)	0.988
Q4	1.02 (0.65 – 1.60)	0.931	0.99 (0.63 - 1.56)	0.927	0.80 (0.42 – 1.54)	0.508	0.77 (0.40 – 1.49)	0.433
Q5	1.05 (0.68 – 1.64)	0.815	1.00 (0.63 – 1.58)	0.992	0.82 (0.43 – 1.60)	0.568	0.77 (0.39 – 1.51)	0.443
Gravidity								
1	Ref							
2	1.21 (0.88 – 1.67)	0.235	1.17 (0.82 – 1.66)	0.380	1.22 (0.76 – 1.98)	0.410	1.01 (0.58 – 1.76)	0.968
3	1.00 (0.66 – 1.51)	0.997	0.97 (0.60 – 1.57)	0.914	1.08 (0.58 – 1.99)	0.816	0.79 (0.37– 1.71)	0.550
4+	0.91 (0.56- 1.47)	0.703	0.83 (0.46 - 1.52)	0.554	0.84 (0.40 - 1.73)	0.629	0.56 (0.21- 1.51)	0.254
Number of ANC visits								
4 or more	Ref							
3 and less	1.78 (1.21 - 2.64)	0.004	1.82 (1.22 – 2.70)	0.003	2.67 (1.56 – 4.57)	<0.001	2.99 (1.73 – 5.18)	<0.001

3.5.2 **Maternal factors associated with low birth weight**

Table 8 shows the prevalence and results from bivariate analysis of factors associated with LBW for the total sample and women with known HIV status. The prevalence of LBW was 12.11% among the total sample of 3724 pregnant women in the Agincourt HDSS who delivered a live birth in the period 2015 -2019.

Maternal age, education status and number of ANC were the only 3 maternal factors found to be significantly associated with LBW deliveries, p=<0.05. More than a quarter of LBW infants were delivered by women aged between 20-24 years and only around 5% were reported among 40-49 years old women. Almost half of LBW infants were reported among women who had secondary education level. Among women who had delivered LBW babies, 92.02% attended 4 or more ANC visits while 94.44 % attended 4 or more ANC visits among women who delivered normal weight babies.

Among women with known HIV status, the prevalence of LBW infants was 11.82%, which was lower compared to the prevalence among total sample. Maternal age and educational status had a significant relationship with LBW. Contrary to the results from the analysis of the total sample analysis, no relationship was observed between ANC visits and LBW.

Like in the total sample, the prevalence of LBW infants was higher at 27.23% among woman within the 20-24 age group compared to the other age groups. Similar trends were reported with regards to education status. More than 45% of LBW were recorded among woman with secondary education level. No other factors had significant association with LBW.

Table 8: Factors associated with low birth weight

Characteristics	Total outcome, regardless of HIV status: n= 3724			Outcomes with known HIV status: 1802		
	Low birth weight (451)	Normal weight (3273)	P - value	Low weight (213)	Normal weight (1589)	P - value
Maternal HIV status						
HIV negative				174 (81.69)	1331 (83.76)	0.444
HIV positive				39 (18.31)	258 (16.24)	
Age						
13 – 19 years	92 (20 .40)	490 (14.97)		52 (24.41)	259 (16.30)	
20-24 years	124 (27.49)	874 (26.70)		58 (27.23)	475 (29.89)	
25 - 29 years	86 (19.07)	839 (25.63)	0.010	35 (16.43)	378 (23.79)	0.011
30 - 34 years	77 (17.07)	573 (17.51)		29 (13.62)	251 (15.80)	
35 – 39 year	49 (10.86)	357 (10.91)		28 (13.15)	162 (10.20)	
40 - 49 years	23 (5.10)	140 (4.28)		11 (5.16)	64 (4.03)	
Residential status						
Permanent	402 (89.14)	2898 (88.54)	0.710	194 (91.08)	1426 (89.74)	0.543
Temporary	49 (10.86)	375 (11.46)		19 (8.92)	163 (10.26)	
Education status						
Primary or less education	46 (10.20)	276 (8.43)		22 (10.33)	105 (6.61)	
Secondary education	213 (47.23)	1387 (42.38)	0.027	101 (47.42)	693 (43.61)	0.039
Complete secondary or more	192 (42.57)	1610 (49.19)		90 (42.25)	791 (49.78)	
Relationship status						
Single	289 (64.08)	2055 (62.79)		143 (67.78)	1077 (67.78)	
Married/cohabiting	146 (32.37)	1129 (34.49)	0.451	61 (28.64)	474 (29.83)	0.283
Widowed/divorced	16 (3.55)	89 (2.72)		9 (4.23)	38 (2.39)	

Socio-economic status						
Q1	81 (17.96)	611 (18.67)		41 (19.25)	261 (16.43)	
Q2	111 (24.61)	701 (21.42)		51 (23.94)	346(21.77)	
Q3	95 (21.06)	659 (20.13)	0.390	50 (23.47)	319 (20.08)	
Q4	92 (20.40)	680 (20.78)		45 (21.13)	357 (22.47)	0.109
Q5	72 (15.96)	622 (19.00)		26 (12.21)	306 (19.26)	
Gravidity						
1	211 (46.78)	1458 (44.55)		101 (47.42)	669 (42.10)	
2	108 (23.95)	901 (27.53)	0.434	47 (22.07)	471 (29.64)	
3	74 (16.41)	529 (16.16)		34 (15.96)	258 (16.24)	0.113
4+	58 (12.86)	385 (11.76		31 (14.55)	191 (12.02)	
Number of ANC visits						
3 and less	36 (7.98)	182 (5.56)	0.040	15 (7.04)	96 (6.04)	0.568
4 or more	415 (92.02)	3091 (94.44)		198 (92.96)	1493 (93.96)	

3.5.3 Univariate and multivariate logistic regression analysis of factors associated with low birth weight

Unadjusted model: univariate analysis

Table 9 shows univariate analysis of factors associated with LWB. The analysis revealed that maternal age (25 -29 years and 30-34 years), and number of ANC visits were significantly associated with LBW. In addition, there was a marginal relation between education status (secondary education level) and LBW (p=0.058). Women who attended 3 or less ANC visits had 47% more risk of giving birth to low-birth-weight infants compared to those attended 4 or more ANC visits, (OR=1.47; 95% CI=1.06 – 2.14).

Among women with known HIV status, like in the total sample, maternal age was found to be a protective factor for LBW. Women aged between 25-29 and those aged between 30-34 had 46% and 43% less risks of delivering LBW infants, respectively. In addition, belonging to a wealthier household (quintile 5) was protective against having LBW infants (OR=0.54; 95% CI=0.32-0.91).

Adjusted model: Multivariate analysis

Results from a total sample analysis show that although education status was significantly associated with LBW in the bivariate analysis and marginally associated in the unadjusted model, it was not significant in the adjusted regression analysis. Also, as much as number of ANC visits were significantly associated with LBW in the bivariate and unadjusted analysis, it turned out to be marginally associated with LBW in the adjusted model (p=0.086).

