PREVALENCE AND FACTORS ASSOCIATED WITH INTRAPARTUM DETECTABLE VIRAL LOAD AMONG PREGNANT HIV POSITIVE WOMEN DELIVERING AT RILEY MOTHER AND BABY HOSPITAL, ELDORET, KENYA.

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DECLARATION

Declaration by the Candidate: This thesis is my original work and has not been presented for a degree in any other university. No part of this research thesis may be reproduced without prior written permission of the author and/or Moi University.

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DEDICATION

I dedicate this work to my mother who brought me to this world and to all pregnant women for whom I desire to see have a memorable journey of pregnancy and have healthy infants.

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ABSTRACT

Background: Vertical transmission of Human Immuno-deficiency Virus (HIV), can occur during pregnancy, labour, and delivery, or in breastfeeding. Detectable viral load (DVL) is it's the strongest predictor. Although several factors have been associated with DVL at delivery, there are few local studies conducted across sub-Saharan Africa countries including Kenya where there is universal Antiretroviral therapy (ART) for all HIV-infected pregnant women. Knowledge of this will inform strategies aimed at eliminating mother to child transmission through the integrated Prevention of Mother to Child Transmission (PMTCT)-Antenatal Care (ANC) Services.

Objective: To describe the patient characteristics, determine the prevalence of detectable viral load and assess factors associated with it among HIV infected women delivering at Riley Mother and Baby Hospital (RMBH), Eldoret Kenya.

Methods: A cross-sectional study conducted at RMBH in Eldoret Kenya among eligible HIV infected expectant women admitted for delivery. They were enrolled consecutively until the desired sample size of 140 was achieved. Maternal sociodemographic and clinical characteristics were collected using structured interviewer administered questionnaire and viral load assay was done by the AMPATH Reference Laboratory at a detection threshold of 40 copies/ml. Descriptive statistics of means and proportions as well as bivariate tests of associations were conducted using statistical package for social sciences (SPSS) version 24. A p-value of ≤0.05 was statistically significant. Logistic regression was conducted on factors that were statistically significant at the bivariate level.

Results: Out of the 140 enrolled HIV positive pregnant women delivering at RMBH, 99 (70.7%) women knew their HIV status before pregnancy. The sero-discordance rate was 24.3% (34/140), while partner disclosure was reported in 111 (79.3%) women. 77 (55.0%) presented late (>16weeks) for their first antenatal visit, while 13 (9.3%) had Syphilis/HIV co-infection. The most common ART regimen was TDF/3TC/EFV. The median duration of antiretroviral therapy was 20 (IQR: 6.0, 60.0) months and moderate or severe ART side effects were reported in 10 (7.1%). Viral load was detectable in 25 (17.9%) of the participants and of these, 5/25 (20%) had Low level viremia (50-1000 copies/ ml) while 17/25 (68%), had > 1000 copies/ml. 16/17 (94%) of those with viral load of >1000copies/ml delivered by spontaneous Vertex Delivery (SVD). When a multivariate analysis was conducted, there was a statistically significant relationship between reporting of moderate or severe ART side effects and having a detectable viral load at delivery (AOR=6.189; 95% CI: 1.330, 28.797; p=0.020).

Conclusions: The prevalence of detectable viral load at delivery was 17.9% with 94% of those with >1000 copies/ml delivering through SVD. The significant predictor of intrapartum of detectable viral load was reporting of moderate or severe ART related side effects.

Recommendations: Adherence counselling in integrated PMTCT and antenatal care should focus on the recognition of ART-related side effects and their management. There is need to institute mechanisms for checking viral load ahead of delivery.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

xi

LIST OF ABBREVIATIONS

3TC	Lamivudine
AIDS	Acquired Immune Deficiency Syndrome
ANC	Antenatal Care
APGAR	(Appearance, Pallor, Grimace, Activity, Respiration)
ART	Antiretroviral Therapy
AZT	Zidovudine
CS	Caesarean section
CTX	Cotrimoxazole
EFV	Efavirenz
EID	Early Infant diagnosis
EMTCT	Elimination of Mother to Child Transmission
HAART	Highly active antiretroviral therapy
HEI	HIV Exposed Infant
IREC	Institutional Research and Ethics Committee
KDHS	Kenya Demographic Health Survey
LBW	Low Birth Weight
MCH	Maternal Child Health
Mls	Millilitres
Mm^3	Millimetres cubed
MTRH	Moi Teaching and Referral Hospital
NNRTI	Non-nucleoside reverse transcriptase inhibitors
NRTI	Nucleoside reverse transcriptase inhibitors
NVP	Nevirapine
PCR	Polymerase Chain Reaction

PI   Protease Inhibitors

PLHIV   Person Living with HIV

PMTCT   Prevention of Mother to Child Transmission

PWID   Persons Who Inject Drugs

RMBH   Riley Mother and Baby Hospital

SDG   Sustainable Development Goals

TDF   Tenofovir

UNAIDS   Joint United Nations Programme on HIV/AIDS.

WHO   World Health Organization

OPERATIONAL DEFINITION OF TERMS

Detectable viral load- Viral copies of more than 40 copies/ ml

Grand multipara- five or more previous viable deliveries

Low level viremia – viral load between 51-1000 copies per ml

Multipara- two to four previous viable deliveries

Option A- Treatment based on CD4 count. ARV prophylaxis if >350cells/mm3. (Mother received AZT from 14weeks gestation, single dose NVP at onset of labour followed by AZT/3TC for one week. Infant received daily NVP till one week after complete cessation of breastfeeding) If CD4< 350 cells/mm3 triple ART was started for life.

Option B- **Al**so based on CD4 count. Triple ARV prophylaxis was given if CD4 was >350cells/mm3, from 14weeks gestation through delivery and till one week after complete cessation of breastfeeding. The infant received Nevirapine and Zidovudine from birth till six weeks of life.

*Option B Plus-*Lifelong HAART as soon as diagnosis is made regardless of WHO stage or CD4 count. Infant receives Zidovudine from birth to six weeks and Nevirapine from birth to 12weeks of life.

Patient characteristics- The sociodemographic and reproductive (obstetric and gynaecologic) characteristics of the participants.

Partner disclosure- declaring your HIV status to your sexual partner

Primigravida- first pregnancy

*Principal investigator-*lead researcher for a particular well-defined research project

CHAPTER ONE

1.0 INTRODUCTION

1.1 Background

The United Nations Factsheet on Kenya (UNAIDS, 2016b) estimates that there are 1.4 million Kenyans were living with Human Immunodeficiency Virus (HIV). Among women of reproductive age, the prevalence rate of HIV is estimated at 5.4% (NASCOP, 2020). This high prevalence among women of reproductive age increases the risk of mother to child transmission (MTCT) which can occur during pregnancy, labour, and delivery or in breastfeeding (WHO, 2015). The World Health Organization's (WHO) aim of eliminating mother to child transmission (**eMTCT) -** defined as less than fifty (50) new infections per 100,000 live births- can be achieved by initiating Antiretroviral Therapy (ART) prior to conception and maintaining a viral loads below detectable levels throughout pregnancy and at delivery (Mandelbrot, Group, et al., 2015). Since 2016, Kenya adopted the test and treat for all people living with HIV (PLWHIV) including pregnant women. In the same year, WHO strongly recommended HIV viral load testing for monitoring treatment progress. The Kenya ART Guidelines of 2022 (NASCOP, 2022) recommended that at confirmation of pregnancy, a viral load test is done for those who are known positive and on HAART. If virally suppressed, the viral load test is repeated after 6 months. For those newly diagnosed with HIV, viral load is done three months after HAART initiation and six-monthly thereafter if suppressed. The WHO guidelines recommend viral load testing at 34–36 weeks of gestation (or at the latest at delivery) to identify women who may be at risk of treatment failure and/or may deliver infants at higher risk of perinatal transmission (World Health Organization, 2021).

Kenya had an estimated PMTCT coverage of 76% in 2018 (NASCOP, 2018b). In the

absence of any intervention, the rates vary from 15% to 45% (WHO, 2015). These rates could be reduced to less than 5% with interventions during pregnancy, labour and delivery as well as breastfeeding. To reduce perinatal transmission as well as preserve the health of various mothers and children, there are some services, that are offered to pregnant women, as well as mothers living with HIV in the various stages of life, which include during the antenatal period, delivery as well as postpartum phases (Loh et al., 2021). In many healthcare facilities in Kenya, approximately thirty-eight percent (38%) of pregnant women are the only ones who are getting and adhering to the appropriate treatment as recommended. The uptake of the ART mainly involved and aided in suppressing the maternal viral load and through this is it enhances the reduction in the transmission of the virus to the infant after during the period of the pregnancy as well as while the mother is breastfeeding. The range of women in the Sub- Saharan African who have a viral load which is unsuppressed range from 6.1–15.4%, while those who experience postpartum episodes of virologic rebound is at 9.4–22% (Barnabas et al., 2020; Jain et al., 2017; Naar et al., 2020; Pintye et al., 2021). There is a reported drop off in postpartum in Option B+ ART adherence (Ngarina et al., 2015; Yotebieng et al., 2019).

Maintaining low viral loads also contributes to the Joint United Nations Programme on HIV/AIDS (UNAIDS) aim of 73 percent viral suppression among people living with HIV (PLHIV) by preventing sexual transmission of HIV, HIV-related maternal sickness, and the emergence of medication resistance. The presence of a non-suppressed viral load during pregnancy could be attributed to a variety of reasons. As the primary predictors of non-suppressed viral load during pregnancy, high viral load levels before ART commencement, delayed ART initiation, new HIV infection during pregnancy, and poor treatment adherence have all been observed.

Published studies have reported that multiple factors predispose an expectant woman infected with HIV to present with detectable viral load at delivery (Aebi-Popp et al., 2014; Jain et al., 2017; Jasseron et al., 2013; Loh et al., 2021). These factors are multifaceted and could include sociodemographic, reproductive as well as clinical factors. Specifically, detectable viral load at delivery is affected by treatment adherence, duration of treatment, side effect profile, drug regimen, partner disclosure, age and enrolment and retention to care (Gill et al., 2016; Yotebieng et al., 2019). Lack of treatment compliance to ART is the most common factor associated with lack of viral suppression. This low adherence could be a function of treatment-related side effects (Chan et al., 2019). Due to health-system factors (such as clinic overcrowding and distance from clinic) and patient-related barriers (such as inadequate knowledge of the importance of early antenatal care (ANC) and slow recognition of unplanned pregnancies), women frequently begin ANC late in their pregnancy in most sub-Saharan African countries (İnkaya et al., 2020; Levi et al., 2016). This delays the start of ART and viral suppression among women who have not been previously initiated on treatment. Aside from intimate sexual partner's HIV status disclosure, other social, behavioral, and biological factors that affect ART compliance and viral suppression during pregnancy include side effect to medication, drug toxicity, treatment exhaustion, substance abuse, and a lack of family support (Biomndo et al., 2021; Odoyo et al., 2019; Yotebieng et al., 2019).

1.2 Problem statement

The presence of a non-suppressed viral load during pregnancy, may be attributed to a variety of causes. Despite availability of evidence that Kenya is on the path to eliminating mother to child transmission, there are still high cases of new vertical

transmissions. In 2018, the National AIDS Control Council (NACC) and National AIDS and STI Control Programme (NASCOP) in Kenya estimated 11.5% of new infections (NASCOP, 2018). There are limited local studies focusing on factors associated with detectable viral load. Detectable viral load at delivery increases the risk of vertical HIV transmission as well as drug resistant mutations. Lack of prompt viral load assessment and knowledge on detectable viral load counters global initiatives such as the 95-95-95 UNAIDS targets. This study addressed the knowledge gap on predictors of detectable HIV viral load at delivery.

1.3 Justification

Strengthening retention in care is essential to improving treatment adherence and monitoring viral load the PMTCT cascade. This is because up to one-third of pregnant women living with HIV (WLHIV) are initiated on ART during antenatal care (İnkaya et al., 2020). As the best indicator of ART efficacy, early ART initiation and adherence, viral load monitoring and the need for increased infant postnatal prophylaxis in newborns at-risk of contracting HIV. There is need to promptly determine the prevalence of detectable viral load at delivery and its associated factors among HIV infected women. Knowledge of this will inform HIV transmission prevention strategies by HIV care givers and policy makers. The findings of this study will provide evidence-based recommendations to health care providers and policy makers both in Kenya and the region.

1.4 Objectives

1.4.1 Broad Objective

To determine the patient characteristics, prevalence of detectable viral load and assess factors associated with it among HIV infected women delivering at RMBH, Eldoret Kenya.

1.4.2 Specific objectives

1. To determine patient characteristics of pregnant HIV infected women delivering at RMBH.

2. To determine the proportion of pregnant women with detectable viral load among HIV infected pregnant women delivering at RMBH.

3. To assess the factors associated with detectable viral load among HIV infected pregnant women delivering at RMBH.

1.5 Research Question

What are the patient characteristics, prevalence of detectable viral load and factors associated with it among HIV infected women delivering at RMBH, Eldoret Kenya?

CHAPTER TWO

2.0 LITERATURE REVIEW

2.1 Introduction

2.1.1 Epidemiology of HIV in pregnancy

There were 36.7 million people living with HIV at the end of 2015 including 1.8 million children. The same year there were 1.1 million AIDS related deaths. The global prevalence of HIV in adults is 0.8% (Barnabas et al., 2020). Majority of these are in low and middle-income countries. 25.5million of persons living with HIV (PLWIV) are in sub-Saharan Africa. 19 million of these live in the Eastern and Southern Africa, which forms 6.2% of the world's population. The adult prevalence of HIV in Sub-Saharan Africa is 7.1% with women (59% of adults) more affected than the men (Joint United Nations Programme on HIV AIDS, 2016). The ART coverage in this region is 54% and only 45% of PLWHIV are virally suppressed. The region experienced 470,000 AIDS related deaths in 2015 (Joint United Nations Programme on HIV AIDS, 2016). Globally, 18.2 million people as of mid-2016 were on antiretroviral drugs (46%). Seven out of 10 HIV positive women (77%) were on ART for PMTCT in 2015. By 2015, Kenya was second to South Africa among the countries with the highest number of persons on treatment with over 900,000 infected persons on treatment (Lecher, 2016). Increase in the number of people on treatment has reduced the annual AIDS related deaths by 43% worldwide since the first global treatment target in 2003, and 26% global reduction since 2010. However, new HIV infections are still a huge Public Health challenge worldwide. There were 2.1 million new HIV infections in 2015 Worldwide. Of these, 960,000 (46%) were in sub-Saharan Africa. There were 150,000 new HIV infection in children in 2015. Most of the children (90%) were in the sub-Saharan Africa and most acquired the infection vertically

(Lecher, 2016). In 2017, there were 1.5 million people living with HIV in Kenya. The prevalence rate among women is 5.4% which is twice that of men (NASCOP, 2020). Since the HIV epidemic began, there have been 471,800 child infections in Kenya that have occurred. However, since 2004, PMTCT has averted over 132,000 new HIV infections in children. In 2017, there were 105,213 (6%) children (0-14years) living with HIV, with an estimated 8000 new infections in this age group (NASCOP, 2020). In most studies, pregnancy has little effect on the surrounding course of HIV infection in women. Nevertheless, as the epidemic spreads, AIDS has increasingly overtaken other causes of maternal death.   In the absence of antiretroviral therapy, statistical approaches of HIV transmission from mother to child range from 15% to over 40% and differ among nations (Joint United Nations Programme on HIV AIDS, 2016). Breast milk can be a postpartum method of transmission as well as during labour and delivery and in utero. Most transmissions are believed to take place in the last stages of pregnancy and during labour.

In absence of any intervention, transmission of HIV from the mother to the infant ranges from 15% to 45%. During pregnancy (15%-20%), labour and delivery (50%), and breastfeeding (25%-30%). These rates can be reduced to less than 1% with effective interventions during pregnancy labor and delivery and breastfeeding. The sub-Saharan Africa has seen a decline of up to 66% (to approximately 56,000) in new HIV infections in children (0-14) years between 2010 and 2015 (UNAIDS, 2016a). This can be explained by increased uptake of PMTCT services coverage in the region. The rates of decline however vary with different countries. In 2014, Kenya was second from Nigeria; with highest number of new HIV infections among children, among the 21 global plan priority countries (Joint United Nations Programme on, 2015). The sustainable development goals put an emphasis on reduction of child

mortality and improving maternal health. Prevention of mother to child transmission (PMTCT) of HIV will allow this to improve maternal and child health. The overall UNAIDS target for elimination of paediatric HIV by 2015 was to reduce new HIV infections in children by 90% and to reduce the number of HIV associated deaths in pregnancy delivery and puerperium by 50% (Lecher, 2016). Elimination of mother to child transmission, which was targeted to be achieved by 2015 is a major objective of UNAIDS. Since this target was unachieved in many countries, as part of building on the global plan (i.e., to eliminate new HIV infections among children and to keep their mothers alive), the UNAIDS has since put in place new strategies and goals to end the AIDS epidemic by 2030. Cuba was the first country to be validated for having eliminated mother to child transmission of HIV (Taylor et al., 2017). This was subsequently followed by three other countries worldwide i.e., Belarus, Thailand, and Armenia. By 2017, Eleven countries in total had been validated for having eliminated mother to child transmission of HIV and /or Syphilis worldwide (Taylor et al., 2017). According to WHO, 69% of pregnant women in sub-Saharan Africa have at least one ANC visit. In Kenya 58% of women received the recommended four Focused ANC visits between 2008 and 2014 (KDHS, 2014). The median months at first ANC visit were 5.4 (23weeks). This implies even though more than half of our pregnant population receives the minimum recommended four ANC visits, many of our women present late at first ANC visit which may impact early detection of HIV infection, treatment and follow up.

Between 2009 and 2014 many countries saw their numbers of new HIV infections in children drop by over 60% (WHO, 2015). Despite the decline in MTCT of HIV in the last two decades, HIV continues to contribute to disease burden in many countries including Kenya. One of the targets of UNAIDS global plan is to reduce the MTCT

rate to less than 5% for breastfeeding populations and less than 2% for non-breastfeeding populations (Taylor et al., 2017). The worldwide transmission rate in breastfeeding is 14% (Joint United Nations Programme on, 2015), which is more than double the desired global plan. This rate was 17% in Kenya with 13,000 new HIV infections in children 2014. In 2018 however, the mother to Child Transmission (MTCT) rate was estimated at 11.5% with 8000 new infections in children 0-14 years (NASCOP, 2020). This rate despite decreasing from prior years is still above the World Health Organization target for validation for elimination of mother to child transmission. In the same year, more than 4000 Aids related deaths occurred in children 0-14 years, showing the high burden of HIV/AIDs in the country when MTCT occurs. The global 90-90-90 UN target by 2020 was to ensure that 90% of Persons living with HIV know their status, 90% of those who know their status are on treatment and 90% of those on treatment have suppressed viral load (Levi et al., 2016). This target has since been revised to 95-95-95, i.e., to ensure that 95 % of those who are living with HIV know their status, that 95% of those who are HIV positive and know their status are on Antiretroviral Therapy and that 95% of those on Antiretroviral Therapy are virally suppressed (with viral loads of less than 50 copies/ml) (UNAIDS, 2015). This can be achieved through strengthened Prevention of Mother to Child Transmission (PMTCT) of HIV/AIDS with improved testing and counselling including at the community level and increased male involvement, integration of PMTCT services with the Maternal Child Health (MCH) services, ensuring routine and timely viral load checks as well as addressing issues related to lack of viral suppression promptly, routine adherence evaluations and ensuring delivery under skilled birth attendance with timely infant prophylaxis and infant HIV testing as per guidelines. Currently Kenya is one of the few countries in Africa that offers HIV testing and counselling at the community (door to door testing)

and has initiated self-testing, however, this is affected by shortage of test kits. Globally, it is estimated that 40% of PLWHIV do not know they are positive (UNAIDS, 2016). In the eastern and southern Africa region, 56% of adults know their status. Detectable viral load has been identified as a predictor of MTCT of HIV (Urase et al 2001, Tanzania). Detectable viral loads in third trimester may mean an increased likelihood of transmission of HIV from the mother to the infant (Denoeud-Ndam et al.).

