PREDICTORS OF ADVERSE PREGNANCY- FETAL OUTCOMES AND THE ASSOCIATION WITH MATERNAL HIV- IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME AMONG WOMEN ATTENDING SELECTED PUBLIC HOSPITALS, NAIROBI, KENYA

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Predictors of Adverse Pregnancy-Fetal Outcomes and the Association with Maternal HIV Immune Reconstitution Inflammatory syndrome among Women Attending Selected Public Hospitals, Nairobi, Kenya

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DECLARATION

This thesis is my original work and has not been presented for a degree in any other university

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DEDICATION

I dedicate this piece of work to Almighty Heavenly God who enables me to overcome all the hurdles in life at my point of weakness. I also dedicate this research paper to my dear wife, Margaret, and daughters (Arvenny, Abby, and Amelia), for constant encouragement and prayers when working on it, relatives for giving me moral support to complete this paper. I sincerely thank them for every effort to stand by me and their support throughout my study. God reward them abundantly.

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ABBREVIATION AND ACRONYMS

AIDS	Acquired Immunodeficiency Syndrome
APFOs	Adverse Pregnancy–Fetal Outcomes
ART	Ant-Retroviral Therapy
ART	Antiretroviral Therapy
CCC	Comprehensive Care Center
CI	Confidence interval
CI	Commutative incidence
CDC	Centre for Disease Control
CMV	Cytomegalo-Virus
Daly's	Disability-adjusted life years
ERC	Ethical Review Committee
EDD	Expected Delivery Date
ERC	Ethical Review Committee
HAART	Highly Active Antiretroviral Therapy
HICs	High Income Contries
HIV	Human Immunodeficiency Virus
IRIS	Immune Reconstitution Inflammatory Syndrome

JKUAT	Jomo Kenyatta University of Agriculture and Technology
KDHS	Kenya Demographic and Health Survey
KEMRI	Kenya Medical Research Institute
KNH	Kenyatta National Hospital
KNH-UoN-ERC	Kenyatta National Hospital–University of Nairobi, Ethical Review Committee
LBW	Low Birth Weight
LMICs	Lower Middle Income Contries
MOH	Ministry of Health
MTCT	Mother to Child Transmission
NACOSTI	National Council for Sciences and Technology
NASCOP	National AIDS and STI Control Program
O. Is	Opportunistic Infections
OR	Odds Ratio
PE	Pre-Eclapsia
PTB	Preterm Birth
RR	Relative Risk
SB	Still Birth

SDGs	Sustainable Development Goals
SGA	Small for Gestational Age
SPSS	Statistical Package for Social Sciences
SSA	Sub-Saharan Africa
STD	Sexually Transmitted Diseases
STI	Sexually Transmitted Infection
TB	Tuberculosis
UN	United Nations
UNAIDS	United Nation Program on HIV/AIDS
UNFPA	United Nations Populations Fund
UNICEF	United Nations International Children's Emergency Fund
uRR	Unadjusted Relative Risk
aRR	Adjusted Relative Risk
USA	United States of America
VCT	Voluntary Counseling and Testing
WHO	World Health Organization

DEFINITION OF OPERATIONAL TERMS

Immune Reconstitution Inflammatory Syndrome (IRIS):	A condition seen in some cases of HIV/AIDS associated immune-suppression, in which the immune system begins to recover (in this case, among women intiated on ART for the first time), but then responds to a previously, acquired opportunistic infection with an overwhelming inflammatory response that, paradoxically makes the symptoms of infection worse (Boulougoura *et al*., 2019).
Clinical definition of IRIS:	In HIV infection, it is an exaggerated inflammatory reaction to a disease-causing microorganism that sometimes occurs when, the immune system begins to recover following treatment with antiretroviral (ARV) drugs.immune reconstitution inflammatory syndrome (IRIS) occurs in two forms: "unmasking" IRIS refering to the flare-up of an underlying, previously undiagnosed infection soon after antiretroviral therapy (ART) is started; "paradoxical" IRIS refering to the worsening of a previously treated infection after ART is started. IRIS can be mild or life-threatening (De Sá *et al*., 2020).
Pregnancy outcome:	Types of pregnancy outcomes include live birth (full-term or preterm birth), stillbirth, spontaneous abortion, and induced abortion (Shelke & Jagtap, 2020).
The fetus and fetal outcome:	A fetus is a developing baby beginning in the 11th week of pregnancy and a fetal outcome is the fetal event occurring from 9^{h} week of gestation on wards until delivery.
Adverse pregnancy-fetal outcomes:	These are pregnancy outcomes other than normal live birth which majorly includes preterm birth, stillbirth, and low birth weight) vii. Any birth defects classified according to International Classification of Diseases.

ABSTRACT

With the enhanced rollout of antiretroviral therapy (ART), HIVimmune reconstitution inflammatory syndrome (IRIS) may remain a public health issue of major concern, moreover in pregnancy. In Kenya, no studies on the incidence and predictors for adverse pregnancy-fetal outcomes with IRIS among ART-naïve women. This study sought to estimate the incidence of, and, determine the predictors for adverse pregnancy-fetal outcomes and the association with maternal-HIV-IRIS. With a prospective cohort design, study subjects were recruited and followed from the end of first trimester for six and half months after confirming their HIV status as positive, on ART treatment with a defined case of HIV-IRIS, from two selected Public Hospitals in Nairobi County, Kenya. A total of 204 women from both cohorts were included in the ultimate analysis post subsequent elimination process at a sample ratio of 1:1. The participants were followed until postpartum through delivery stage. Bivariate analyses with a chi-square test was used to measure the association between the variables at p-value < 0.05 and multiple logistic regression was performed to identify the independent predictors of adverse pregnancy-fetal outcomes (APFOs). The APFOs incidence, both cumulative and rate was 26.47% and 0.012 per person's week and 10.78% and 0.0045 per person's week among IRIS cases and non-IRIS cases respectively. The incidence rate of APFOs was higher at delivery time, 164/10000 person's week with a cumulative incidence of 18.6%. Overall, 38 (18.6%) APFOs ocurred, most, at delivery and within two weeks after delivery, with LBW, mostly being noted; LBW (10.8%), PTB (2.9%) and LBW (7.8%), PTB (2.9%) in IRIS and non-IRIS exposed, respectively. Miscarriage was the most common APFO before delivery. Two newborn intensive care unit admissions and one severe newborn jaundice in IRIS and non-IRIS cases respectively were noted within two weeks post-delivery. Over the entire period, IRIS cases had three times, odds of experiencing an APFO compared to non-IRIS cases [OR=3; 95% CI: 1.4-6.4; P=.004], at, bivariate analysis but the multiple logistic regression analysis did not sustain it [AOR=1.6; 95% CI: 0.4-5.8; P =.508], a similar trend of experiencing an APFO at the delivery time among IRIS cases compared to non-IRIS at bivariate analysis [OR=2.5; 95% CI: 1.295-8.121; P=.006]. Other outcome measurement times; at the end of the second trimester and within two weeks after delivery, had [OR=2.1; 95% CI: 0.502-8.482; P=.16] and [OR=2.4; 95% CI: 0.216- 27.286; P=.71] respectively. Multiple logistic regression revealed the HIV-RNA viral load of above 50 copies/ml at baseline [AOR=2.7; 95% CI: 1.2-6.3; P=.017], an hypertensive event implicated by maternal placental syndrome [AOR=0.1; 95% CI: 0.0-1.0; P =.052] and , majorly, the general health of the woman at delivery stage [AOR= 4; 95% CI: 4.0:1.8-9.1; P=.001] as independent predictors of APFOs. This study demonstrates a higher incidence of APFOs with maternal HIV-IRIS diagnosed women. Empirical research should study interventions aimed at minimizing the associated risk factors identified in this analysis for their effects on reducing APFOs incidence. Public health and to an extent, clinical interventions should also target the modifiable risk factors associated with APFOs in ART-naive pregnant women, as an integrative approach with PMTCT, to ameliorate any possible adverse pregnancy-fetal incidences.

CHAPTER ONE

INTRODUCTION

1.1 Background

Pregnancy outcomes refer to life events that occur to a newborn infant from the age of viability (28 weeks) to the first week of life. The transition of a fetus immersed in the amniotic fluid to live outside the womb is not always smooth and can result in an adverse outcome. Adverse pregnancy outcomes are those pregnancy outcomes other than normal live births which majorly include; preterm birth, stillbirth, and low birth weight, which are the major cause of neonatal morbidity, mortality, and long-term physical and psychological problems (Figuero *et al*., 2020). These adverse birth outcomes; prematurity, low birth weight, and stillbirth represent significant problems in both developing and developed countries. Adverse pregnancy-fetal outcomes lead to serious health consequences to the mother and the baby (Yeshialem *et al*., 2017).

Immune Reconstitution Inflammatory Syndrome (IRIS), is an immune recovery disorder referring to pathogen-specific inflammatory responses in HIV after starting or re-initiating anti-retroviral therapy (ART) treatment or changing to an active ART regimen. IRIS is usually associated with an increase in CD4 cell count and a rapid decrease in HIV-RNA viral load. The time of presentation is usually within the first 4 to 8 weeks after initiation of antiretroviral therapy; however, it has occurred weeks after starting and in sequestered sites (Sereti, 2020). For most patients, starting antiretroviral treatment (ART) improves immune responses to a wide range of other opportunistic pathogens (Chen *et al*., 2018).

IRIS describes two distinct outcomes; an exacerbation of partially or completely treated opportunistic diseases, paradoxical IRIS, and an inflammatory response to a previously undiagnosed, often more pronounced than the typical presentation of the opportunistic infection, the unmasking IRIS (Walker *et al*., 2018). HIV-infection rates in women is

generally higher than in men in Africa (Girum *et al*., 2018), and based on several factors, this translates to pregnant women at large. This is associated with adverse birth outcomes such as neonatal mortality, as found in a Kenyan based study (Kaguthi *et al*., 2018).

The disorder, IRIS in HIV-infected patients starting antiretroviral therapy originates from a restored immunity to certain antigens. Paradoxical clinical extremities of a known condition or the appearance of a new condition after initiating therapy usually characterize the syndrome. Mechanisms are; a partial recovery of the immune system or excess immunological responses to pathogenic or antigenic stimuli. The incidence of overall IRIS is not known but depends on the population in question and its existing and underlying opportunistic infections burden. Most frequently associated pathogens linked with immune reconstitution syndrome have been documented in the existing literature. There is currently no stipulated specific treatment option that exists and this solely depends on the underlying infectious agent and its general clinical presentation.

A variety of mycobacterium, viral, fungal, and parasitic opportunistic infections are linked with Immune Reconstitution Inflammatory Syndrome (Nakiwala *et al*., 2018). Mortality related to IRIS is uncommon; however, the associated high morbidity contributes to the burden on the health-care system (Sereti *et al*., 2020). This has become a public health concern, as ART use has been linked with increased IRIS inform of opportunistic and other non-infectious conditions. HIV disease is also coupled with a rapid plasma pro-inflammatory and anti-inflammatory cytokine responses in antiretroviral naive individuals. While ART typically decreases both immune activation and inflammatory markers, there is still currently an evidence that, these markers remain elevated in many HIV infected patients (Osuji *et al*., 2018).

The clinical outlook of each case of IRIS is variable and data from trials has not been published this far to give sound guidelines. Recommendations are based on clinical experience, case reports, case series, and other expert opinions (Murthy *et al*., 2015). To diagnose IRIS, the presence of a new OI or other illness, failure of HIV treatment, and

failure of treatment for a known OI (such as; owing to drug resistance, inadequate treatment, or poor adherence) must be ruled out. The severity of IRIS varies widely, from mild to life-threatening outcomes. Treatment varies according to the specific pathogen and clinical situation but typically includes continuing ART if possible, treating the OI as indicated, and adding anti-inflammatory therapy including corticosteroids as needed (Meya *et al*., 2016).

The presentation is largely a clinical diagnosis, and other conditions must be eliminated, as indicated above. To consider IRIS in the differential diagnosis, clinicians must recognize the clinical findings as typical or atypical of a specific OI and the temporal relationship with treatment (usually after ART initiation, but IRIS may occur with treatment of the OI alone). For example, for a patient with TB who has recently been initiated on ART after responding to treatment of TB, the "red flags" for a diagnosis of IRIS (and not TB progression) would include new or worsening fever, new effusions, and new or worsening lymphadenopathy, in the absence of poor adherence to TB treatment or drug-resistant TB (Narendran *et al*., 2019).

In HIV-infected pregnant women, the administration of ART during pregnancy and/or intrapartum significantly reduces the risk of mother-to-child transmission (MTCT) of HIV (Hurst *et al*., 2015). Although the beneficial effects of antiretroviral (ARV) therapy for preventing mother-to-child transmission are indisputable, studies in developed and developing countries have reported conflicting findings on the association between ART exposure and the adverse birth outcomes. ART also has directly and indirectly been found to significantly contribute to poor pregnancy outcomes (Saleska *et al*., 2018). Also, the subgroup of patients experiences a clinical deterioration as a consequence of the rapid and dis-regulated restoration of antigen-specific immune responses during the treatment (Günthard *et al*., 2016), with studies showing some specific maternal chemistry with triple combination of anti-retroviral agents having moderate adverse pregnancy outcomes (Fowler *et al*., 2015).

Given that the evidence for the occurrence of up to 30 percent of ART responders developing one or more inflammatory syndromes consistent with IRIS (Pérez-Rueda *et al*., 2017), this has the greatest impact in resource-poor countries, where patients are often very immune-deficient, including pregnancy-associated immune-depression and opportunistic pathogens when therapy is commenced (Santosa *et al*, 2019).

Findings from some studies prove an increased relative risk of adverse birth outcomes associated with the use of highly active antiretroviral therapy during pregnancy among women and generaly, poor maternal outcome (Tshivuila-Matala *et al*., 2020). Perinatal deaths account for 7% of the global burden of disease, with developing countries contributing to about 98% of deaths (Chaibva *et al*., 2019). Between 2018 and 2030, it is projected that 27·8 million children will die in their first month of life if each country maintains its current rate of reduction in NMR, particularly in sub-Saharan Africa and south Asia (Hug *et al*., 2019).

Birth outcomes have improved dramatically worldwide in the past 40 years yet, there is still a large gap between the outcomes in developing and developed countries. Human immunodeficiency virus (HIV) infection is likely to have untoward effects on pregnancy and its outcomes where studies have shown that, adverse pregnancy outcomes are significantly associated with HIV positive status (Ikpim *et al*., 2016). HIV infection is associated with adverse pregnancy outcomes such as low birth weight and perinatal mortality. However, the association is conflicted by the effect of antiretroviral therapy (ART) on pregnancy outcomes and it remains unexamined (Twabi *et al*., 2020).

HAART in pregnant African women with advanced HIV disease substantially has reduced mother-to-child transmission, but it is associated with LBW (Rasmussen *et al*., 2020), with findings suggesting that, women treated with combined ART have a higher rate of SGA compared to those untreated women ($P < 0.05$), but without tangible differences in early infant growth being observed among the different treatment regimens (HU *et al*., 2019).

Women and girls in sub-Saharan Africa, the world's region with the largest HIV epidemics are particularly affected. In 2018, women accounted for 59% of new infections among adults over 15 years in the region and figures have remained unchanged since 1995. Being HIV-positive is associated with negative health outcomes, including an increased risk of intrauterine infection. While progress has been made towards increasing HIV-testing during pregnancy and providing antiretroviral therapy for PMTCT, insufficient integration of HIV services into reproductive, maternal, newborn, child, and adolescent health care is a major challenge (Hassan *et al*., 2020).

Antiretroviral therapy during pregnancy is considered the main and most effective method for reducing the vertical transmission of HIV infection. However, there is no consensus over potential associations between antiretroviral therapy and adverse pregnancy-fetal outcomes (Abdi *et al*., 2019). Of the 17 goals in the SDGs, goals number 1, 2, 4, 5, 6, 8, 11, and 13 are indirectly related to maternal and neonatal health, while only goal number 3 explicitly deals with health problems, including maternal and newborn health issues showing a great focus to mitigate maternally, pregnancy and birth-related adverse outcomes (Bali & Taaffe, 2017).

There is a dearth of studies evaluating the incidence and predictors of adverse pregnancy-fetal and the related birth outcomes among HIV-positive ART-naïve pregnant women regarding the association with maternal HIVimmune reconstitution inflammatory syndrome in Kenya.

1.2 Statement of the problem

While antiretroviral therapy (ART) during pregnancy is considered the main and most effective method of reducing the risk of vertical transmission of infection, this method might be associated with fetal consequences such as preterm delivery, low birth weight, decreased neural function, and low APGAR score (Abdi *et al*, 2019). There is also lack of consensus over the relationship between ART during pregnancy and fetal

complications and, consequently, with a significant population of HIV-positive women of reproductive age which may implicate simi pregnancy outcomes despite PMTCT.