In the adjusted logistic regression for women with known HIV status, there was no observed relationship between LBW and number of ANC visits, education status and maternal age as observed in the total sample analysis. Women from wealthier households (quintile 5) had 0.60 odds of having LBW infants compared to women from poorest households (OR=0.35; 95% CI= 0.45 – 1.03). However, the association was marginally significant (p=0.06).

Table 9: Univariate and multivariate analysis of factors associated with low birth weight

	Total sample, n=3724				Known HIV status, n=1802			
Variable	**Univariate**		**Multivariable**		**Univariate**		**Multivariable**	
	Unadj OR (95% CI)	**P-value**	**Adj OR (95% CI**	**P-value**	**Unadj OR (95% CI)**	**P-value**	**Adj OR (95% CI**	**P-value**
HIV status								
HIV positive								
HIV negative					1.16 (0.80 -1.68)	0.444	1.19 (0.80 – 1.78)	0.389
Age								
13 – 19 years	Ref							
20-24 years	0.76 (0.56 – 1.01)	0.060	0.81 (0.59 -1.11)	0.190	0.61 (0.41– 0.91)	0.016	0.65 (0.41 – 1.01)	0.057
25 - 29 years	0.55 (0.40 – 0.75)	<0.001	0.56 (0.39 - 0.81)	0.002	0.46 (0.29 – 0.73)	0.001	0.48 (0.27 – 0.86)	0.013
30 - 34 years	0.72 (0.52- 0.99)	0.044	0.70 (0.45 – 1.05)	0.084	0.58 (0.35 – 0.94)	0.026	0.57 (0.30 -1.11)	0.097
35 – 39 year	0.73 (0.50 – 1.06)	0.099	0.69 (0.43 – 1.10)	0.119	0.86 (0.52– 1.42)	0.557	0.77 (0.37 – 1.62)	0.495
40 - 49 years	0.87 (0.53– 1.43)	0.596	0.79 (0.43 - 1.44)	0.445	0.87 (0.42- 1.73)	0.666	0.70 (0.27– 1.79)	0.459
Residential status								
Permanent	Ref							
Temporary	0.94 (0.69 – 1.29)	0.710	1.03 (0.75 -1.43)	0.843	0.86 (0.52 – 1.41)	0.543	0.98 (0.58 - 1.64)	0.935
Education status								
Primary/ less education	Ref							
Secondary education	0.92 (0.65 – 1.30)	0.641	0.98 (0.62 – 1.27)	0.509	0.70 (0.42 – 1.15)	0.159	0.69 (0.40 – 1.20)	0.188
Complete secondary or more	0.72 (0.51– 1.01)	0.058	0.77 (0.53– 1.11)	0.163	0.54 (0.33 – 0.90)	0.019	0.68 (0.38 – 1.19)	0.178
Relationship status								
Single	Ref							
Married/cohabiting	0.92 (0.74 – 1.14)	0.438	0.99 (0.78 – 1.24)	0.873	0.97 (0.70 – 1.33)	0.848	1.07 (0.72 -1.60)	0.730

Widowed/divorced	1.29 (0.74 – 2.21)	0.378	1.27 (0.71 – 2.24)	0.421	1.78 (0.84– 3.77)	0.129	1.69 (0.38 – 3.84)	0.211
Socio-economic status								
Q1	Ref							
Q2	1.19 (0.88 – 1.62)	0.256	1.23 (0.90 – 1.67)	0.197	0.94 (0.60 – 1.46)	0.777	0.98 (0.62– 1.53)	0.924
Q3	1.09 (0.79- 1.49)	0.603	1.13 (0.83 – 1.57)	0.424	1.00 (0.64 – 1.56)	0.992	1.10 (0.70 – 1.72)	0.687
Q4	1.02 (0.74 – 1.40)	0.900	1.07 (0.78 - 1.48)	0.675	0.80 (0.51 – 1.26)	0.340	0.88 (0.56 – 1.40)	0.595
Q5	0.87 (0.62 – 1.22)	0.430	0.96 (0.68 – 1.36)	0.810	0.54 (0.32– 0.91)	0.020	0.60 (0.35 – 1.03)	0.063
Gravidity								
1	Ref							
2	0.83 (0.65 – 1.06)	0.134	0.98 (0.74 – 1.29)	0.897	0.66 (0.46– 0.95)	0.026	0.79 (0.51 – 1.21)	0.275
3	0.97 (0.73 – 1.28)	0.814	1.17 (0.82 – 1.66)	0.384	0.87 (0.58 – 1.32)	0.520	0.99 (0.55 – 1.75)	0.961
4+	1.04 (0.76- 1.42)	0.801	1.12 (0.73 - 1.72)	0.602	1.08 (0.70 - 1.66)	0.743	0.60 (0.45 - 1.83)	0.782
Number of ANC visits								
4 or more	Ref							
3 and less	1.47 (1.06 - 2.14)	0.041	1.39 (0.95 – 2.03)	0.086	1.19 (0.67 – 2.07)	0.569	1.12 (0.63 – 1.99)	0.701

3.6. Objective 3b To determine maternal factors associated infant survival amongst HIV infected and non-infected women in Agincourt over the period of 2015 to 2019.

3.6.1. Factors associated with infant survival:

Table 12 presents results of the bivariate analysis of the relationship between infant survival and maternal factors. Results shows a total of 90 deaths out of 11001 live births reported in the total sample.

Maternal education status, number of ANC visits and pregnancy term were significantly associated with infant mortality, $p<0.005$. High prevalence of more than 50 infant mortality was reported among women who had attained secondary education level and almost a quarter was reported among those with primary education level. More than three quarter of infants who died withing the first 12 months of life were delivered by women who attended 4 or more ANC visits. Results also showed that the majority of infants who died were born full term, less than 10 % were born pre-term.

The analysis of women with known HIV status showed that the prevalence of infant mortality was 0.74% (n=34), which was lower compared to the overall sample. Maternal HIV status, education status and number of ANC visits had significant relationship with infant mortality. Contrary to the total sample analysis, no relationship was observed between infant mortality and pregnancy term. There were more deaths reported among children of HIV negative women compared to HIV positive women (70. 59% and 29.41% respectively). More than 60% of the infants who died their mothers had attained secondary school level and only less than 10% had primary or less education. Similar to total sample results, less than 10% infants were delivered before term.

<u>Kaplan Meier estimates of mean survival time:</u>

The Kaplan Meier survival curves in Figures 10 and 11 show that the survival probability is the same from birth for the first few weeks. However, maternal HIV infection is associated with poor survival from first month up to 6 months of life. At 6 to 8 months, survival is equal for both HIV exposed and unexposed infants although probability of survival among HIV unexposed drops at 9 months.