2.1.2 Pathogenesis of HIV in pregnancy

Human Immunodeficiency Virus is the virus that causes HIV infection and subsequently AIDS. It is a lentivirus (subgroup of Retrovirus), a positive sense enveloped RNA virus. There are two types of HIV, HIV 1, and HIV 2. HIV 1 has high virulence and infectivity and is prevalent globally whereas HIV 2 has lower virulence and infectivity and is prevalent in West Africa. HIV is transmitted from one person to another sexually, through blood and blood products and vertically from an infected mother to the infant, the most common mode of HIV transmission in children. The most common mode of transmission of HIV in women is via the sexual route. Studies show that 84% of new infections in women are acquired sexually Mother to child transmission can occur in utero, during labour and delivery and during breastfeeding. Transmission correlates with high levels of virus in the body fluids and with the nature and duration of contact with the fluids.

HIV type 1 is the most prevalent source of HIV infection worldwide (HIV-1). Most HIV infections in West Africa are caused by another viral strain, HIV-2, which is seldom ever found outside of that region. Human-affecting retroviruses like HIV-1 are members of the Lentiviridae subfamily. These infections are distinguished by their protracted clinical latency and chronic viremia, both of which compromise

immunological function. The viral gp120's attachment to the CD4 molecule, the HIV receptor on the surface of the host cell, starts the replication cycle of HIV in its target cell. The shape of the glycoprotein changes after gp120 attaches to CD4, making it easier for it to connect to a cellular receptor. Infection is established after fusion with the host cell membrane. The development of the chronic and recurrent infection that is a defining feature of HIV illness is greatly aided by an initial burst of viremia and the swift diffusion of the virus to lymphoid organs, notably the gut-associated lymphoid tissue. The virus manages to evade immune-mediated eradication given the substantial cellular and humoral reactions seen during basic HIV infection.

During pregnancy, the placenta provides a physical as well as an immune barrier between maternal and fetal circulations and is also thought to protect against HIV infections (BMJ, 2017). Majority of infections in utero occur in late pregnancy (WHO, 2015). The exact mechanism of MTCT of HIV is unknown; however, factors such as disruption of placental barrier e.g., following infections like intraamniotic infection may play a role. The type of virus and genetic factors may also influence in utero transmission. This includes the Human Leukocyte Antigen (HLA) type or Chemokine receptor genotype (BMJ, 2017).

During labour, contractions can allow maternal-fetal transfusion. The infant could also swallow fluids in the genital tract leading to infection of lymphoid cells when fluid passes the gastrointestinal mucosa of the infant and subsequently systemic dissemination (BMJ, 2017). Studies have shown that breast milk contains high levels of the virus and transmission can occur at any point during lactation (BMJ, 2017). Several factors can increase the risk of infant transmission in utero, during labor and delivery as well as lactation including a high maternal viral load, Chorioamnionitis,

prolonged labour, harmful practices in labour such as many vaginal exams, advanced disease in the mother, breast diseases such as mastitis or cracked nipple and low maternal CD4 count indicating lower maternal immune status. Similarly, infant gastrointestinal diseases may enhance viral transmission e.g., oral candidiasis (BMJ, 2017).

2.2 Prevention of Mother to Child Transmission (PMTCT)

2.2.1 Evolution of PMTCT

One of the greatest achievements in public health over the past 20 years has been the prevention of mother-to-child transmission (PMTCT) of HIV. In environments where adequate prophylaxis can be implemented, very low rates of PMTCT of HIV have been achieved because of scientific efforts and diligent and focused labour. Global paediatric HIV infection eradication is now more possible than ever before, despite the fact that there are still a number of achievement as well as implementation challenges. Throughout the last decade, Central and Eastern Europe (CEE) and the Commonwealth of Independent States (CIS) nations have made great progress in PMTCT. Significant reductions in the incidence of HIV transmission to newborns have been made possible by political will and dedication and the expertise of maternity and child health services. In all low- and middle-income nations globally, the CEE/CIS area seems to have the greatest prevalence of HIV-infected pregnant women and the newborns with antiretroviral prophylaxis, including an approximated 53% of diagnosed pregnant women getting antiretrovirals for PMTCT in 2009.

Globally accepted strategies for prevention of mother to child transmission of HIV (PMTCT) include four prongs:

1. Primary prevention of HIV (Keeping those who are HIV negative- negative)

2. Preventing unintended pregnancy in women with HIV through Family planning

3. Preventing vertical transmission of HIV from infected women to their infants (PMTCT)

4. Providing care treatment and support for mothers with HIV and their infants including their partners and family involvement.

The PMTCT of HIV/AIDS was started 21years ago when (Connor et al., 1994) did an RCT on reduction of perinatal transmission using Zidovudine (AZT) and showed a 2/3 reduction in MTCT using AZT in Second trimester (T2) and Third Trimester (T3) and in neonatal period. PMTCT in Kenya largely follows the World Health organization (WHO) recommendations. There has been an increase in the uptake of PMTCT in the East and Southern region of the sub-Saharan Africa over the years from 62% to 90 % in 2015 (UNAIDS, 2016). The PMTCT coverage in Kenya in 2018 was estimated at 76% according to the Kenya Population HIV impact Assessment preliminary report, (NASCOP, 2020). In this report, It was estimated that in 2017, 69,500 pregnant women were in need of PMTCT services. This number was a decrease compared to 83,200 women in 2005. PMTCT uptake was also noted to have increased from 23% in 2005 to the current 76% (NASCOP, 2020).

Prevention of Mother to Child Transmission of HIV/AIDS has evolved in the last decade from option A to Option B and currently option B plus or Lifelong HAART since 2015 (Cherutich et al., 2016; GOK, 2016). Option A and B involved treatment or ARV prophylaxis of the mother based on CD4 count of 350 cells/mm3. In option A, with CD4 counts of less than 350 cells/mm 3, triple Antiretroviral was started as soon as a diagnosis was made. When CD4 count was more than 350, antepartum Zidovudine as early as 14 weeks gestation was given. In addition, intrapartum, at the onset of labour, a single dose nevirapine and a first dose of Zidovudine and Lamivudine was given, the latter of which was continued until 7 days postpartum.

The infant received daily nevirapine from birth until 1 week after complete cessation of breastfeeding, or until 4-6 weeks if the mother was on treatment or opted not to breastfeed. With Option B, the same ARVs (triple ARV) was used for both CD4 counts of less than 350 and more than 350. In this case, if CD4 was less than 350, then ART was initiated for life, however if CD4 counts were more than 350, triple ARV was started at 14 weeks and continued until 1 week after complete cessation of breastfeeding or after childbirth if not breastfeeding. The infant received daily nevirapine or zidovudine from birth till 4-6 weeks of life regardless of the feeding method. Option B plus replaced option B where lifelong HAART is usually started as soon as a diagnosis of HIV is made in pregnant woman regardless of CD4 status or WHO clinical stage. Infants receive Zidovudine for 6weeks from birth and Nevirapine for 12 weeks regardless of the feeding method. Cotrimoxazole prophylaxis is started at six weeks and is continued until after complete cessation of breastfeeding. The infant receives all other immunizations as scheduled with addition of measles vaccine at six weeks. Option B plus has shown improvements in HIV prevention in vertical transmission. In a study in Malawi, it was found that many women who enrolled to care after option B plus implementation were retained on treatment through to delivery compared to prior to option B plus implementation(Kim et al., 2015). Implementation of the test and treat protocol in management and care of pregnant women with HIV has also augmented prevention of HIV transmission through other modes such as sexual transmission. This is especially so in cases where ART is working, and viral suppression is achieved and therefore the campaign of undetectable equals untransmissible can hold as was seen in a study where no sexual transmissions were found in 144,000 sexual encounters where a viral load of less than 200 copies per ml was maintained, (For et al., 2020).

Perinatal transmission has decreased because of improvements in HIV treatment, particularly since the implementation of the mother-to-child transmission prevention Programme (PMTCT). PMTCT entails using antiretroviral therapy (ART) to lower viral replication in the pregnant woman and the risk of HIV transmission to the fetus and infant (vertical transmission). ART for PMTCT has progressed from prophylaxis in Option A and Option B and now treatment for all Option B+, i.e., lifetime Highly Active Antiretroviral Therapy (HAART) at diagnosis. HIV counselling and testing at first contact (typically the first ANC visit) and commencement of HAART at diagnosis is advised for all HIV positive pregnant women, according to the World Health Organization (*Guideline on When to Start Antiretroviral Therapy and on Pre-Exposure Prophylaxis for HIV*, 2015). Women on Option A are switched to the appropriate first-line regimen.

PMTCT is currently offered as an integrated service in all government facilities where ANC and ART services are offered together. Several studies have shown benefits of option B plus over the others. A study in Malawi found that many women were enrolled to care following implementation of option B plus and were retained on treatment through delivery compared to prior to option B plus implementation (Kim et al., 1999). Integration has been shown to strengthen health systems. It is however complex, and transition must be done well (Vo et al., 2012).

Kenya guidelines (NASCOP, 2018) recommend that HIV counselling and testing for all pregnant women is done in the first ANC visit in trimester 1 (T1) as part of ANC profile tests. A repeat test is done in third trimester for all who test negative in T1. If found negative, a repeat test is done in labor and delivery, 6weeks after delivery and 6months after delivery if negative, every six months for all breastfeeding mothers. All pregnant women found HIV positive are started on lifelong HAART at diagnosis. They

are then enrolled to care, receive counselling and support with assisted disclosure, if necessary, linked to care and follow up. The guidelines also recommend that spouses of all pregnant and breastfeeding women be offered HIV counselling and testing and all children <14years tested if mother is found positive.

All infants born to women who are HIV positive are started on ARV prophylaxis and a Polymerase Chain Reaction (PCR) test is done at birth within 72 hours of delivery (NASCOP, 2018). Birth testing helps to diagnose antenatal infections (In utero) versus intrapartum infections (diagnosed with a positive PCR at 6weeks, that was negative at birth). A baseline viral load for confirmed infected infant is also done. Infants with a positive PCR at birth are presumed infected and offered ART with a confirmatory PCR and baseline viral load sample taken at time of ART initiation. Infants who are found to be negative are then continued ARV prophylaxis and are managed as per HIV Exposed Infant (HEI) protocol. A repeat DNA PCR is done at 6weeks or at the earliest time, the child would be seen after six weeks. However, in MTRH, the first routine infant testing is done at six weeks using point of care test kits and results stored in the AMPATH Medical Record System (AMRS).

According to the PMTCT care cascade-infant diagnosis, a rapid HIV test is done at nine months, and if found positive, it is confirmed by a PCR and ART is started after confirmation. If negative, the infant continues Cotrimoxazole (CTX) prophylaxis.

If HIV PCR results come positive, the infant is started on ART and continues CTX prophylaxis. If negative, CTX is stopped, and a rapid HIV antibody test is done at 18 months; if breast feeding, do HIV antibody test every 6 months while breast feeding and 6 weeks after complete cessation of breastfeeding (NASCOP, 2022). If results turn positive, HIV PCR is done to confirm the result. ART is then started if the test

turns positive. If the rapid test as well as PCR test turn negative, the infant exits PMTCT care and is declared HIV negative.

2.2.2 Treatment monitoring (Viral load testing).

A routine examination of the maternal viral load is significant because it allows for the detection of excessive levels of maternal viral load and so aids in the early treatment of this problem, which aids in suppressing and reducing the risk of transmission. Since 2016, the World Health Organization recommended test and treat for all HIV positive individuals including pregnant women. It also recommended viral load testing as the treatment monitoring modality of choice (*Guideline on When to Start Antiretroviral Therapy and on Pre-Exposure Prophylaxis for HIV*, 2015). It is important to test the viral load of HIV infected pregnant women on ART to monitor treatment as well as to reduce the risk of transmission; however, in poor and middle-income countries, there are various hurdles that occur making it a problem, including budgetary issues and clinical operational issues. Viral load testing was quite low at 36%-57%, according to research on pregnant women who had certain viral load tests in Senegal, Mozambique, as well as Kenya (Inzaule et al., 2016).

Viral load testing is an important guide for monitoring treatment, evaluating adherence to optimize first line regimen, and making clinical decisions on when to switch to second line in treatment failure. It has been unavailable in low-income countries for long, but with increased need, technologies for viral load determination have become simpler and costs decreasing (Calmy et al., 2007). The WHO recommendation of viral load testing for monitoring HIV treatment has been adopted in our Kenyan ART guidelines (NASCOP, 2018).

For patients who are virally suppressed, viral load testing provides a financially viable

and sustainable programmatic technique for tracking the effectiveness of therapy. This enables patients to visit the doctor less frequently. Monitoring viral loads permits rapid and precise diagnosis of therapy failure prior to immunologic deterioration. A test for HIV viral load (VLT) measures the number of HIV RNA copies per milliliter of serum or plasma and is usually reported as number of viral copies/ml depending on the Laboratory's Lowest Detectable Limit (LDL). LDL is the lowest viral threshold that the laboratory can detect, depending on their machine and has been reported as 20 copies/ml, 40 copies/ml, 50 copies/ml, 200 copies/ml, 400 copies/ml and 1000 copies/ml. Measuring HIV viral load, reveals viral replication if detectable and is routinely done to track antiretroviral medication use. For the purposes of assessing the immune system, CD4 lymphocyte counts are also determined. Both clinical outcomes and suppression of viremia below 50 copies/mL in two subsequent assessments are used to assess the efficacy of antiretroviral treatment. The WHO defines viral suppression as having a viral load of less than 50 copies/ml. Maintaining viral suppression is key to preventing HIV transmission and confirms adherence to ART. Failure of this may indicate lack of adherence or treatment failure which may necessitate testing for drug resistance mutations as well as possibly changing therapy.

Commercially accessible diagnostics called nucleic acid testing (NAT) can detect HIV nucleic acid (either RNA or proviral DNA). The concepts of polymerase chain reaction (PCR), real-time PCR, nucleic acid sequence-based amplification, and ligase chain reaction are used in these tests. NAT tests are beneficial in specific conditions, such as during the window period of contamination when anti-HIV antibodies are missing in serum, and in newborns of HIV-infected mothers whereby maternal anti-HIV antibodies are detectable in the newborn's serum. The identification of immune cells harboring quiescent provirus and cells afflicted with continuously replicating

HIV is made possible by the amplification of proviral DNA. Health care providers of Infants and young toddlers up to the age of 18 months who were born to mothers who were HIV-positive can utilize this test to diagnose their HIV infection. Negative result DNA PCR test findings, unfortunately, can happen in kids on antiretroviral treatment and can force an unwarranted end to that treatment.

Currently, PMTCT requires that for those who are known positive and are already on ART, a baseline viral load is conducted at the time of confirmation of pregnancy. If suppressed (less than 50 copies/ml), the gravid lady is allowed to continue her antiretroviral Therapy and a repeat vial load is done every six months until complete cessation of breast feeding. However, for all newly diagnosed pregnant HIV positive women, a viral load test should be done 3 months after ART initiation. With proper adherence to ART, it is expected that by this time the viral load should be below the LDL. If a woman is found to have a detectable viral load after 3 months of ART, potential reasons for viremia are assessed and addressed. Adherence support is enhanced intensively, and a repeat viral load is done 3 months later. If viral load is found to be ≥1000 copies/ml, the pregnant woman is changed to an effective regimen. If the viral load is found to be more than the LDL but less than 1000copies/ml, the mother is referred to the regional or national HIV Clinical Technical working Group (NASCOP, 2018a). This is referred to as low level viremia (LLV) i.e., viral load of between 50-1000 copies/ml. Drug resistance testing is done if the patient is on a protease inhibitor regimen or if the client was on second line regimen. The WHO defines treatment failure as plasma viral load of >1000copies/ml on 2 different occasions 3 months apart in the setting of proper adherence counselling. This necessitates change to second line regimen (*Guideline on When to Start Antiretroviral Therapy and on Pre-Exposure Prophylaxis for HIV*, 2015). Baseline viral load (at

diagnosis of HIV) is not done in Kenya as per our guidelines.

The three most used assays for measuring viral load are HIV-1 RNA polymerase chain reaction (PCR), Branched chain DNA (bDNA) and Nucleic acid sequence-based amplification. Each test has characteristics, specificity and varying costs and results from different labs may not be strictly comparable. In MTRH and AMPATH center Lab, the Abbott HIV-1 RNA PCR is the most common method used. It measures viral copies to as low as 40copies/ml. Before viral load monitoring was available in Kenya, treatment was monitored using CD4 count (Immunologic criteria) and clinical criteria. However, these have not been validated since immunologic responses to treatment have individual variations. A study in Botswana suggested that use of CD4 count to predict virologic failure is limited (Bisson et al., 2006). Furthermore, clinical failure may occur late and be identified late and therefore defining treatment failure based on clinical grounds is not optimal (Calmy et al., 2007). Similar studies in low resource income countries have shown a discrepancy between CD4 counts and Viral load with high Viral loads in patients with high CD4 counts and low CD4 counts in patients with undetectable viral load. This leaves viral load monitoring as the best test for monitoring treatment as per the WHO recommendations.

2.2.3 Detectable Viral Load

Viral suppression has been defined with changing terminologies. In 2015, it was defined as less than 1000 copies/ml of HIV. WHO put it at <400copies/ml. WHO proposed that 70% of patients should achieve virologic suppression (<400copies/ml) at 6months of ART in resource limited settings) (WHO, 2015). Due to the confusing terminologies in defining viral suppression and treatment failure, the WHO currently put in place universal thresholds for viral load to define suppression as well as

treatment failure. The current definition of viral suppression is viral load of ≤ 50 copies/ml. Similarly, WHO defined the threshold for treatment failure as ≥ 1000 viral copies/ml (World Health Organization, 2021). Detectable viral load differs with different laboratory tests and sensitivity. The laboratory thresholds range from <5copies/ml to <50 copies/ml. When viral replication is suppressed to undetectable levels, resistance mutations cannot emerge and a durable treatment response occurs (Calmy et al., 2007). Replication of virus in the presence of treatment favors selection of resistance mutations and hence a development of treatment failure. Detectable viral load in a woman who is on ART puts the infant at risk of transmission of drug resistant virus (Calmy et al., 2007). A study of 1684 infants enrolled in an RCT in Brazil, South Africa, Argentina, and the United States of America (USA) found that higher maternal viral load was significantly associated with vertical transmission (DenoeudNdam et al.). In sub-Saharan Africa, detectable viral load has been identified as a predictor of MTCT of HIV. Maternal virologic suppression is a keystone of PMTCT. Increase in number of HIV pregnant women on treatment with detectable viral load will increase the need for aggressive treatment and counselling. A higher viral load in a pregnant HIV woman in a sero-discordant relationship may mean and increased risk of HIV transmission to the partner. Studies have shown that having undetectable viral loads will protect the HIV negative partner from acquiring HIV through sexual transmission, the basis for the campaign for Undetectability equals Un transmissibility (U=U) (For et al., 2020). This campaign is however only for sexual transmission of HIV as there is insufficient evidence for the same campaign for breastfeeding as well as other modes of transmission whereby transmission could still occur albeit at very low risk.