Past research on the relationship between pregnancy complications in HIV-infected women with or without ART have also yielded inconsistent findings (Sebikari *et al*., 2019), in which IRIS could be a key role factor in this relationship. Antiretroviral therapy use in pregnancy has proven to be associated with adverse pregnancy outcomes including preterm birth, low birth weight and small for gestational age infants. However, there are conflicting findings in the existing research with respect to the specific inter-play between ART and HIV infection, that is, IRIS. This may be related to other factors and the confounding of maternal HIV infection and ART effects on immune responses.

There has been findings showing that a significant association exists between HIV infection and anemia, antenatal and postpartum infections, lower maternal weight gain, cesarean section, low birth weight in neonate and duration of neonatal hospitalization (Manogna *et al*., 2017), a phenomena which silently could be propelled by the interaction between ART and HIV, that is; the immune reconstitution inflammatory syndrome, as evidenced in the recent past in a multi-site, multifactorial PROMISE trial which found that, antiretroviral therapy in pregnancy reduced vertical transmission, but also increased the frequency of several adverse birth outcomes (Fowler *et al*., 2016).

A fundamental change in management approach of HIV with earlier initiation of ART is expected to decrease the burden of HIV in developed countries (WHO, 2016); however, with the enhanced roll out of ART following PMTCT inception in recent years and the associated burden of opportunistic infections in developing countries (AVERT, 2020), IRIS may remain a public health area of major concern especially in pregnancy, compromising realization of SDGs related to maternal and child health, mostly, reduction of neonatal mortality. There is increasing evidence of the benefits of ART given to pregnant women (Sebitloane & Moodley, 2017); however, there is a paucity of data that distinguishes HIV or ART as the cause or exacerbation of preëxisting medical conditions or conditions specific to pregnancy with more than 10% of the global disease

burden being due to pregnancy complications, adverse pregnancy, and, related birth outcomes (Sina, 2017).

Despite the recent advances in obstetrics medicine, pregnancy complications and adverse birth outcomes are a growing public health concern and an economic burden on the health-care system. Perinatal deaths account for 7% of the global burden of disease, with developing countries contributing to about 98% of deaths (Tichenor & Sridhar, 2020). An estimated 220,000 adverse pregnancy-fetal outcomes among women with probable infections have been experienced in Africa as an aggregate value (Kuznik *et al*., 2015). However, country-specific data is vital because health care policy is generally set at the national level and comparisons of the public health burden across disease states are important to define priorities for each country.

Adverse pregnancy-fetal outcomes especially preterm birth and low birth weight have a significant cause of newborn morbidity and mortality and strains society's healthcare resources due to its long-term effects on the health of the newborn. This consequently impacts negatively on the maternal quality of life. Preterm births account for 11.1 percent of the world's live births, sixty percent of them in South Asia and sub-Saharan Africa. In the poorest countries, on average, 12 percent of babies are born too soon, compared to 9 percent in higher-income countries (Lincetto & Banerjee, 2020).

There has been a substantial burden of adverse pregnancy-fetal outcomes with the prevalence of PTB, LBW, and SGA infants of 19.8%, 14.2%, and 12.6%, respectively, and prevalence of SB and neonatal death of 1.9% and 0.4%, respectively in one of the largest cohort study among HIV positive pregnant women (Kreitchmann *et al*., 2014). Pregnancy, delivery and post-delivery periods are associated with fast changes leading to decreased self-confidence, anxiety, stress, or even maternal depression impairing the woman's quality of life (QOL) (Jakubauskiene *et al*., 2019). This poor quality of life may further be propagated by any related adverse pregnancy-fetal outcome or a maternal complication such as SGA, LBW, and neonatal mortality.

The proportion of women experiencing APFOs due to IRIS linked to ART in Kenya and to an extent, sub-Saharan Africa, is not well described. The risk of HIV transmission to newborns is the major concern, but there also may be an increased risk for other adverse pregnancy-fetal outcomes associated with maternal-HIV-IRIS. The incidence of Immune reconstitution inflammatory syndromes is decreasing globally due to the implementation of antiretroviral therapy rollout programs and increased access to treatment (Mu *et al*., 2017), though its effect on pregnancy outcomes has not been researched.

Although different studies have shown IRIS incidence in a variety of epidemiological settings (Janssen *et al*., 2017; Melzani *et al*., 2020; Novak *et al*., 2012; Sainz-de-la-Maza *et al*., 2016), published data is scarce on the incidence and associated risk factors of the syndrome in the context of adverse pregnancy-fetal outcomes in East and Central African regions, similarly lacking such pertinent data in Kenya. Research studies have provided substantial evidence about the predictors, mediators, and, other factors of poor pregnancy outcomes in other parts of the world (Abbafati *et al*., 2020; Çelik *et al*., 2019; Z. Li *et al*., 2020; Tucker Edmonds *et al*., 2014). However, such shred of comprehensive research evidence lacks in Kenya and the contextual aspects here doesn't apply for Kenya due to difference in settings.

The HIV among pregnant women bear a delicate particularity mostly associated with an exceptionally high risk of poor pregnancy outcomes in the absence of clinical intervention (Sebitloane & Moodley, 2017). Research on outcomes among infants from HIV-positive pregnant women, the ART effects has been acknowledged among predictors of poor birth outcomes with some 9.3% stillbirths and 9.3% low birth weights respectively, and also 15.2% preterm births (Tobin-West, 2017). However, there is limited knowledge on the indirect effects associated with the immune response syndrome due to ART use. This unknown conclusion has been demonstrated by a study depicting adverse pregnancy outcomes occurring at 35.1% of all the enrolled HIV-infected women and conflicted by the fact that the rates of adverse pregnancy outcomes, spontaneous abortion, ectopic pregnancy, stillbirth, infant death, and perinatal HIV infection were higher among women not receiving ART, compared to those treated with

cART or mono/dual ART ($P < 0.05$). However, it demonstrated a higher rate of SGA, compared to untreated women (HU *et al*., 2019).

Pregnancy in HIV-infected women is associated with adverse maternal and newborn complications (Arab *et al*., 2017). As though to climax the problem, a systematic review analysis indicates that, ART regimens vary substantially in their association with LBW and PTB (Saleska *et al*., 2018). Adverse pregnancy-fetal outcomes generally lead to serious health consequences to the mother and/or the baby.

The possible risk of the adverse pregnancy-fetal outcome associated with maternal HIV-immune reconstitution syndrome due to the ART intervention in PMTCT has not yet been documented by such studies in Kenya. The fact that there is a dearth of information concerning the relationship between ART during pregnancy and pregnancy complications, it is crucial to evaluate the effects of HIV-IRIS during pregnancy on adverse pregnancy-fetal consequences.

1.3 Justification of the study

Due lack of reliable data on the association between maternal HIV immune reconstitution syndrome and adverse maternal and related pregnancy outcomes among HIV-positive women on ART in Kenya, the study is necessary to identify the key predictors of adverse pregnancy-fetal outcomes among women diagnosed with maternal HIV-IRIS. This is further necessitated by the fact that the risk of adverse pregnancy outcomes among HIV-positive women on ART is only known broadly in terms of direct teratogenic effects of antiretroviral therapy on the developing fetus. Additionally, adequate clinical evidence of the indirect effects of ART is of paramount importance in enhancing maternal and child health achievement as outlined towards sustainable development goals, 2030.

Preterm birth, intrapartum-related complications (birth asphyxia or lack of breathing at birth), infections, and birth defects cause most neonatal deaths. Despite the disparities in

these findings and the existing evidence, further studies are needed to determine the moderating effect of maternal HIV–IRIS on the relationship between maternal HIV-infection and the ART, in ART naïve pregnant women within the reproductive age. Findings from some studies demonstrate an increased relative risk of adverse birth outcomes associated with the use of highly active antiretroviral therapy during pregnancy among women and general poor maternal outcomes (Delicio *et al*., 2018). Again much of the efforts have seen infant mortality decline substantially over time in developed and developing countries, but the number of LBW infants declined, in 2014. However, the prevalence of LBW has not changed significantly (6.9% in 2005 to 6.7% in 2014) with African-American women having a persistent 2.4-fold greater prevalence of having an LBW infant compared with white women (Ratnasiri *et al*., 2018).

Robust research is thus required to investigate the underlying mechanisms and come up with the common IRIS related opportunistic infections during pregnancy among HIV-infected women, utilize an analytical multi-center approach, and investigate the role of immune reconstitution inflammatory response using the indices of immunity, such as CD4 counts (as a marker of immune competence or suppression or exacerbation), even in HIV-negative women.

Physicians treating very immune-deficient HIV-infected clients with ART are coming across the syndrome. The conditions have their greatest effects in resource-poor nations or settings more so in sub-Saharan Africa, where patients are often very immune-deficient and also have multiple opportunistic pathogens associated with pro and anti-inflammatory cytokines (Akase *et al*., 2017). This is not different among the pregnant population with diminished immune responses. Thus, the related study should increase knowledge on the immune-pathogenesis of these conditions and adverse pregnancy and related birth complications, so that measures based on; diagnostic tests, prevention, and treatment can be improved.

Given the mystery of IRIS presentation coupled with mixed opportunistic infections across the general population with HIV at first, there is a need to research the risk of

adverse pregnancy-fetal outcomes and IRIS in maternal HIV among pregnant women newly on ART, based on the little known issues of IRIS at moment. Although the ART use and known IRIS outcomes have been well documented, there is no current data on maternal HIV- IRIS, and the incident risk of adverse pregnancy-fetal outcomes among pregnant women, with the only major concern being inclined towards TB with HIV infection among this group, and, only on adverse consequences to the pregnant woman.

The findings of this study will be of benefit to the Ministry of Health, policymakers and other key stakeholders in their efforts towards improved implementation of PMTCT in the era of the increasing rollout of ART in pregnancy among HIV diagnosed women. It shall promote informed public health and clinical approaches pertinent to HIV and immune reconstitution syndrome in pregnancy towards enhancing health SDGs related to maternal and child health. The study will also be important to health-related researchers and concerned entities with the goals of improving maternal outcomes and implementing the desired projects at the National and County Government levels to mitigate the negative impact of ART and HIV among the ART naïve pregnant women as supported by MoH policy documents on HIV/AIDS in section 10.

Therefore, this research study investigates the incidence, relative risk, the predictors and frequencies of specific adverse pregnancy-fetal outcomes in maternal HIV-IRIS to elucidate adverse birth outcomes related to antiretroviral therapy due to HIV infection as it is needed in African settings. This research will also be beneficial in exploring the relationship between HIV infection, antiretroviral therapy, and the development of predictors of poor birth outcomes. Moreover, it is expected to serve as a baseline for those who may wish to make further research in the area, especially the existing and complicated, but, the salient phenomena of IRIS in more prone sub-populations.

1.4 Objectives

1.4.1 General objective

To determine the incidence and predictors of adverse pregnancy-fetal outcomes and the association with maternal-HIV-immune reconstitution inflammatory syndrome among women attending selected Public Hospitals, Nairobi, Kenya.

1.4.2 Specific objectives

i. To determine the incidence of adverse pregnancy-fetal outcomes among women with and without maternal–HIV immune reconstitution inflammatory syndrome attending selected Public Hospitals, Nairobi, Kenya.
ii. To determine the social-demographic and economic predictors of adverse pregnancy-fetal outcomes among women attending selected Public Hospitals, Nairobi, Kenya.
iii. To determine the clinical predictors of adverse pregnancy-fetal outcomes among among women attending selected Public Hospitals, Nairobi, Kenya.
iv. To assess the relationship between maternal–HIVimmune reconstitution inflammatory syndrome and the adverse pregnancy-fetal outcome among women attending selected Public Hospitals, Nairobi, Kenya.

1.5 Hypothesis

1.5.1 Null hypothesis

There is no significant difference in the incidence of adverse pregnancy-fetal outcomes between women with maternal HIV–Immune Reconstitution Inflammatory Syndrome and women without maternal HIV–Immune Reconstitution Inflammatory Syndrome women attending selected public hospitals, Nairobi, Kenya.

CHAPTER TWO

LITRATURE REVIEW

2.1 HIV-Immune Reconstitution Inflammatory Syndrome

2.1.1 Definition

Immune reconstitution inflammatory syndrome (IRIS) is a paradoxical deterioration of a preexisting illness following abrupt improvement in an individual's immune function. It is classically seen in HIV/AIDS patients following initiation of highly active antiretroviral therapy (HAART). Increasingly, however, it is also seen in the setting of other diseases treated with immunomodulation. Symptoms typically develop within 60 days following the initiation of ART and generally mimic worsening of the underlying condition despite rising CD4 counts and a falling viral load. It has been reported to affect 10-25% of patients with AIDS. Treatment is usually by corticosteroid therapy, alongside ongoing ART. Fatal cases have been reported in under 5% of cases with the common differential diagnosis being non-IRIS-associated opportunistic infection and central nervous system lymphoma (Boeva & Belyakov, 2018; Wong *et al*., 2017).

2.1.2 Clinical Presentaion and Epidemiology

The precise clinical picture depends on the underlying condition and body region involved and, there is an associated immune dysfunction characterized by a persistent inflammatory state and unhealthy elaboration of both pro-and anti-inflammatory cytokines (Akase *et al*., 2017). Timely correlation to immune restoration, distinct clinical appearance, particular immunologic and genetic characteristics, and different therapeutic requirements justify the assumption of an independent entity for IRIS. The immune recovery associated with ART is crucial for the survival of severely immune-compromised patients but can be complicated byimmune reconstitution inflammatory syndrome (IRIS). IRIS is an often inflammatory deterioration of clinical manifestations of an infection or tumor that follows successful suppression of HIV viremia with ART in

5%–50% of patients who have developed AIDS (Boulougoura & Sereti, 2016). IRIS is particularly common in patients who have underlying opportunistic infections, especially tuberculosis (TB), Mycobacterium avium complex (MAC), cryptococcosis, and herpesviruses including varicella-zoster virus (VZV), Kaposi sarcoma herpesvirus (KSHV), and cytomegalovirus (CMV) (Nelson *et al*., 2017). Generally, IRIS may present as "paradoxical" worsening of symptoms of a known infection at a new body site or at the original body site, or the "unmasking" of an occult opportunistic disease, in which disease that was not clinically apparent before ART manifests during ART (Nelson *et al*., 2017). The degree of clinical events is broad in general, with occurrence ranging from 10% to 23% in all individuals starting ART and from 8% to 43% of all individuals with existing opportunistic diseases (Sereti *et al*., 2020).

2.1.3 Diagnosis of IRIS

Diagnostic creteria has been developed to aid in the differentiation of IRIS from immunodeficiency disease among patients presenting with an opportunistic infection during ART. These diagnostic criteria are based on 2 major and 3 minor criteria for diagnoses. The first major is essential and must be accompanied by evidence of either a therapeutic response to ART in the form of $\geqslant$1 log decrease in human immunodeficiency virus type 1 (HIV-1) viral load or 2 minor criteria where an increase in the CD4 cell count is feasible (Lewis J. Haddow *et al*., 2009; Sereti, 2020). Physicians have used a definition proposed by the AIDS Clinical Trials Group, which was adapted from a definition proposed by findings where 20 cases of IRIS associated with major opportunistic infections were evaluated and found a high level of agreement with expert physicians (Sereti *et al*., 2020). The definition encompasses 3 essential criteria which include: new or worsening infectious or inflammatory symptoms, $\geqslant$1 log decrease in viral load, and the absence of 3 other explanations (newly acquired infection, predicted course of previously diagnosed infection, and adverse drug effects) (Dellière *et al*., 2018; Lewis J. Haddow *et al*., 2009).

2.1.4 Treatment and Management of IRIS

Clinicians should initiate appropriate treatment of opportunistic infections, as well as symptomatic treatment and supportive care according to the severity of immune reconstitution inflammatory syndrome. Clinicians should also consult with an experienced HIV care provider for the management of severe IRIS, including the decision of whether to interrupt ART if IRIS is severe. Nonsteroidal anti-inflammatory agents for discomfort associated with mild inflammation or fevers, drainage of abscesses, excision of inflamed and painful lymph nodes and inhaled steroids for bronchospasm or cough associated with mild pulmonary inflammation are applicable in mild IRIS while corticosteroid therapy to suppress inflammatory response is the most commonly used intervention in cases of severe IRIS.

2.2 Incidence, etiology, and trends of adverse pregnancy outcomes

2.2.1 Global context in developed and developing nations

Differences among developed and developing nations are recognized for maternal health and related mortality, infant, stillbirth as well as low birth weight (LBW). The higher rates of low birth weight in developing settings are due to intrauterine growth restriction than preterm birth. Much of the excess intrauterine growth restriction is caused by short maternal stature; low pre-pregnancy body mass index and low gestational weight gain (Vogel *et al*., 2018). Infant mortality has substantially decreased over time both in developed and developing settings despite non-decline in low birth weight. Developed settings have reported a temporal upsurge in fetal growth among infants born at term, a reduction in stillbirth outcomes, and the prevention of neural tube defects in a multinational prospective observational longitudinal study of fetal growth in low-risk singleton pregnancies of women of high or middle socioeconomic status and without known environmental constraints on fetal growth (Kiserud *et al*., 2017). The determinants that influence maternal health also affect pregnancy outcomes, infant and child health. Racial and ethnic disparities exist in infant mortality and can be partly

attributed to disparities in social determinants of health (Braveman *et al*., 2015). More progress is needed, however, in understanding the origin and prevention of commonly experienced adverse infant outcomes as it has been recommended by the world health organization in 2020.