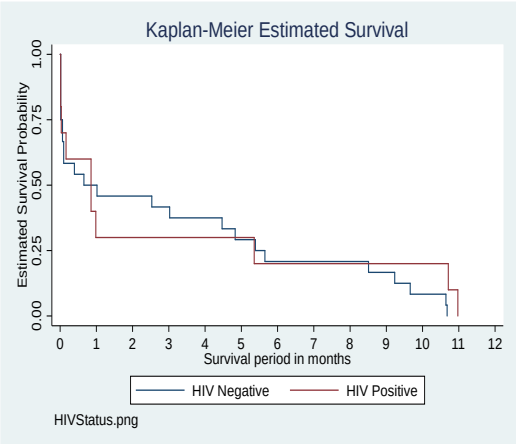


Figure 10: Kaplan Maier survival curve for HIV sample

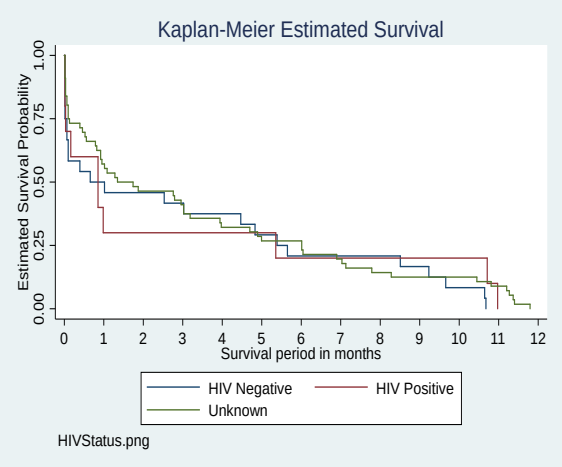


Figure 11: Kaplan Maier survival curve for total sample

<u>The log rank estimates of infant mortality by maternal HIV status:</u>

In this analysis, we assumed that the survival distribution is the same. Maternal age and number of ANC showed statistically significant evidence that there is equal survival in the total sample and a sample of women with known HIV status respectively. There was no statistically significant evidence that the survival distributions are not the same in the same analysis for women with known HIV status. However, there was a marginal relationship with maternal age and pregnancy duration (p=0.097 and 0.079 respectively).

Table 11: Log rank estimates of infant survival

Total sample		Known HIV status	
Variable	Log rank estimate	Variable	Log rank estimate
HIV status		HIV status	X^2 = 0.00 P-value = 0.963
Maternal age	X^2 = 13.13 P-value = 0.022	Maternal age	X^2 = 9.32 P-value = 0.097
Resident status	X^2 = 0.01 P-value = 0.919	Resident status	X^2 = 0.32 P-value = 0.574
Education status	X^2 = 3.03 P-value = 0.220	Education status	X^2 = 1.14 P-value = 0.566
Relationship status	X^2 = 0.64 P-value = 0.727	Relationship status	X^2 = 2.08 P-value = 0.353
SES	X^2 = 3.41 P-value = 0.492	SES	X^2 = 1.21 P-value = 0.876
Gravidity	X^2 = 1.85 P-value = 0.603	Gravidity	X^2 = 0.20 P-value = 0.977
Number of ANC visit	X^2 = 3.96 P-value = 0.047	Number of ANC visit	X^2 = 3.15 P-value = 0.076
Pregnancy attended	X^2 = 0.12 P-value = 0.725	Pregnancy attended	X^2 = 0.16 P-value = 0.693
Pregnancy duration	X^2 = 1.38 P-value = 0.241	Pregnancy duration	X^2 = 3.10 P-value = 0.079

Table 12: Bivariate analysis of the relationship between infant survival and maternal factors

Characteristics	All infants N= 11001	Status of infant survival		P value	All infants N= 4620	Status of infant survival		P-Value
		Died, n= 90	Survived, n= 10911			Died, n= 34	Survived n= 4586	
HIV status								
HIV –				**0.112**	3857 (83.48)	24 (70.59)	3833 (83.53)	0.042
HIV+					763 (16.52)	10 (29.41)	753 (16.42)	
Age								
13 – 19 years	1746 (15.87)	15 (16.67)	**1731 (15.86)**		883 (19.11)	8 (23.53)	875 (19.08)	
20-24 years	2840 (25.82)	24 (26.67)	**2816 (25.81)**		1353 (29.29)	8 (23.53)	1345 (29.33)	
25 – 29 years	2777 (25.24)	22 (24.44)	**2755 (25.25)**	**0.987**	1065 (23.05)	9 (26.47)	1056 (23.03)	0.135
30 – 34 years	1997 (18.15)	14 (15.56)	**1983 (18.17)**		682 (14.76)	2 (5.88)	680 (14.83)	
35 – 39 year	1184 (10.76)	11 (12.22)	**1173 (10.75)**		460 (9.96)	3 (8.82)	457 (9.97)	
40 – 49 years	457 (4.15)	4 (4.44)	**453 (4.15)**		177 (3.83)	4 (11.76)	173 (3.77)	
Residential status								
Permanent	8947 (81.33)	78 (86.67)	**8869 (81.28)**	**0.192**	4029 (87.21)	31 (91.18)	3998 (87.18)	0.487
Temporary	2054 (18.67)	12 (13.33)	**2042 (18.72)**		591 (12.79)	3 (8.82)	588 (12.82)	
Education status								
Primary or less education	956 (8.69)	**13 (14.44)**	943 (8.64)	**<0.001**	335 (7.25)	3 (8.82)	332 (7.24)	
Secondary education	4620 (42.00)	**52 (57.78)**	4568 (41.87)		2108 (45.63)	22 (64.71)	2086 (45.49)	0.051
Complete secondary or more	5425 (49.31)	**25 (27.78)**	5400 (49.49)		2177 (47.12)	9 (26.47)	2168 (47.27)	
Relationship status								
Single	7078 (64.34)	**54 (60.00)**	7024 (64.38)	**0.596**	3248 (70.30)	23 (67.65)	3225 (70.32)	

Married/cohabiting	3616 (32.87)	**34 (37.78)**	3582 (32.83)		1267 (27.42)	11 (32.35)	1256 (27.39)	0.572
Widowed/divorced	307 (2.79)	**2 (2.22)**	305 (2.80)		105 (2.27)	0 (0.00)	105 (2.29)	
Socio-economic status								
Q1	1972 (17.93)	19 (21.11)	**1953 (17.90)**		767 (16.60)	8 (23.53)	759 (16.55)	
Q2	2293 (20.84)	22 (24.44)	**2271 (20.81)**	**0.664**	983 (21.28)	11 (32.35)	972 (21.19)	
Q3	2192 (19.93)	18 (20.00)	**2174 (19.92)**		940 (20.35)	4 (11.76)	936 (20.41)	0.171
Q4	2256 (20.51)	17 (18.89)	**2239 (20.52)**		1004 (21.73)	8 (23.53)	996 (21.72)	
Q5	2288 (20.80)	14 (15.56)	**2274 (20.84)**		926 (20.04)	3 (8.82)	923 (20.13)	
Gravidity								
1	4891 (44.46)	33 (36.67)	**4858 (44.52)**		2062 (44.63)	15 (44.12)	2047 (44.46)	0.897
2	3140 (28.54)	31 (34.44)	**3109 (28.49)**	**0.270**	1301 (28.16)	8 (23.53)	1293(28.19)	
3	1705 (15.50)	12 (13.33)	**1693 (15.52)**		689 (14.91)	6 (17.65)	683 (14.89)	
4+	1265 (11.50)	14 (15.56)	**1251 (11.47)**		568 (12.29)	5 (14.71)	563 (12.28)	
Number of ANC visits								
3 and less	952 (8.65)	22 (24.44)	**930 (8.52)**	**<0.001**	371 (8.03)	10 (29.41)	361 (7.87)	
4 or more	10049 (91.35)	68 (75.56)	**9981 (91.48)**		4249 (91.97)	34 (70.59)	4225 (92.13)	<0.001
Delivery attendant								
Health professional	9945 (90.40)	83 (92.22)	**9862 (90.39)**	**0.556**	4325 (93.61)	32 (94.12)	4293 (93.61)	0.904
Other	1056 (9.60)	7 (7.78)	**1049(9.61)**		295 (6.39)	2 (5.88)	293 (6.39)	
Pregnancy term								
Term	10791 (98.09)	82 (91.11)	**10709 (98.15)**	**<0.001**	92 (1.99)	2 (5.88)	90 (1.96)	0.103
Pre-term	210 (1.91)	8 (8.89)	**202 (1.85)**		4528 (98.01)	32 (94.12)	4496 (98.04)	