It is generally known that viremia and the spread of the HIV virus among individuals go hand in hand. Additionally, results from clinical trials and epidemiological studies show that antiretroviral medication (ART)-induced viral load (VL) reduction lowers the risk of HIV transmission via breastfeeding and intercourse. Thus, it is now essential for global public health that viral load in the population is suppressed. The prevalence of HIV is high in Kenya, where there is a widespread HIV epidemic. 1.5 million individuals were thought to be living with HIV/AIDS in 2017, and 52000 more are thought to have contracted the disease in the same year. Kenya is one of the high HIV load nations that has pledged to attain 90% viral suppression in ART-treated patients, thus it is crucial to monitor how this policy target is being carried out. Viral Load measurements are mostly used to diagnose and monitor postoperative complications in Sub-Saharan Africa, and they are seldom used to track population-level infection rate. They are also used to make clinical decisions such as mode of delivery in HIV infected women.

Detectable viral load in a woman who is on HAART puts the infant at risk of transmission of drug resistance virus. Many women in sub-Saharan Africa start antenatal care late and their treatment response (viral suppression) not available prior to delivery. A high viral load around the time of delivery increases the risk of mother to child transmission of HIV. The Kenyan ART guidelines recommend delivery via Pre labour Caesarean section (Elective Caesarean section) where available if Viral load at 36 weeks gestation or more is ≥ 1000copies/ml (NASCOP, 2018). This is also the same recommendation by WHO. Several factors have been associated with detectable viral load at delivery including adherence, duration of HAART, drug regimen, partner disclosure, partner HIV status, Side effect Profile, Gestation at first Antenatal Care (ANC) Visit, Number of ANC visits, Timing of HIV diagnosis

(whether in this pregnancy or prior), Illness in the current pregnancy and some socio demographic factors. There are few studies on viral load and factors associated with detectable viral load in the setting of option B plus of PMTCT in sub–Saharan Africa and Kenya.

2.3 Factors associated with detectable viral load.

Several factors have been associated with lack of viral suppression and subsequently detectable viral loads in late pregnancy. These include duration of treatment, adherence to ART, partner disclosure, certain socio-demographic factors, regimen used, gestation at first ANC visit, side effect profile.

2.3.1 Adherence

Adherence to ART is a major factor that affects viral suppression. Non-adherence to ART is the most common factor associated with lack of viral suppression. According to Margaret Chesney, adherence rates of <80% were associated with detectable viremia (Chesney, 2000). Poor adherence has been noted to accelerate development of drug resistant HIV. There are several factors that affect adherence including patient factors (age, sex, alcohol, ethnicity and family planning, presence of a treatment buddy, pill burden, and nutrition), drug regimen, dosing schedules, side effect profile, patient health care provider relationship and system of care (Chesney, 2000).

There is evidence that adherence affects time to viral suppression. In a study done in US, time to viral suppression was assessed in ART naive and ART experienced HIV positive pregnant women. Pregnant women with more than 50% adherence whether ART naive or experienced on average achieved viral load levels of less than 400copies/ml within a median of 26 days and viral load of 1000 copies/ml within a median of 14 days of HAART initiation. Increased adherence and lower baseline viral load were all statistically significant predictors of earlier time to achieve viral

suppression (Aziz et al., 2013).

According to Myer L and co-workers in study on viral suppression in pregnancy in South Africa found that in HIV positive women who were on ART at first ANC visit, having a viral load of 1000copies/ml was associated with missing more than three doses in the last ninety days (Myer et al., 2016). In a study in Rwanda assessing extent of viral suppression in women on option B plus, adherence was not a significant predictor of detectable viral load at enrolment (Gill et al., 2016). The method used to assess adherence was self-reported missed doses in the last three days, which overestimated adherence levels limiting detection of any significant difference (Gill et al., 2016). The time on ART initiation can affect adherence. In a study of 50 cases and 135 controls in 31 public facilities in Kenya found that women who first learned of their HIV status during pregnancy were 2.85 times less likely to adhere to ART and 2.42 times more likely to have a home delivery compared to women who were on ART prior to pregnancy (Turan et al., 2012). This may contribute to having detectable viral loads in third trimester and subsequently possible vertical transmission of HIV. The reason for the low adherence in the group diagnosed in the pregnancy may be due to the challenges of pregnancy including nausea and vomiting. In addition, the side effects of the Anti-retroviral treatment as well as possible psychological effects of the new diagnosis and anxious thoughts or fears of the fetus/newborn being infected may affect the mother's well-being and impact adherence negatively.

Adherence can be measured using several methods including Self-reporting, Pill counts, Drug assay levels, electronic monitoring systems (Medication Electronic Monitoring Systems-MEMS) and lastly Viral load monitoring. Studies have shown that self-reporting using questionnaires or recall is simple but has the disadvantage of

overestimating adherence. This was evidenced by a study comparing self-report of adherence versus pill count that found that self-reports inflated the estimates of adherence (MA Chesney). Reporting of missing pills requires that the clinician counts the remaining pills at the next drug refill. Its disadvantage is that it may overestimate adherence when pill dumping occurs and when the patient forgets the packaging. Assay of drug levels is not practical in many settings including Kenya as well as many other sub-Saharan countries. Electronic monitoring systems use computer chips in bottle caps of antiretroviral medication that records the time of opening and closing of the bottle. This method assumes that only one pill is taken with every opening and is therefore inaccurate when multiple doses are received at once (MA Chesney). Electronic methods of drug assessment, like drug assay level is not available in our setting currently.

The Kenya ART guidelines recommend adherence monitoring at every clinic visit using a standardized validated tool i.e., the Morisky Medication Adherence Scale 4 (MMAS-4) as well as Pill count. The pill count is done until viral suppression. The Morisky Medication Adherence Scale 8 (MMAS-8) is done where the Healthcare worker suspects adherence issues e.g., in suspected or confirmed treatment failure, or for patients who have missed appointments. The MMAS-4 has a set of four questions with a score of one for any question answered with a yes and zero for any question answered with a no. A score of 0 is good and the patient is encouraged to continue with her medication. A score of 1-2 is considered inadequate and calls for assignment of a case manager, assessment of barriers to adherence, engagement of a person of support during adherence counseling sessions and closer follow up of between two to four weeks. A score of 3-4 is considered poor and calls for the same measures as for inadequate score and with the addition of a Direct Observed Therapy (DOT) method

of drug administration as well as an even closer follow up of between one to two weeks. The MMAS-8 tool is more advanced with four more questions (eight in total) with a score of one for every yes and a score of zero for every questioned answered with a no. A score of 0 is considered good and the patient is encouraged to continue being adherent. A score of 1-2 is considered inadequate just like for MMAS-4 and calls for similar measures as for MMAS-4 scoring while a poor score is 3-8, calling for the same measures as for MMAS-4. As for pill counts, this method grades adherence based on number of missed doses per month for once daily dosing as well as for twice daily dosing. If a patient misses one dose for once daily (OD) dosing or between one to three doses for twice daily (BD) dosing, then this is considered as good adherence and the patient is encouraged to continue taking her medication. This gives a percentage of total pills taken of more than or equal to 95% which is desirable. If a patient misses two to four doses for once daily dosing or four to eight doses for twice daily dosing, then the adherence is rated as inadequate, and the measures taken are similar as for MMAS-4. Such a patient is considered to have taken 85%-94% of her total medication. When a patient misses more than or equal to 5 doses of her medication for once daily dosing or more than or equal to 9 doses for twice daily dosing then the adherence rating is considered as poor and the same measures as for MMAS-4 are instituted. Such a patient is considered to have taken less than 85% of her medication in that month (NASCOP, 2018). This study used self-reported seven-day Recall to measure for adherence where participants were asked if they missed any dose of their ART in the last seven days and if they did (answering yes), they were considered non-adherent, whereas if they did not (answering no), they were considered adherent. Missing one dose in a week would give the worst picture of adherence of 85% of pills taken. This method has the disadvantage of recall bias as

well as it doesn't give the true picture of the month's adherence level. This has been mentioned as a limitation. Barriers to adherence that are assessed when adherence is considered suboptimal include one, Awareness of HIV status, i.e., if the client is aware of their positive status and id they have accepted or not, two, Understanding of HIV infection and ART, i.e., if they have any side effects to ART, if they understand the risks of transmission, the benefits of adherence and the consequences of non-adherence including drug resistance mutations as well as treatment failure and increased risk of transmission, three, Patient's daily routine including if work schedules are conflicting with timing of taking their ART or if there have been any travels and reminders to carry their medication in case of travelling as well as remembering to take any missed doses as soon as possible within 12 hours of the scheduled time, Fourthly, Assessment of patient's psychological circumstances, fifthly, a mental health screening including assessing for depression using standardized scales and lastly, assessing if there have been any referrals such as nutritional referrals and if they were followed or not (NASCOP, 2018a).

When using viral load to assess for adherence, an undetectable vial load is considered as adequate adherence to ART and patients are encouraged to continue as so. However, since all patients are still at risk of barriers to adherence counseling and support continue but less frequently. Such patients are referred to as stable patients and are scheduled for facility revisits and drug refill at less frequent intervals (3-6monthly) and may also be enrolled in the community-based ART program, which is one of the benefits of maintaining a virally suppressed status. For women with Detectable viral load, enhanced adherence is conducted and barriers to adequate adherence are assessed. A repeat viral load is done after 3 months of confirmed adequate adherence to assess for treatment failure which is diagnosed when the repeat

viral load is ≥1000 copies/ml. Enrolment into viremia clinic is done to allow for the close monitoring of such patients.

Other ways of enhancing adherence in HIV positive pregnant women is the use of peer counseling as well as use of mentor mothers. In a cluster randomized controlled trial in South Africa, peer mentors supporting women living with HIV together with their infants resulted in significantly fewer depressive symptoms, fewer underweight babies and greater adherence to guidance at the time of prevention of vertical transmission (Rotheram-Borus et al., n.d.). Similarly, in an evaluation of mentoring programs in health facilities in Uganda for mothers living with HIV, there was a significant increase in retention to care among HIV infected women on triple ART compared to facilities without support. There was also a significant reduction in vertical transmissions from 6.8% in facilities with mentor mothers compared to 8.7% in facilities without mentor mothers. The MTRH integrated MCH-PMTCT clinic has adopted the use of mentor mothers who support infected women living with HIV together with their infants.

2.3.2 Duration of treatment

Duration of treatment with ART has been shown to affect detectable viral load in pregnancy and subsequently perinatal transmission. Findings from a retrospective study in Canada show that, perinatal transmission rates for women who were on continuous ART (cART) for more than 4 weeks was 0.4% while for those on cART for less than 4weeks transmission rate was 9% (Jitratkosol et al., 2012). This suggests that duration of ART has a direct impact on viral load suppression and vertical transmissibility. A prospective French perinatal cohort study found zero perinatal transmissions in women who received preconception ART, continued throughout pregnancy, and

delivered with viral load of <50 copies/ml. This however was a non-breastfeeding population (Mandelbrot et al., 2015). In that study, regardless of viral load at delivery, the perinatal transmission rate increased from 0.2% for women starting ART prior to conception, to 0.4% for women starting ART in the first trimester, 0.9% for second trimester and 2.2% for third trimester. However, regardless of when ART was initiated, perinatal transmission was higher for women whole viral load near delivery was between 50-400copies/ml than those with less than 50 copies per ml denoting the importance of having a detectable viral load near or at delivery. A similar study in UK found that with viral loads of > 10,000 copies/ml at initiation of treatment, the probability of achieving undetectable viral loads (<50copies/ml) was reduced by initiating HAART after 20.4 weeks gestation. Baseline viral load (at the diagnosis of HIV) is not routine in our setting, but majority of our women start ANC at > 20weeks gestation (KDHS, 2014). This can delay HIV diagnosis for those who are living with HIV but are unaware of their status, and late diagnosis will delay ART initiation. Late ART initiation in pregnancy due to late presentation and diagnosis may lead to a HIV infected pregnant woman to present with detectable viral load at delivery. Several other studies show an association between duration of ART and risk of vertical transmission. Luzuriaga & Mofenson (2016) noted that the risk of perinatal transmission rises after 28weeks of pregnancy and so initiating ART by at least 6 months reduces the risk. The PACOME study in Benin of 217 HIV positive pregnant women found that ART must be started prior to third trimester for a woman to achieve undetectable viral loads by delivery (Denoeud-Ndam et al., 2013). Duration of ART also has been shown to have an impact on maternal morbidity and mortality which has direct negative impact on viral load as well as HIV transmissibility. In a retrospective observational cohort in Malawi and Mozambique (DREAM study), among 8661

women living with HIV, mortality among women who received triple ART for 30 days prior to delivery was three times that of those who received ART for three months or more prior to delivery (Liotta et al., n.d.). Another retrospective study in Zambia that analyzed data on 1,813 pregnant women attending Antenatal Care to assess various exposures of mother to child transmission of HIV, the odds of vertical transmission increased 5.5 times among women of ART for four weeks or less before delivery compared to thirteen weeks or more. In that study, for each additional week on ART up to thirteen weeks prior to delivery, the odds of transmission were reduced by 14%. In that study whose primary outcome was infant HIV infection, apart from duration of ART, other factors including maternal age, infant weight at birth, maternal body mass index (BMI), Hemoglobin levels (Hb), maternal CD4 counts, Gestational age were not found to be associated with infant HIV infection by 12 weeks (Chibwesha et al., 2011). Another retrospective cohort that followed 418 HIV infected mother and infants in a Cameroon PMTCT program found that ART regimes lasting less than four weeks during pregnancy led to 4.7-fold higher risk of early vertical transmission of HIV i.e., before 10 weeks of life (Tchendjou et al., n.d.). According to the Woman and Infants Transmission Study (WITS), pre-pregnancy ART exposure was a significant predictor of detectable viral load at delivery. The prevalence of detectable viral load in that study was 32% (Katz et al., 2010)

In the Kabeho study Rwanda 2015, shorter duration of ART was associated with higher risk of detectable viral load in third trimester (enrolment). Among women who were not on ART at the first antenatal, 66% had detectable viral load at enrolment (third trimester), (Gill et al., 2016). According to KDHS 2014, the average gestation at first ANC visit in Kenya was 23 weeks. This may mean a late diagnosis of HIV for undiagnosed pregnant women and may lead to delay in initiating ART compared to if ANC was started earlier. The status of viral suppression may not be apparent until

after delivery in these women and could lead to detectable viral loads in late pregnancy (KDHS, 2014).

2.3.3 Drug regimen

HIV treatment has evolved from initiating treatment based on immunologic (CD4) criteria or clinical criteria to the current practice of test and treat. There are at least twenty-five HAART medications found in six major classes that are in use worldwide. These medication work of the HIV life cycle that has six steps including, entry i.e., binding and fusion, reverse transcription, integration, replication (transcription and translation), assembly and lastly budding and maturation. Entry inhibitors include maraviroc, Enfuvirtide and Fostemsavir, which are not very common. Nucleoside/Nucleotide reverse transcriptase inhibitors (NRTIs) include Abacavir sulphate (ABC) (a guanosine analog), Emtricitabine (FTC) and Lamivudine (3TC), (Cytosine analogs), Tenofovir Alafenamide (TAF) and Tenofovir Disoproxil fumarate (TDF) -Adenosine derived NRTIs, and lastly Zidovudine (AZT) (thymidine analog). Zidovudine and Stavudine (D4T) are rarely used due to their side effects of peripheral neuropathy and Lipodystrophy as well as mitochondrial toxicity respectively. Zidovudine is however still used in special situations such as in K65R mutations when patients have difficulty in achieving viral suppression with more common regimes as well as in intrapartum care in resource rich settings depending on maternal HIV viral load within four weeks of delivery. When indicated at delivery, it is given intravenous at a loading dose of 2mg/kg followed by a maintenance dose of 1mg/kg/hour till delivery and is given regardless of presence of drug resistance to zidovudine. NTRIs are usually administered in pairs and the most common and current combinations include TDF/FTC (Truvada), or in combination ART with other classes such as integrase inhibitors like Dolutegravir (DTG) as TDF/3TC/DTG. Non-

Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) are generally administered with dual NRTIs. The first-generation drugs in this group include Efavirenz and Nevirapine. Others in the group are, Dapivirine, Doravirine, Etravirine and Rilpivarine. Dapivirine ring is a new agent that has been recommended by the WHO for HIV prevention in women, through vaginal sex since November 2021. This agent is placed in the vagina for twenty-eight days, after which it should be replaced with a new ring (World Health Organization, 2021). The ring study showed a reduction in HIV transmission by 35%, while the ASPIRE study showed a reduction to 27% (Garcia et al., 2021). These drugs (NNRTIs), work only against HIV 1 but not against HIV 2 and they work at a site different from the NRTIs to prevent chain elongation. They have a low barrier to resistance with a major mutation K103N leading to cross resistance in the group. Etravirine can be used in treatment of patients with resistance to the first generation NNRTIs (Anta et al., 2013). An important property of the orally administered drugs in this group is their long half-life of more than 24 hours in adults which can lead to monotherapy or the commonly referred to 'NNRTI tail' when an NNRTI containing regimen is stopped, which can lead to development of drug resistance (Hare et al., 2008). Efavirenz 600mg once daily or 400mg once daily with no difference in its time to viral suppression when comparing the two doses (Carey et al., 2015). Efavirenz has been used with good potency and durability in treatment naïve patients, but the Integrase strand inhibitors are generally preferred due to Efavirenz related side effects including Central Nervous System (CNS) toxicity and elevated transaminases and is therefore avoided in psychiatric patients as well as patients with liver disease (Saag et al., 2020). Efavirenz is taken on an empty stomach to reduce side effects since fatty meals increase its absorption. Nevirapine is no longer in use in many parts of the world including the USA and in Kenya due to its toxicity

especially in the first three months of treatment including hepatic necrosis, skin reactions including Steven Johnsons Syndrome that could lead to death. If Nevirapine is to be considered, studies show that it should not be given to female patients with a CD4 count of more than 250 cells/ml or male patients with a CD4 count of more than 400 cells/ml (Zhang et al., 2013).