Worldwide, an estimated 11.1% of all live births in 2010 were born preterm (14.9 million babies born before 37 weeks of gestation), with preterm birth rates increasing in most countries with reliable trend data. Direct complications of preterm birth account for one million deaths each year, and preterm birth is a risk factor in over 50% of all neonatal deaths (Blencowe *et al*., 2013). The estimated global preterm birth rate for 2014 was 10•6% (uncertainty interval 9.0–12.0), equating to an estimated 14.84 million (12.65 million–16.73 million) live preterm births in 2014. 12.0 million (81.1%) of these preterm births occurred in Asia and sub-Saharan Africa. Regional preterm birth rates for 2014 ranged from 13.4% (6.3–30.9) in North Africa to 8.7% (6.3–13.3) in Europe. India, China, Nigeria, Bangladesh, and Indonesia accounted for 57.9 million (41×4%) of 139.9 million live births and 6.6 million (44×6%) of preterm births globally in 2014. Of the 38 countries with high-quality data, preterm birth rates have increased since 2000 in 26 countries and decreased in 12 countries. Globally, we estimated that the preterm birth rate was 9×8% (8×3–10×9) in 2000, and 10×6% (9×0–12×0) in 2014 (Chawanpaiboon *et al*., 2019). Data from four birth cohorts show that preterm births increased markedly. Mean birth weights remained stable over a 33-year period. Increased prevalence of preterm and early term births, associated with high levels of obstetric interventions, has offset the expected improvements due to reduction in risk factors for low birth weight (Silveira *et al*., 2019).

2.2.2 Incidence in African context and Kenyan Perspective

An African context-based study which sought to estimate and compare adverse pregnancy-fetal outcomes and associated factors revealed that, one third of women reported an adverse pregnancy-fetal outcome; 10.8 % (abortion = 8.4 %, stillbirth = 2.4 %) by method 1 and 8.5 % (abortion = 7.2 %, stillbirth = 1.3 %). Abortion rates were

similar (10.8 vs 10.5) per 1000 women and stillbirth rates differed (26.2 vs 13.8) per 1000 births by methods 1 and 2 respectively. Abortion risk increased with the age of the mother, non-attendance of antenatal care, and proximity to the road. Lifetime stillbirth risk increased with age. Abortion and stillbirth risk reduced with increasing parity (Asiki *et al*., 2015). For all 43 sub-Saharan Africa countries, the estimated incidence of adverse pregnancy-fetal outcomes was 205,901 (95% confidence interval [CI], 113,256-383,051) per year, including stillbirth (88,376 [95% CI, 60,854-121,713]), neonatal death (34,959 [95% CI, 23,330-50,076]), low birth weight (22,483 [95% CI, 0-98,847]), and congenital syphilis (60,084 [95% CI, 29,073-112,414]), resulting in approximately 12.5 million DALYs (Kuznik *et al*., 2015). An Ethiopian based study showed that the prevalence of adverse birth outcomes among women who delivered was 31. 8% and further establishing that, living in rural area (AOR = 1.8; 95% CI 1.13, 2.78), age ≥ 34 years (AOR = 2.2; 95% CI 1.21, 4.05), mid-upper-arm circumference < 23 cm (AOR = 3.1; 95% CI 1.90, 4.94), multigravida women (AOR = 1.8; 95% CI 1.08, 3.06), lack of antenatal care visit (AOR = 2.1; 95% CI 1.02, 4.40) and complications during pregnancy (AOR = 2.1; 95% CI 1.23, 3.55) were significantly associated with adverse birth outcomes (Kassahun *et al*., 2019).

In a Kenyan survey, among 50,981 deliveries, 91.3% were born alive and, of those, 1.6% died before discharge. An additional 0.5% of deliveries were early stillbirths, 3.6% late stillbirths, and 4.7% spontaneous abortions. There were 64 documented maternal deaths (0.1%). Preterm and low birth weight infants represented a disproportionate number of stillbirths and pre-discharge deaths, yet very few were born at ≤1500g or <28w. More pre-discharge deaths and stillbirths occurred after maternal referral and with cesarean section. Half of the maternal deaths occurred in women who had undergone cesarean section (Waiswa *et al*., 2020).

2.3 Occurrence of adverse pregnancy and related birth outcomes

An adverse infant or pregnancy outcomes are far more frequent in developing nations in general due to several factors associated with such, as depicted in an African based

study, where low gravidity and young age predict perinatal death and PTD (Andemel *et al*., 2020), and, adverse pregnancy outcome has been also reported higher in grand multiparas (Muniro *et al*., 2019), similar to stillbirth (Yimer *et al*., 2020). Broad differences probably also exist in the rate of late fetal deaths, although fetal deaths in developing countries are rarely reported. The global incidence of LBW is around 17%, although estimates vary from 19% in developing countries like Bangladesh to 5-7% in the developed countries (Begum *et al*., 2017).

In an Ethiopian study, a total of 580 respondents 106(18.3%) respondents had child-related adverse birth outcomes (Tsegaye & Kassa, 2018). A Nigerian based case-control study found that several pregnancies ≥4 (AOR: 5.02; 95% CI: 1.97-12.82) were associated with adverse outcomes (Sadiq *et al*., 2016). In a study done in Rico, in overall, among pregnant women residing in Puerto Rico, socioeconomic status was associated with preterm birth but few other factors were associated with this or other adverse outcomes of pregnancy (Ferguson *et al*., 2019), with the risk of delivering babies with LBW being 1.12 times higher among mothers who were ≤ 36 weeks of gestation (AOR, 1.12; 95% CI, 0.06–0.25; p = < 0.001) (Mikomangwa *et al*., 2019).

2.4 Measures of APFOs

Despite the recognized benefits of mortality and severe morbidity as measures of adverse pregnancy outcomes, much of the published work in the areas of adverse infant outcomes, especially those related to maternal nutrition are based on trigger outcomes for death and severe illnesses with a narrow focus on the inter-links with IRIS. The most commonly studied of these proxies are; low birth weight (LBW), including its constituents, preterm delivery and intrauterine growth restriction (IUGR) as well as congenital anomalies and related infant outcomes (Bansal *et al*., 2018; Dessu *et al*., 2020; Kananura *et al*., 2016; Mekie & Taklual, 2019; Ogunkunle *et al*., 2020).

2.4.1 Birth weight as a common measure of adverse pregnancy outcomes

The prevalence of LBW is greater in resource-limited countries. While current data show that up to 10% of term infants in developed countries have LBW, that figure is 20% in developing countries. A recent report indicates that 19% of infants in resource-limited areas are born with LBW, and 22% of reported neonatal deaths occur in infants with LBW. In 2012, the Child Health Epidemiology Reference Group evaluated 14 birth cohorts and applied the birth weight standards specified by the International Fetal and Newborn Growth Consortium for the twenty-first Century (INTERGROWTH-21st). Using this definition, LBW was found in 19.3% of live births in low-income and middle-income countries, and 22% of neonatal deaths occurred in infants born small for gestational age ("Erratum: Estimates of Burden and Consequences of Infants Born Small for Gestational Age in Low and Middle Income Countries with INTERGROWTH-21st Standard: Analysis of CHERG Datasets (BMJ (Clinical Research Ed.) (2017) 358 (J3677))," 2017). Perinatal mortality increases in infants with LBW, whether they are born at term or preterm (Ray *et al*., 2017). Neonates with low birth weight have a >20 times greater risk of dying than neonates with a birth weight of >2500 g with a prevalence of term low birth weight of 10% (Desta *et al*., 2019). Low birth weight is a result of preterm birth (PTB), short gestation <37 completed weeks, intrauterine growth restriction (IUGR, also known as fetal growth restriction), or both. Globally, it is estimated that 15–20% of all births, or > 20 million newborns annually, are low birth weight infants. Low and middle-income countries account for a disproportionate burden of LBW; over 95% of the world's LBW infants are born in LMICs. There are marked global and regional variations in LBW rates. An estimated 6% of infants are born with LBW in East Asia and the Pacific, 13% in Sub-Saharan Africa, and up to 28% in South Asia (Slyker *et al*., 2014).

Low birth weight is a valuable public health indicator of maternal health, nutrition, healthcare delivery, and poverty. Neonates with low birth weight have a >20 times greater risk of dying than neonates with a birth weight of >2500 g. A baby's low weight at birth is either the result of preterm birth (before 37 weeks of gestation) or of restricted

fetal (intrauterine) growth. Low birth weight is closely associated with fetal and neonatal mortality and morbidity, inhibited growth and cognitive development, and chronic diseases later in life (Slyker *et al*., 2014). Additionally, low birth weight is associated with long-term neurological disability, impaired language development (Zerbeto *et al*., 2015), impaired academic achievement, and increased risk of chronic diseases including cardiovascular disease and diabetes. Preterm infants carry additional risk due to immaturity of multiple organ systems, including intracranial hemorrhage, respiratory distress, sepsis, blindness, and gastrointestinal disorders. Preterm birth is the leading cause of all under-5 child mortality worldwide (You *et al*., 2015).

Low birth weight (LBW) of less than 2500 g is an important marker of maternal and fetal health, predicting mortality, stunting, and adult-onset chronic conditions. Global nutrition targets set at the World Health Assembly in 2012 include an ambitious 30% reduction in LBW prevalence between 2012 and 2025 (Blencowe *et al*., 2013). The prevalence of IUGR is different among developing nations: 30–55% of infants born in South Central Asia versus 15–25% in Africa and 10–20% in Latin America as per the research findings. Caution is again advised in interpreting the values because of the lack of universal birth registration and the poor gestational age data in many developing nations. Absolute birth weight is associated with mortality, with birth weight<1.5 kg giving the largest association (OR 48.6, 95% CI 28.62-82.53). When using centile charts, regardless of the threshold, the summary odds ratios were significant but closer to 1 than when using absolute birth weight. For all tests, summary predictive ability comprised high specificity and positive likelihood ratio for neonatal death, but low sensitivity and a negative likelihood ratio close to 1 (Malin *et al*., 2014).

2.4.2 Determinats of APFOs

LBW is generally associated with situations in which uterine malnutrition is produced due to alterations in placental circulation. There are many known risk factors, the most important of which are socioeconomic factors, medical risks before or during gestation, and maternal lifestyles (Begum *et al*., 2017). The underlying causes of both PTB and

IUGR are multifactorial, and the biological pathways and preventive strategies for these two conditions are quite different, (Sharma *et al*., 2016).

The exact cause of PTB may be unknown in many cases; however numerous maternal, fetal, and placental factors may contribute to PTB (Cutland *et al*., 2017). Moderate to strong statistically significant associations between outcomes of last pregnancy, gestational age at delivery, mode of delivery, and the timing of antenatal care booking with maternal mortality, neonatal mortality, and low birth weight, even after controlling for other covariates (Ameh *et al*., 2016). Research has shown patterns of increased risk of LBW and PTB for women who smoke, have elevated pre-pregnancy body mass index (BMI), or with insufficient pregnancy weight gain. SGA was associated with maternal smoking, alcohol use, insufficient weight gain, and nausea and vomiting during pregnancy. The risk of cesarean section is also associated with having a diagnosed illness before pregnancy, elevated BMI, greater pregnancy weight gain, and less pregnancy exercise (Bird *et al*., 2017).

Predictors of low birth weight have been identified with several maternal and newborn characteristics. Commonly, variables such as sex of the newborn, prenatal care follow-up, pregnancy-induced hypertension, preterm delivery, and residence of the mother have been significantly associated with LBW (Katiso *et al*., 2020).

2.5 Temporal trends of pregnancy outcomes

The trend in the consequences of pregnancy has provided a mixture of good and bad news. The good news is that infant mortality has fallen in many parts of the world. It is important to explain that the decrease in infant mortality has occurred in the history of small or no effective LBW. Instead, infant mortality has decreased in both births, including children of normal birth weight (Abbafati *et al*., 2020). From 2008 to 2010, there were 51,080 deliveries to women with stillbirth, giving a rate of 4.08 per 1000 live births. Women with stillbirth were more likely to be African American (OR, 2.12; 95% CI, 2.07-2.17), with an age less than 25 years (OR, 1.19; 95% CI, 1.16-1.22) or older

than 35 years (OR, 1.40; 95% CI, 1.37-1.44) compared with women without stillbirth. Medical conditions such as cardiac, rheumatological, and renal disorders; hypertension; diabetes; thrombophilia; and drug, alcohol, and tobacco use, were independent predictors of fetal demise in multi variable logistic regression modeling. From 2000 to 2010, despite an increase in the total number of births to women with comorbidities, there was a significant decrease in the stillbirth rate, which was more pronounced among women with comorbidities compared with women without comorbidities (P=.021) (Patel *et al*., 2015).

2.6 General immunological changes during pregnancy and the postpartum period

Pregnancy represents an integrated orchestration of physiological processes to establish systemic, neuroendocrine, and immunological harmony facilitating the semi-allogenic fetal growth in the maternal entity. According to the cytokine profile alterations in immune mediation of pregnancy, the latter can be demarcated into three phases. The first immune phase of pregnancy, being dominated by pro-inflammatory cytokines, suffers from inflammatory propagation to enable successful implantation. In the second phase, a probable shift from pro-inflammatory Th1 cytokines to anti-inflammatory Th2 cytokines establishes the symbiotic existence of fetal with maternal components ensuring robust fetal development. The final immune phase of pregnancy is again characterized by the induction of inflammatory and cytolytic cytokines reinforcing inflammatory phases to facilitate parturition (Dutta & Sengupta, 2017).

As gestation evolves, the developing embryo becomes isolated within a semi-permeable environment. The anatomic organization of the maternal-fetal interface, absence of classical MHC molecules on the trophoblast surface, uterine NK cells, the cytokine milieu, macrophages, T and B cell populations, antibody production, indoleamine 2,3-deoxygenase, complement regulatory proteins, and sex hormones allow for the integrity of the maternal-fetal interface and provide an example of cellular recognition. As immunologic changes develop, the balance required for host defense and control of

autoimmunity is transformed and the pregnant female becomes susceptible to infections and changes in disease activity (Bronchud *et al*., 2016).

2.7 Epidemiology of IRIS in HIV-infected populations

Despite several descriptions of the infectious and noninfectious causes of IRIS, the incidence of the syndrome itself remains unknown widely. Among 599 eligible patients monitored prospectively between 2012 and 2014, there were 59.3% males, with mean age 36.6 + 7.8 years.immune reconstitution inflammatory syndrome incidence rate was 51.3 per 100 person-years (95% confidence interval: 44.5-59.2). One-third (31.4%) experienced at least 1 IRIS event, at a median of 27 days since ART initiation (Thambuchetty *et al*., 2017).

In the analysis of a large retrospective study examining types and presentations of IRIS, 33/132 of patients exhibited one or more disease episodes after initiation of ART (Walker *et al*., 2015). The variation in reported frequency reflects differences in case definitions, and more importantly, differences in study populations with differing risk profiles and underlying burden of opportunistic infections. Some studies suggested that up to 30 percent of ART uses developed one or more inflammatory syndromes matching with IRIS (Meya *et al*., 2016).

Subsequent data have suggested that the incidence is probably much lower. Data from other studies suggest that the incidence of IRIS following ART is largely dependent on the likelihood of a preexisting infection and the likelihood of viral and immunologic response to ART. A Kenyan based study established that most patients with HIV had an opportunistic infection. The three most common OIs being TB (35%), Herpes Zoster (HZ; 15.4%) and oral thrush (OT; 8%). Years of HIV infection significantly predicted TB (p=0.01) concluding that, there is a complex management of HIV and its associated OIs (Chepkondol *et al*., 2020).

IRIS is a common complication in patients starting ART. This is particularly common in patients with history of CMV retinitis, cryptococcal meningitis, and tuberculosis, and in patients who start ART at low CD4 cell counts. It is probably underdiagnosed in resource-limited settings and may contribute to the high early mortality in these settings (Walker *et al*., 2015). IRIS is expected to become more common in resource-constrained settings, where access to ART is increasing owing to matching HIV infections. The underlying prevalence of OI like Mycobacterium tuberculosis (TB) is high in this settings and the patients initiating ART are more likely to have advanced immune-suppression. Overall, prevalence of most OIs have declined especially after the introduction of ART. However significant variations exist in the trends of different OIs in different geographical areas. (Rubaihayo *et al*., 2015). Reported incidence varied also widely depending on associated pathogen; 37.7% of patients with a diagnosis of cytomegalovirus (CMV) retinitis before ART initiation developed IRIS, compared to 6.4% of patients with a diagnosis of Kaposis Sarcoma(Manzardo *et al*., 2015) (Manzardo *et al.*, 2015).