3.6.2. Cox regression analysis:

In the bivariate analysis of the total sample, education status, number of ANC visits and pregnancy duration were associated with survival status. However, only number of ANC visits was marginally associated with infant survival in the cox regression analysis as presented in Table 13 (p=0.091). Infants born from women who attended 3 or less ANC visits had 2 times higher hazards of dying in the first 12 month of life as compared to infants born from women who attended 4 or more ANC visits (AHR: 1.55; 95% CI: 0 .93 – 2.57).

Contrary to the total sample, bivariate analysis conducted among women with known HIV status revealed that pregnancy duration was not statistically associated with infant survival. However, education status and number of ANC visits remained associated with infant survival in the analysis. In addition, HIV status was statistically associated with infant survival. Cox regression analysis showed similar results to findings from the total sample. The risk of mortality among infants born from women who had attended 3 or less ANC visits was also twice higher than those born from women who attended 4 or more ANC visits (AHR: 1.96; 95% CI: 0.91 – 4.23).

Table 13: Crude and adjusted hazards of maternal factors associated with infant mortality

	Total sample, n= 4444				**Known HIV status, n=4620**			
Variable	**Univariate**		**Multivariable**		**Univariate**		**Multivariable**	
	CHR (955 CI)	**P-value**	**AHR (95% CI**	**P-value**	**CHR (95% CI)**	**P-value**	**AHR (95% CI**	**P-value**
HIV status								
HIV positive								
HIV negative					1.02 (0.49 -2.13)	0.964	1.2 (0.52 – 2.39)	0.780
Education status								
Primary/ less education	Ref							
Secondary education	0.96 (0.52– 1.76)	0.885	0.94 (0.50 – 1.77)	0.856	1.21 (0.36 – 4.05)	0.756	0.98 (0.28 – 3.44)	0.977
Complete secondary or more	1.16 (0.59 – 2.27)	0.667	1.11 (.56 – 2.22)	0.753	1.74 (0.47– 6.48)	0.406	1.53 (0.41 – 5.77)	0.531
Number of ANC visits								
4 or more	Ref							
3 and less	1.61 (1.00 - 2.62)	0.052	1.55 (0 .93 – 2.57)	0.091	1.91 (0.91 – 4.01)	0.089	1.96 (0.91 – 4.23)	0.085
Pregnancy duration								
Term	Cons							
Preterm	1.53 (0.74 – 3.18)	0.252	1.29 (0.60 -2.80)	0.519	0.16 (0.04 – 0.65)			

CHAPTER 4: DISCUSSION

In this discussion chapter, a brief overview of the results will be presented. The aim of this study was to assess the effect of maternal HIV infections on perinatal and infant survival outcomes in Agincourt, rural South Africa over the period 2015-2019. We will discuss the trends of adverse perinatal outcome and infant survival, and maternal factors associated with adverse perinatal and infant survival outcome. To conclude the chapter, the strengths and limitation of the study as well as the conclusion and recommendations drawn from the study will be outlined.

4.1. Overview of the study findings:

In this study, we estimated a 16.58% prevalence of maternal HIV infections among women aged 13 – 49 years. The reported prevalence was lower compared to a national prevalence of 26% estimated in 2019 (UNAIDS, 2020). The lower prevalence in our study may be explained by the fact more than 50% of our sample had missing data on HIV status. The primary study only collected HIV data among women who accessed ANC services at one of the 9 government health facilities in the Agincourt study area. As a result, HIV data for women who sought ANC services at private facilities or outside the Agincourt study area is unknown.

Regarding the trends of adverse outcomes, trends of PTD gradually increased over the period of 5 years. There was no significant change in perinatal deaths from 2015 - 2018 and then a drop in 2019. A similar study conducted in Mpumalanga province reported a decrease in perinatal deaths owing to implementation of 2016 WHO reviewed and published recommendations on the number and timing of ANC visits (Lavin *et al.*, 2020). LBW trends also remained constant in the total sample and HIV negative women however, there were fluctuations among the HIV positive women where the highest was recorded in 2015. Similar results reported in other settings, (Marete *et al.*, 2020) did not observe a significant change in LBW trends from 2013-2018 although LBW burden was reportedly higher among the Asian sites than African sites.

Overall prevalence of perinatal deaths which consisted of abortions, miscarriage and stillbirths was 0.76% and 0.88% for the total sample and known HIV-subgroup, respectively. Contrary to our findings, there is high prevalence of perinatal deaths reported in Africa and other parts of South Africa. Two African studies reported a prevalence of around 10% (Madhi *et al.*, 2019; Ameyaw, Ahinkorah and Seidu, 2020). Another similar study done at an urban area of Durban reported a

prevalence of 37% perinatal deaths associated with maternal factors (Naidoo, Sartorius and Tshimanga-Tshikala, 2016).

We expected to observe lower prevalence as an indication of effectiveness of ART that promote better outcomes in pregnant women. However, in this study the lower prevalence may have been due issues associated with health systems. Under reporting of abortions owing to unsafe pregnancy terminations that involves ending a pregnancy by an untrained person, or in an unauthorized facility with minimal medical standards or both (Ameyaw, Ahinkorah and Seidu, 2020). In addition, data was collected in a rural setting with limited resources. Therefore, lack of standardized criteria for reporting lost pregnancies may also be a contributing factor (Blondel *et al.*, 2018). This is self-reported data which does not have medically confirmed records. Therefore, under reporting of perinatal deaths may be because of stigma associated with abortions.

We reported the PTD prevalence of around 2% for the total sample and the HIV sub-group. The prevalence was lesser compared the 10% -11% global prevalence reported in 2015 and around 10% reported in previous and recent SA studies done in KZN (Naidoo, Sartorius and Tshimanga-Tshikala, 2016; Jeena *et al.*, 2020). The study population of Agincourt HDSS comprises about a third former Mozambican refugees (Kahn *et al.*, 2012). We assume that the portion of pregnant women in our study form part of the immigrants who may not have legal South African citizenship. It is likely that some women did not access ANC services during early pregnancy due to factors associated with being a migrant, and only presented to the health facilities during delivery and without documented pregnancy history. There is evidence that women refugees face challenges such as medical xenophobia and language barriers in attempt to access reproductive health services in South Africa (Africa and Munyaneza, 2019). The low prevalence of PDT in our study may be due to under reporting of preterm infants in our facilities.