The other group of ART are the Integrase Strand Transfer Inhibitors (ISTI) which include the oral agents Dolutegravir, Raltegravir, Bictegravir, and Cabotegravir which is given intravenously. These agents are used in combination with two nucleoside analogues as the preferred third agent in treating ART naïve patients. Due to their little or no effect on cholesterol and Triglycerides, they are specifically good for treating patients with abnormal lipid profile or risk factors for coronary artery disease compared to efavirenz or the protease inhibitors. They act by blocking the enzyme integrase that is needed for HIV replication at the integrase strand transfer step, whereby viral DNA is integrated into the host cell genome. Drug resistance to Dolutegravir as well as Bictegravir (not available in Kenya), is very uncommon and since Dolutegravir is cleared by glucuronidation, it rarely interacts with other drugs (few drug-drug interactions). It is generally well tolerated except for weight gain (Sax et al., 2020), insomnia, and dizziness (C Hoffmann et al., 2017). The last group of ART medication are the Protease inhibitors which include Atazanavir/ritonavir, as well as Lopinavir/ritonavir and Darunavir/ritonavir. These agents are boosted with ritonavir and are the commonly used drugs in this group. They are given usually with a dual NRTI combination such as TDF/3TC/ATV/r. Boosted Atazanavir and Darunavir are more preferred and effective as first-line in treatment naïve patients in combination with NRTIs. They work against HIV 1 and 2 and have a higher genetic barrier to resistance when compared to the NNRTIs. Lopinavir/ritonavir is currently

not recommended due to issues regarding its potency as well as toxicity (Saag et al., 2020). In a study comparing TDF/3TC/FTC combination versus LPV/r/3TC dual therapy, viral suppression at 48 weeks of therapy with the two regimens was the same in the two groups (88% vs 83%) (Cahn et al., 2014).

Drug regimen in HIV prevention of mother to child transmission has been shown to affect detectable viral load in some studies whereas other studies have shown no association. In an analysis of infants delivered in the US and Ireland from 2000 to 2011, regardless of ARV regimen or mode of delivery, there was significantly lower risk of transmission with viral load of less than 50 copies/ml (0.09%) compared to if viral load was between 50-399 copies/ml (1%). Several studies have shown non-nucleoside reverse transcriptase inhibitors (NNRTI's) better predictors of viral suppression compared to protease inhibitors. A European collaborative study found that patients on Protease inhibitors regimen took longer to be virally suppressed compared to those on Nevirapine, suggesting that patient's regimen can affect the duration to achieve undetectable viral loads. Similarly, in assessing viral suppression in ART naive and ART experienced pregnant women, Aziz and associates found that Non-nucleoside Reverse Transcriptase inhibitors (NNRTI) based regimen was a statistically significant predictor of viral load of less than 400 copies/ml (Aziz et al., 2013). A systematic review on virologic outcomes in treatment naive patients on regimens containing Efavirenz or Nevirapine based ART in RCTs and observational cohorts between 1996 and 2013 concluded that Efavirenz is significantly less likely to lead to virologic failure compared to Nevirapine; a finding that supports the use of Efavirenz in the first line regimen of ART especially in resource limited settings (Pillay, Ford, Shubber, & Ferrand, 2013).

The first line ART regimen in our setting at the time of the study was Tenofovir/Lamivudine/Efavirenz (TDF/3TC/EFV) as per our antiretroviral guidelines of 2018 and in keeping with the WHO recommendations at the time. The adult drug recommendation in Kenya at that time was and still is Dolutegravir based regimen consisting of Tenofovir/Lamivudine and Dolutegravir (TDF/3TC/DTG). Dolutegravir (DTG), was however not recommended in women and adolescents of childbearing potential because of the potential risk of neural tube defects. However, it was considered safe during pregnancy and breastfeeding if initiated after 8weeks of pregnancy. Women and adolescent girls of reproductive potential ought to have been counseled appropriately. Those who were on effective contraception could opt to use Dolutegravir; and were to be supported in their decision. However, if a woman found she was pregnant already while on DTG, she was not to be changed to an Efavirenz based regimen. This is because the neural tube is usually already formed by the time a pregnancy is diagnosed. Dolutegravir has the advantages of being better tolerated, having a high genetic barrier to resistance and with less drug interactions (Vitoria et al., 2018). The risk of neural tube defects with DTG were raised from a study in Botswana that found a slightly increased prevalence of neural tube defects with DTG exposure at the time of conception than with other ART exposures at conception (3/1000 versus 1/1000) (Zash et al., 2019). In 2016, the WHO recommended TDF/3TC/EFV as the first line ART with DTG as an alternative (*Guideline on When to Start Antiretroviral Therapy and on Pre-Exposure Prophylaxis for HIV*, 2015). Botswana was the first African country to transition from efavirenz based first line ART to integrase based (DTG) regimen in 2016 (Zash et al., 2019). By the end of 2017, most Low- and middle-income (LMICs) countries in the world including Brazil, Uganda and Kenya had transitioned to the DTG regimen. However, the safety and efficacy of DTG

was still not clear especially in special groups such as pregnant and breastfeeding women as well as in TB/HIV co infection (Vitoria et al., 2018). Since then, many studies have been done to give clarity on the new ART regimens and have given evidence leading to the development of the WHO guidelines on ART between 2019-2021 (World Health Organization, 2021). The current Kenya ART guidelines of 2018 is undergoing review to incorporate safer and more efficacious molecules that have since been developed especially for children and adolescent girls of childbearing potential in accordance with the WHO recommendations. The current first line regimen for all above 15 years is TDF/3TC/DTG including pregnant and breastfeeding women. This change was brought to full practice from late 2020 following communication via circulars from the National Aids/STI Control Program (NASCOP) as well as the Ministry of Health.

2.3.4 Partner disclosure

Partner disclosure means declaring your HIV status to your sexual partner. It is a part of four other levels of disclosure including family, friends, health care providers and employment/work settings disclosure (GOK, 2016). Disclosure of HIV status to sexual partners is an important goal emphasized by WHO and Center for Disease Control and Prevention (CDC). HIV status disclosure has advantages to the positive partner as well as the public. According to Matthews C (1999), partner disclosure increases social support among many women. Other benefits of disclosure included improved access to HIV prevention and treatment programmes, increased opportunities for risk reduction and ability to plan (WHO, 2015). According to a WHO bulletin of 2004, awareness of HIV status in couples helps lower number of unintended pregnancies in HIV positive women as couples make informed choices.

HIV status disclosure will also help women access PMTCT services freely and with a good social support this reducing the risk of MTCT (Medley, Garcia-Moreno, McGill, & Maman, 2004). Access to treatment care and support services for HIV positive women with undisclosed status is limited. This may have a direct impact on maternal treatment, adherence, monitoring of treatment and subsequently detectable viral loads in late pregnancy. This may also increase the risk of MTCT of HIV.

A French perinatal cohort study from 2005-2009 found that 15% of women did not disclose their HIV status to their partners (Jasseron et al., 2013). Non- disclosure was more frequent in women diagnosed in late pregnancy originating from Sub Saharan Africa or living alone and if the partner was not tested for HIV. Non-disclosure was independently associated with non-optimal PMTCT, late initiation of ART, detectable viral load at delivery and lack of neonatal prophylaxis. However, their rates of perinatal transmission did not differ according to disclosure status (Jasseron, Mandelbrot, Dollfus, Trocmé, Tubiana, & Teglas, 2013). Women testing in the setting of Antenatal Care are less likely to disclose their HIV status compared to women testing on Voluntary basis. Optimal uptake and adherence to treatment care and support is difficult for women whose partners are unaware of their status or not supportive of their participation (Medley et al., 2004). There is evidence that in Africa women often do not make decisions regarding their health and those of their children (Molyneux, Murira, Masha, & Snow, 2002). It is difficult for HIV positive women to seek medical and social support from treatment programs for them and their children without first disclosing their HIV status to their partners. With this evidence, failure of disclosure means inadequately treated/ poorly adherent pregnant HIV positive women and their infants with increased risk for detectable viral load in late pregnancy and increased risk of perinatal transmission. Non-disclosure of HIV status affects optimal

adherence to treatment as was seen in a study in south Africa on treatment failure, drug resistance and CD4 decline on women on ART (CJ Hoffmann et al., 2016). According to a study in Lesotho of pregnant HIV positive women enrolled in a French perinatal cohort, lack of disclosure of HIV was associated with virologic failure in adults on ART for more than six months (Labhardt et al., 2014). Most women do not disclose their status for fear of loss of economic support, abandonment, blame, physical and emotional abuse, discrimination and disruption of family relationships(Stinson & Myer, 2012). Failure to disclose HIV positive status has potential risks including the risk of transmitting the virus to an unsuspecting HIV negative partner (Jasseron, Mandelbrot, Dollfus, Trocmé, Tubiana, & Teglas, 2013). Disclosure rates increase as time from diagnosis increases. This is evidenced by studies reviewed from 14 countries in sub-Saharan Africa (SSA) with three studies from Kenya, for a period of between two weeks to almost four years that found disclosure rates of between 16.7% to 86% (Medley et al., 2004). Another systematic review in SSA on disclosure rates among pregnant and postpartum women, timing of disclosure and factors associated with disclosure decisions between 2000 to 2014 found that disclosure rates (to any person) ranged from 5% to 97%. Women disclosed more often to their partners compared to other persons i.e., family, friends, or religious leaders. Factors that were associated with decisions to disclose included personal factors such as a younger age, being in their first pregnancy, knowing someone who was living with HIV and low levels of stigma. Among the partner related factors, higher partner education level and partner HIV testing were associated with disclosure decision (Tam et al., 2015). Low rates of disclosure have an influence all the four prongs of PMTCT. On prong 1, disclosure of serostatus by positive partners will help to keep the negative woman negative due to protective sexual

behaviours. Secondly, infected HIV women will begin contraception early to prevent unintended pregnancy and only conceive when treatment is effective(viral suppression), Thirdly pregnant HIV women will be able to start ART early with good support and participation in support groups (Medley et al., 2004). In the study in Rwanda on factors associated with detectable viral load in late pregnancy, in the setting of Option B plus, the odds of having a detectable viral load were significantly higher in women with undisclosed HIV status. The disclosure rates in this study were at 56% (81.9% to partner and 13.7% to persons other than the partner). Non-disclosure rate was at 44%. In a study in rural Lesotho, disclosure of HIV status to less than 5 persons was associated with virologic failure in adults on ART for more than six months (Daniel Labhardt et al., 2014). It is of great value for health care workers to know the importance of disclosure and the challenges surrounding it especially for the pregnant woman and therefore emphasize on the need for continued support in order to overcome the barriers to disclosure to allow the pregnant infected woman enjoy the benefits of disclosure which include adherence to medication and subsequently viral suppression, ANC attendance, having an individualized birth plan, skilled birth attendance and neonatal prophylaxis all with a bid to prevent vertical transmission.

2.3.5 Initial CD4 Count

Before viral load monitoring was available in Kenya, treatment was monitored using CD4 count and clinical criteria. However, these have not been validated as immunologic response to treatment has individual variations (GOK, 2016). Aziz and colleagues in USA 2013 in a retrospective study to assess time to viral suppression in ART naive and ART experienced pregnant women on HAART found a statistically significant association between increased CD4 and earlier time to achieve viral load

of less than 1000 copies/ml (Aziz et al., 2013). Denound found that a higher CD4 count at enrolment was a positive predictor for undetectable viral load at the end of pregnancy (Denoeud-Ndam et al., 2013). However, Bisson G and co-workers suggested that the use of CD4 count to predict virologic failure is limited (Bisson et al., 2006). Alexandra Calmy and associates noted that similar studies in resource limited settings have shown a discrepancy between CD4 counts and viral load with increased CD4 counts in patients with higher viral load and reduced CD4 counts in patients with undetectable viral load. This leaves viral load monitoring as the best tool for monitoring treatment. Currently according to the WHO guidelines, (World Health Organization, 2021). According to the Kenyan ART guidelines which is in line with the WHO recommendations, CD4 count is currently used to identify Advanced HIV Disease. It is routinely done for all at baseline and reported as cells/µl for all above 5 years and CD4% for children below 5 years. Advanced HIV disease is defined as CD4 counts of less than 200 cells/µl or CD4% of $\leq 25\%$ for those $\leq$ 5years. Such patients receive different care including intensive management of those presenting with illness and those who are malnourished, identification management and prevention of opportunistic infections including Gene Xpert for Tuberculosis (TB) diagnosis, Serum CRAG, Cotrimoxazole prophylaxis, Isoniazid preventive therapy (IPT), priority for initiation of antiretroviral therapy with caution if there is suspected or confirmed TB, TB meningitis or cryptococcal Meningitis and finally close monitoring for development of Immune Reconstitution Inflammatory Syndrome (IRIS) (NASCOP, 2018).

2.3.6 Socio-demographic and other clinical factors

There is evidence that some socio-demographic factors in HIV positive pregnant women are associated with detectable viral loads. Katz and associates in assessing risk factors for detectable viral load at delivery, in positive pregnant women on HAART in the USA, found that younger age at delivery was a significant predictor for detectable viral load. In their study, black race and maternal illicit drug use were also significant predictors of detectable viral load at delivery (Katz et al., 1999). The Kabeho study in Rwanda on detectable viral loads in late pregnancy on women who were on option B plus found that maternal age was not associated with detectable viral load at enrolment (Gill et al., 2016). This may be because teenage pregnancy is not common in Rwanda. The rate of teenage pregnancy in Rwanda is 0.3% compared to other countries in sub-Saharan Africa like Mozambique (12%) (WHO, 2015), and 8% in Kenya (KDHS, 2014). The odds of having a detectable viral load in women with no education were higher than for those with primary or secondary school education. Early diagnosis of HIV in pregnancy enables early initiation of PMTCT services including ART initiation which results in a reduction in MTCT of HIV by reducing viral loads in late pregnancy. Katz and co-workers in a retrospective study in 2010 in USA showed that parity was not significant to detectable viral load at delivery (Katz et al., 1999). HIV diagnosis prior to current pregnancy was significant risk factor to detectable viral load at delivery. However other studies show evidence that there is higher virologic suppression in Multigravida women than primigravida women as seen by Denound and colleagues in a prospective study in Benin (sub study of the PACOME trial) who found that virologic suppression was 60% in primigravida and second gravid women and 77% in Multigravida women (p=0.01) (Denoeud-Ndam et al.). This may be because the primigravida women may have challenges adjusting to

first pregnancy as well as the diagnosed HIV status which may impact on their adherence to treatment and follow up as well as partner disclosure. In the same study, Partner status was not associated with detectable viral load, similar to marital status. Higher weight and higher CD4 count at enrolment increased the probability of virologic suppression at the end of pregnancy. A regular job, higher baseline detectable viral load and virologic failure at enrolment reduced the probability of having undetectable viral load by more than 30-fold. Early ART initiation more than eight weeks before detectable viral load measurement as well as high ANC attendance of more than six visits during pregnancy was associated with undetectable viral loads at delivery. The WHO recommends antenatal care models with a minimum of eight contacts to reduce perinatal mortality and improve women's experience of care (Luis & Moncayo, n.d.).

2.3.7 Side Effect profile

There are many side effects of antiretroviral drugs that have been studied and reported some of which are class specific while others cut across most drugs. Since the beginning of HIV treatment, drug options have evolved with newer agents having less side effects than the older ones. Similarly, concerns over safety of these agents in special groups such as in pregnancy and breastfeeding period (fetal safety) have become clearer. WHO endeavours to recommend the safest most effective combinations based on latest evidence, with many countries adopting the safest regimens into their protocols/guidelines including Kenya. Side effects to ART can affect treatment by affecting adherence. Side effects can range from mild, not affecting daily activities or adherence, to severe affecting adherence and subsequently viral load. Some side effects could be severe enough to warrant change of therapy.

Pregnancy physiology may affect pharmacokinetics of some drugs that may need dose adjustment in pregnancy. The class effect of the NRTIs is majorly mitochondrial toxicity. Others include fatigue, nausea diarrhoea and abdominal pain (Al-Dakkak et al., 2013). Mitochondrial toxicity may present as myopathy, peripheral neuropathy, hepatic steatosis with lactic acidosis (more common in females and could be life threatening in some cases) (Currier, 2007). These side effects usually resemble pregnancy symptoms (nausea, bloating and fatigue) and they may overlap sometimes. Hepatic steatosis with Lactic acidosis may resemble a severe, life threatening complication of preeclampsia called HELLP (Haemolysis, Elevated liver enzymes, Low Platelets) syndrome. Mitochondrial toxicity happens because of inhibition of Deoxyribonucleic Acid (DNA) polymerase gamma, that results in mitochondrial DNA depletion and dysfunction. Inhibition of DNA polymerase by the NRTIs occurs at different levels with the highest inhibition seen with Zidovudine whereas, other agents such as Tenofovir, Emtricitabine, Lamivudine and Abacavir have much less inhibition and hence less mitochondrial toxicity. Mitochondrial toxicity has been studied and seen to be a cause of potential neurologic toxicity in infants (Barret et al., 2003). Looking at common specific drugs used in our setting, in the group, Emtricitabine has been shown to have fetal safety with no dose adjustments required in pregnancy. Even though pharmacokinetic studies show a decrease in exposure of this drug by 25% in third trimester compared to postpartum, this was not associated with failure to achieve viral suppression or vertical transmission of HIV (Colbers et al., 2013). Lamivudine has been shown to be safe for the fetus and has no dose adjustment requirements (Benaboud et al., 2012). Tenofovir Disoproxil Fumarate has been shown to have the side effects of renal toxicity and modest bone mineral density loss in non-pregnant population. In the African trial of breastfeeding women with

HIV and a CD4 count of more than or equal to 350 cells/µl, decline in bone mineral density of the spine and hip from 14 days to 74 weeks after delivery was more in those who were randomly assigned to tenofovir based regimen (with protease inhibitor) compared to those not on ART (infants were given nevirapine instead). Whether the bone mineral density reverses or not after cessation of breastfeeding is not clear (Stranix-Chibanda et al., 2021). TDF does not need dose adjustments in pregnancy. Studies have shown some modest decrease in drug levels in third trimester and therefore careful viral load monitoring in pregnancy is important. Similarly, pharmacokinetic studies have shown a decrease in the area under curve (AUC) concentration in third trimester compared to postpartum or non-pregnant. However, these decreases were not associated with virologic failure or mother to child Transmission of HIV (Best et al., 2015). Tenofovir is not given with Lopinavir/ritonavir because of concerns about fetal safety (Siemieniuk et al., 2017). Findings from the PROMISE trial in which one arm of HIV infected pregnant women were put on Zidovudine/Lamivudine/Lopinavir/ritonavir while the other arm was on zidovudine only and later Tenofovir/Lamivudine/ Lopinavir ritonavir, revealed a higher rate of preterm births (<34 weeks) in the tenofovir group versus the zidovudine group (Fowler et al., 2016). Zidovudine is an NRTI that is used currently as part of second line agents in resource limited settings including Kenya. On the side-effects of the NNTRIs, the class side effects include rash and hypersensitivity (worse with the older agents such as Nevirapine and less with Efavirenz and least with Etravirine) and Central nervous system disorders, liver toxicity and mood disorders (NASCOP, 2018). Efavirenz, the most commonly used NNRTI in our setting, has been found to be safe for the fetus from many studies with no increased risk of congenital anomalies compared to other ART regimen (Ford et al., 2014).

Maternal side effects of Efavirenz include Central Nervous System toxicity, Rash, and elevated hepatic transaminases levels. Studies have shown that the adverse effects of efavirenz based regimen are similar to those of integrase inhibitor regimen (Lockman et al., 2021). No dose adjustment is required for efavirenz during pregnancy. This is evidenced by a study that found no difference in the pharmacokinetics of efavirenz in the pregnant versus non-pregnant women (Cressey et al., 2012). Nevirapine is another NNRTI that is no longer in use in many high-income countries and is being phased out in Low- and middle-income countries. Despite being safe for the fetus and with no dose adjustments requirements in pregnancy, it is associated with severe side effects such as, rash including Steven Johnson's Syndrome, and hepatotoxicity with fulminant hepatitis as well as liver failure in other cases (Lyons et al., 2006).