2.7.1 HIV-Immune response syndrome from resource-poor regions of the world

East and Southern Africa is the region the hardest hit by HIV. It is home to around 6.2% of the world's population but over half (54%) of the total number of people living with HIV in the world (20.6 million people). In 2018, there were 800,000 new HIV infections, just under half of the global total (Del Rio, 2019). Uncontrolled viral replication and higher co-infection prevalence may alter the immunological milieu of individuals in LMIC and increase the size of the HIV reservoir. Differences in HIV sub types could also influence the measurement and size of the HIV reservoir. Immune activation may differ due to late presentation to care, presence of chronic infections, increased gut translocation of bacterial products, and poor nutrition (Rossouw *et al*., 2017). In a study done in South Africa, mucocutaneous conditions accounted for 68% of IRIS events, mainly folliculitis, warts, genital ulcers, and herpes zoster**.** Tuberculosis (TB) accounted for 25% of IRIS events. 18/135 (13.3%) patients with major pre-ART OIs (e.g. TB, cryptococcosis) developed paradoxical IRIS related to the same OI. Risk

factors for this type of IRIS were baseline viral load >5.5 vs. <4.5 log10 (adjusted hazard ratio 7.23; 95% confidence interval 1.35–38.76) and ≤30 vs. >30 days of OI treatment before ART (2.66; 1.16–6.09). Unmasking IRIS related to major OIs occurred in 25/498 patients (5.0%), and risk factors for this type of IRIS were baseline C-reactive protein ≥25 vs. <25 mg/L (2.77; 1.31–5.85), hemoglobin <10 vs. >12 g/dL (3.36; 1.32–8.52), ≥10% vs. <10% weight loss prior to ART (2.31; 1.05–5.11) and mediastinal lymphadenopathy on pre-ART chest x-ray (9.15; 4.10–20.42). IRIS accounted for 6/25 (24%) deaths, 13/65 (20%) hospitalizations and 10/35 (29%), ART interruptions (Haddow *et al*., 2012).

2.8 Immune Reconstitution Inflammatory Syndrome

2.8.1 In HIV infected patients

The incidence of IRIS in patients in whom ART is started varies with the preexisting illness. Studies have reported IRIS in 63% of HIV-infected patients with cytomegalovirus retinitis, 30% – 34% of those with inactive cryptococcus, and 30% of those with M. tuberculosis infection (Chang *et al*., 2014). The spectrum of HIV-associated IRIS is described, with a particular focus on three important pathogen-associated forms: tuberculosis-associated IRIS, cryptococcal IRIS, and Kaposi's sarcoma IRIS. While the clinical features and epidemiology are well described, there are major gaps in understanding of pathophysiology and as a result, therapeutic and preventative strategies are sub-optimal. Timing of ART initiation is critical to reducing IRIS-associated morbidity (Walker *et al*., 2015).

Neurological disorders have also been described with varying bacterial, spirochetal, and viral infections including several patients with HIV. However, specific immunopathological mechanisms that may lead to opsoclonus-myoclonus in HIV-positive patients are unknown (S. R. Sharma *et al*., 2017). Clinical presentations of Histoplasma-related IRIS can present with worsening lymphadenopathy, small bowel obstruction, and worsening pulmonary symptoms. The emergence of IRIS appears to be

very common in people with HIV and disseminated histoplasmosis but the underlying trigger may be Histoplasma, other co-infections, or both (Boulougoura *et al*., 2019). Research has demonstrated that HIV infection causes changes in intestinal microbial diversity and the specific bacterial composition. Nevertheless, the regulatory effect of gut microbiota on immune function is well-known. The diversity and composition of the gut microbiota change in infected individuals with poor immune recovery, which may be the key factor for poor immune reconstitution in some infected individuals (Geng *et al*., 2020).

HIV is associated with posterior reversible encephalopathy syndrome in a patient with HIV/AIDS and immune reconstitution syndrome, a neurotoxic condition caused by damage to the blood-brain barrier. IRIS may be an unrecognized risk factor via massive T-cell activation (Weiss *et al*., 2018). The introduction of HAART was quickly followed by numerous reports of patients in whom recovery of immune responses led to clinical worsening allowing the host to respond to and control infection, but a significant number of patients will have atypical inflammatory syndromes during the recovery period presenting with other myriad symptoms associated with it (Nelson *et al*., 2017).

2.8.2 Inflammatory Activation in HIV-infected persons and IRIS Development

The pathophysiology and immunopathology of IRIS remain unclear, though it is believed to involve an interplay between regulation of restored immune system cells, type and burden of inciting pathogen, changes in T-helper (Th) cells profile and host genetic susceptibility (Lai *et al*., 2016). HIV-associated systemic and persistent background inflammation may independently lead to inadequate regulation of inflammatory activation, thereby contributing to systemic homeostatic disruptions (Furman *et al*., 2019). The inflammatory milieu of dysregulated immune responses of PLWH to an opportunistic pathogen combined with immune reconstitution after ART initiation creates the perfect environment for IRIS development, though it may be circumvented as early therapy appears to lead to better prognosis and decrease IRIS incidence (Narendran *et al*., 2019; Sereti, 2020). Chronic systemic inflammation (SI) is

characterized by persistent activation of both immune and non-immune cells, mainly driven by underlying infectious or inflammatory processes (Furman *et al*., 2019).

Chronic inflammation disrupts the well-coordinated mobilization of immune responses leading to unregulated immune activation and homeostatic disruption. Notably, chronic systemic inflammation is associated with viral persistence in PLWH and may lead to a persistent inflammatory background and the development of noninfectious comorbidities, such as age-related noninfectious comorbidities (NICMs) and IRIS (Deeks, 2011). Prior work indicates that, in the absence of treatment, HIV-driven systemic inflammation is associated with increased systemic levels of proinflammatory cytokines such as interleukin (IL)-6, tissue necrosis factor (TNF)-α, and IL-1β(Hilburg et al., 2020) (Borges *et al*., 2015). After ART initiation, most individuals have a pronounced decline in some circulating cytokine concentrations, while other markers such as IL-6 and C-reactive protein (CRP) remain elevated (Hsu *et al*., 2018). While reconstitution of the immune system through ART is critical to the reduction of mortality in PLWH, uncontrolled inflammation through the development of IRIS may rapidly lead to clinical deterioration (Ramanathan *et al*., 2018).

2.8.3 Non-HIV immune-compromised patients

Immune reconstitution inflammatory syndrome (IRIS) is a phenomenon initially described in patients with the human immunodeficiency virus. Upon initiation of combination antiretroviral therapy, recovery of cellular immunity triggers inflammation to a preexisting infection or antigen that causes paradoxical worsening of clinical disease. A similar phenomenon can occur in human immunodeficiency virus-negative patients, including pregnant women, neutropenic hosts, solid-organ or stem cell transplant recipients, and patients receiving tumor necrosis factor inhibitors. Common with this is Tuberculosis-associatedimmune reconstitution inflammatory syndrome (IRIS) in an HIV-negative patient that presents with a multitude of clinic-radiological presentations that are often confused with drug resistance/treatment failure (Aggarwal *et al*., 2020).

Non-HIV immune-compromised host develop immune reconsetitution inflammatory syndrome when the sudden change in the dominant T helper responses to inflammation is not well-balanced by anti-inflammatory responses. Primary diseases in which non-HIV IRIS is secondary include severe cutaneous adverse drug reactions, such as autoimmune diseases, collagen diseases, pregnancy, and internal malignancies. Potential triggers of recovery from an immune deterioration state include discontinuation or abrupt tapering of systemic steroids and/or immunosuppressants, withdrawal or reduced effects of anti-tumor necrosis factor-α antibodies, and the use of immune-checkpoint antagonists for the advanced stages of malignancies (Sueki *et al*., 2018). However, it has also been seen in non-HIV patients following corticosteroid withdrawal, discontinuation of anti-TNF therapy, or recovery of neutropenia after cytotoxic chemotherapy. It can also rarely, occur in TB patients without any underlying predisposing factor (Aggarwal *et al*., 2020).

2.9 Maternal HIV and related adverse Birth outcomes

The most prevalent adverse pregnancy-fetal outcomes are low birth weight, preterm birth, and stillbirth. Several studies have shown that maternal HIV infection is associated with adverse pregnancy-fetal outcomes such as low birth weight and perinatal mortality (Chaibva *et al*., 2019).

Maternal HIV infection harmed birth weight and perinatal mortality in 2010. Birth weight was not dependent on ART uptake but perinatal mortality was higher among infants of HIV-infected mothers who were not on ART (Twabi *et al*., 2020). Several studies have shown that maternal HIV infection is associated with adverse pregnancy outcomes such as low birth weight and perinatal mortality which was higher among infants of HIV-infected mothers who were not on ART (Twabi *et al*., 2020). Infant mortality and morbidity persist in the sub-Saharan African (SSA) region in which the HIV prevalence among pregnant women is high and HIV infection continues to be associated with significant maternal morbidity and poor neonatal health outcomes with the risk of stillbirths doubling in HIV-infected women (RR, 2.16 [95%CI 1.17; 3.96], p

= 0.013). Fetal anemia was also increased among infants born to HIV-infected women (10.6% versus 7.3%, p = 0.022) (González *et al*., 2017).

A growing number of studies have shown conflicting evidence on the association between maternal HIV and adverse pregnancy-fetal outcomes such as LBW. Some studies have shown that antiretroviral therapy (ART) among HIV-infected mothers is associated with adverse outcomes such as low birth weight (LBW), intrauterine growth restriction (IUGR), preterm delivery (PTD), and stillbirths (Gibango *et al*., 2018). On the other hand, several studies have found that sustained intake of ART among HIV-infected mothers reduces adverse pregnancy-fetal outcomes such as stillbirths, low birth weight, and prematurely delivered babies (R. M. Patel & Manuck, 2018).

HIV infection is responsible for significant adverse obstetric outcome irrespective of anti-retroviral treatment with rates for low birth weight (28.04 per 100 pregnancy outcomes), spontaneous abortion (4.85 per 100), stillbirth (2.64 per 100), and MTP (9.25 per 100 live birth) were found to be significantly high for HIV-infected pregnancies on ART, as compared to the general population. MTP rates and low birth weight rates for general pregnancies did not fall within the 95% confidence interval of those rates for HIV-infected pregnancies (Ganguly *et al*., 2020). In other similar studies, mother to child transmission of HIV infection rate of 0.99% showed that it is possible to achieve an MTCT rate of less than 1 % in African settings. The risk of preterm birth is high in HIV-infected mothers (Zack *et al*., 2014).

2.9.1 HIV with LBW and preterm delivery outcome

HIV-infected women have a higher risk of having a low birth weight and preterm infants compared with uninfected women (Xiao *et al*., 2015). It has been reported that HIV-infected women are more likely to encounter adverse pregnancy-fetal outcomes, such as low birth weight (LBW) and preterm delivery (PTD). In a study among 2549 singleton live births, 10.4% (n = 264) were PTD and 10.4% (n = 265) SGA. PTD declined from 16.3% in 2010 to 9.3% in 2015 and SGA remained stable from 9.9% in 2010 to 10% in

2015 (Chetty *et al*., 2018). HIV management has generally improved the pregnancy outcomes, although the benefits of ART during pregnancy for the prevention of MTCT are undisputed, studies have indicated that ART regimens vary substantially in their association with LBW and PTB.

Although challenging, optimization of ART regimens could simultaneously promote maternal health, prevent MTCT, and also minimize risks of PTB and LBW (Saleska *et al*., 2018). Other than direct HIV infection predicting the adverse pregnancy outcome, a study found that LBW was associated with prematurity, odds ratio (OR) 7.15, 95% confidence interval (CI) 5.18 to 9.89; premature rupture of membranes OR 7.33, 95% CI 2.43 to 22.12 and attending fewer than five antenatal care (ANC) visits OR 1.30, 95% CI 1.06 to 1.61. Male infants were less likely to be LBW, in this population (Tshotetsi *et al*., 2019).

In published studies, there were more than 16 million female adults who had been infected with HIV by the end of 2012 (Girum *et al*., 2018). There is also a possibility that maternal HIV infection has severe impacts on pregnancy outcomes as it has been implicated in several studies though not clearly established. HIV-infected women are more likely to encounter adverse infant outcomes (Xiao *et al*., 2015). A significant heterogeneity among studies for maternal HIV infection associated with LBW/PTD (I^2 = 71.7 %, $P < 0.05$, and I^2 = 51.8 %, $P < 0.05$ for LBW and PTD, respectively) suggesting that the summary measures need to be interpreted with caution. Similarly, pooled ORs for LBW and PTD from random effect models were presented and the summary OR was 1.73 (95 % CI: 1.64, 1.82, $P < 0.001$) for LBW and 1.56 (95 % CI: 1.49, 1.63) for PTD, indicating that HIV infected women had approximately 2-fold risk to deliver low birth weight or preterm babies compared with uninfected ones. The beneficial effects of antiretroviral (ARV) are indisputable; studies in developed and developing countries have reported contradicting results on ARV exposure and adverse birth outcomes (Li *et al*., 2016).

2.10 Risk factors for development and diagnosis of HIV-IRIS

Risk factors for the developments of IRIS include an advanced state of immunosuppression and high infective antigen at ART initiation (Walker *et al*., 2015). Findings have demonstrated that, people living with HIV with severe immunosuppression initiating ART, baseline low BMI and hemoglobin, and high C-reactive protein (CRP) and D-dimer levels may be clinically useful predictors of IRIS and death risk (Sereti *et al*., 2020). High alkaline phosphatase levels and increased CD8+ T-cell activation with low CD4 counts at ART initiation have been found to warrant suspicion for subsequent development of mycobacterium avium complexim mune reconstitution inflammatory syndrome in a contemporary cohort of patients with HIV (Breglio *et al*., 2020). There may also be a genetic predisposition and certain genes have been associated with increased susceptibility to the development of IRIS in the presence of mycobacteria and herpes viruses (Walker *et al*., 2015).

2.11 Pathogenesis of IRIS

Despite numerous descriptions of the manifestations of IRIS, the immunopathogenesis of IRIS remains only partially understood. Qualitative and quantitative reconstitution of the immune system, host genetic susceptibility, and mycobacterial load are supposedly involved in the pathogenesis of IRIS (Hamada & Adachi, 2020). The immunopathogenesis of the syndrome appears to be the result of unbalanced reconstitution of effector and regulatory T-cells, leading to an exuberant inflammatory response in patients receiving ART (Walker *et al*., 2015). The syndrome is precipitated by the degree of immune restoration following ART. An alternative immunological mechanism may involve qualitative changes in lymphocyte function or lymphocyte phenotypic expression. For instance, following ART an increase in memory CD4 cell types is observed possibly as a result of redistribution from peripheral lymphoid tissue. This CD4 phenotype is primed to recognize previous antigenic stimuli, and thus may be responsible for manifestations of IRIS seen soon after ART initiation. After this redistribution, naive T cells increase and are thought to be responsible for the later

quantitative increase in CD4 cell counts (Perdomo-Celis *et al*., 2019). Thus, IRIS may be due to a combination of both the quantitative restoration of immunity and qualitative function and phenotypic expression observed soon after the initiation of ART (Meya *et al*., 2016). The third purported pathogenic mechanism for IRIS involves host genetic susceptibility to an exuberant immune response to the infectious or noninfectious antigenic stimulus upon immune restoration. Although evidence is limited, carriage of specific HLA alleles suggests associations with the development of IRIS and specific pathogens (Dellière *et al*., 2018).

2.12 The Conceptual Framework

The conceptual framework explains the relationship and the interaction between independent, confounding, and dependent variables. Dependent variable was the 'the overall adverse pregnancy-fetal outcomes' whereas the independent included factors grouped into two broad categories. The first category was the exposure variable of interest that is, Maternal HIV-immune reconstitution inflammatory syndrome, in the context of this study, distinguished by a falling plasma viral load as a more important indicator combined with a typical presentation of opportunistic infection in response to antiretroviral therapy (Main criterion) with minor being; increase in CD4 count, spontaneous disease resolution following ART and increase in immune responses.

The second broad category were the other factors which were sub-grouped as follows: first, The maternal and clinical factors; maternal placental syndrome, chronic hypertension, maternal anemia, maternal substance abuse during pregnancy, prophylaxis for opportunistic infection, cesarean section delivery, gestational diabetes, RH factor, hemoglobin level, maternal body mass index (BMI), clinical, laboratory characteristics and obstetrical history; the second was social demographic factors such as maternal age, occupation, marital status, residence, income, education, and religion; the third was health care services: antenatal clinic attendance and antenatal clinic care.

In the context of this study, ‘adverse pregnancy-fetal outcome” implies the presence of at least one or more of the following conditions in the current pregnancies. These included fetal loss/miscarriage, low birth weight, preterm birth, any congenital anomaly, neonatal sepsis, early neonatal mortality, abnormal Apgar score SGA, and “others”. Thus, if the HIV-infected women initiated on ART experienced either of the above at intrapartum, at delivery, or, postpartum were labeled as “women with a pregnancy-fetal related adverse outcome’’.