Our study found a LBW prevalence of 12.11% and 11.82% for the total sample and HIV sub-group, respectively. The prevalence was slightly lower than a 15 - 20 % reported in low and middle income countries and 13% reported in Sub-Saharan Africa (Girma *et al.*, 2019). A recent South African study prevalence of 13.5% (Jeena *et al.*, 2020). There is a similar prevalence of LBW across the globe suggesting an effectiveness of improved interventions that were implemented to combat LBW globally.

An estimated infant mortality rate in our study was low at 0.82% and 0.74% for the total sample and HIV subgroup respectively. The reported results in our study are in line with the global decline in infant mortality. In 2018 infant mortality was reported at 2.27% globally (OECD/WHO, 2021). A recent study conducted in an urban area in Durban also reported low rate of 1.4% for infant mortality (Jeena *et al.*, 2020). Although we expect lower prevalence in this study, we acknowledge that our results may be influenced by unregistered infant deaths that do not reach the health systems because they occurred at home.

4.2. Maternal factors associated with adverse perinatal outcomes and infant mortality:

The third objective in this study was to determine maternal factors associated with adverse outcome. The study has revealed several interesting findings, maternal HIV infections were associated with preterm deliveries and there was no relationship with other adverse perinatal outcomes. Maternal age was associated with LBW but no relationship with other outcomes. In addition, number of ANC visits were associated with preterm abortion/stillbirths, PTD and infant mortality and no association with low birth weight.

4.2.1. Relationship between maternal HIV infections and adverse perinatal outcome and infant mortality

4.2.1.1. Maternal HIV infections and adverse perinatal outcome

Maternal HIV infection continues to make an important contribution towards adverse perinatal outcome and infant mortality (Zack *et al.*, 2014; Paulo, 2015). As an intervention to combat negative pregnancy outcomes, WHO and UNICEF in 2013 recommended that all HIV positive pregnant women start ART in pregnancy regardless of CD4+ cell count and continue ART for life (Stringer *et al.*, 2018). ART aims at reducing the negative impact of HIV infections on the women and the infants. Therefore, we would expect to find no difference in outcomes between HIV positive and HIV negative women.

We observed that HIV-infected women had more perinatal deaths compared to HIV-uninfected women (24.39% and 16.52% respectively). Additionally, HIV-infected women had increased risk of perinatal deaths although not statistically significant. Results are consistent with previous African study (González *et al.*, 2017) that found no association between HIV infections and adverse outcomes. These results reject the hypothesis that maternal HIV infections has impact on

the perinatal deaths, suggesting that there are other factors contributing to occurrence of perinatal deaths among HIV positive women.

An interesting finding in this study is that preterm deliveries were significantly associated with maternal HIV infections. The prevalence of PTD was 27.17% among HIV-infected women compared to 16.30% among HIV uninfected women. HIV infected women had twice the odds of having PTD as compared to HIV uninfected women. (Naidoo, Sartorius and Tshimanga-Tshikala, 2016) also reported similar findings. Although Santosa *et al.*, (2019) did not find relationship between maternal HIV infections and PTD, findings from studies done in Africa and globally (Zack *et al.*, 2014; Macdonald *et al.*, 2015; Mathews *et al.*, 2015; Kochanek *et al.*, 2019; Yang *et al.*, 2019) confirm that maternal HIV infection is a significant risk factor for PTD. There is adequate evidence to accept the hypothesis that maternal HIV infections contribute to occurrence of PTD. These findings could be attributed to medical and social factors.

Placental abnormalities such as fibrotic lesion and intervillous thrombi which are mostly common among HIV infected women maybe be the cause of PDT among these women (Macdonald *et al.*, 2015) . In addition to the medical risks of maternal HIV for PDT, maternal social factors such as stigma, racism and stresses associated with HIV which are not included in this study may augment the negative effect of underlying HIV infection in women (Macdonald *et al.*, 2015).

There is no consensus regarding the effect of HIV infections on infant birth weight as some studies link LBW to maternal HIV infections (Macdonald *et al.*, 2015; Dara *et al.*, 2018; Yang *et al.*, 2019; Jeena *et al.*, 2020) while González *et al.*(2017) and Wu *et al.*(2018) found no relationship between LBW and maternal HIV status. In this study, although the prevalence of LBW was higher among HIV infected women, maternal HIV infection had no significant impact on birth weight in the multivariate analysis**.** Based on the findings, infant LBW is not significantly associated with maternal HIV infections, implying that it may be caused by other factors such as maternal age and preterm deliveries which were not significant in this study. These contradictory findings may suggest the protective role of ART uptake among HIV infected women as ART has found to improve the immune system of the mother enabling her to supply adequate nutrients to the unborn fetus.

4.2.1.2. Maternal HIV infections and infant mortality

Although high infant mortality was found among HIV infected women in the bivariate analysis, maternal HIV infections had no impact on the survival of the infant in the cox regression analysis. On the contrary, previous studies found infants born from HIV positive mothers to be at high risk of dying compared to those born from HIV negative women. (González *et al.*, 2017; Yang *et al.*, 2019; Twabi, Manda and Small, 2020).

4.2.2. ANC visits:

Antenatal care provides healthcare services in an attempt to make sure that pregnant women have a smooth pregnancy and deliver healthy infants (Jinga *et al.*, 2019). The ANC service includes screening for complications, assessment of pregnancy risk, provision of information and support to pregnant women. WHO recommends a minimum of four ANC visits. Early and frequent ANC visits is also vital in promoting positive perinatal outcomes (Stringer *et al.*, 2018).

In this study we noted that women who attending three or less ANC were three times more likely to lose pregnancies such as abortion, stillbirths or miscarriage compared to those who attended four or more visits. Attending three or less ANC visits was three times more significantly associated with the risk of having PTD (WHO, 2016). Lastly, inadequate attendance of ANC during pregnancy was associated with LBW in the total sample. However, the relationship was not significant in the HIV sub-group. These findings suggest that attending more than 4 ANC visits reduces the risk of adverse pregnancy outcomes.

Findings in our study concur with findings from other studies that show that poor ANC attendance is a risk factor for PTD (Baldewsingh *et al.*, 2020) supporting the assumption that the more the number of contacts with a healthcare provider through ANC visits, the more the opportunities of reducing risks of pregnancy complications such as PTD through treatment.

Results indicated that although prevalence of infant mortality was high among women who attended 4 or more ANC visits, the hazards ratio for infant mortality was twice compared to infants born from mothers who attended 3 or less ANC visits. Findings are consistent with a systemic review and meta-analysis study that included studies from low-middle income countries to assess ANC care follow-up on neonatal health outcomes (Shiferaw *et al.*, 2021)

These findings suggest that ANC visits are associated with reduced infant mortality through post-partum information that are provided by health care workers during visits. Similarly, (Tekelab *et al.*, 2019) in their systematic review and meta-analysis also found that women in SSA who met WHO recommendation of minimum of 4 ANC had 55% lower risk of neonatal mortality.