The Protease inhibitor class effects include: Gastrointestinal intolerance with diarrhoea and abdominal pain, Insulin resistance, Hyperglycaemia, Diabetes Mellitus, Lipodystrophy, and side effects caused by drug-to-drug interactions when used with other drugs metabolized by the liver (NASCOP, 2018a). The risk of gestational diabetes in pregnant women on protease inhibitors is however not increased (Hitti et al., 2007) and glucose monitoring should be as for the standard ANC protocol and not special. The preferred protease inhibitor in pregnant women is ritonavir boosted Atazanavir. It has the side effect of elevated unconjugated bilirubin due to its inhibition of the enzyme Uridine 5'-diphospho-glucuronosyl transferase in the liver. This side effect may lead to increase bilirubin in the neonates (Ripamonti et al., 2007). ATV/r is a second line agent in our guidelines. Dose adjustment in pregnancy may be required. Studies have shown that an increase from the usual 300mg of ATV and 100mg of ritonavir, to 400mg of ATV with 100mg of ritonavir resulted in an AUC equivalent to that seen in non-pregnant patients with HIV receiving the standard

dose of 300mg ATV/100mg ritonavir (Mirochnick et al., 2011). Lopinavir/ritonavir is not recommended in pregnancy but has been used as a second line agent in our setting. It has no fetal safety concerns; however, a dose increase is recommended in pregnancy to 600mg Lopinavir/50mg ritonavir twice daily, especially in protease inhibitor experienced patients with return to the standard 400mg/100mg twice daily dose immediate postpartum. This is because of studies showing a reduction in drug levels in second and third trimester compared to postpartum and outside pregnancy. Viral load monitoring where available is usually indicated and a once daily dose is not recommended in pregnancy (Mirochnick et al., 2008). Integrase inhibitors form part of first line regimens in all populations of HIV infected persons including pregnant and breastfeeding women as well as women of child bearing potential (World Health Organization, 2021). Dolutegravir is the most used agent in the group. As pertains fetal safety, a study in Botswana showed a small risk of Neural Tube Defects (NTD) with DTG, which is not statistically significant when compared to other regimens that are non DTG based (0.15% versus 0.1%), and is limited to if DTG was used around the time of conception (Vitoria et al., 2018). In another study, the risk of NTDs for women who started DTG in pregnancy was 0.05% while the risk for women without HIV was 0.07% which is lower than for DTG around the time of conception. Other risks for DTG to the fetus (Still birth rates, Preterm births, Neonatal deaths, Small for gestational age) were the same as the population risks. There is no dose adjustment required for DTG in pregnancy. Considering drug to drug interactions, if Tuberculosis treatment is being given concurrently, an increase in DTG dose of 50mg in the evening is given to all patients on rifampicin for the duration of rifampicin use and for an additional two weeks (NASCOP, 2018a). This is because of the enzyme induing properties of Rifampicin that causes a reduction in DTG that may lead to suboptimal

treatment. Side effects have been shown to affect adherence to ART(Al-Dakkak et al., 2013). It is not clear as to which side effects have an impact on adherence to ART the most and some may while others may not affect adherence (Al-Dakkak et al., 2013). Side effects to ART can be severe enough to warrant stopping of treatment by the patients. In an Italian cohort of ART naïve patients, 21% stopped their regimen due to toxicity while only 5% stopped due to treatment failure (Monforte et al., 2005). The more the side effects, the more likely one is to stop therapy. With regards to specific side effects, for instance, confusion could lead to impaired adherence since ART needs specific drug combinations sometimes with different timing. Loss of appetite and taste disturbances as well as nausea all which resemble pregnancy can lead to poor adherence (Al-Dakkak et al., 2013). It is not easy to separate side effects to a single antiretroviral drug due to adoption of combination ART currently.

ART side effects are graded from grade 1 to 4 with grade 1 being mild side effects while grade 4 being life-threatening. Grade 1 (Mild) side effects are those which are transient, resulting in no limitation in daily activities and requires no investigations. They are self-limiting. Grade 2 (Moderate) side effects are those that limit daily activity moderately, with some assistance to do daily activities needed but with none or little medical intervention. Grade 3 (Severe) side effects are those in which daily activities are markedly reduced and assistance is needed and sometimes may require hospitalization. Grade 4 (Life threatening) side effects are those in which significant assistance is required. Side effect profile in this study was graded as mild moderate and severe depending on limitation of daily activities, excluding the life-threatening (Grade4) side effects, since very ill patients were not eligible for the study. Looking at side effect profile in relation to viral suppression, Detectable viral load was associated with women who reported ART side effects in the past month at enrolment in the

Kabeho study in Rwanda, which may reflect poor adherence among the group. The odds of having detectable viral load at enrolment were higher in women with side effect to ART (AOR =2.63; (1.72, 4.03) (p<0.0001) (Gill et al., 2016).

2.4 Conceptual framework

This study hypothesized that clinical characteristics such as duration of HAART, Drug regimen, Side effect profile, HAART adherence, Hospitalization or illness in the current pregnancy among others were predictors of detectable viral load. This relationship was influenced by the patient's sociodemographic and reproductive characteristics that were intervening variables. The reproductive characteristics of interest were gravidity, gestation at first ANC, Number of ANC visits, Partner disclosure, partner HIV status, timing of HIV diagnosis (whether in this pregnancy or prior), among others (Figure 2.1).

INDEPENDENT VARIABLES

DEPENDENT VARIABLE

Clinical Characteristics
Duration of HAART
Drug regimen
Side effect profile
Adherence
Illness in current pregnancy
Partner disclosure
Timing of HIV diagnosis

Detectable Viral Load
(at Delivery)

Patient Characteristics
(Sociodemographic and Reproductive)

INTERVENING VARIABLES
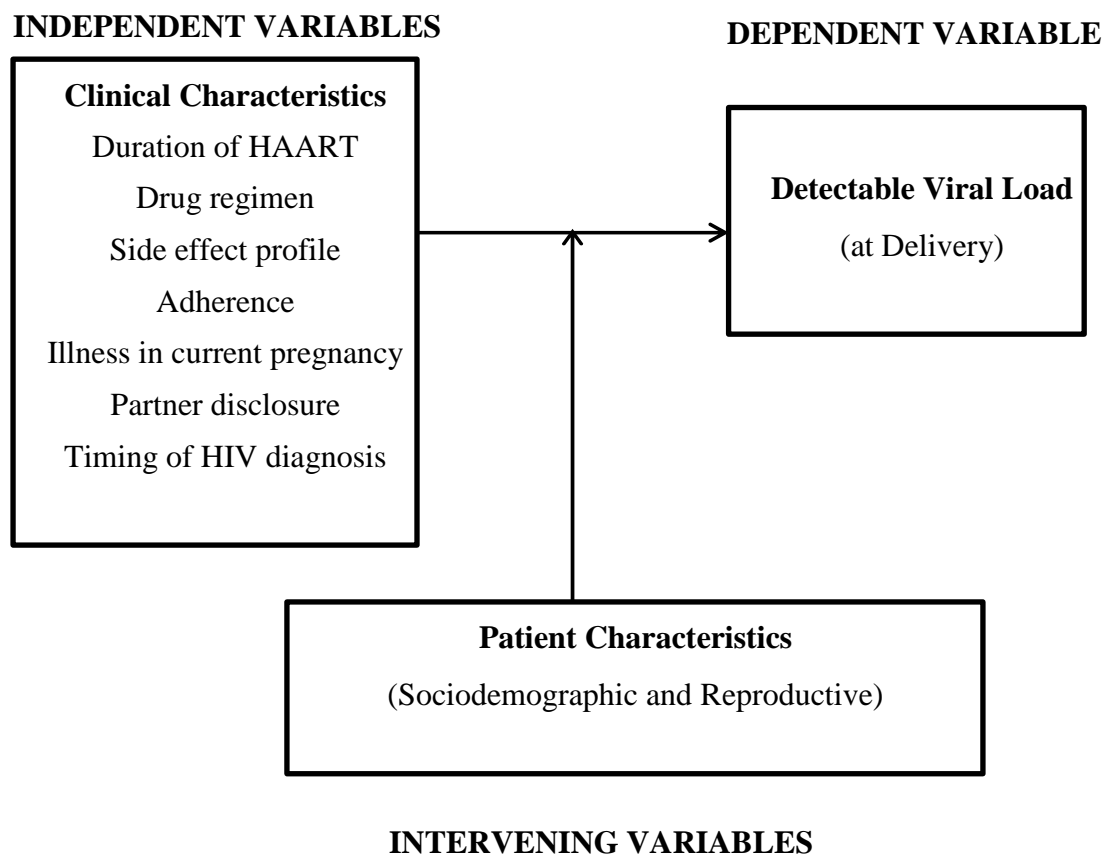
Figure 2. 1: Conceptual Framework

CHAPTER THREE

3.0 METHODOLOGY

3.1 Study site

The study was conducted at the Riley Mother Baby hospital, the maternity unit of Moi Teaching and Referral Hospital (MTRH) as well as the Post-natal Clinic. This is the second largest national referral hospital in Kenya located in Eldoret town in the western part of Kenya. The hospital has a 1000 bed capacity and serves population of western and the North rift regions of Kenya, parts of Eastern Uganda, and the Southern Sudan. The Obstetrics unit of MTRH has a bed capacity of approximately 160 of which 28 are specifically for antenatal mothers and 17 for labour and delivery. Through the academic model providing access to healthcare (AMPATH), the hospital provides comprehensive care for individuals infected with human immunodeficiency virus (HIV). The study setting (MTRH/AMPATH) adopted option B+ and integrated the care of HIV positive pregnant women in MCH clinic around 2015. Of the approximately 1200 deliveries conducted in a month within MTRH, about 20 are for HIV-infected women and this makes it a suitable site to conduct a study on the factors associated with detectable viral load at delivery among HIV positive women.

3.2 Study Design

This was a cross-sectional study conducted among HIV-infected women delivering at Moi Teaching and Referral Hospital's maternity unit and those admitted at the postnatal unit.

3.3 Study population

The study population were HIV infected expectant mothers seeking labour and delivery services at MTRH.

3.4 Eligibility Criteria

3.4.1 Inclusion Criteria

1. All confirmed or Known HIV infected pregnant women 28weeks gestation and above admitted for labour and delivery regardless of their age.

2. All HIV infected pregnant women who provided, informed consent to participate in this study.

3.4.2 Exclusion Criteria

1. All confirmed or known HIV positive pregnant women more than 28 weeks gestation that were too ill to participate.

3.5 Sample Size calculation

Using the Cochran formula (1977) to calculate the sample size,

$$n_0 = \frac{z^2 * p * (1-p)}{e^2} \qquad \text{Where:}$$

n_0 = required sample size of HIV positive pregnant women

z = z-value at 95% confidence interval (1.96)

p = proportion of detectable viral load estimated at 9% (Landes et al., 2019)

q = 1-p (91%).

e = desired level of precision (margin of error), set at 0.05

Therefore:

$$n_0 = \frac{1.96^2 * 0.09 * (0.91)}{0.05^2} = 126. \text{ Calculated minimum sample size=126}$$

Adjusting for the likelihood of incomplete data 10% =13.

We therefore needed to recruit 140 participants.

3.5.1 Sampling

This study adopted a consecutive sampling technique due to the low number of HIV infected pregnant women delivering at the Riley Mother and Baby Hospital (RMBH) within Moi Teaching and Referral Hospital (MTRH) in Eldoret Kenya. According to the hospital's statistics, there are nearly 900 deliveries monthly; of these 30 are from women infected with HIV. With this backdrop, it was more appropriate to use the consecutive sampling technique due to the low numbers of the target population. Specifically, the research team was informed by the nursing team of a new delivery or admission for delivery by a HIV infected mother. The woman was then approached by a trained research assistant, who informed her about the study as well its objectives and procedures. In the event she agreed to participate in the study, a written informed consent was administered in a private room and all her questions were conclusively answered. In the event she declined to participate, the next new delivery or admission for the same, who met the eligibility criteria was approached. This procedure was repeated until the desired sample size was achieved.

3.6 Study Procedure

Pregnant HIV infected mothers admitted for labour and delivery at RMBH MTRH diagnosed either antenatally or at admission who met the inclusion criteria were consented to participate in the study and were subjected to an interviewer administered questionnaire. Data on age, weight, height, body mass index, physical examinations (general exam and vital signs), gestational age at first ANC visits, number of ANC visits, parity, gestational age at enrolment, duration on ART, self-reported non-adherence, side effects related to ART use, partner disclosure of HIV, and WHO HIV clinical staging among others. Events at labour including duration,

mode of delivery and hours since membrane rupture were recorded from the patient's files. After enrolment, a viral load sample was collected by the interviewer, observing the recommended standards for handling a viral load sample as required by the laboratory. The samples were taken to the Academic Model Providing Access to Healthcare (AMPATH) reference lab within the first hour of collection. Viral load at delivery was analysed by the AMPATH Lab using the Abbott real time PCR analyser with a 40 copies/ml detection threshold. Results were recorded in the patient's questionnaire as a continuous variable. Adherence was measured using self-reporting at enrolment, (delivery). Women were considered non-adherent if they reported missing Highly Active Antiretroviral Therapy (HAART) at the 7-day recall.
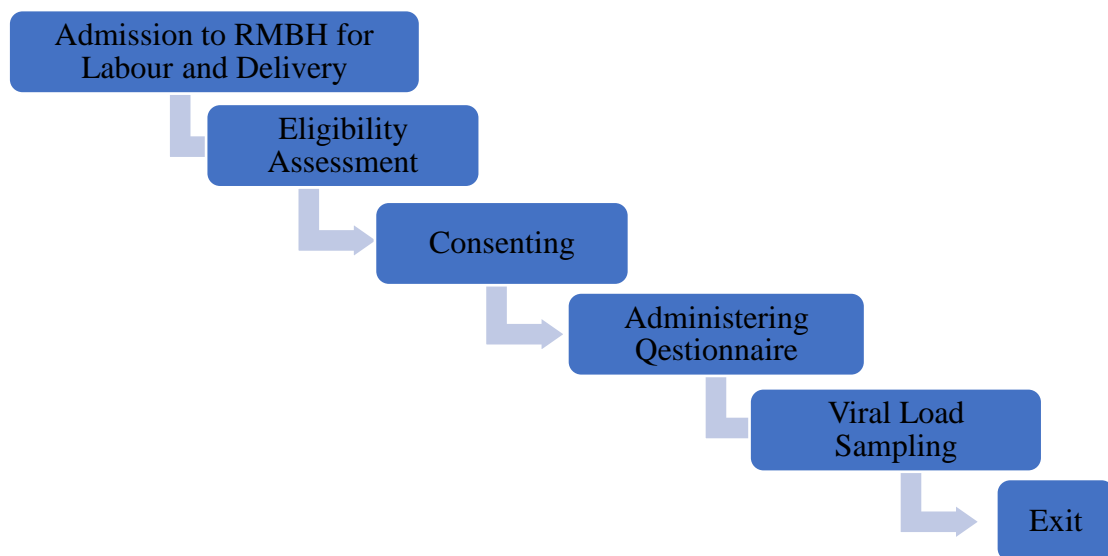
Figure 3.1: Study Procedure

3.7 Data Management

3.7.1 Data Collection

Data was collected using structured questionnaires. The filled questionnaires were entered into an electronic database.

3.7.2 Data Analysis

Data analysis was done using software for statistical computation known as SPSS Version 24. Continuous variables such as age, viral load among others were summarized using mean and the corresponding standard deviation. Pearson Chi-Square test of association between patient characteristics and the occurrence of detectable viral load at the time of delivery was conducted, where a $p \leq 0.05$ was considered statistically significant. Odds ratios were computed at 95% confidence interval. Where a statistically significant association was obtained at the bivariate level of analysis (using Pearson Chi-Square test), a multivariate logistic regression was conducted to control for the probable confounders.

3.8 Ethical considerations

1. Approval was sought from IREC – Institutional Research and Ethics Committee as well as Moi Teaching and Referral Hospital.

2. Individual informed consent was sought before carrying out the study from each participant. The participants were informed that their decision to participate or not to participate in the study would NOT affect their medical care. Informed consent was obtained by the researcher assistant who was not directly providing care to minimize coercion.

3. Those who declined to give informed consent were not at any circumstance denied medical care that best suited their needs.

The entered data was de-identified to ensure that the confidentiality of the participants was maintained, and the database was encrypted to protect against unauthorized access. The questionnaires were converted to the electronic form and were kept in a safe cabinet under a lock and the key kept by the primary investigator. Consenting process took place in private.

CHAPTER FOUR

4.0 RESULTS

4.1 Patient characteristics of pregnant HIV infected women delivering at RMBH.

This study enrolled 140 expectant and seropositive women with a mean age of 29.42 years. Of these, more than two-thirds (67.9%) were married, 40.7% had a primary level of education, nearly all (99.3%) professed the Christian faith with nearly equal proportion of unemployed (42.9%) and self-employed (44.2%) women as shown on Table 4.1.

Table 4. 1: Participants Sociodemographic Characteristics (N=140)

Characteristic		n (%)
Maternal age (years)	Mean (SD)	29.42 (±7.07)
	Median (IQR)	29.0 (17.0, 45.0)
Marital Status	Single	31 (22.1)
	Married	95 (67.9)
	Separated	13 (9.3)
	Widowed	1 (0.7)
Highest Level of Education attained	None	7 (5.0)
	Primary	57 (40.7)
	Secondary	47 (33.6)
	Tertiary	29 (20.7)
Religion	Christian	139 (99.3)
	Muslim	1 (0.7)
Occupation	Employed	18 (12.9)
	Unemployed	60 (42.9)
	Self-employed	62 (44.2)

The median gravidity of the women enrolled was 3.0 (IQR: 1.0, 8.0). More than half (55%) of the study participants presented late (>16 weeks) for their first antenatal visit. The median number of antenatal visits was 4 (IQR: 1.0, 5.0). Following an

antenatal profile, 123 (87.1%) of the women were Rhesus positive, 62 (44.3%) had

blood group O, 122 (87.1%) were non-reactive to venereal disease research laboratory

(VDRL) serum tests and 13 (9.3%) were reactive to VDRL serum tests as shown on

table 4.2a.