In this cohort study, all cases of TB infection or therapy were eliminated from the study among the both cohorts. This fact was due to; among co-infections in PLWH, mycobacteria are the most common OI, primarily by Mtb. In 2019, the World Health Organization (WHO) estimated 456,426 new cases of tuberculosis (TB) among PLWH with 208,000 deaths (Global Tuberculosis Report 2020, 2020). A previous study over a very long period in memory found an incidence of MAC coinfection ranging from 6% to 43% in PLWH (Gilks *et al*., 1995). Above, co-infection with pathogenic mycobacterium can lead to increased systemic inflammation in PLWH. TB infection itself leads to changes in inflammatory proteins and lipid mediators that persist even after completion of antitubercular therapy, culminating in intense inflammatory imbalance (Breglio *et al*., 2020; Oliveira-de-Souza *et al*., 2019; Vinhaes *et al*., 2019). In comparison to persons with mono-infections, those with HIV-TB coinfection express higher levels of inflammatory cytokines such as IL-6, TNF-α, IL-10, and IL-1-β (Schutz *et al*., 2019; Shivakoti *et al*., 2015). Its management also is prone to establishing itself with responses related to IRIS which in the context of this study, it would compromise the indentification of IRIS which was a very key step moving forward with the follow-up.

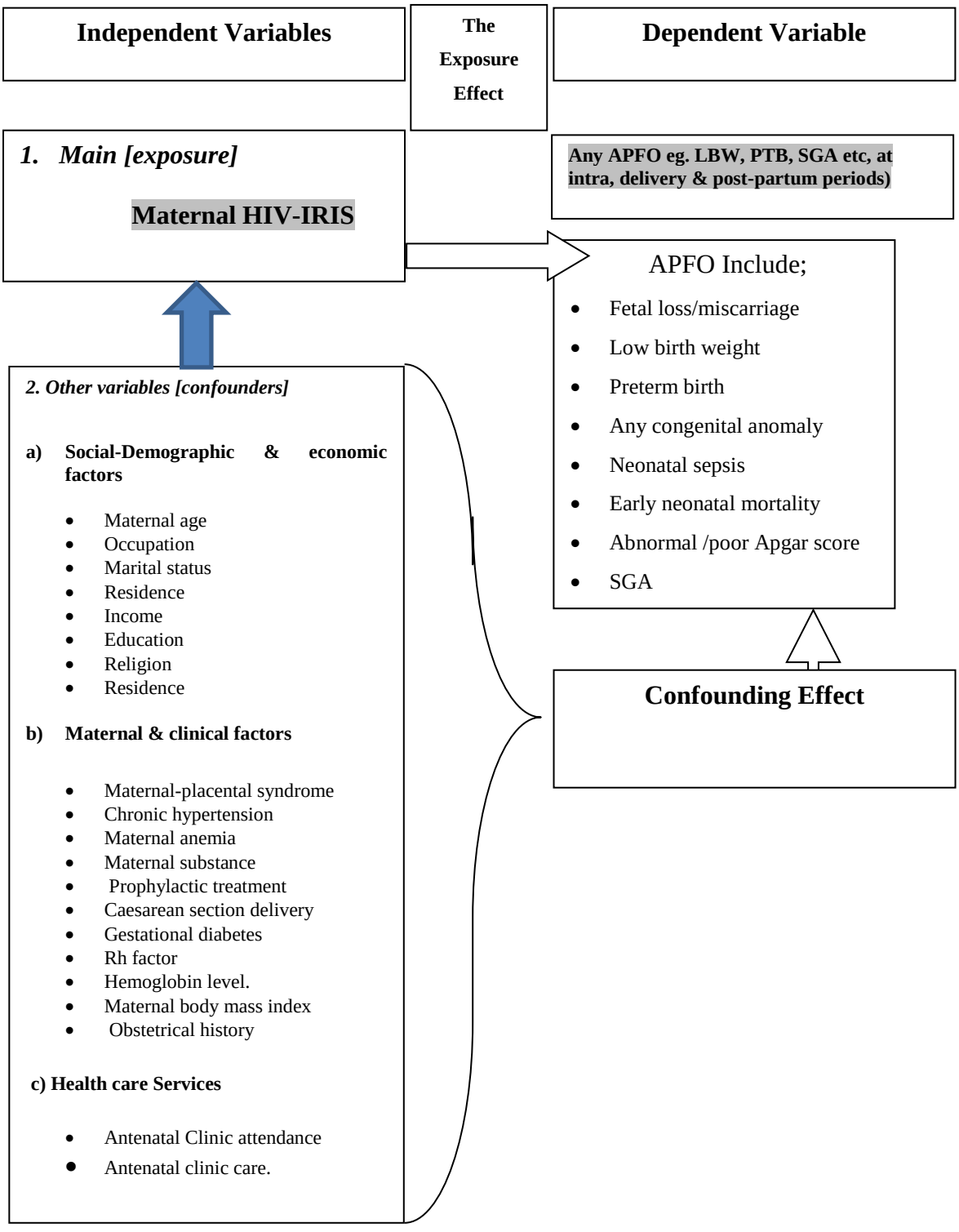


Figure 2.1: The conceptual framework

CHAPTER THREE

MATERIALS AND METHODS

3.1 Study sites

This was carried out at two referral facilities in Kenya; Kenyatta National Hospital, Mbagathi level 5 Hospital. The facilities offer also preventive care services and participate in public health programs for the local community and the total primary health care system. With their concentration of resources and personnel, these teaching and referral hospitals contribute to providing solutions to local and national health problems through research, as well as contributing to policy formulation. The hospitals have specific roles in providing information on various health problems and diseases**.**

3.1.1 Kenyatta National Hospital

The hospital is located in the area to the immediate west of Upper Hill in Nairobi, the capital and largest city of Kenya. The location is about 3.5 kilometers west of the city's central business district. The hospital complex measures 45.7 acres. KNH is the largest public referral hospital in Kenya, Eastern, and Central Africa and also serves as a teaching hospital for the University of Nairobi and the Kenya Medical Training College. It is located in Nairobi which is the capital city of Kenya with a population of about 4 million. The hospital has a busy maternity unit registering over 10,000 deliveries annually. It also has a busy newborn unit (NBU) that offers specialized neonatal care. Being a teaching and referral hospital, KNH handles many high-risk pregnancies and other related obstetrical complications and outcomes.

3.1.2 Mbagathi District Hospital

This medical facility was originally known as “Infectious Diseases Hospital” (IDH) under the then “King George VI Hospital,” historically. This facility is situated in Kenyatta Golf Course Location; Dagoretti District of Nairobi County. The facility offers

integrated health services for nearly 9800 HIV patients, supporting the supply of critical life-saving HIV treatment; nutrition education and commodities; family planning; and direct support, including staff training and community outreach. The facility has a maternity wing with an estimated capacity of over 300 beds where mothers deliver. Comprehensive care clinics for HIV patients are in place, and, this is also used in maternal health services both antenatal and post-natal. With also a capacity of over 40 incubators for preterm deliveries and neonatology unit, it has medical specialists in and visiting ones.

3.2 Study design

A prospective cohort study design was used. Study participants were recruited during the first trimester (first 2-3 months, with HIV status being confirmed not later than one month post conception) and followed until delivery and two week postpartum period so that the association between APFOs) and IRIS among the study participants would be established. Matching by age and parity among pregnant women infected with HIV, confirmed by test at least in the first trimester was performed. These protocols were designed to describe the characteristics of enrolled pregnant women, use of ART regimens, and, pregnancy-fetal adverse events. Women enrolled in the study were followed during pregnancy for six and half weeks months (using active case progressive records where current clinical and primary outcome measure, the APFOs were noted and the expert opinions to retreave any outcome measure), at 6^{th} month, through delivery, and two weeks postpartum. During each study visit, the participants' clinical characteristics were assessed through a physical examination, the evaluations of laboratory results, and a review of medical diagnoses made since the last visit.

3.3 Study population

The reference population included HIV-positive confirmed cases, ART-naive pregnant women as a single population from the selected facilities attending antenatal care unit (ANCu) from the first trimester of their pregnancies and not later than one-month post-

conception. The cohort was then initiated to ART as a single population and baseline data on the exposure was obtained prior to specific cohort allocation. IRIS was assessed and confirmed within the first 2-12 weeks using International Network for the Study of HIV-associated IRIS (INSHI) and experts' opinions as per IRIS case definitions was done to ensure internal validity was maintained.

3.3.1 Inclusion criteria

3.3.1.1 Enrollment of Study Cohorts

535 HIV-positive, ART-naïve pregnant women were enrolled and intiated on ART and followed for two weeks to three months to indentify IRIS in this first phase of the study, and obtained the two cohorts (first being the IRIS cohort of 133, followed by the non-IRIS cohort of 133 from the same initial population).The study instrument incorporated an assessment of the frequency and forms of adverse pregnancy-fetal outcomes.

Exposed Cohort (Maternal HIV-IRIS):

i. A woman willing to be delivered in a selected referral health facility
ii. A cohort of pregnant women diagnosed with HIV-IRIS and confirmed to be HIV-seropositive at least in the first trimester.
iii. Women receiving or initiated on ART care and support at VCT center after being confirmed to be HIV- seropositive at least in the first trimester.
iv. Women willing to participate in the study and be a resident in the study area for at least 1 year.

Non-Exposed Cohort (Comparison group) (Non-maternal HIV- IRIS)

i. A woman willing to be delivered in a selected referral health facility.

ii. A cohort of pregnant women not diagnosed with HIV-IRIS and confirmed to be HIV-seropositive at least in the first trimester.
iii. Women receiving or initiated on ART care and support at VCT center after being confirmed to be HIV- seropositive at least in the first trimester.
iv. Women/mothers willing to participate in the study, be a resident in the study area for at least one year.

3.3.2. Exclusion Criteria

Exposed Cohort (Maternal HIV-IRIS):

i. Pregnant women not ART-naïve at first in the first trimester.
ii. A cohort of pregnant women diagnosed with HIV-IRIS but not yet on ART.
iii. Women with high-risk pregnancies or special needs who required specialist care or with a history of high-risk pregnancy outcomes.
iv. Women with known TB disease or on regular anti-tubercular medication, rather than the normal TB prophylaxis.
v. Pregnant women meeting the selection criteria but not consenting to the study
vi. Subject with insufficient data.
vii. Women with an ultrasound scan results showing more than one fetus during the study.

Non-Exposed Cohort (Non-maternal HIV- IRIS)

i. Pregnant women, not ART-naïve at first in the first trimester.
ii. Women not diagnosed with IRIS during pregnancy and not on ART.
iii. Women with high-risk pregnancies or special needs who require specialist care or with a history of high-risk pregnancies.

iv. Women with known TB disease or on regular anti-tubercular medication rather than the normal TB prophylaxis.
v. Pregnant women meeting the selection criteria but not consenting to the study
vi. Subject with insufficient data.
vii. Women with an ultrasound scan results showing more than one fetus.

3.4 Sample size determination

3.4.1 IRIS and non-IRIS exposed cohorts

Using the formulae by Kelsey for unmatched/independent cohort study;

To be 90% confident of rejecting H_o: RR=1 in favor of the alternative H_a: RR≠1, performing the test at α=0.05 level and with P_0=0.35 and P_1=0.175 in exposed and unexposed population respectively, the incidence rate of outcome (related APFO events) under investigation from the literature review on maternal HIV and use of ART (Dadhwal, *et al*., 2017).

$\alpha = 0.05$

$\beta = 0.1$

P_0=0.355[in the exposed]

P_1=0.175[in the unexposed]

r=1

Hypothesised (assumed) relative risk in exposed) =2

Technical validation using the formular:

$$N_{Kelsey} = \frac{\left(z_{\alpha/2} + z_{\beta}\right)^2 p(1-p)(r+1)}{r(p_0 - p_1)^2}$$ (Kelsey *et al*, 1996)

The estimated sample size n is calculated as:

N_{Kelsey} = (1.960+1.282)2*0.2625*0.7375*2 / (0.355-0.175)2= 133

Therefore, using Kelsey's formula, a total of 266 HIV positive ART-naive pregnant women were enrolled in the study and obtained 133 per arm (cohort) of the participant for comparative analysis on the risk of adverse pregnancy-fetal outcomes and maternal HIV-IRIS.

3.4.2 Projected population size to obtain the IRIS exposed cohort

ART in some cases leads to the phenomenon ofimmune reconstitution inflammatory syndrome (IRIS). The overall incidence of IRIS is unknown; it is rather dependent on the population being studied and the burden of underlying opportunistic infections. In this study, 17.01 % was utilized to obtain the population size of HIV–positive, ART-naïve pregnant women where the arm of 133 who developed IRIS would be obtained. The calculator that uses the below formula was applied as follows:

Formula

This calculator uses the following formula for the sample size n:

n = N*X / (X + N – 1),

Where,

X = Zα/2 ¬*p*(1-p) / MOE2,

Zα/2 is the critical value of the Normal distribution at α/2 (e.g. for a confidence level of 95%, α is 0.05 and the critical value is 1.96),

MoE is the margin of error, P=0.175 is the sample proportion (event of interest in normal population) (Dadhwal *et al*., 2017).

N is the population size.

Therefore, to obtain the arm of 133 women who would develope IRIS, a crude initial population at ANC of at least 535 HIV-Positive ART-naïve women was needed, following systematic rule of sampling that was applied. This was based on the projected population of 535 HIV positive ART-naïve women where the 133 identified arm would be obtained as; 535 / 133= 4 (being the interval).

3.5 Sampling technique

The investigator, through a systematic sampling, initially included subjects with the numbers; 4, 8, 12, 16, 20 and so on to obtain the 535 HIV positive ART-naïve women where the 133 of the exposed arm would be identified. A consecutive approach as IRIS developed was then applied in the selection of the participants (both IRIS and non-IRIS cohorts) from the initial projected 535 population as the sampling frame. For the exposed cohort, the participants were picked as IRIS developed prospectively irrespective of the time intervals for the same within the first trimester as it was expected to occur. The sampling was based on the development of IRIS such that, until the 133 IRIS exposed group was attained, the sampling was not stopped. The 133 non-IRIS cohort was then randomly selected from the same initial crude population among the participants who did not develop IRIS (remnants of 535 after the indentification of the 133 IRIS cases), thus with a ratio of 1:1, a total of 266 participants as the sample size.

3.6 Study Procedures

3.6.1 Recruitment and consenting of study subjects

3.6.1.1 Recruitment

This was based at each study site as per the selected medical referral facility which was conducted among all the eligible subjects based on the inclusion criteria. The women were seeking maternal healthcare services and this took place during the first visit in the

first trimester to the facility at the level of a single population followed by a random selection of subjects who would participate in the study. This phase took place irrespective of whether they would develop IRIS or not with time and later was split into two cohorts at 133 subjects per arm using n=266 based on who developed IRIS and who did not.

3.6.1.2 Consenting of the study subjects

This was a continuous process of communication between the investigator and the research subjects more so in the first phase of recruitment and enrollment. This was based on the fact that, the body of knowledge impacting this study was subject to be frequently changing. The study participants received information from the investigator after they had been enrolled in this study. Significant new findings that could affect their decision to participate in research or clinically useful test results were communicated especially the diagnoses of the IRIS as the exposure status among the exposed cohort during the first trimester of pregnancy. Consequentially, during the follow-ups stages where applicable, based on the outcome indicators, the consenting took place among the study participants, though this as expected, was rare onwards.

3.6.2 Enrollment of study subjects

Study participants were recruited prior to the enrollment in this study during the first trimester (10–12 weeks) of their pregnancies (after establishing their IRIS status) and followed until delivery so that the incidence of outcomes and associations between exposure and outcome variables among the study participants would be measured. This was systematically recruited where antenatal clinics are held, at the reproductive and child health units of the KNH (Clinic 18) and Mbagathi (CCC Unit) facilities using the ANC register of the facility.