It is important to note that in this current study we found that more than 80% of the women attended more than 4 ANC visits thus there are possibilities that even women who attended ANC visits had adverse outcome. We therefore suspect that although there was adequate ANC attendance there may be inadequate use of ANC interventions by women or inadequate counselling of pregnant women by health care professionals during visits, or both. During ANC visits health care workers provide pregnant women with information such as postpartum care, newborn care including appropriate feeding practices.

4.2.3 Maternal age:

Results in this study indicate a significant high risk of LBW among women aged 20-24 years and an increased risk with increased age from 25 years and older although not statistically significant. We also reported an increased risk for women 35 years and older although the relationship was not found among the known HIV sub-group. Our results are in line with a study conducted among women attending public clinics in Durban SA, that showed that women aged 30 years and older had increased risks of LBW (Jeena *et al.*, 2020). Contrary to our findings, (Baldewsingh *et al.*, 2020) did not found a relationship between maternal age and LBW. In our sample, majority of the women (more than 80%) were below the age of 35 years. This self-contradiction in our study may suggested that LBW may be attributed to risky lifestyle associated with this age group. Behaviors such as smoking and drinking alcohol are likely to causes LBW delivery through inhibiting supply of nutrients to the infant.

CHAPTER 5: CONCLUSION AND RECOMMENDATIONS

In conclusion, our study documented that there is no difference in risk of having adverse perinatal outcomes including infant mortality between HIV infected and non-infected mothers. The result from this study suggests that introduction of ART to all pregnant women regardless their CD4 counts in the past 5 years made a huge impact in combatting adverse perinatal outcomes. The

cases of pregnancy loss, LBW, PTD and infant mortality are found to have dropped over these days. The study further showed that attendance of ANC visits plays a vital role in promoting positive pregnancy outcomes and reducing infant mortality.

5.1. Recommendations:

We therefore recommend raising awareness about the importance of attending ANC visits during pregnancy and strengthening of already existing PMTCT programs that aims at promoting frequent and regular attendance of ANC visits during pregnancy especially in the rural areas such as Agincourt. In addition, there is a need for more skilled healthcare professionals who are adequately trained to provide both pre-natal and post-partum quality services during the ANC visits and to ensure that all HIV positive women are enrolled on ART. While the study shows that there is no difference in risk of having adverse perinatal outcome between HIV and non-HIV infected women it is still unknown whether the results is linked to ART uptake or non-pharmaceutical interventions such as healthy eating therefore further work is required to assess the relationship between ART uptake among women and perinatal outcome.

5.2. The strength and limitations of the study

The strength of this study lies in the fact that the information gathered is derived from a large carefully examined sample where rigorous primary data collection methods were employed to ensure high data quality. It is important to note that this is the first study to assess the impact of maternal HIV infections on perinatal outcomes in the rural Mpumalanga province, South Africa.

There are several epidemiological and statistical limitations to the study, including the fact that the study relied on retrospective, routine data which means the completeness and the quality of the data could not be controlled. For example, we had more than 50% unknown HIV status. To address this, analysis was conducted for the total sample and the known HIV subgroup to compare the differences. The diagnosis of perinatal deaths was based on self-report data from the mother and is subject to misclassification bias as many may report still birth instead of self-induced abortions, as a result both stillbirths, abortions and miscarriage analyzed as one variable. The analysis was

based on data collected in a rural area, therefore estimates from this study cannot be generalizable to the national population however representative of the rural settings.

The study did not include data on ART care history status to explain the differences in risks among HIV positive women. The study did not include information on other social variables such as smoking and drinking history, maternal weight which have been found to contribute to adverse perinatal outcome. We could not make inferences on some of the outcome variables reported due to inadequate sample size e.g birth weight. In addition, most information in the data were retrospective self-reported which has high risk of recall bias.

REFERENCES

Africa, S. and Munyaneza, Y. (2019) ‘Challenges of women refugees in utilising reproductive health services in public health institutions in’, pp. 1–8.

Ameyaw, E. K., Ahinkorah, B. O. and Seidu, A. A. (2020) ‘Does knowledge of pregnancy complications influence health facility delivery? Analysis of 2014 Bangladesh Demographic and Health Survey’, *PLoS ONE*, 15(8 August), pp. 1–14. doi: 10.1371/journal.pone.0237963.

Babb, B. A. and Pruett, M. K. (2019) ‘July 2019’, *Family Court Review*, 57(3), p. 293. doi: 10.1111/fcre.12416.

Baldewsingh, G. K. *et al.* (2020) ‘Adequate antenatal care and ethnicity affect preterm birth in pregnant women living in the tropical rainforest of Suriname’, *BMC Pregnancy and Childbirth*, 20(1), pp. 1–9. doi: 10.1186/s12884-020-03364-2.

Barron, P. *et al.* (2013) ‘Eliminating mother-to-child HIV transmission in South Africa’, *Bulletin of the World Health Organization*, 91(1), pp. 70–74. doi: 10.2471/blt.12.106807.

Blondel, B. *et al.* (2018) ‘How do late terminations of pregnancy affect comparisons of stillbirth rates in Europe? Analyses of aggregated routine data from the Euro-Peristat Project’, *BJOG: An International Journal of Obstetrics and Gynaecology*, 125(2), pp. 226–234. doi: 10.1111/1471-0528.14767.

Burton, R., Giddy, J. and Stinson, K. (2015) ‘Prevention of mother-to-child transmission in South Africa: an ever-changing landscape’, *Obstetric Medicine*, 8(1), pp. 5–12. doi: 10.1177/1753495X15570994.

Dara, J. S. *et al.* (2018) ‘Low birth weight in human immunodeficiency virus–exposed uninfected infants in Bronx, New York’, *Journal of the Pediatric Infectious Diseases Society*, 7(2), pp. E24–E29. doi: 10.1093/jpids/pix111.

Dzanibe, S. *et al.* (2019) 'HHS Public Access', 105(2), pp. 281–289. doi: 10.1002/JLB.MR0318-120R.Impact.

Evans, C., Jones, C. E. and Prendergast, A. J. (2016) 'HIV-exposed, uninfected infants: new global challenges in the era of paediatric HIV elimination', *The Lancet Infectious Diseases*, 16(6), pp. e92–e107. doi: 10.1016/S1473-3099(16)00055-4.

Fuchs, F. *et al.* (2018) 'Effect of maternal age on the risk of preterm birth: A large cohort study', *Obstetrical and Gynecological Survey*, 73(6), pp. 340–342. doi: 10.1097/01.ogx.0000541308.53092.4a.

Girma, S. *et al.* (2019) 'Factors associated with low birthweight among newborns delivered at public health facilities of Nekemte town, West Ethiopia: A case control study', *BMC Pregnancy and Childbirth*, 19(1), pp. 1–6. doi: 10.1186/s12884-019-2372-x.

González, R. *et al.* (2017) 'Effects of HIV infection on maternal and neonatal health in southern Mozambique: A prospective cohort study after a decade of antiretroviral drugs roll out', *PLoS ONE*, 12(6), pp. 1–17. doi: 10.1371/journal.pone.0178134.

Ikpim, E. M. *et al.* (2016) 'HIV infection in pregnancy: maternal and perinatal outcomes in a tertiary care hospital in Calabar, Nigeria', *Tropical Doctor*, 46(2), pp. 78–86. doi: 10.1177/0049475515605003.