Table 4.2a: Participants Reproductive Characteristics (N=140)

Characteristic		Mean (SD)/ Median (IQR) / n (%)
Gravidity	Median (IQR)	3.0 (1.0, 8.0)
Gestation at First ANC Visit (weeks)	Late (>16 weeks)	77 (55.0)
	Early (≤16 weeks)	63 (45.0)
Number of ANC Visits	Median (IQR)	4.0 (1.0, 5.0)
VDRL Status	VDRL (Non-Reactive)	122 (87.1)
	VDRL (Reactive)	13 (9.3)
	Missing VDRL	5 (3.6)
Gestation at Delivery (weeks)	Mean (SD)	38.24 (±3.29)
Mode of Delivery	ELCS EMCS SVD	12 (8.6) 31 (22.1) 97 (69.3)

A small proportion of participants 23 (16.3%) reported an illness in the current

pregnancy and 15 (10.7%) of the participants were hospitalized at some point during

their pregnancy. The mean gestation at the time of delivery was 38.24 (±3.29) weeks,

body mass index (BMI) at 26.64 (± 4.23) kg/m2, and the median duration of highly

active antiretroviral (HAART) use was 20 (6.0, 60.0) months. Majority of the women

delivered by Spontaneous Vertex Delivery (SVD) 94 (67.1%). The most used

HAART was an NNRTI-based HAART regimen specifically TDF/ 3TC/ EFV among

124 (88.6 %) of all the women enrolled and a majority 130 (92.9) had mild HAART

related side effects. A large proportion 99 (70.9%) of the participants knew their

positive HIV status prior to getting pregnant. On partner HIV status, approximately

one fifth of the participants 29 (20.7%), did not know their partners HIV status while

a majority 111 (79.3%) did. About half of the participants 77 (55%) had a HIV positive partner while almost a quarter 34 (24.3%) were in a sero-discordant relationship. Majority of the women in this study 103 (73.6%) had disclosed their HIV status to their partners (Table 4.2b).

Table 4.2b: Participants' Clinical Characteristics (N=140)

Characteristic		Mean (SD)/Median (IQR) / n (%)
Hospitalization during current pregnancy	Yes	15 (10.7%)
Illness in current Pregnancy (n=23)	Anaemia	9 (6.4)
	Asthma	1 (0.7)
	Hypertension	7 (5.0)
	Lower Back Pain	1 (0.7)
	Opportunistic infections	2 (1.4)
	Other illness	3 (2.1)
Current HAART Regimen	Protease inhibitors	6 (4.3)
	Integrase inhibitors	10 (7.1)
	NNRTI-based	124 (88.6)
Duration of HAART use (months)	Median (IQR)	20 (6.0, 60.0)
WHO Clinical Staging	Stage I	132 (94.3)
	Stage II	8 (5.7)
HIV Diagnosis Status	Diagnosed in this pregnancy	41 (29.3)
	Known HIV Positive	99 (70.7)
Partner's HIV Status	Positive	77 (55.0)
	Sero-discordant	34 (24.3)
	Unsure	29 (20.7)
Partner HIV Disclosure	Yes	103 (73.6)
	No	37 (26.4)
Side Effects	Moderate/Severe	10 (7.1)
	Mild	130 (92.9)

4.2 Proportion of pregnant women with detectable viral load among HIV infected pregnant women delivering at RMBH.

This study determined that 25 (17.9%) of all the expectant women diagnosed with HIV and enrolled into the study had detectable viral load at the time of delivery, (Figure 4.1)
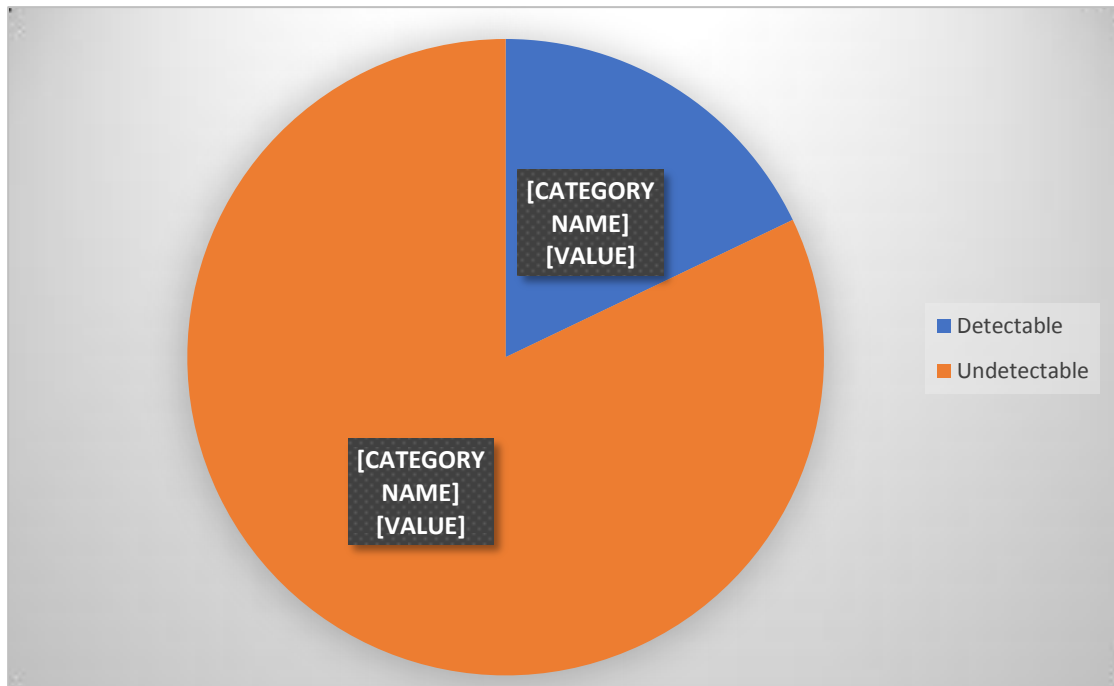
Figure 4. 1: Proportion of Participants with Detectable Viral Load

4.2.1 Distribution of Detectable Viral Load

Among the 25 participants with a detectable viral load (>40 copies/ml) at delivery, , 3/25 (12%) were between 41-50copies/ml, 5/25 (20%) had low level viremia (51-1000copies/ml), while 17/25 (68%) had more than 1000 copies/ml (Figure 4.2)
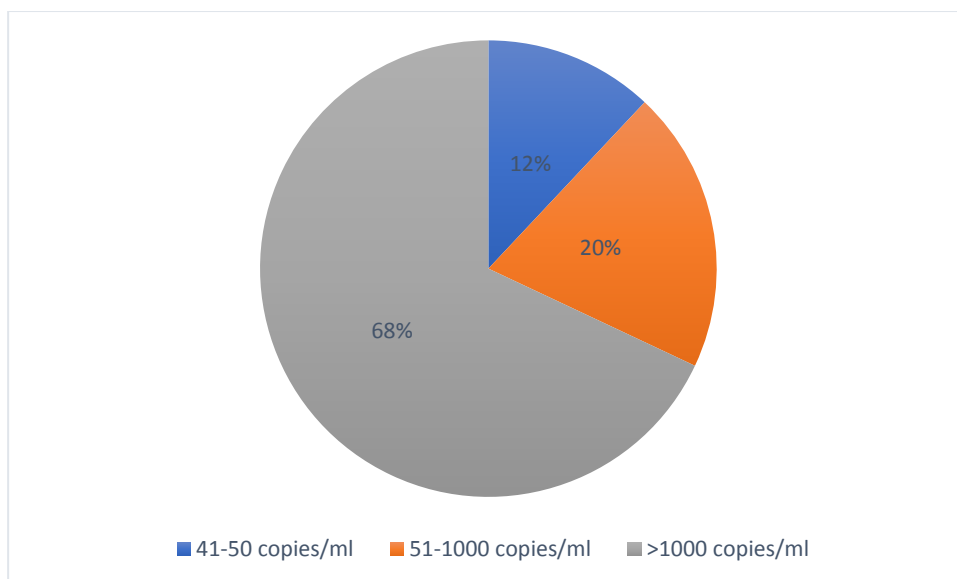
Figure 4. 2: Distribution of detectable viral load

4.2.2 Mode of Delivery Stratified by Viral Load.

In this study, 94.1% of women with viral load copies of >1000copies/ml delivered via Vaginal delivery (Table 4.3).

Table 4. 3: Mode of Delivery (stratified by viral load)

Mode of Delivery	Viral load >1000 copies/ ml	
	Yes	No
ELCS	0	12 (9.7%)
EMCS	1 (5.9%)	29 (23.6%)
SVD	**16 (94.1%)**	82 (66.7%)
Total	**17 (100.0%)**	**123 (100.0%)**

4.3 Factors associated with detectable viral load among HIV infected pregnant women delivering at RMBH.

This study found that women who reported moderate or severe antiretroviral use side effects were significantly more likely to have detectable viral load compared to those with mild side effects (OR=3.250; 95% CI: 1.552, 6.808; p=0.017). Although lack of adherence to HAART medication or regimen change, shorter duration of HAART use (less than 3 years), being married and having a lower level of education (primary education or less) increased the likelihood of a detectable viral load, the relationship between these predictors and detectable viral load was not statistically significant.

99 (70.9%) of the women enrolled already knew their HIV status (known positives). However, there was a greater likelihood (OR = 1.610; 95% CI: 0.789, 3.283) of those diagnosed in the current pregnancy to have a detectable viral load; a relationship that was however not statistically significant (p=0.227). Although majority of the women enrolled had WHO stage I of the disease, those with WHO stage II were two times more likely (OR=2.400; 95% CI: 0.900, 6.401; p=0.152) to have detectable viral load, despite this relationship not being statistically significant. Most women were on NNRTI-based (Tenofovir, Lamivudine and Efavirenz) highly active antiretroviral therapy (HAART) regimen while those on protease inhibitors were more likely (OR=0.780; 95% CI: 0.369, 1.648; p=0.639) to have a detectable viral load compared to those on other form of HAART. Women who had a late first ANC visit (of more than 16 weeks gestation) were more likely to have detectable viral load compared to those who came earlier (OR= 2.104; 95% CI: 0.939, 4.715; p=0.076); however, this relationship was not statistically significant (Table 4.4).

Table 4. 4: Factors associated with detectable viral load among HIV infected pregnant women.

Factor		Detectable Viral Load		Total	p-value	OR (95% CI:)
		Yes	No			
Diagnosis	In this pregnancy	10 (24.4)	31 (75.6)	41	0.227	1.610 (0.789, 3.283)
	Known positive	15 (15.2)	84 (84.8)	99		
WHO Staging	Stage 2	3 (37.5)	5 (62.5)	8	0.152	2.400 (0.900, 6.401)
	Stage 1	20 (15.6)	110 (84.4)	132		
HAART Regimen	Protease-Based HAART	2 (33.3)	4 (66.7)	6	0.639	0.780 (0.369, 1.648)
	Integrase-based HAART	1 (10.0)	9 (90.0)	6		
	NNRTI-based HAART	21 (16.9)	103 (83.1)	124		
Protease Inhibitors	Yes	2 (33.3)	4 (66.7)	6	0.298	1.913 (0.581, 6.294)
	No	25 (18.7)	109 (81.3)	134		
Gestation at first ANC	Late First visit (>16 weeks)	18(23.4)	59 (76.6)	77	0.076	2.1044 (0.939, 4.715)
	Early First visit (≤16 weeks)	7(11.1)	56 (88.9)	63		
HAART Adherence	No	11 (20.0)	44 (80.0)	55	0.654	1.214 (0.595, 2.478)
	Yes	14 (16.5)	71 (83.5)	85		
HAART Regimen Change	No	20 (19.2)	84 (80.8)	104	0.616	1.066 (0.907, 1.253)
	Yes	5 (13.9)	31 (86.1)	36		
Duration of HAART use	≤ 3 years	20 (20.6)	77 (79.4)	97	0.239	1.773 (0.712, 4.413)
	>3 yea4s	5 (11.6)	38 (88.4)	43		
Side Effects	Moderate/Severe	5 (50.0)	5 (50.0)	10	**0.017**	3.250 (1.552, 6.808)
	Mild	20 (15.4)	110 (84.6)	130		
Gravidity	≥5 (High)	6 (21.4)	22 (78.6)	28	0.587	1.263 (0.557, 2.865)
	1-4 (Low)	19 (17.0)	93 (83.0)	112		
Level of Education	≤ Primary	14 (21.9)	50 (78.1)	64	0.407	1.857 (0.863, 3.995)
	≥ Secondary	11 (14.5)	65 (85.5)	76		
Marital Status	Married	20 (21.1)	75 (78.9)	95	0.167	1.895 (0.760, 4.724)
	Not married	5 (11.1)	40 (88.9)	45		
Partner's Disclosure	No	9 (21.6)	29 (78.4)	37	0.617	1.310 (0.618, 2.772)
	Yes	17 (16.5)	86 (83.5)	103		

When a multivariate logistic regression statistical analysis was conducted, (controlling for HAART regimen, no HAART regimen change, Protease inhibitor use, lack of treatment adherence, partner use of HAART and Partner disclosure); these confounders did not affect the statistically significant association between HAART related side effects and patient presenting with a detectable viral load at the time of delivery, (AOR=6.189; 95% CI: 1.330, 28.797; p=0.020) as shown on Table 4.5.

Table 4. 5: Factors associated with detectable viral load among HIV infected pregnant women (Adjusting for Confounders)

Factor		Detectable Viral Load		Total	p-value	AOR (95% CI :)
		Yes	No			
Side	Moderate/Severe	5 (50.0)	5 (50.0)	10	**0.020**	6.189 (1.330, 28.797)
Effects	Mild	20 (15.4)	110 (84.6)	130		

CHAPTER FIVE

5.0 DISCUSSION

In this cross-sectional study of 140 HIV positive pregnant women enrolled at Riley Mother and Baby Hospital (RMBH), 17.9% of them had a detectable viral load (more than 40 copies/ml) at the point of delivery. There was a statistically significant association between women presenting with a moderate or severe HAART related side effects and intrapartum detectable viral load. These women were six times significantly more likely to present with detectable viral load at delivery. This proportion of detectable viral load at delivery is higher than the set limit of 5% by the Joint United Nations Programme on HIV/AIDS (UNAIDS), which aims to end the consequences of HIV infection including transmission and deaths from Acquired Immune Deficiency Syndrome (AIDS) by 2030. Lack of prompt viral load assessment and knowledge on detectable viral load counters global initiatives such as the UNAIDS 95-95-95 targets; where 95% of those who are HIV positive should know their status, 95% of those who know they are HIV infected should be on treatment and 95% of those on treatment should be virally suppressed. From the most recent national survey on HIV findings in Kenya (NASCOP, 2020), 82.7% of Kenyan women aged between 15 to 64 years who tested positive to HIV already knew their status, 96.6% who knew their status were already on treatment and 90.4% on treatment had already achieved viral load suppression. This implies that Kenya is yet to achieve the UNAIDS 95-95-95 targets but is on the pathway to achieving it. This study documents higher rates of detectable viral load at delivery on pregnant HIV infected women compared to NASCOPs finding on all women as well as the 95-95-95 UNAIDS target. The second major finding in this study was that there was a statistically significant association between women presenting with a moderate or

severe HAART related side effects and intrapartum detectable viral load. These women had a six-fold increased likelihood of presenting with detectable viral load at delivery. These findings suggests that there is need for additional effort to improve adherence counselling focusing on side effects to ART in this special sub-population of pregnant women who experience unique challenges of pregnancy, especially in clinical settings where both PMTCT and antenatal care services are integrated, as in our case at MTRH. The counselling offered should include ways of how to manage the side effects. It has been previously documented that ART related side effects have a negative effect on patient adherence to medications (Mukose et al., 2021; Stinson & Myer, 2012). This finding is close to that reported in Rwanda (Gill et al., 2016) where women who reported side effects had a higher likelihood of detectable viral load (OR=2.63; 95% CI: 1.72, 4.03, p<0.0001).

Other studies that reported higher detectable viral load levels at delivery were conducted in countries within the East African Community. In the Democratic Republic of Congo (DRC), a cross-sectional baseline assessment was conducted in 35 provincial health zones within Kinshasa where the proportion of detectable viral load at delivery stood at 52% (Yotebieng et al., 2019). Although both studies used a similar viral load cut-off (>40 copies/ml), the study conducted in Kinshasa enrolled more participants (N=1623) from multiple (n=35) study sites compared to the 140 enrolled in a single site in the current study. This difference in study population and sample size could have a direct effect in the overall proportion of detectable viral load eventually reported, as the relationship could be confounded by more factors than those that could be witnessed in a single national referral hospital setting.

 In Rwanda, (Gill et al., 2016) reported a proportion of 47.8% which is higher than the current study. The difference between these two studies could be attributed to methodological variance. Sample collection in our study was at delivery which is at the tail end of a pregnancy journey while in Rwanda it was from the beginning of third trimester (28weeks) to delivery (Gill et al., 2016). Many women with detectable viral load at 28 weeks would have a lower or undetectable viral load if tested at delivery assuming satisfactory adherence to ART. Labor and delivery carries the highest risk of mother to child transmission, which advised the timing of viral load testing in this study. Secondly, the study in Rwanda used a lower threshold for detectable viral load of 20 copies per ml compared to our study of 40 copies per ml.

In South Africa, 22% of the 574 women enrolled and were on HAART, were found to have a detectable viral load (Myer et al., 2016) a relatively comparable finding to our study. Higher proportions (36.4%) of detectable viral load at delivery were reported in a second study from South Africa (Moyo et al., 2020) conducted among 2769 HIV infected women delivering at four tertiary obstetric units in Gauteng –South Africa between June 2018 to March 2019. The study (Moyo et al., 2020) adopted a relatively higher viral load cut-off (>50 copies/ml) compared to this current study (>40 copies/ml).

5.1. Distribution of detectable viral loads and mode of delivery

A sub-analysis on the distribution of detectable viral loads in this study was done. Of the 25/140 (17.9 %) who had detectable viral load, defined as more than 40 copies/ml, 3/25 (12%) of them had viral loads of between 41-50 copies/ml, hence were virally suppressed. Viral suppression has been defined by the World Health Organization currently as having less than 50 copies per ml (World Health Organization, 2021). 5/25 (20%) had low level viremia (between 51-1000 copies/ml), and the majority 17/25 (68%) had more than 1000 copies/ml. Focusing on viral copies of more than 1000/ml, studies have shown a reduction in mother to child transmission of HIV if delivery is done through pre labour caesarean section (Elective Caesarean) for women with a viral loads of more than 1000 copies/ml. This study found that almost all 16/17 (94%) of the participants who had a detectable viral load of more than 1000 copies/ml had a vaginal delivery. According to the Kenya ART guidelines at the time of this study, where available a pre labour caesarean delivery was recommended for women with viral load of > 1000 copies/ml (NASCOP, 2018). From the findings in this study, these women 16/17 (94%) had their infants exposed to an increased risk of intrapartum HIV vertical transmission that would have been reduced by Elective caesarean section. This finding could possibly be explained by the lack of a routine term viral load assessment policy on pregnant women and subsequently unclear delivery plans that would lead to such women presenting in already established labour where the benefit of pre-labour caesarean section for delivery would essentially be lost. This finding therefore suggests that there is need to review the viral load assessment policy at the Academic Model Providing Access to Healthcare (AMPATH) program for this special sub-population of pregnant women, to ensure a term viral load is done with subsequent delivery plans in line with the viral load

status. Elective caesarean section has been shown to reduce the risk of vertical transmission from a meta-analysis of fifteen prospective studies that found mother to child transmission rates of 8.4% versus 16.7% for elective caesarean delivery versus vaginal delivery, even after controlling for intrapartum zidovudine (Andiman et al., 1999). A subsequent randomized trial of caesarean delivery versus vaginal delivery found that caesarean delivery significantly reduced the risk of MTCT compared to vaginal delivery, without increasing postpartum complications of Caesarean section significantly (Parazzini et al., 1999). These two studies were however done in resource rich settings. A more recent meta-analysis (Kennedy et al., 2017) found that elective Caesarean section reduced infant HIV transmission overall as well as in low and middle income countries, in women with viral loads of more than 400 copies/ml.