3.6.3 Identification of pregnant women developing IRIS

Criteria by the International Network for the Study of HIV-associated IRIS (INSHI) for defining IRIS events were utilized to indentify cases of Immune Reconstitution Inflammatory Syndrome soon after the commencement of ART. The clinical presentation of an IRIS was applied as it was expected to occur between 2 weeks and 3 months after ART commencement of ART intensification or earlier (within days) as it may be possible. The temporal onset of an IRIS was particularly difficult to attribute among women who portrayed erratic ART adherence. Diagnosis of an IRIS was also made clinically based on the temporal relationship between starting ART and disease onset; disease manifestations included the exclusion of alternative diagnoses; and a fall in plasma HIV viral load. The major differential diagnosis was a relapse of the infection that triggered the IRIS or occurrence of another infection (French, 2009; Lewis J. Haddow *et al*., 2009; Sereti *et al*., 2020). Differentiation of these conditions was essential as the clinical presentation may occur with mixed conclusions. Therefore, to identify the cohort developing IRIS, Criteria for the diagnosis of an IRIS was the guiding principle as per the table below. Above all, medical experts' opinion (more than two per IRIS event definition) was relied upon and this required major and minor criteria as below;

Table 3.1: Immune Recinstitution Inflammatory Response Syndrome Diagnosis Creteria

Major criteria
1. Initial presentation or exacerbation of disease associated with an HIV-related infection or cancer following commencement of effective ART, especially when disease manifestations are exaggerated and/or atypical, with exclusion of recurrent or new infections and drug hypersensitivity reactions 2. Decrease in plasma HIV RNA level by >1log10 copies/mL
Minor criteria 1. Atypical inflammatory response in affected tissues, eg. - Granulomas in the context of severe $CD4^+$ T cell depletion - Tissue necrosis and suppuration - $CD8^+$ T cell infiltrates in PML-IRIS
2. Increased blood $CD4^+$ T cell count after ART 3. Increase in an immune response specific to the relevant pathogen, eg. delayed-type hypersensitivity skin test response to mycobacterium antigens 4. Spontaneous resolution of disease without specific antimicrobial therapy or tumor chemotherapy with continuation of anti-retroviral therapy

3.6.4 Follow-up

Follow-up began post IRIS identification and cohort allocation during the first trimester. The first visit was at 22–24 weeks and the second at 36–37 weeks of gestation during the pregnancy and the third, two weeks postpartum. The two obtained cohorts (IRIS and non-IRIS cases) were followed all through at the same visits with the subsequent recording of the outcome measures, the adverse pregnancy-fetal outcomes. Systolic and diastolic blood pressure was measured at recruitment and each visit, as well as any adverse pregnancy-fetal outcome. To maintain follow up, subjects who were easier to track were established during the initial stages of recruitment. The use of doctors and nurses was also utilized because they were more likely to remain interested in the study.

3.7 Data collection

Data collection was on initial enrollment followed by consequential visits more so until the final visit of delivery and the postpartum period (the final outcome measure stage). The study instrument incorporated the baseline demographic characteristics such as age, marital status, and so on. Baseline assessment of HIV and tuberculosis status for early and initial elimination as per inclusion criteria was performed. Each scheduled visit included an examination of/ and monitoring of plasma HIV-1 RNA (where possible although the initial phase was considered more feasible in the context of this study), CD4, WBC, RBC, and platelet counts as per the medical experts' reports and opinions where it was applicable and doable based on resources. Notably, plasma HIV-1 RNA was ascertained after three-month duration post ART initiation as the most standard procedure and most accurate compared to CD4 values. The data collection also featured a passive surveillance component for opportunistic infections throughout the study. This was after enrollment to identify potential IRIS development as per the described IRIS case diagnosis criteria. Finally, the measurable outcomes were ascertained at the defined three stages of follow-up; intrapatum, delivery and postpartum as the final stage. There was a developed operation manual used by all study personnel describing the standardized procedures for collecting and managing data. The chart below gives a summary of data collection at every single expected visit for the six and half month follow-up period.

General demographic characteristics' data and the staging of HIV and medical history including previous illnesses and opportunistic diseases were obtained at the enrollment. Further physical exam was performed; a basic neurological exam and inspection of the skin for cutaneous abnormalities were ascertained. At visits, information on any new health complaints and self-reported outcomes was recorded. At enrollment and follow-up visits, full blood counts and basic chemistry tests information was recorded. HIV viral loads and CD4 counts were measured post ART initiation three months after where it was applicable. Signs and symptoms of TB and the related information were accounted for. In the instance of any TB symptoms at follow-up visits, elimination from

the study was done. All clinical visit information was pegged on the assistance of the study physicians/ medical officers to ascertain the best definition of IRIS cases. Type of ART combination was recorded and physical exam repeated.

The predictors and outcome variables were collected and recorded on the data collection tool. At phase one, data on IRIS and non-IRIS cases were obtained. Onward from the second trimester to delivery and the two week postpartum period, the data on pregnancy-fetal outcomes were obtained from the two cohorts identified in the first phase. In each study visit for both cohorts, the inclusion criteria guided the researcher on whether to continue with a particular study subject or not. Relevant data for the study in each visit at enrollment, selection of two cohorts, and data on APFOs were obtained respectively at each visit. At phase one, women with IRIS were identified based on published and recent criteria as per the case definition of IRIS presentation as per operational terms. Physical/clinical examination was performed with the assistance of a qualified team of gynecologists, a pediatrician with an interest in HIV, and general physicians to ascertain a case of IRIS among pregnant women put on ART in the first phase all through to the postpartum period.

3.7.1 General information

Socio-demographic, economic characteristics, and general data were collected using the structured questionnaire.

3.7.2 Blood pressure measurements

To the nearest 0.5 mm Hg using a digital arm sphygmomanometer after a 10-minute rest while in a supine position, the blood pressure of subjects was measured. The measurements were performed at each visit and if not so, active records were used to obtain such information from the health specialist’s notes attending to the study subjects.

3.7.3 Measurement of pregnancy outcomes

After delivery, pregnancy outcome records were obtained from physician's notes on the Maternal Heath Record Book and/or the woman herself using a simple checklist.

3.8 Research Variables

3.8.1 Depedent Variable

Adverse pregnancy-fetal outcome in utero, at delivery and, postpartum periods(s) including, miscarriage (spontaneous abortion), preterm delivery (PT), low birth weight (LBW), small for gestational age (SGA), stillbirth (SB), neonatal death, poor Apgar scores, neonatal sepsis, and "others".

3.8.2 Independent variables

3.8.2.1 The Main independent variable (exposure)

Maternal HIV-Immune Reconstitution Inflammatory Syndrome, in the context of this study, distinguished by a falling plasma viral load as a more important indicator combined with a typical presentation of opportunistic infection in response to antiretroviral therapy (Main criterion) with minor being; Atypical inflammatory response, increase in CD4 count, spontaneous disease resolution following ART and increase in immune responses.

3.8.2.2 Potential confounders

1. The Clinical factors

    i. Maternal placental syndrome

    ii. Chronic hypertension

iii. Maternal anemia

iv. The maternal substance/ drug abuse during pregnancy

v. Prophylaxis for opportunistic infection

vi. Cesarean section delivery

vii. Gestational diabetes

viii. Rh factor

ix. Hemoglobin level.

x. Maternal body mass index (BMI)

xi. Clinical, laboratory characteristics

xii. Obstetrical history

2. Social Demographic Factors

i. Maternal age

ii. Occupation

iii. Marital status

iv. Residence

v. Income

vi. Education

vii. Religion

viii. Age

3. Health care Services

i. Antenatal Clinic attendance
ii. Antenatal clinic care.

3.9 Data management and analysis

3.9.1 Data management

The collected data from the abstraction tool was double entered into a computer database designed using the MS-Access application approach. File back-up was done to avoid the loss or tampering with the stored data and information. Back up files were stored in CDs and/flask discs in multiples to ensure safety and reduce loss chances. Data cleaning and validation were performed to achieve a clean data set that was exported into a Statistical Package format (using SPSS version 20.0) for analysis.

3.9.2 Data analysis

Only the potential confounders that changed the relative risk of our pre-specified adverse–fetal pregnancy outcomes by more than 10%, with less than <10% missing data, were included in our final logistic regression model.

3.9.2.1 Univariate Analysis

Simple descriptive analysis comparing the frequency and distribution of the identified potential confounders between the exposure groups were performed using measures of central tendency and presented in graphs and pie charts.

3.9.2.2. Bivariate Analysis

The data were analyzed using the chi-square statistic test to establish the association between the dependent and independent variables. The level of statistical significance was then set at a p-value < 0.05.

3.9.2.3. Logistic regression

A logistic regression analysis was performed for confounding in the relationship between adverse pregnancy-fetal outcomes and maternal HIV-IRIS. Unadjusted risk estimates (uRR) for adverse pregnancy-fetal outcomes were compared between women with and without maternal HIV-IRIS using multiple logistic regression. Only potential confounders that changed the relative risk of our pre-specified adverse infant outcomes by more than 10%, with less than <10% missing data, were included in the final regression model. Adjusted odds ratio (aOR) was calculated using logistic regression models. Relative risk estimates were reported with 95% confidence intervals (CI) and the significance level was set at an alpha of 0.05 and used for all statistical analysis.

3.10 Quality Control

Research assistants were trained and pretesting on medical records and checking for their completeness was done daily. Data verification took place to ensure that the correct information was collected as well as correct data entry.

3.11 Ethical considerations

The approval to carry on with the research was sought from KNH/UON-ERC (Ethical Review Committee). A permit from NACOSTI was also obtained. Informed consent was sought from the study participants in this study. Benefits from the study at any point were maximized and confidentiality of the data collected was managed and maintained using identity codes to conceal the information on subjects. Minimization of harmful publicity was ensured. Permission and consent were sought from section heads to access active records. Authorization from hospital administrators has been sought accordingly. The results on information abstracted were treated with confidentiality and for the purpose of this study. The entry to the facility permission was sought from the hospital administration on specific visits to data collection. Principal investigator informed the heads of the purpose of entering that specific section in order to obtain the permission. Conflict of interest was identified in advance and evaded. Above all, objectivity, carefulness, openness, integrity, honesty, and responsible dissemination of findings through publication was ensured by the principal researcher.

3.12 Study limitations

Identification of IRIS was limiting based on the fact that this is a syndrome of elimination diagnosis. However, with medical experts in the areas of HIV, nurses, and clinicians with broad expertise and experience in ART, the objective to determine the IRIS cases was achieved within a 2 week-3 month-period post ART initiation. This was done by the use of International Network for the Study of HIV-associated IRIS (INSHI) Consensus Case Definition for the Diagnosis of IRIS to ensure clarity in mapping the IRIS and non-IRIS cases.

The TB infected and TB-IRIS related events and treatment affected the arm of IRIS-exposed women prior to follow-up after IRIS development and allocation of the groups, but this was taken care of by subsequently reducing the unexposed arm in-order to obtain a balance in the ratio as needed. Cosequently, IRIS occurred much later among

some non-exposed cohort (precisely, in five participants) after three months, but were also eliminated from the follow-up.

The criteria for diagnosing the exposure of interest, IRIS, was compromised by lack of sufficient resources to monitor in whole, the CD4 counts (although not much relied up on currently as fluctuayions can occur differently in cases on or not on ART) but Plasma HIV-RNA loads taken during the IRIS identification at 2-week to 3 month-period post ART initiation was used in combination with developing opportunistic infections attributable to IRIS. Again, the common nature of inflammatory responses associated with IRIS was used to ascertain the diagnosis of the latter.

3.13 Dissemination

The findings of this study have been shared with the ministry of health Nairobi County (Kenyatta National and Mbagathi hospitals). The results have also been published with the International Journal of Public Health (IJPH), the African Journals On-line (East African Medical Journal), and, Biomed Central (BMC)-pregnancy and child birth [pre-print] and the international aids society journal as an abstract. The preliminary findings have also been partially presented at a medical conference at Tanzania Health Summit in November, 2020 and the the IAS conference 2021

CHAPTER FOUR

RESULTS

4.1 Characteristics of the study participants

From August 2019 to May 2020, over 500 HIV-infected, ART-naive pregnant women were screened; 266 participants were recruited, of which 204 were included in the final analysis. Fifteen (15) of the IRIS exposed were excluded because of presenting with TB associated IRIS which was not supposed to be included in the follow-up and initiated on anti-tubercular therapy (n=15), cases with insufficient clinical data during subsequent visits (n = 6), transferred (n = 3), lack of plasma HIV-RNA profile (n=2), loss to follow up (n=5). Among the non-exposed group, the following were eliminated/loss to follow-up; cases with insufficient information (n=7), cases with TB (n=4), loss to follow-up (n=7), , developed serious complication and hospitalized (n=1) transferred out (n=3), developed symptoms of IRIS later, and eliminated (n=5) and four (4) were removed deliberately to ensure the balance of a ratio of 1; 1 (n=4). Of the remaining 204 women at the end of the follow-up, 103 (50.5%) were within the age category of 30-39, 109 (53.4%) had acquired secondary education, and 131 (64.2%) were married women. The study subjects comprised of 88 (43.1%) women with a parity of 1 and 96 (47.1%), parity of 2-3. Majority were Christians 189 (92.6%) and 102 (50.0%) had a normal weight range of 18.5 – 25.0 kg/m² with 53(26%) being overweight and above at a range of 25.0 - 29.9 kg/m².

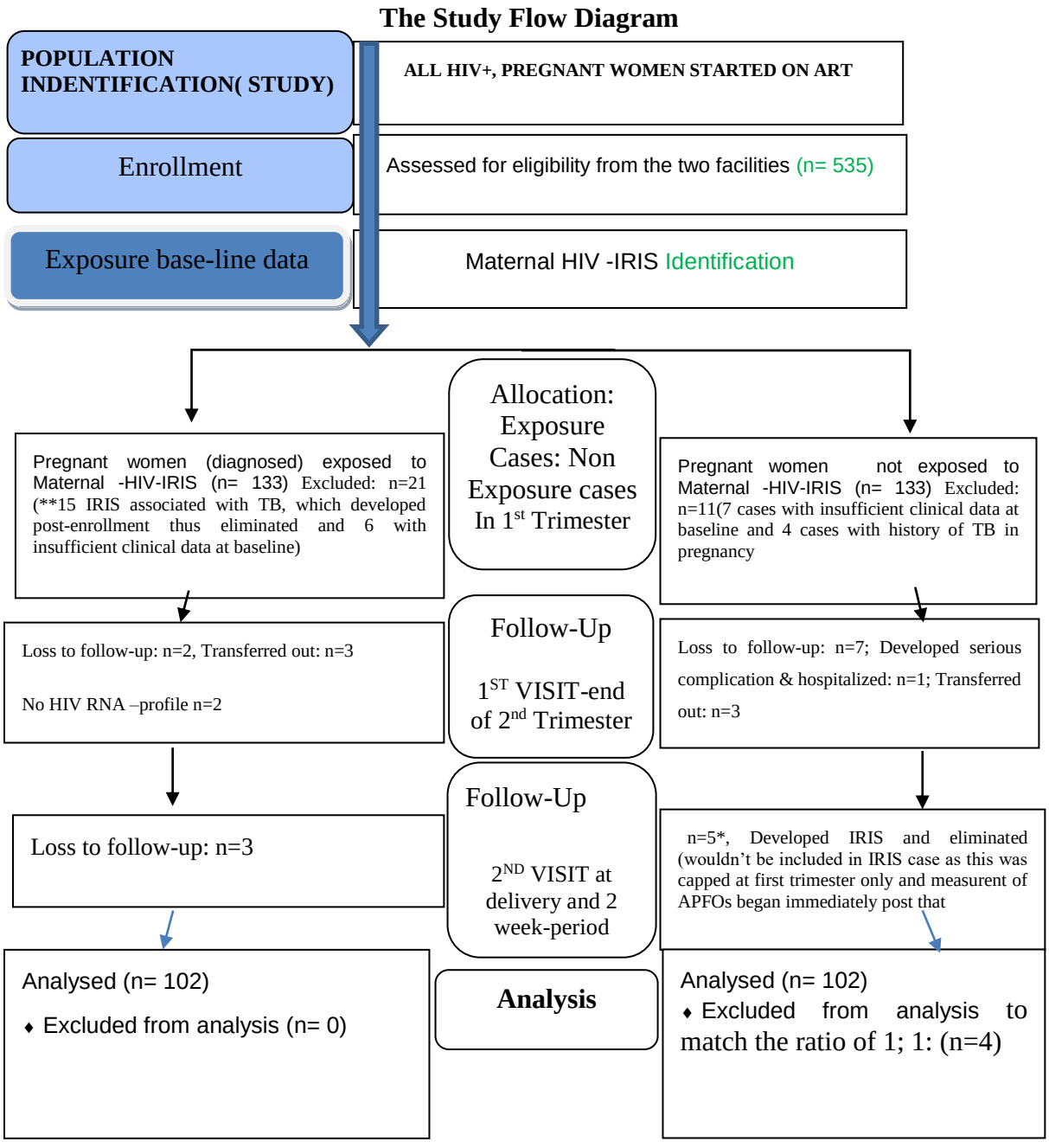


Figure 4.1: The Prospective Cohort Study flow diagram

4.2 Social-demographic and economic characteristics of HIV-positive ART initiated pregnant women

Data was collected from a total of 204 HIV-positive ART initiated pregnant women, that is, 102 diagnosed with maternal HIV Immune Reconstitution Inflammatory Syndrome and 102 not diagnosed with the syndrome, seeking antenatal care services at Mbagathi District and Kenyatta National Hospitals in Nairobi County. Most, 103 (50.5%) HIV positive ART initiated women were aged between 20-39 years. The majority, 163 (79.9%) were from the Nairobi region while the rest from other counties, with most, over sixty percent being married women. Over ninety percent of HIV positive ART initiated women were Christians with only 15 (7.4%) being Muslims. The majority of HIV-positive ART initiated 109 (53.4%) had secondary education. Only 49 (24.0%) had tertiary education. Almost half of them, 101 (49.5%) were self-employed and about a similar proportion of them 86 (42.2%) were unemployed. Only 16 (7.8%) were in civil service. On income source, 46 (22.5%) were housewives while the majority, 142 (69.6%) had some income generating activity. Only 16 (7.8%) were not known of their income source status. This ordinarily depicted that, on income generation, most of this pregnant population is not employed and most income is from self-employment as shown in table 4.1 below.