Jeena, P. M. *et al.* (2020) 'Maternal demographic and antenatal factors, low birth weight and preterm birth: findings from the mother and child in the environment (MACE) birth cohort, Durban, South Africa', *BMC Pregnancy and Childbirth*, 20(1), pp. 1–11. doi: 10.1186/s12884-020-03328-6.

Jinga, N. *et al.* (2019) 'Reasons for late presentation for antenatal care, healthcare providers' perspective', *BMC Health Services Research*, 19(1), pp. 1–9. doi: 10.1186/s12913-019-4855-x.

Joseph, O., Biodun, O. and Michael, E. (2011) 'Pregnancy outcome among HIV positive women receiving antenatal HAART versus untreated maternal HIV infection', *Journal of the College of Physicians and Surgeons Pakistan*, 21(6), pp. 356–359.

Kabudula, C. W. *et al.* (2014) 'The promise of record linkage for assessing the uptake of

health services in resource constrained settings: A pilot study from South Africa', *BMC Medical Research Methodology*, 14(1), pp. 1–10. doi: 10.1186/1471-2288-14-71.

Kahn, K. *et al.* (2007) 'Research into health, population and social transitions in rural South Africa: Data and methods of the Agincourt health and demographic surveillance system', *Scandinavian Journal of Public Health*, 35(SUPPL. 69), pp. 8–20. doi: 10.1080/14034950701505031.

Kahn, K. *et al.* (2012) 'Profile: Agincourt health and socio-demographic surveillance system', *International Journal of Epidemiology*, 41(4), pp. 988–1001. doi: 10.1093/ije/dys115.

Klaas, N. E., Thupayagale-Tshweneagae, G. and Makua, T. P. (2018) 'The role of gender in the spread of HIV and AIDS among farmworkers in South Africa', *African journal of primary health care & family medicine*, 10(1), pp. 1–8. doi: 10.4102/phcfm.v10i1.1668.

Kochanek, K. D. *et al.* (2019) 'treatment in sub-Saharan Africa (POISE Study)', *PLoS ONE*, 13(1), pp. 1–10. doi: 10.1093/jpids/pix111.

Kurewa, E. N. *et al.* (2010) 'Effect of maternal HIV status on infant mortality: Evidence from a 9-month follow-up of mothers and their infants in Zimbabwe', *Journal of Perinatology*, 30(2), pp. 88–92. doi: 10.1038/jp.2009.121.

Lavin, T. *et al.* (2020) 'The impact of implementing the 2016 WHO Recommendations on Antenatal Care for a Positive Pregnancy Experience on perinatal deaths : an interrupted time- - series analysis in Mpumalanga province , South Africa'. doi: 10.1136/bmjgh-2020-002965.

Macdonald, E. M. *et al.* (2015) 'Adverse Neonatal Outcomes Among Women Living With HIV: A Population-Based Study', *Journal of Obstetrics and Gynaecology Canada*, 37(4), pp. 302–309. doi: 10.1016/S1701-2163(15)30279-6.

Madhi, S. A. *et al.* (2019) 'Causes of stillbirths among women from South Africa: a prospective, observational study', *The Lancet Global Health*, 7(4), pp. e503–e512. doi: 10.1016/S2214-109X(18)30541-2.

Malaba, T. R. *et al.* (2017) 'Antiretroviral therapy use during pregnancy and adverse birth outcomes in South African women', *International Journal of Epidemiology*, 46(5), pp. 1678–1689. doi: 10.1093/ije/dyx136.

Marete, I. *et al.* (2020) 'Regional trends in birth weight in low - and middle - income countries 2013 – 2018', *Reproductive Health*, 17(3), pp. 1–9. doi: 10.1186/s12978-020-01026-2.

Marinda, E. *et al.* (2007) 'Child mortality according to maternal and infant HIV status in Zimbabwe', *Pediatric Infectious Disease Journal*, 26(6), pp. 519–526. doi: 10.1097/01.inf.0000264527.69954.4c.

Mathews, T. J. *et al.* (2015) 'National Vital Statistics Reports Infant Mortality Statistics From the 2013 Period Linked Birth / Infant Death Data Set', 64(9), pp. 2000–2013.

Van Der Merwe, K. *et al.* (2011) 'Birth outcomes in South African women receiving highly active antiretroviral therapy: A retrospective observational study', *Journal of the International AIDS Society*, 14(1), pp. 1–11. doi: 10.1186/1758-2652-14-42.

Moodley, T. *et al.* (2016) 'Improved pregnancy outcomes with increasing antiretroviral coverage in South Africa', *BMC Pregnancy and Childbirth*, 16(1), pp. 1–10. doi: 10.1186/s12884-016-0821-3.

Mugwaneza, P. *et al.* (2011) 'Under-two child mortality according to maternal HIV status in Rwanda: Assessing outcomes within the National PMTCT Program', *Pan African Medical Journal*, 9, pp. 1–13.

Naidoo, M., Sartorius, B. and Tshimanga-Tshikala, G. (2016) 'Maternal HIV infection and preterm delivery outcomes at an urban district hospital in KwaZulu-Natal 2011', *Southern African Journal of Infectious Diseases*, 31(1), pp. 25–28. doi: 10.4102/sajid.v31i1.101.

Ndirangu, J. *et al.* (2012) 'Maternal HIV infection associated with small-for-gestational age infants but not preterm births: Evidence from rural South Africa', *Human Reproduction*, 27(6), pp. 1846–1856. doi: 10.1093/humrep/des090.

OECD/WHO (2012) *Health at a glance*, *Tuberculosis*.

Olagbuji, B. N. *et al.* (2010) 'Obstetric and perinatal outcome in HIV positive women receiving HAART in urban Nigeria', *Archives of Gynecology and Obstetrics*, 281(6), pp. 991–994. doi: 10.1007/s00404-009-1186-x.

Paulo, S. (2015) 'PRETERM BIRTH AND FETAL GROWTH RESTRICTION IN HIV-INFECTED', 57(2), pp. 111–120.

Pfeifer, C. and Bunders, M. J. (2016) 'Maternal HIV infection alters the immune balance in the mother and fetus; Implications for pregnancy outcome and infant health', *Current Opinion in HIV and AIDS*, 11(2), pp. 138–145. doi: 10.1097/COH.0000000000000239.

Rao, C., Lopez, A. D. and Hemed, Y. (2006) *Causes of Death*, *Disease and Mortality in Sub-Saharan Africa*. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21290659 (Accessed: 9 July 2019).

Rollins, N. C. *et al.* (2013) 'Exclusive breastfeeding, diarrhoeal morbidity and all-cause mortality in infants of HIV-infected and HIV uninfected mothers: An intervention cohort study in KwaZulu natal, South Africa', *PLoS ONE*, 8(12), pp. 1–10. doi: 10.1371/journal.pone.0081307.

Santosa, W. B. *et al.* (2019) 'Perinatal outcomes associated with maternal HIV and antiretroviral therapy in pregnancies with accurate gestational age in South Africa', (February). doi: 10.1097/QAD.0000000000002222.