Despite varying recommendations for resource rich versus resource limited settings on the mode of delivery for HIV infected women, MTRH is a relatively resource rich setting and it would be feasible to have term viral loads for pregnant HIV infected women and subsequent elective caesarean delivery for those with viral loads of more than 1000 copies/ml in view of the benefit of reducing intrapartum infant transmission of HIV.

5.2 Factors associated with detectable viral load among HIV infected pregnant women delivering at RMBH.

Other factors in this study were not found to have to have significant associations with detectable viral load at delivery. Women diagnosed with HIV in the current pregnancy were more likely to have a detectable viral load (OR=1.610; 95% CI: 0.789, 3.283; p=0.227) at their time of parturition, however this relationship was not statistically significant. Late diagnosis of HIV status and immunosuppression associated with pregnancy could explain the higher plasma viral load among this group of women (Gill et al., 2016; Nielsen-Saines et al., 2012; Stinson & Myer, 2012). Many programs have been put in place to encourage HIV surveillance, early detection and prevention of mother to child transmission of HIV (Calmy et al., 2007; Moseholm & Weis, 2020; NASCOP, 2020).

Women enrolled in this study presented with either stage I or II clinical staging of HIV according to the World Health Organization guidelines. Women who had stage II of the disease had a two-fold (OR=2.400; 95% CI: 0.900, 6.401; p=0.152) increased likelihood of having a detectable viral load compared to those with the first stage. Although this relationship was not statistically significant, a higher stage of the disease is often a result of the immune system's inability to regulate viral replication, hence a higher plasma viral load finding (Jobanputra et al., 2015; Levi et al., 2016).

The HAART regimens were classified as protease-based, integrase-based, and non-nucleoside reverse transcriptase-based HAART regimen. Patients on protease-based inhibitors were more likely (OR= 1.913; 95% CI: 0.581, 6.294; p=0.298) to have a detectable viral load compared to those on NNRTI and Integrase-based HAART (Read et al., 2012) but this relationship was not statistically significant. Integrase

inhibitor-based regimen in our setting includes Tenofovir/Lamivudine and Dolutegravir combination ART. Studies had shown a small risk of neural tube defects with Dolutegravir at the time of the study, and it was therefore only started after 8weeks of pregnancy and after counseling of the mother. According to the Kenyan national guidelines on ART 2018, the first line therapy for women and adolescents of childbearing potential was Tenofovir/Lamivudine and Efavirenz (TDF/3TC/EFV) unless the woman is on effective contraception. This has since changed to the current regimen that is Dolutegravir (DTG)-based, specifically (TDF/3TC/DTG). Dolutegravir has been shown to have the advantage of dropping the viral load faster, have less drug-to-drug interactions and is generally well tolerated. It also has been shown to have the advantage of having a high genetic barrier to resistance. This has since been changed and the current regimen id DTG based.

A woman's late gestation (>16 weeks) at first antenatal clinic visit increased the likelihood of detectable viral load (OR= 2.104; 95% CI: 0.939, 4.715; p=0.076); however, this relationship was not shown to be statistically significant in the current study. Previous authors (İnkaya et al., 2020), have demonstrated that early ANC visit increases the likelihood of early HAART initiation and use. Furthermore, based on the health education provided to this group of women, there is an increased likelihood of improved HAART adherence. This was also evidenced by the fact women enrolled in this study who did not adhere to their HAART regimen were more likely (OR= 1.282 (0.607, 2.708) to have a detectable viral load. It has been previously documented (Landes et al., 2019) that lack of optimal adherence to HAART treatment is a strong predictor of unsuppressed viral load. In an Option B+ study conducted in Uganda (Mukose et al., 2021), early adherence to HAART among newly diagnosed HIV positive expectant mothers initiated on HAART was 76.8%. This low HAART

adherence, soon after treatment initiation, was reported to be worrying as the women were expected to be more motivated to comply with their treatment as part of prevention of mother to child transmission cascade. Multiple factors were associated with this low adherence level such as HAART related side effects, lack of partner disclosure and the perception that the newborn will be safe post-delivery (Mukose et al., 2021). In Rwanda (Musiime et al., 2011), a HAART adherence rate of 91% was reported; a proportion that was higher than many other African countries under comparison. This stark variation could also be attributed to the temporal difference on when the current and the study in Rwanda were conducted. Furthermore, the difference in data collection approaches could be attributed. In Rwanda, the authors used therapeutic drug monitoring approaches including pill count for the patients on a Triomune single-pill fixed dose combinations of stavudine, lamivudine and nevirapine (Musiime et al., 2011), while the current study used a 7-day recall approach. This could portend a recall bias to the current study participants. In the event of a treatment resistance, the clinical guidelines recommend a regimen change (Nielsen-Saines et al., 2012; Read et al., 2012). In Benin (Denoeud-Ndam et al., 2013), Women with a gestation more than 21 weeks at enrollment were less likely (OR=0.61; 95% CI: 0.34, 1.10) to have undetectable viral load. A high antenatal attendance: if the women had attended more than four antenatal visits during pregnancy was associated (OR=3.55; 95% CI: 1.30, 9.72) with increased likelihood of undetectable viral load (Denoeud-Ndam et al., 2013) though not statistically significant.

Women who are consistent with their overall HIV comprehensive care will have their regimen promptly changed when indicated to improve the clinical outcome, in the event of a treatment failure due to drug resistance. In this study, women who had never had a HAART regimen change, had an increased likelihood (OR= 1.583; 95%

CI: 0.579, 4.330) of presenting with a detectable viral load compared to those who had their regimen changed at any point of their HIV treatment period. This lack of change could be attributed to either recent treatment initiation or hence a short duration of HAART use to warrant any change (Aziz et al., 2013; Chibwesha et al., 2011; Musiime et al., 2011).

This study determined that lack of partner disclosure of HIV status increased the likelihood of a woman presenting with a detectable viral load at the point of delivery, however, this relationship was not statistically significant. Contrasting findings were reported in Rwanda (Gill et al., 2016) where women who had not disclosed their HIV status to their sexual partners were two times (OR=2.11; 95% CI: 1.51, 2.95) significantly (p<0.001) more likely to have a detectable viral load. Similarly, lack of HIV disclosure significantly increased the likelihood of detectable viral load in a study conducted in Kinshasa- Democratic Republic of Congo (Yotebieng et al., 2019).

In a study conducted in Busia County (Makwaga et al., 2020), majority of the patients with treatment resistance were on TDF+3TC+EFV regimen. Although majority of the patients on HAART in both this study and in the country were on this regimen, both the current study and the one conducted in Busia still reported a higher treatment failure rate for this cohort of HIV infected patients. This creates a need for routine HAART resistance testing to improve treatment outcomes.

There is need to initiate women on HAART prior to conception because of its multiple benefits. They should be chosen based on the woman's pregnancy related issues, treatment tolerance as well as prior information on adherence to treatment so as to ensure continuity between pre-conception and prenatal care (Mandelbrot et al., 2015). These medications provide additional benefit by protecting male partner in the

conception attempt. The authors (Mandelbrot et al., 2015) reported no perinatal transmissions in women who received preconception ART, continued throughout pregnancy and delivered with viral load of <50 copies/ml.

In this study, when duration of HAART use was stratified, women who had been on HAART for not more than three years had an increased likelihood (OR=1.773; 95% CI: 0.712, 4.413; p=0.239) of presenting with detectable viral load compared to those who had been on treatment of more than three years. Although the current study did not find any statistically significant association between duration of HAART use and presenting with a detectable viral load at the time of delivery, this finding matches a retrospective study conducted among 707 women in Brazil (Joao et al., 2012) enrolled between 1996 to 2006 where there was a significantly increased likelihood of detectable viral load among the women who had been on HAART for less than 12 weeks and presenting with a detectable viral load (OR=2.51; 95% 1.72, 3.65). In Gauteng-South Africa (Moyo et al., 2020), there was a four-fold (OR=4.11; 95% CI: 2.20, 7.66) increased likelihood of detectable viral load among expectant women who had a shorter duration (<3 months) of HAART use compared to their counterparts who had been on HAART for 3 or more months. In Kinshasa- Congo (Yotebieng et al., 2019), women who had been on HAART for at least 12 months were more likely to have viral load suppression compared to their counterparts who had used antiretroviral for a shorter duration. The longer the duration of HAART use the greater the likelihood of viral suppression. However, prolonged HAART use (greater than 3 years) predisposes the women to HAART resistance, which could counter the intended benefit of viral suppression. These women have been reported to have a detectable late pregnancy (>28 weeks) viral load (Gill et al., 2016).

In Benin (Denoeud-Ndam et al., 2013), women who did not have impaired HAART adherence were less likely to have a detectable viral load. The authors further noted that the probability of an undetectable plasma viral load was four times higher among those who had been on treatment for 8 weeks or more. These long durations could only be feasible if the treatment was initiated before 28 weeks of gestational (Denoeud-Ndam et al., 2013). In the United Kingdom, the authors (Patel et al., 2007) reported that women with viral loads above 10,000 copies/ml at initiation of treatment, the probability of achieving undetectable viral loads (<50copies/ml) was reduced by initiating HAART after 20.4 weeks gestation.

This study did not find any significant association between a woman's gravidity, level of education, marital status, partner disclosure and detectable HIV viral load at delivery. This is despite the median gravidity in this study of 3.0 (IQR: 1.0, 8.0) being comparable to studies conducted in Kenya's Southern Nyanza region (Turan et al., 2015) and Malawi (Landes et al., 2021) at 3.0 (IQR: 2.0, 4.0). This similarity in gravidity could be attributed to the fact that both this study and that in Southern Nyanza (Turan et al., 2015) were both conducted in Western Kenya. Similarly, there is a lot of sociodemographic similarities between Malawi and Kenya as was evidenced by comparable median gravidity.

Secondly, the highest proportion (40.7%) of the new mothers enrolled in this study had attained a primary school level of education followed by those with a secondary education at 33.6%. This finding is lower than that reported in Rwanda where 60.2% (Gill et al., 2016) had a primary level of education. Socioeconomically, Kenya is ranked higher than Rwanda and this could explain the higher literacy levels in Kenya compared to Rwanda. Although Kenya has a higher literacy level than most African

countries, in very rural communities such as those found in the islands of Lake Victoria, the literacy levels are much lower. This was evidenced by the findings reported in the study conducted in Southern Nyanza where 85% of the women enrolled had some primary or no education at all (Turan et al., 2015). This rural population had a much higher proportion of women with basic education compared to the predominantly urban population living in Eldoret that reported a much higher proportion of women with an advanced level of education.

Lastly, more than two thirds (67.9%) of those enrolled were married a proportion like that reported in Rwanda where 79.1% of the 608 women enrolled and followed prospectively reported to be married. However, the proportion of married women enrolled in this study is much higher than the national averages from the Kenya AIDS indicator survey (KAIS) conducted in 2012 (Cherutich et al., 2016). From the review of the findings, the authors (Cherutich et al., 2016) noted that 29.6% of the participants claimed to be single while 25.9% were married or cohabiting. This variation in study findings could be attributed to the whole population difference compared to a specific demographic targeted. When you only review a specific demographic (such as expectant women), certain proportions may be higher than those of an entire population as was the case in the proportion of married women. In another randomized controlled trial (RCT) conducted in the Southern Nyanza region within Western Kenya between 2009 and 2011 (Turan et al., 2015), 84% of the women enrolled into the PMTCT program were either married or cohabiting, a proportion which is much higher than the current study. This variation could be attributed to the difference in the target population. The southern Nyanza population was more rural compared to the urban population of the women enrolled in this study from Eldoret.

5.3. Study Strengths and Limitations

5.3.1 Study Strengths

1. This is the first local study assessing detectable viral load status at delivery and its associated factors among HIV infected pregnant women.

2. All samples were analysed at one laboratory.

5.3.2 Study Limitations

1. Since this was a cross-sectional study, it did not assess the relationship between maternal viremia and infant outcomes.

2. This was a hospital-based study, and the findings may not be generalizable to the entire population.

CHAPTER SIX

6.0 CONCLUSIONS AND RECOMMENDATIONS

6.1 Conclusions

This is the first local study assessing detectable viral load status at delivery and its associated factors among HIV infected pregnant women; to inform PMTCT strategies. From the findings of this study that enrolled 140 HIV infected women delivering at Riley Mother and Baby Hospital in Eldoret-Kenya, we infer the following conclusions:

i   The prevalence of detectable viral load at delivery reported among HIV infected women is 17.9% with 94% of those with detectable viral load of more than 1000 copies/ml delivering vaginally.

ii   The significant predictor of detectable viral load was having moderate or severe HAART related side effects.

6.2 Recommendations

To eliminate HIV mother-to-child transmission, there is need for sustained suppression of plasma viral load during pregnancy, delivery and breastfeeding among women living with HIV. From the findings of this study, the following are the recommendations:

i.   There is need to institute pre-labor (34 to 36 weeks gestation) viral load assessment for all HIV infected pregnant women and schedule elective caesarean sections for those with viral load of more than 1000 copies per ml.

ii.   There is need to enhance counselling of HIV positive pregnant women on possible side effects of HAART and how to manage those side effects; especially in view of the unique challenges that pregnancy physiology brings along.

iii.   Future prospective studies should be conducted to determine infant outcomes and their relationship to maternal viremia.

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APPENDICES

APPENDIX I: BUDGET

Items	Quantity	Unit Price (Kshs)	Total (Kshs)
Stationery and Equipment			
Printing Papers	5 reams	500.00	2500.00
Writing Pens	10	20.00	200.00
Box Files	2	200.00	400.00
Document Wallets	2	50.00	100.0
Subtotal			**3,200.00**
Research Proposal Development			
Printing drafts & final proposal	6 copies	500.00	3000.00
Photocopies of final proposal	6 copies	250.00	900.00
Binding of copies of proposal	6 copies	250.00	900.00
Subtotal			**4,800.00**
Personnel			
Biostatistician	1	35000.00	45000.00
Research assistants	2	15000.00	30000.00
Subtotal			**75,000.00**
Communication			**1,000.00**
Laboratory Charges			
Hiv viral load	140	4000.00	**561,000.00**
Subtotal			**561,000.00**
Thesis Development			
Printing of drafts and final thesis	6 copies	800.00	4800.00
Photocopy of final thesis	6 copies	250.00	900.00
Binding of thesis	6 copies	300.00	1800.00
Subtotal			**7,500.00**
Total			
Miscellaneous Expenditure (2% of Total)			**13000.00**
Grand Total			**664,500.00**

Note.

The intrapartum maternal viral load was done and not abstracted from the file. The cost for this was met by the principal investigator.

APPENDIX II: TIME FRAME

ACTIVITY	NOV 2017	DEC 2017-FEB 2018	MAR-MAY 2018	SEP 2019		DEC 2021	FEB 2022	MAR 2022	APRIL 2022	MAY 2022	JUNE 2022
Proposal Submission to IREC	■										
IREC Review		■									
Piloting of data collection tools			■								
Finalization of data collection tools			■								
Data Collection				■	■	■	■	■			
Data entry and Analysis									■		
Thesis Write up (Results, discussion)									■		
Notice of intent to submit									■	■	
Mock defense										■	
Thesis submission										■	
Thesis Defense and Presentation											■

APPENDIX III: INFORMED CONSENT FORM

My name is Susan J. Matetai. I am currently pursuing a master's degree in medicine-

Reproductive health at Moi University. I'm doing a study on the factors associated with detectable viral load at delivery among HIV infected women delivering at RMBH. You are among many women that have been considered to be part of this study. I wish to ask you questions about your socio demographic and reproductive health characteristics, obtain a viral load sample from you. You are free to participate in this study and have the right to opt out. If you opt out your management in the hospital will not be affected in any way. You will benefit from the study by knowing the factors associated with a detectable at delivery and this will improve your HIV care and that of other infected pregnant women from the findings of the study. The purpose of this study is to identify what proportion of HIV infected pregnant women at MTRH have detectable viral load and assess the predictors of detectable viral load at delivery which can be addressed to reduce risk for transmission to your child. There are no risks in the study except for a little pain may be experienced on removal of the viral load sample for you. By agreeing to participate you will be agreeing for information on your child to be collected too.

CONFIDENTIALITY OF INFORMATION

Your participation in this study will not affect in any way the treatment plan that your doctors have planned for you. Your decision to participate will not change or prejudice your care in this hospital. Information gathered will be treated with utmost confidentiality; your identity will be protected, and your name will not be used anywhere in this study.

This study has been approved by the Institutional Research and Ethics Committee (IREC) of Moi University and the Moi Teaching and Referral Hospital Board.

For any question or further clarification, please feel free to contact me on 0720612206 or contact the chairperson of IREC, MOI TEACHING AND REFERAL HOSPITAL BUILDING, second floor room 219 P.O BOX 3-30100 ELDORET, Phone number 0787723677.

YOUR CONSENT:

Adults aged 18yrs and above I have been adequately informed that am being recruited into a study to determine the relationship between maternal HIV viral load at delivery and infant outcomes at six weeks. The investigator has also informed me that my participation in this study is voluntary and will not exclude me from my routine care even if I opt out.

 Sign …………………Date………….

Phone number.….…………………….

Kiswahili

CHETI CHA KUTOA IDHINI KWA HIARI

Jinalanguni   Susan   Matetai.   Kwa sasa,
Mimi ni mwanafunzi wa shahada ya afya ya uzazi katika   Chuo   Kikuu   cha
Moi. Ninafanya utafiti juu ya uhusiano wa kiwango cha virusi vya HIV katika damu
ya mama wakati wa kuzaa, na sababu ambazo zinasababisha kuonekana kwa virusi
kwa kiwango cha Zaidi ya ile ya chini Zaidi kwenye maabara yetu ya Ampath hapa
MTRH. Wewe ni mmoja ya wanawake wengi ambao wamefikiriwa kuhusika katika
utafiti huu. Ningependa kukuuliza maswali juu ya jamii na afya yako ya uzazi kisha
utatolewa sampuli ya damu ya kupima kiwango cha virusi vya

HIv. Unao uhuru wa kushiriki katika utafiti huu na unaweza kujiondoa. Ukijiondoa,
Matibabu yako katika hospitali haitaathirika vyovyote.

Sababu ya utafiti huu ni kuweza kujua ni sababu gani zinazochangia wanawake
wajawazito walio na virusi vya HIV kuwa na kiwango cha juu cha virusi ili kujua ni
nini kitaangaliwa kwa kina mama kwa kina kusaidia kurudisha chini virusi hivyo.
Utafiti huu utakusaidia kujua kiwango chako cha virusi wakati wa kuzaa na sababu
zinazochangia kiwango cha juu cha virusi. Ukikubali kuhusika, utakua umetoa idhini
yako na mwanao.   Hakuna athari zozote katika utafiti huu isipokuwa uchungu
mdogo wakati wa kutoa sampuli ya damu kwako.

USIRI WA HABARI

Kushiriki kwako katika huu utafiti hautaadhiri kwa njia yoyote mpango wa matibabu
ambao madaktari wamekupangia. Kukubali kwako kushiriki au kutokubali
hakutaadhiri matibabu yako katika hosipitali hii. Taarifa zitakazopatikana zitawekwa
fiche, na hazitatambulishwa kwa vyovyote. Jina lako halitatumiwa popote katika
utafiti huu.