Table 4.1: HIV-positive ART initiated pregnant women social-demographic and economic characteristics

Variable	Frequency (%)
Maternal age Category in years	
20-29	73 (35.8)
30-39	103 (50.5)
40-49	28 (13.7)
Location/address	
Nairobi	163 (79.9)
Outside Nairobi	41 (20.1)
Education level	
No formal education	21 (10.3)
Primary	24 (11.8)
Secondary	109 (53.4)
Higher/university	49 (24.0)
Not recorded	1 (0.5)
Occupation	
Unemployed	86 (42.2)
Civil servant	16 (7.8)
Self-employed	101 (49.5)
Not recorded	1 (0.5)
Religion	
Christian	189 (92.6)
Muslim	15 (7.4)
Marital status	
Single	60 (29.4)
Married	131 (64.2)
Separated	9 (4.4)
Windowed	1 (0.5)
Not recorded	3 (1.5)
Income source	
Working (Self employed or employed)	142 (69.6)
House wife	46 (22.5)
Not recorded	16 (7.8)

4.3 Distribution of all women (n=204) by age category

The majority of women (both exposed to and not exposed to IRIS) were within the age category of 30-39 years 103(50.5%), followed by those within the age category of 20-29 years 73 (35.8%) and only 28 (13.7%) within the age category of 40-49 years, figure 4.2.

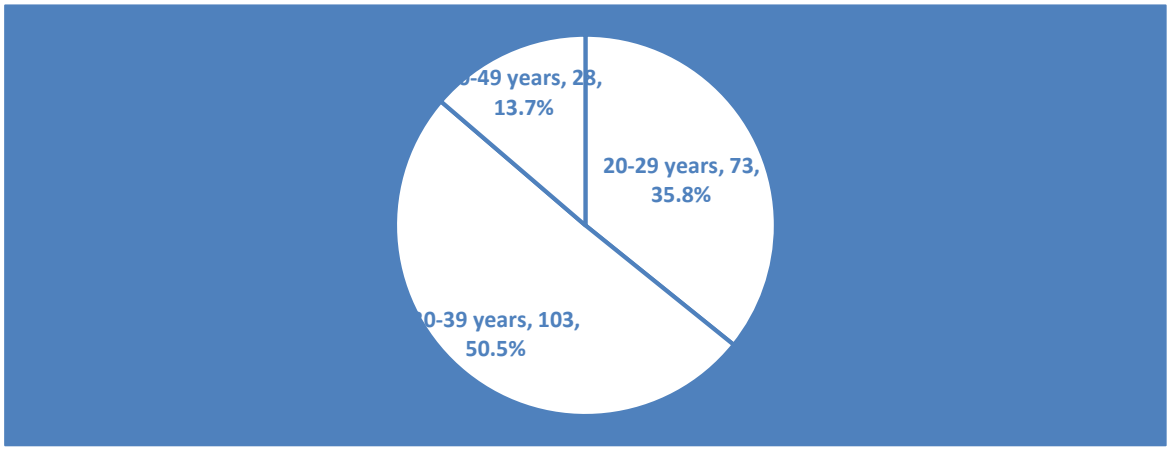


Figure 4.2: Age category distribution of all women (n=204)

4.4 Parity distribution among all women (n=204

Figure 4.3 shows that the majority of women (47.1%) had a parity of 2-3 followed closely by women who had a parity of 1 at 43.1%. Women with a parity of 6-7 were only 1 % of the total.

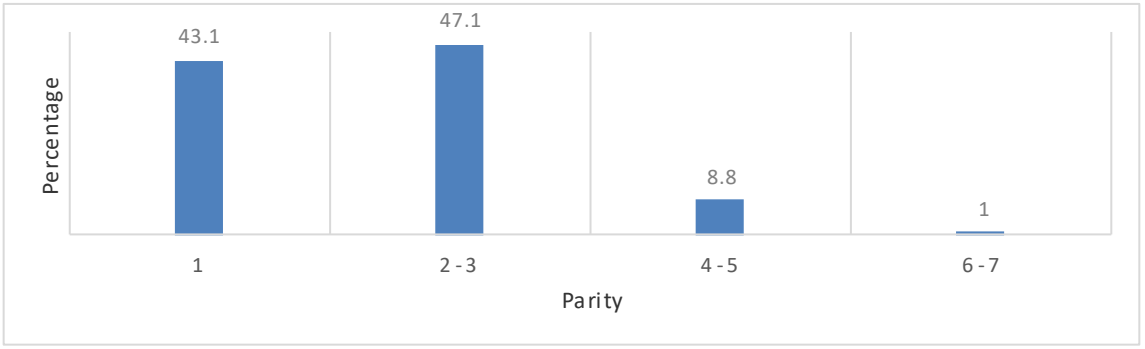


Figure 4.3: Parity distributions among all women

4.5 Proportion of women experiencing APFOs compared to women not experiencing APFOs

Figure 4.4 below shows that out of 102 exposed women to IRIS, 27 experienced adverse pregnancy-fetal outcomes compared to 11 among 102 women not exposed to IRIS

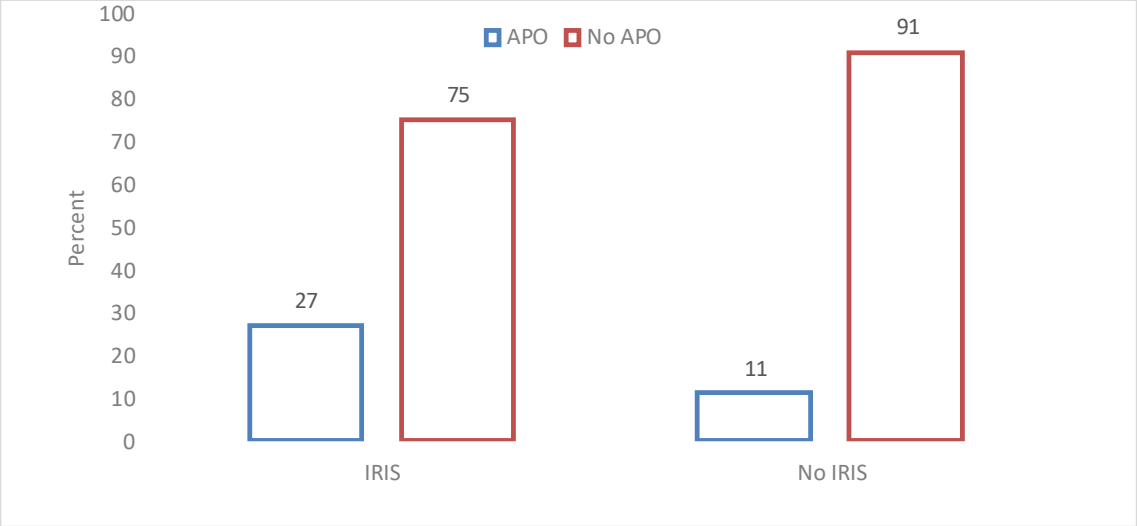


Figure 4.4: Distribution of adverse pregnancy-fetal outcomes among the IRIS exposed and non-IRIS exposed women

4.6 Distribution of WHO-HIV staging among all women (n=204) at baseline measurements

Figure 4.5 below shows that 54.9% of women were at the HIV-clinical stage one and closely, 51.9% being at the primary stage of HIV as per the World Health Organization. Only 1.5% were at clinical stage three.

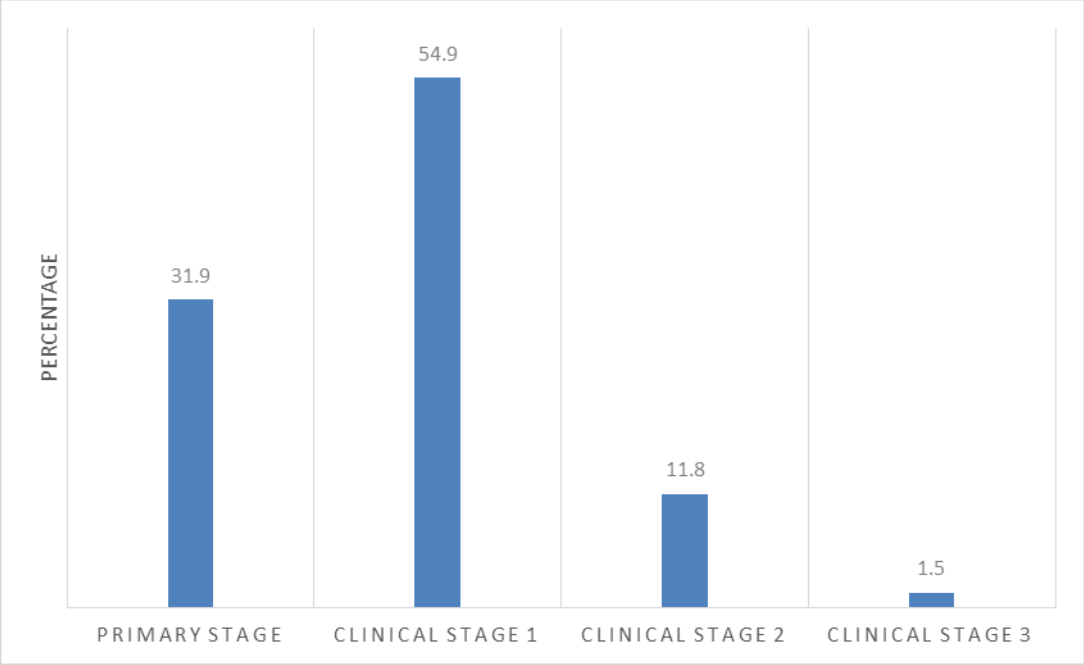


Figure 4.5: WHO-HIV Staging distributions

4.7 Woman's general health during intrapartum and at delivery among all women both exposed to IRIS and not exposed to IRIS

Fifty-seven women had some illness during intrapartum and at delivery representing 27.9 % of the total number. Seven lacked information on health status during intrapartum and at delivery representing 3.4 % as shown in figure 4.6.

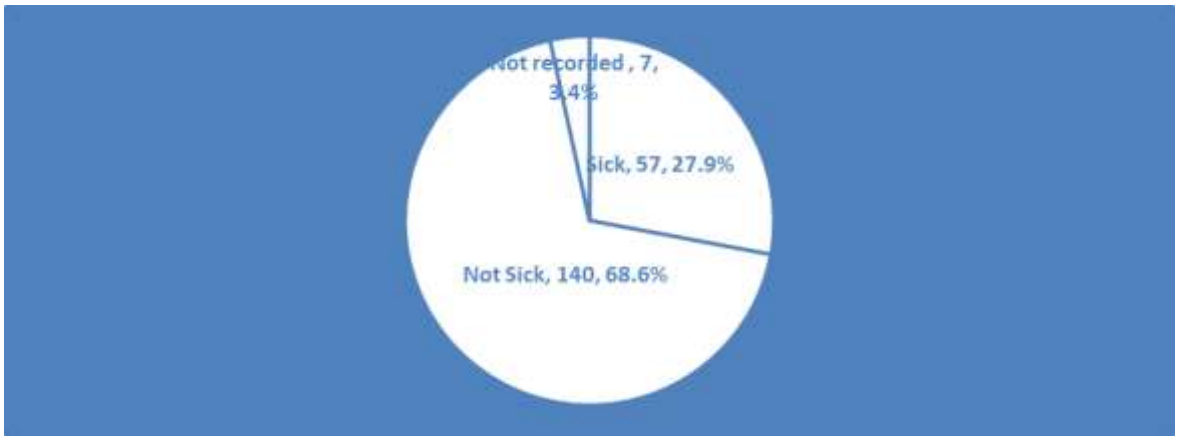


Figure 4.6: Women's general health percent distribution during pregnancy and at delivery

4.8 Comparison of mothers' general health during delivery

Analysis of the mother's general health during delivery with adverse pregnancy-fetal outcomes is shown in figure 4.7. Being sick at delivery predicted for adverse pregnancy-fetal outcomes showing a greater percentage 18 (31.6%) among all women who were sick as compared to 15 (10.7%) of all women who were not sick, showing a significant difference between the two [OR=3.8; 95% C. I; 1.8-8.3; P=<0. 001], this depicts that; the indirect effect ofimmune reconstitution inflammatory syndrome on mother's health could be connected to experiencing adverse pregnancy-fetal outcomes.

Figure 4.7: Mother's General health during delivery

4.9 Social-demographic factors associated with maternal HIV- IRIS among women attending selected facilities in Nairobi, Kenya

On maternal HIVimmune reconstitution inflammatory syndrome diagnoses as the exposure variable with social-demographic and economic characteristics of HIV-positive ART initiated pregnant women, occupation and income source was significant at P< .05, while the other characteristics were insignificant (P=/>0.05) as shown in table 4.2 below.

Table 4.2: Social-demographic factors associated with with maternal HIV-IRIS among women attending selected facilities in Nairobi, Kenya

Variable	Maternal HIV-IRIS		P value
	YES(n=102)	NO (n=102)	
Maternal age in years			
20-29	31 (30.4)	42 (41.2)	0.133
30-39	53 (52.0)	50 (49.0)	
40-49	18 (17.6)	10 (9.8)	
Location/address			
Nairobi	79 (77.5)	84 (82.4)	0.382
Outside Nairobi	23 (22.5)	18 (17.6)	
Education level			
No formal education	11 (10.8)	10 (9.8)	0.056
Primary	16 (15.7)	8 (7.8)	
Secondary	57 (55.9)	52 (51.0)	
Higher/university	17 (16.7)	32 (31.4)	
Not recorded	1 (1.0)	0	
Occupation			
Unemployed	51 (50.0)	35 (34.3)	0.036
Civil servant	9 (8.8)	7 (6.9)	
Self-employed	41 (40.2)	60 (58.8)	
Not recorded	1 (1.0)	0	
Religion			
Christian	97 (95.1)	92 (90.2)	0.180
Muslim	5 (4.9)	10 (9.8)	
Marital status			
Single	32 (31.4)	28 (27.5)	0.165
Married	60 (58.8)	71 (69.6)	
Separated	6 (5.9)	3 (2.9)	
Windowed	1 (1.0)	0	
Not recorded	3 (2.9)	0	
Income source			
Employed	7 (6.9)	5 (4.9)	0.042
Self employed	58 (56.9)	72 (70.6)	
House wife	24 (23.5)	22 (21.6)	
Not recorded	13 (12.7)	3 (2.9)	

4.10 Social-demographic predictors of APFOs

Of the 204 women, 38 (18.62%) experienced an adverse pregnancy-fetal outcome (of a particular nature. The common maternal age among the women was between 30-39 years with a larger proportion of this age category being in women who did not experience adverse pregnancy-fetal outcomes but this observation was not significant 19 (18.4); 84 (81.6) [OR = 0.9; 95% CI: 0.7-2.4; P= .728]. Mothers' status of being separated as regards marital status was found to be significant for experiencing an adverse pregnancy-fetal outcome. Adverse pregnancy-fetal outcomes were more likely among mothers with separated marital status fourfold compared to women without adverse pregnancy-fetal outcomes OR=4.2; 95%CI: 1.0-16.9; P=0.044]. There was a difference in the proportion of woman's level of education among women experiencing adverse pregnancy-fetal outcomes and those not experiencing but this observation was not significant (P>0.95). Besides, there was statistically insignificant observation at (P>0.05) between the other women's' social-demographic characteristics and adverse pregnancy-fetal outcome as indicated in table 4.3

Table 4.3: Comparison of Social-demographic characteristics between women experiencing APFOs and those who did not

Variable	APFO		OR (95% CI)	P value
	Yes n (%)	No n (%)		
Maternal age in years				
20-29	15 (20.5)	58 (79.5)	1.0	
30-39	19 (18.4)	84 (81.6)	0.9 (0.4-1.7)	0.728
40-49	4 (14.3)	24 (85.7)	0.6 (0.2-2.1)	0.473
Location/address				
Nairobi	29 (17.8)	134 (82.2)	0.8 (0.3-1.8)	0.541
Outside Nairobi	9 (22.0)	32 (78.0)	1.0	
Education level				
No formal education	1 (4.8)	20 (95.2)	1.0	
Primary	4 (16.7)	20 (83.3)	4.0 (0.4-39.0)	0.233
Secondary	22 (20.2)	87 (79.8)	5.1 (0.6-39.8)	0.123
Higher/university	11 (22.4)	38 (77.6)	5.8 (0.7-48.1)	0.104
Occupation				
Unemployed	16 (18.4)	71 (81.6)	1.0	
Civil servant	4 (25.0)	12 (75.0)	1.6 (0.4-5.6)	0.479
Self-employed	18 (17.8)	83 (82.2)	1.0 (0.5-2.2)	0.946
Religion				
Christian	36 (19.0)	153 (81.0)	1.5 (0.3-7.1)	0.742
Muslim	2 (13.3)	13 (86.7)	1.0	
Marital status				
Single	11 (18.3)	49 (81.7)	1.2 (0.5-2.6)	0.693
Married	21 (16.0)	110 (84.0)	1.0	
Separated	4 (44.4)	5 (55.6)	4.2(1.0- 17.0)	0.02
Windowed	2 (66.7)	1 (33.3)	10 (0.9-120)	0.03
Income source				
Employed	3 (25.0)	9 (75.0)	1.4 (0.3-6.1)	0.680
Self employed	25 (19.2)	105 (80.8)	1.0 (0.4-2.3)	0.961
House wife	10 (21.2)	37 (78.8)	1.0	

OR = Odds Ratio, CI= Confidence Interval, *Significant P≤ 0.05 level.