Schulte, J. *et al.* (2015) 'Declines in Low Birth Weight and Preterm Birth Among Infants Who Were Born to HIV-Infected Women During an Era of Increased Use of Maternal Antiretroviral Drugs : Pediatric Spectrum of HIV Disease , 1989 – 2004'. doi: 10.1542/peds.2006-1123.

Shiferaw, K. *et al.* (2021) 'The effect of antenatal care on perinatal outcomes in Ethiopia: A systematic review and meta-analysis', *PLoS ONE*, 16(1 January), pp. 1–11. doi: 10.1371/journal.pone.0245003.

Stringer, E. M. *et al.* (2018) 'Pregnancy outcomes among HIV-infected women who conceived on antiretroviral therapy', *PLoS ONE*, 13(7), pp. 1–12. doi: 10.1371/journal.pone.0199555.

Tekelab, T. *et al.* (2019) ‘The impact of antenatal care on neonatal mortality in sub-Saharan Africa: A systematic review and meta-analysis’, *PLoS ONE*, 14(9), pp. 1–15. doi: 10.1371/journal.pone.0222566.

Twabi, H. S., Manda, S. O. and Small, D. S. (2020) ‘Assessing the effects of maternal HIV infection on pregnancy outcomes using cross-sectional data in Malawi’, *BMC Public Health*, 20(1), pp. 1–15. doi: 10.1186/s12889-020-09046-0.

UNAIDS (2019) ‘Global HIV and AIDS statistics 2019 Fact sheet’, *Global HIV and AIDs ststistics, World AIDS day 2019 Fact Sheet*.

UNAIDS (2020) ‘Data 2020’, *Programme on HIV/AIDS*, pp. 1–248. Available at: https://www.unaids.org/en/resources/documents/2020/unaids-data%0Ahttp://www.unaids.org/sites/default/files/media_asset/20170720_Data_book_2017_en.pdf.

UNSAID (2018) ‘UNAIDS Data 2018’, *Programme on HIV/AIDS*, pp. 1–376. Available at: http://www.unaids.org/sites/default/files/media_asset/unaids-data-2018_en.pdf%0Ahttp://www.unaids.org/sites/default/files/media_asset/20170720_Data_book_2017_en.pdf.

Venkatesh, K. K. *et al.* (2011) ‘Morbidity and mortality among infants born to HIV-infected women in South Africa: Implications for child health in resource-limited settings’, *Journal of Tropical Pediatrics*, 57(2), pp. 109–119. doi: 10.1093/tropej/fmq061.

Wedi, C. O. O. *et al.* (2016) ‘Perinatal outcomes associated with maternal HIV infection: A systematic review and meta-analysis’, *The Lancet HIV*, 3(1), pp. e33–e48. doi: 10.1016/S2352-3018(15)00207-6.

WHO (2016) ‘WHO recommendations on antenatal care for a positive pregnancy experinec’.

Wu, J. *et al.* (2018) ‘Neurodevelopmental outcomes in young children born to HIV-positive mothers in rural Yunnan, China’, *Pediatrics International*, 60(7), pp. 618–625. doi: 10.1111/ped.13584.

Xiao, P. L. *et al.* (2015) ‘Association between maternal HIV infection and low birth

weight and prematurity: A meta-analysis of cohort studies', *BMC Pregnancy and Childbirth*, 15(1). doi: 10.1186/s12884-015-0684-z.

Yang, M. *et al.* (2019) 'Impact of maternal HIV infection on pregnancy outcomes in southwestern China – A hospital registry based study', *Epidemiology and Infection*, 147. doi: 10.1017/S0950268818003345.

Zack, R. M. *et al.* (2014) 'Risk Factors for Preterm Birth among HIV-Infected Tanzanian Women: A Prospective Study', *Obstetrics and Gynecology International*, 2014, pp. 1–9. doi: 10.1155/2014/261689.

APPENDICES:

Appendix 1: Plagiarism declaration report

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I _____Denny Mabetha_____ (Student number: __1915798_____)

am a student registered for the degree of _MsEpidemiology Epidemiology___ in the academic year

___2018____. I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.
- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

Signature: Date: 13 May 2021

_____ _____

Appendix 2: Ethics clearance certificate

UNIVERSITY OF THE

WITWATERSRAND, JOHANNESBURG

RI 4/49 Miss Denny Mabetha

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M200103 MED19-12-049

NAME: (Principal Investigator)	Miss Denny Mabetha
DEPARTMENT:	MRC/Wits Rural Public Health Transitions Research Unit (Agincourt)
PROJECT TITLE:	The effect of maternal HIV infection on perinatal and infant survival outcomes in Agincourt, rural northeast South Africa, 2015-2019
DATE CONSIDERED:	31/01/2020
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Chodziwadziwa Kabudula

APPROVED BY: Dr C Penny, Chairperson, HREC (Medical)

DATE OF APPROVAL: 07/02/2020

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 January and will therefore be due in the month of January 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 3: Ethics clearance certificate of the primary study

UNIVERSITY OF THE WITWATERSRAND. V JOHANNESBURG	HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

09/01/2019

Professor SM Tollman, et al

School of Public Health

MRC/Wits Rural Health and Health Transitions

Research Unit (Agincourt)

Sent by e-mail to: Kathleen.Kahn@wits.ac.za

Dear Professor Kahn

Re: Protocol Ref No: M151162

Protocol Title: Record-linkage of health facility registries with the Agincourt Health

Demographic Surveillance System (HDSS) Database Principal Investigator: Professor SM Tollman, et al

Thank you for your letter of 08/12/2018.

I confirm that the proposed study amendment has been noted and approved. For the record, the amendment is:

- inclusion of all willing patients presenting at the nine health facilities in the Agincourt HDSS area, regardless of age; previously only adult patiénts were included

Thank you for keeping us informed.

Yours Sincerely

J. Burns

.....

Mr I Burns

For the Human Research Ethics Committee (Medical)

Works2000/lain0007/AcknowIedge.docx

Appendix 4: Letter for permission to access data.

MRC/Wits Rural Public Health and Health Transitions Research Unit (Agincourt)

School of Public Health, University of the Witwatersrand, 27 St Andrew's Road, Parktown, Johannesburg, South Africa, 2193
Tintswalo Hospital, Main Road, Acornhoek, Mpumalanga, South Africa, 1360
Telephone: +27 11 717 2085 (Johannesburg) | +27 13 795 5076 (Acornhoek) | www.agincourt.co.za | twitter@wealcount2

To whom it may concern,

Authorisation to use the MRC/Wits Agincourt Research Unit data

The reason for this letter is to authorize Denny Mabetha, a Field Epidemiology Master's student at Wits to use the unit's data for the purpose of fulfilling her Master.

Denny Mabetha, will have to fill in the Data Request form that can be found at the Agincourt website to request which data is needed for his research and the main objective of his work.

Please do not hesitate to contact me if you require further information.

Yours sincerely, Prof. F. Xavier Gómez-Olivé

Research Manager

MRC/Wits Rural Public Health and Health Transitions Research Unit (Agincourt) School of Public Health

University of the Witwatersrand

Tel/Fax: +27 (0)13 795 50 76

Cell: +27 (0)76 378 82 55

E-mail: F.Gomez-OliveCasas@wits.ac.za