Utafiti huu umeidhinishwa na Kikao cha Maadili na Utafiti cha Chuo Kikuu cha Moi (IREC).Kwa ufafanuzi au swali lolote, tafadhali usisite kuwasiliana nami kwenye nambari hii: 0720612206 au kuwasiliana na Mwenyekiti wa IREC,JENGO LA MOI TEACHING AND REFERAL HOSPITAL,OROFA YA PILI -CHUMBA 219, S.L.P 3-30100, ELDORET.

IDHINI YAKO

Kwa watu wazima wenye umri wa miaka 18 na Zaidi

Nimeelezwa kikamilifu kwamba nasajiliwa katika utafiti kuhusu uhusiano wa kiwango cha virusi vya HIV kwa mama wakati wa kuzaa na sababu zinazochangia kiwango cha juu cha virusi

Mtafiti pia amenieleza kwamba kushiriki kwangu katika huu utafiti ni kwa hiari na hutaadhiri matibabu yangu hatanikijiondoa.

Sahihi…………..Tarehe…………...

NAMBARI YA SIMU- …………………..

APPENDIX IV: QUESTIONNAIRE

<u>**PART I**</u>

Interview number………………………………….Date…………………………………

<u>**DEMOGRAPHIC DATA**</u>

Age(yrs).......................................

Marital status- Single ⬜ Married ⬜ Separated ⬜ Widowed ⬜

Highest level of Education- None ⬜ Primary ⬜ Secondary ⬜ Tertiary ⬜

Occupation- Student ⬜ Unemployed ⬜ Farming ⬜ Business ⬜ Casual ⬜ Formal ⬜ Other ⬜

Religion- Christian ⬜ Muslim ⬜ None ⬜ Other ⬜

OBSTETRIC HISTORY

Parity...........................

LNMP………………. EDD…………………. GDB………………………….

Gestation at delivery (weeks).................................

Gestation at 1st ANC visit(weeks).......................

Number of ANC visits................................ANC profile done Yes ⬜ No ⬜

ANC profile

Blood group- O ⬜ A ⬜ B ⬜ AB ⬜

Rhesus Positive ⬜ Negative ⬜

VDRL status Reactive Treated Reactive not treated Non-reactive ⬜

Partner Company to ANC clinic; Never ⬜ Once ⬜ More than once ⬜

Hospital admission in this pregnancy Yes ⬜ No ⬜

Hospital admission in this pregnancy Yes No

Illness in this pregnancy (Circle where appropriate)

(Hypertension, Anaemia, Opportunistic Infections, Others- diabetes, DVT, malaria, obstetric complication, etc.)

MEDICAL EXAMINATION

Weight (kgs)……………………………**Height (m)**………………………

Blood pressure(mm/hg). systolic……………/ diastolic……………

Temperature (degrees Celsius.) ....

Pulse rate(bpm)...........................

Respiratory rate (breaths/min) ....

General examination (circle what is appropriate)

(Pallor, Jaundice, Cyanosis, Lymphadenopathy, Thrush, Oedema, Dehydration)

HIV History

Diagnosis In this pregnancy ☐ Known Positive ☐ ☐

WHO clinical stage (Appendix V): Stage I ☐ Stage II ☐ Stage III ☐ Stage IV

Duration of HAART (months).....................

Current regimen (Tick appropriately)

1. (AZT+3TC+NVP)
2. (AZT+3TC+EFV)
3. (AZT+3TC+LPV/r)
4. (TDF+3TC+NVP)
5. (TDF+3TC+LPV/r)
6. (TDF+3TC+LPV/r)
7. (TDF+3TC+EFV)
8. (AZT+3TC+ATV/r)
9. (TDF+3TC+ATVr)
10. (TDF+3TC+DTG)

Ever changed regimen Yes ☐ No ☐

Protease Inhibitor (PI) based regimen currently Yes ☐ No ☐

Adherent

Yes (missed no dose in last 7days) ⬓

No (missed pill in the last 7 days) ⬓

Partner HIV Status Positive ⬓ Negative ⬓

Partner on HAART Yes ⬓ No ⬓ Sero discordant ⬓

Partner Disclosure Yes ⬓ No ⬓

If no, reason why?

………………………………………………………………………………………

Partner Occupation

Unemployed ⬓ farming ⬓ Casual ⬓ Business ⬓ Formal ⬓

Last CD4 count (cell/mm³) ....

Last viral load (copies/ml) ....

Date done ……………...

Side effects to drugs

Mild (tolerable, doesn't affect daily activities) ⬓

⬓

Moderate (doesn't affect adherence) ⬓

Severe (affects adherence) ⬓

Delivery

Viral load at delivery (copies/ml) ....

Mode of delivery SVD ⬓ ELCS ⬓ EMCS ⬓ AVD ⬓ Episiotomy

Duration of labour (hours)...........................

Duration of membrane rupture (hours)..............

Outcomes of labour and infant outcomes

Live birth ⬓ Still birth ⬓

Apgar score at 5minutes.................................

Baby admitted to NBU Yes ⬓ No ⬓

Baby Died Yes ⬓ No ⬓

Birth weight (Grams)...................

Estimated blood loss (mls)…...........

Documented vaginal examinations......................

Assisted vaginal delivery (vacuum/Episiotomy) done Yes ⬭ No ⬭

Infant prophylaxis given

AZT only ⬭ NVP only AZT and NVP ⬭ None ⬭

Reason for not getting both drugs……………………………………………………………

Infant hospital duration of stay after delivery (days)....................

Maternal hospital duration of stay after delivery (days)...........

APPENDIX V: WHO CLINICAL STAGING FOR HIV

CLINICAL STAGE 1

- Asymptomatic
- Persistent generalised lymphadenopathy

CLINICAL STAGE 2

- Moderate and unexplained weight loss (less than 10% of presumed or measured body weight)
- Recurrent respiratory tract infections (such as sinusitis, bronchitis, otitis media, pharyngitis)
- Herpes Zoster
- Recurrent oral ulcerations
- Papular pruritic eruptions
- Angular Cheilitis
- Seborrheic dermatitis
- Onychomycosis (fungal nail infections)

CLINICAL STAGE 3

- Unexplained chronic diarrhoea for longer than one month
- Severe weight loss (> 10% of presumed or measured body weight)
- Unexplained persistent fever (intermittent or constant for longer than one month)
- Oral candidiasis
- Oral hairy leucoplakia
- Pulmonary Tuberculosis (TB) diagnosed in last two years
- Severe presumed bacterial infections (e.g., pneumonia, empyema, meningitis, bacteraemia, pyomyositis, bone or joint infection)
- Acute necrotizing ulcerative stomatitis, gingivitis, or periodontitis
- Unexplained anaemia (hb< 8g/dl, and /or neutropenia (<500/ul) for more than on month

CLINICAL STAGE 4

- HIV wasting syndrome
- Pneumocystis pneumonia
- Recurrent severe or radiological bacterial pneumonia
- Chronic Herpes simplex infection (orolabial, genital, anorectal of more than one month's duration)

- Oesophageal Candidiasis

- Extra pulmonary Tuberculosis

- Kaposi's Sarcoma

- Central nervous System Toxoplasmosis

- HIV Encephalopathy

- Extra pulmonary Cryptococcosis

- Disseminated non-tuberculous mycobacteria infection

- Progressive multifocal leukoencephalopathy

- Candida of trachea, bronchi or lungs

- Cryptosporidiosis

- Isosporiasis

- Visceral herpes simplex infection

- Cytomegalovirus (CMV) infection, (retinitis or of any organ other than the liver spleen or lymph nodes)

- Any disseminated mycosis (e.g., Histoplasmosis, Coccidiomycosis, Penicilliosis)

- Recurrent non-typhoidal salmonella septicaemia

- Lymphoma (cerebral or B cell non Hodgkin)

- Invasive cervical carcinoma

- Visceral Leishmaniasis

APPENDIX VI: IREC APPROVAL

MTRH/MU-INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE (IREC)

MOI TEACHING AND REFERRAL HOSPITAL
P.O. BOX 3
ELDORET
Tel: 33471//2/3

MOI UNIVERSITY
COLLEGE OF HEALTH SCIENCES
P.O. BOX 4606
ELDORET
Tel: 33471/2/3

Reference: IREC/2017/233
Approval Number: 0002060

1st March, 2022

Dr. Susan Jepchirchir Matetai,
Moi University,
School of Medicine,
P.O. Box 4606-30100,
ELDORET-KENYA.

Dear Dr. Matetai,

RE: CONTINUING APPROVAL

The Moi Teaching and Referral Hospital/Moi University College of Health Sciences- Institutional Research and Ethics Committee has reviewed your request for continuing approval to your study titled:-

"Detectable Viral Load at Delivery and Factors Associated among Pregnant HIV Positive Women Delivering at Riley Mother and Baby Hospital Eldoret, Kenya".

Your proposal has been granted a Continuing Approval with effect from 1st March, 2022. You are therefore permitted to continue with your study.

Note that this approval is for 1 year; it will thus expire on 28th February, 2023. If it is necessary to continue with this research beyond the expiry date, a request for continuation should be made in writing to IREC Secretariat two months prior to the expiry date.

You are required to submit progress report(s) regularly as dictated by your proposal. Furthermore, you must notify the Committee of any proposal change (s) or amendment (s), serious or unexpected outcomes related to the conduct of the study, or study termination for any reason. The Committee expects to receive a final report at the end of the study,

Sincerely,

PROF. E. WERE
CHAIRMAN
INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE

INSTITUTIONAL RESEARCH & ETHICS COMMITTEE
1 4 MAR 2022
APPROVED
P.O. Box 4606-30100 ELDORET

cc: CEO   -   MTRH
      Principal -   CHS
      Dean   -   SOM
      Dean   -   SPH
      Dean   -   SOD
      Dean   -   SON

INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE (IREC)

MOI TEACHING AND REFERRAL HOSPITAL
P.O. BOX 3
ELDORET
Tel: 33471//2/3

MOI UNIVERSITY
COLLEGE OF HEALTH SCIENCES
P.O. BOX 4606
ELDORET
Tel: 33471/2/3

1st March, 2020

Reference: IREC/2017/233
Approval Number: 0002060

Dr. Susan Jepchirchir Matetai,
Moi University,
School of Medicine,
P.O. Box 4606-30100,
ELDORET-KENYA.

Dear Dr. Matetai,

RE: CONTINUING APPROVAL

The Institutional Research and Ethics Committee has reviewed your request for continuing approval to your study titled:-

"Association between Intrapartum Maternal HIV Viral Load and Infant HIV Status at Six Weeks Postpartum for Women Delivering at MTRH, Eldoret, Kenya".

Your proposal has been granted a Continuing Approval with effect from 1st March, 2020. You are therefore permitted to continue with your study.

Note that this approval is for 1 year; it will thus expire on 28th February, 2021. If it is necessary to continue with this research beyond the expiry date, a request for continuation should be made in writing to IREC Secretariat two months prior to the expiry date.

You are required to submit progress report(s) regularly as dictated by your proposal. Furthermore, you must notify the Committee of any proposal change (s) or amendment (s), serious or unexpected outcomes related to the conduct of the study, or study termination for any reason. The Committee expects to receive a final report at the end of the study.
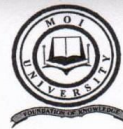
Sincerely,

PROF. E. WERE
CHAIRMAN
INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE

cc: CEO   -   MTRH
        Principal -   CHS
        Dean   -   SOM
        Dean   -   SPH
        Dean   -   SOD

INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE (IREC)

MOI TEACHING AND REFERRAL HOSPITAL
P.O. BOX 3
ELDORET
Tel: 33471//2/3

MOI UNIVERSITY
COLLEGE OF HEALTH SCIENCES
P.O. BOX 4606
ELDORET
Tel: 33471/2/3

1st March, 2019

Reference: IREC/2017/233
Approval Number: 0002060

Dr. Susan Jepchirchir Matetai,
Moi University,
School of Medicine,
P.O. Box 4606-30100,
ELDORET-KENYA.

INSTITUTIONAL RESEARCH &
ETHICS COMMITTEE
0 1 MAR 2019
APPROVED
P.O. Box 4606-30100 ELDORET

Dear Dr. Matetai,

RE: CONTINUING APPROVAL

The Institutional Research and Ethics Committee has reviewed your request for continuing approval to your study titled:-

"Association between Intrapartum Maternal HIV Viral Load and Infant HIV Status at Six Weeks Postpartum for Women Delivering at MTRH, Eldoret, Kenya".

Your proposal has been granted a Continuing Approval with effect from 1st March, 2019. You are therefore permitted to continue with your study.

Note that this approval is for 1 year; it will thus expire on 28th February, 2020. If it is necessary to continue with this research beyond the expiry date, a request for continuation should be made in writing to IREC Secretariat two months prior to the expiry date.

You are required to submit progress report(s) regularly as dictated by your proposal. Furthermore, you must notify the Committee of any proposal change (s) or amendment (s), serious or unexpected outcomes related to the conduct of the study, or study termination for any reason. The Committee expects to receive a final report at the end of the study.

Sincerely,

DR. S. NYABERA
DEPUTY-CHAIRMAN
INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE

cc: CEO   -   MTRH
        Principal -   CHS
        Dean   -   SOM
        Dean   -   SPH
        Dean   -   SOD

MTRH/MU-INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE (IREC)

MOI TEACHING AND REFERRAL HOSPITAL
P.O. BOX 3
ELDORET
Tel: 33471//2/3

MOI UNIVERSITY
COLLEGE OF HEALTH SCIENCES
P.O. BOX 4606
ELDORET
Tel: 33471/2/3

14th March, 2022

Reference: IREC/2017/233
Approval Number: 0002060

Dr. Susan Jepchirchir Matetai,
Moi University,
School of Medicine,
P.O. Box 4606-30100,
ELDORET-KENYA.

Dear Dr. Matetai,

RE: APPROVAL OF AMENDMENT

The Moi Teaching and Referral Hospital/Moi University College of Health Sciences- Institutional Research and Ethics Committee has reviewed the amendment made to your proposal titled:-

"Detectable Viral Load at Delivery and Factors Associated among Pregnant HIV Positive Women Delivering at Riley Mother and Baby Hospital Eldoret Kenya"

We note that you are seeking to make amendments as follows:-

- To change the study title to above from *"Factors Associated with Detectable Viral Load at Delivery among HIV Positive Women at Riley Mother and Baby Hospital Eldoret Kenya".*
- To change the study design from prospective cohort to cross sectional study.
- To change sample size from sample size of 97 for each cohort to 140 for the study population.
- To change broad objective to assess the extent of viral suppression and factors associated with detectable viral at delivery among HIV infected mothers delivering at RMBH, Eldoret, Kenya.
- To change specific objectives to (i) To determine the patients characteristics of pregnant HIV infected women delivering at RMBH. (ii) To determine the proportion of pregnant women with detectable viral load among HIV infected pregnant women delivering at RMBH. (iii) To assess the factors associated with detectable viral load among HIV infected pregnant women delivering at RMBH.

The amendments have been approved on 14th March, 2022 according to SOP's of IREC. You are therefore permitted to continue with your research.

You are required to submit progress(s) regularly as dictated by your proposal. Furthermore, you must notify the Committee of any proposal change(s) or amendment(s), serious or unexpected outcomes related to the conduct of the study, or study termination for any reason. The Committee expects to receive a final report at the end of the study.

INSTITUTIONAL RESEARCH &
ETHICS COMMITTEE

1 4 MAR 2022
APPROVED
P. O. Box 4606 - 30100 ELDORET

Sincerely,

PROF. E. WERE
CHAIRMAN
INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE

cc:	CEO	-	MTRH	Dean	-	SPH	Dean	-	SOM
	Principal	-	CHS	Dean	-	SOD	Dean	-	SON

INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE (IREC)

MOI TEACHING AND REFERRAL HOSPITAL
P.O. BOX 3
ELDORET
Tel: 33471//2/3

MOI UNIVERSITY
COLLEGE OF HEALTH SCIENCES
P.O. BOX 4606
ELDORET

Reference: IREC/2017/233
Approval Number: 0002060

1st March, 2018

Dr. Susan Jepchirchir Matetai,
Moi University,
School of Medicine,
P.O. Box 4606-30100,
ELDORET-KENYA.

INSTITUTIONAL RESEARCH &
ETHICS COMMITTEE

0 1 MAR 2018

APPROVED
P. O. Box 4606 - 30100 ELDORET

Dear Dr. Matetai,

RE: FORMAL APPROVAL

The Institutional Research and Ethics Committee has reviewed your research proposal titled:-

"Association between Intrapartum Maternal HIV Viral Load and Infant HIV Status at Six Weeks Postpartum for Women Delivering at MTRH, Eldoret, Kenya".

Your proposal has been granted a Formal Approval Number: *FAN: IREC 2060* on 1st March, 2018. You are therefore permitted to begin your investigations.

Note that this approval is for 1 year; it will thus expire on 28th February, 2019. If it is necessary to continue with this research beyond the expiry date, a request for continuation should be made in writing to IREC Secretariat two months prior to the expiry date.

You are required to submit progress report(s) regularly as dictated by your proposal. Furthermore, you must notify the Committee of any proposal change (s) or amendment (s), serious or unexpected outcomes related to the conduct of the study, or study termination for any reason. The Committee expects to receive a final report at the end of the study.

Sincerely,

PROF. E. WERE
CHAIRMAN
INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE

cc	CEO	-	MTRH	Dean	-	SOP	Dean	-	SOM
	Principal	-	CHS	Dean	-	SON	Dean	-	SOD

APPENDIX VII: HOSPITAL APPROVAL

IREC/2017/233

An ISO 9001:2015 Certified Hospital

MOI TEACHING AND REFERRAL HOSPITAL

Telephone:(+254)053-2033471/2/3/4
Mobile: 722-201277/0722-209795/0734-600461/0734-683361
Fax: 053-2061749
Email: ceo@mtrh.go.ke/directorsofficemtrh@gmail.com

Nandi Road
P.O. Box 3 – 30100
ELDORET, KENYA

Ref: ELD/MTRH/R&P/10/2/V.2/2010

8th March, 2018

Dr. Susan Jepchirchir Matetai
Moi University,
School of Medicine,
P.O. Box 4606-30100,
ELDORET-KENYA.

APPROVAL TO CONDUCT RESEARCH AT MTRH

Upon obtaining approval from the Institutional Research and Ethics Committee (IREC)

to conduct your research proposal titled:-

"Association between Intrapartum Maternal HIV Viral Load and Infant HIV Status at Six Weeks Postpartum for Women Delivering at Moi Teaching and Referral Hospital, Eldoret, Kenya".

You are hereby permitted to commence your investigation at Moi Teaching and Referral Hospital.

MOI TEACHING AND REFERRAL HOSPITAL
C E O
APPPOVED
0 8 MAR 2018
SIGN

DR. WILSON K. ARUASA, *MBS*
CHIEF EXECUTIVE OFFICER
MOI TEACHING AND REFERRAL HOSPITAL - 30100, ELDORET

cc - DCEO, (CS)
   - Director of Nursing Services (DNS)
   - HOD, HRISM

All correspondence should be addressed to the Chief Executive Officer
Visit our Website: www.mtrh.go.ke
A WORLD CLASS TEACHING AND REFERRAL HOSPITAL