4.11 Incidence of APFOs in IRIS compared to non-IRIS women

4.11.1. Over the entire follow-up period

4.11.1.1 Cumulative Incidence of APFOs in IRIS and non-IRIS cases

The contingency table 4.4 below shows that out of 102 IRIS exposed women, 26.47% experienced adverse pregnancy-fetal outcomes compared to 10.78% among 102 IRIS non-exposed women. Cumulative incidence of adverse pregnancy-fetal outcomes in the IRIS exposed group was over double compared to that of the IRIS unexposed group. The relative risk of experiencing an adverse pregnancy outcome was 26.47 / 10.78 = 2.46. This suggests that women with IRIS had 2.46 times the relative risk of experiencing adverse pregnancy-fetal outcomes. Exposure to IRIS contributed to adverse pregnancy-fetal outcome [OR=3; 95%CI: 1.4-6.4; P=.004].

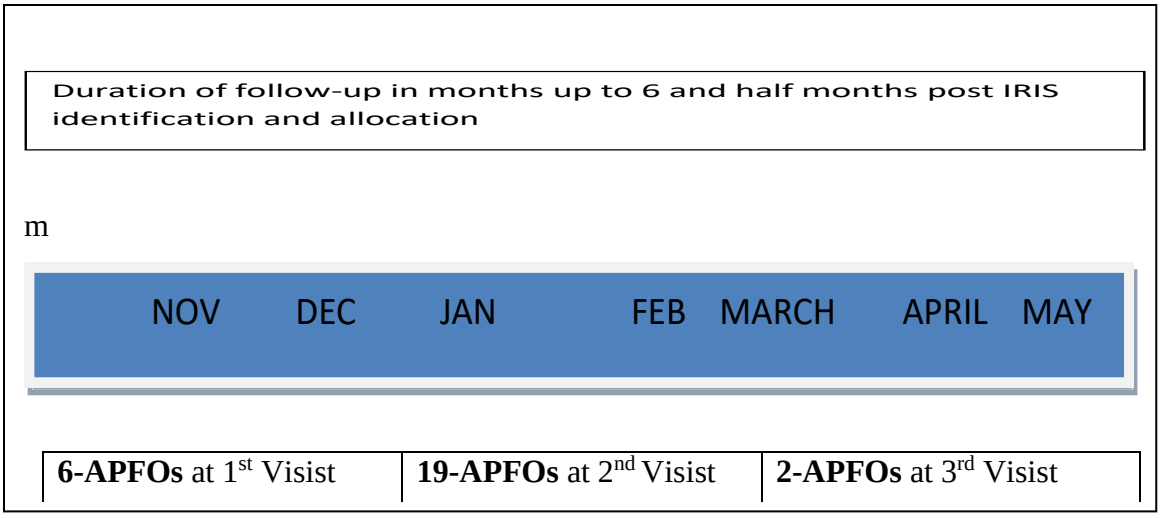
Table 4.4: Cumulative incidence and OR of APFOs in IRISRIS compared to non-IRIS women

Variable	**APFO**		**uOR**	**(95%CI)**	**P value**
	Yes	**No**			
	n (%)	**n (%)**			
IRIS					
Yes	27 (26.5)	75 (73.5)	**3.0**	**(1.4-6.4)**	**0.004**
No	11 (10.8)	91 (89.2)	1.0		

4.11.1.2 Incidence rate estimate of APFOs in IRIS and non-IRIS cases

Subjects were followed for six and half months (26weeks) post IRIS identification and allocation, with a two-week postpartum period included as the last phase of follow-up as per table 4.5.

Table 4.5: Incidence rate estimate of APFOs over the entire follow-up period (six and a half month-period post-IRIS identification



	APFOs	No-APFOs	Person-time at risk
IRIS	27	75	2259 Person-weeks = 0.012 / Week
NO IRIS	11	91	2448 Person-weeks = 0.0045/Week
Total	38	166	4707 Person-weeks
			Rate Ratio=.012/.0045=2.7

4.12.2 APFOs at specific follow-up visits

4.12.2.1 Cumulative incidence

Out of 102 IRIS exposed women, 5.8 % at the end of the second trimester, 18.6 % at delivery, and 1.96% within two weeks after delivery experienced adverse pregnancy-fetal outcomes compared to 2.9 % at the end of the second trimester, 6.9 % at delivery and 0.98 % within two weeks after delivery among 102 IRIS non-exposed women respectively. Cumulative incidence of adverse pregnancy-fetal outcomes in the IRIS exposed women was therefore higher compared to that of the IRIS unexposed women, with the incidence of APFOs at delivery being the highest in both groups at; IRIS cases, 18.6 % and non-IRIS cases at 6.9 %. The relative risks of experiencing an APFO were; 2.0 at the end of the second trimester, 2.69 at birth, and 2.0 within two weeks after delivery. Exposure to IRIS contributed to adverse pregnancy-fetal outcomes at specific points of visitation as follows; after the second trimester [OR=2.1; 95%CI: 0.502 - 8.482; P=.0.16]; at delivery [OR=2.5; 95%CI: 1.295 -8.121; P=.0.006] and within two weeks after delivery [OR=2.4; 95%CI: 0.216- 27.286; P=0.71]. This indicates a strong evidence against the null hypothesis in regard to the association between IRIS and APFOs at delivery.

Table 4.6: Incidence and OR of APFOs in IRIS compared non-IRIS women at different measurement visit times

First Visit				
Variable	**APFO**		**OR (95% CI)**	**P value**
	Yes	**No**		
	n (%)	**n (%)**		
IRIS				
Yes	6 (5.9)	96 (94.1)	2.1 (0.502-8.482)	0.16
No	3(2.9)	99 (97.1)	1.0	
Second Visit				
Variable	**APFO**		**OR (95% CI)**	**P value**
	Yes	**No**		
	n (%)	**n (%)**		
IRIS				
Yes	19(19.8)	77(80.2)	2.5 (1.295 -8.121)	**0.006**
No	7(7.1)	92(92.9)	1.0	
Third Visit				
Variable	**APFO**		**OR (95% CI)**	**P value**
	Yes	**No**		
	n (%)	**n (%)**		
IRIS				
Yes	2(2.6)	75(97.4)	2.4 (0.216- 27.286)	0.71
No	1(1.1)	91(98.9)	1.0	

4.12.2.2 Incidence rate of APFOs at different measurement visit times

Since the exact time at risk could not be determined easily, each subject was allocated 50% of the duration of time at risk of the adverse pregnancy-fetal outcome at each specific point/time of visit among the two cohorts. The first, second, and last visits, the IRIS exposed versus IRIS non-exposed women had the following adverse pregnancy-fetal outcomes each;

Table 4.7: Incidence rate of APFOs at different outcome measurement visit times

1st VISIT	APFOs	No-APFOs	Person-time at risk
IRIS	6	96	612 Person-weeks = 0.0098/ Week =98/10000 person-weeks
NO IRIS	3	99	612 Person-weeks = 0.0049/Week=49/10000 person-weeks
Total	9	195	
			Rate Ratio=98/49=2.
2nd VISIT	APFOs	No-APFOs	Person-time at risk
IRIS	19	77	1152 Person-weeks = 0.0164 / Week =164/10000 person-weeks
NO IRIS	7	92	1188 Person-weeks = 0.0058 / Week =58/10000 person-weeks
Total	26	169	
			Rate Ratio=164/58=2.8
3rd VISIT	APFOs	No-APFOs	Person-time at risk
IRIS	2	75	1001 Person-weeks = 20 / 10000 person-weeks
NO IRIS	1	91	1196 Person-weeks = 8/10000 person-week
Total	3	166	
			Rate Ratio=20/8=2.5

4.13 Adverse pregnancy-fetal outcomes and subjects' enrollment baseline clinical characteristics

Adverse pregnancy-fetal incidence was higher in women with opportunistic infections (27.8%) compared to women without opportunistic infections [OR= 2.3; 95%CI: 1.1-4.8; P=.013]**.** The incidence of adverse pregnancy-fetal outcomes was marginally associated with the cluster of differentiation (CD4 Count) of 350 cells per cubic millimeter and below at (23.6%) higher than women who had a cluster of differentiation (CD4 Count) of 350 cells per cubic millimeter and above at (13.6%) [OR=2.1; 95%CI: 1.0-4.4; P=.051]. HIV ribonucleic acid viral loads level of 50 copies/ml and above was protective for adverse pregnancy-fetal outcomes 18(31.0%) as compared to 50 copies and below 20(13.7%) [OR=0.4; 95%CI: 0.2-0.7; P=.004]. Adverse pregnancy-fetal outcomes incidence was a bit higher (25.0%) in women who experienced extensive skin

physical examination compared to (17.4%) women who did not experience extensive skin physical examination. However, there was no significant difference concerning woman's HIV staging (P >.05), previous medical history (P=0.096), neurological extensive physical examination (P= .392), full blood count (p=.141), and basic blood chemistry (P = 1.000) among the women experiencing adverse pregnancy-fetal outcomes and women not experiencing adverse pregnancy-fetal outcomes as shown in table 4.8.

Table 4.8: Clinical predictors of APFOs among HIV positive ART naïve women attending selected hospitals, Nairobi, Kenya

Variable	APFO		OR (95% CI)	P value
	Yes n (%)	No n (%)		
WHO-HIV Staging-2016				
Primary stage	12 (18.5)	53 (81.5)	1.0	-
Clinical stage 1	17 (15.2)	95 (84.8)	0.8 (0.4-1.8)	0.570
Clinical stage 2	8 (33.3)	16 (66.7)	2.2 (0.8-6.3)	0.141
Clinical stage 3	1 (33.3)	2 (66.7)	2.2 (0.2-26.4)	0.531
Medical History				
Previous illnesses				
Yes	8 (32.0)	17 (68.0)	2.3 (0.9-5.9)	0.096
No	30 (16.8)	149 (83.2)	1.0	
Opportunistic infections				
Yes	20 (27.8)	52 (72.2)	2.3 (1.1-4.8)	**0.013**
No	18 (13.6)	114 (86.4)	1.0	
Extensive Physical exam				
Neurological				
Yes	6 (26.1)	17 (73.9)	1.6(0.6-4.5)	0.392
No	32 (17.7)	149 (82.3)	1.0	
Skin				
Yes	9 (25.0)	27 (75.0)	1.6 (0.7-3.7)	0.287
No	29 (17.4)	138 (82.6)	1.0	
CD4 counts				
<350	26 (23.6)	84 (76.4)	2.1 (1.0-4.4)	**0.051**
>350	12 (12.9)	81 (87.1)	1.0	
HIV viral loads				
> 50 copies/ml	20 (13.7)	126 (86.3)	0.4 (0.2-0.7)	**0.004**
< 50 copies/ml	18 (31.0)	40 (69.0)	1.0	
Full Blood Count				
Abnormal	7 (31.8)	15 (68.2)	2.3 (0.9-6.0)	0.141
Normal	31 (17.0)	151 (83.0)	1.0	
Basic blood Chemistry				
Abnormal	1 (16.7)	5 (83.3)	0.8 (0.1-7.7)	1.000
Normal	37 (18.7)	161 (81.3)	1.0	

4.14 Comparison of women with APFOs and women without APFOs by Maternal health (during pregnancy) and/or at birth and Type of ARV Combination

The comparison of women with APFOs and women without APFOs by Maternal health (during pregnancy) and/or at birth and type of ARV Combination is presented in Table 4.9. The table indicates that a BMI value of 25.0 - 29.9 kg/m² (overweight) was not significant with APFO expirirnce [OR= 2.1; 95%CI: 1.34-6.02; P=0.08]. On the contrary, as it would be expected, the odds of adverse pregnancy-fetal outcomes in women with any maternal placental syndrome defining event (hypertensive disorder) was 80% less than in the women without maternal placental syndrome defining event with the true population effect between 100% and 10% [O.R=0.2;95% CI: 0.1-1; P=0.031]. Prophylaxis during pregnancy, maternal substance abuse, maternal anemia, cesarean section delivery, obstetrical interventions, Rhesus factor, parity, and any previous adverse infant outcome showed no significant association with experiencing an adverse birth outcome. Type of ART combination relative to adverse pregnancy-fetal outcomes was not significant and no difference in the three clusters of combinations of the ART (P> 0.05).

Table 4.9: Women with APFOs and women without APFOs by Maternal health (during pregnancy and by type of ARV Combination)

Variable	APFO		OR (95% CI)	P value
	Yes n (%)	No n (%)		
Prophylaxis during Pregnancy				
Yes	22 (21.6)	80 (78.4)	1.5 (0.7-3.0)	0.281
No	16 (15.7)	86 (84.3)	1.0	
Maternal Substance Abuse				
Yes	1 (7.1)	13 (92.9)	0.3 (0.04-2.5)	0.475
No	37 (19.5)	153 (80.5)	1.0	
MPS				
Yes	2 (5.7)	33 (94.3)	0.3(0.09-1.2)	**0.041**
No	36 (21.3)	133 (78.7)	1.0	
Maternal anemia				
Yes	3 (27.3)	8 (72.7)	1.7 (0.43-6.7)	0.433
No	35 (18.1)	158 (819)	1.0	
Caesarean section delivery				
Yes	5 (21.7)	18 (78.3)	1.2 (0.4-3.6)	0.776
No	33 (18.2)	148 (81.8)	1.0	
Maternal Body Mass index (BMI)				
< 18.5 kg/m² (Underweight)	5 (15.6)	27 (84.4)	1.1 (0.4-3.2)	0.899
18.5 – 25.0 kg/m²(normal)	15 (14.7)	87 (85.3)	1.0	
25.0 - 29.9 kg/m² (overweight)	14 (26.4)	39 (73.6)	2.1 (0.9-4.7)	0.080
> 30 kg/m² (obese)	4 (23.5)	13 (76.5)	1.8 (0.5-6.2)	0.363
Any other maternal infections/conditions/co-morbidities				
Yes	4 (23.5)	13 (76.5)	1.4 (0.4-4.5)	0.531
No	34 (18.3)	152 (81.7)	1.0	
Obstetrical Interventions				
Stress test	2 (33.3)	4 (66.7)	1.0	-
Amniocentesis	27 (18.8)	117 (81.3)	0.5 (0.08-2.7)	0.386
Tocolysis	1 (9.1)	10 (90.9)	0.2 (0.01-2.9)	0.237
Rhesus factor				
Positive	35 (19.3)	146 (80.7)	1.6 (0.5-5.7)	0.580
Negative	3 (13.0)	20 (87.0)	1.0	
Parity				
1	12 (13.6)	76 (86.4)	1.0	-
2-3	21 (21.9)	75 (78.1)	1.8 (0.8-3.9)	0.149
4-5	5 (27.8)	13 (72.2)	2.4 (0.7-8.1)	0.145
6-7	0	2 (100)		
Any previous adverse infant outcome				
Yes	6 (25.0)	18 (75.0)	1.5 (0.6-4.2)	0.406
No	32 (17.8)	148 (82.2)	1.0	

4.15 Cumulative incidences of specific APFOs and their significance with Maternal –HIV-IRIS

The incidence of miscariange (2.9% vs 2%), preterm birth (PTB) (7.8% vs 2.9%), low birth weight (LBW) (10.8% vs 2.9 %), poor Apgar score (2.0% % vs 1.0%), were higher among the HIV-IRIS case women than HIV-IRIS non-case women, with adjusted ORs of 1.5 (95%CI: 0.243 , 9.078), 2.8 (95%CI: 0.723 , 10.905), 3.8 (95%CI: 1.079 , 14.754) and 2.02 (95%CI: 0.180 , 22.633), respectively. No differences were found in the APFOs (neonatal sepsis (1% vs 0%), small for gestational age (SGA) (0.0 % vs 1.0%), and newborm intensive care unit admission (2.0% vs 0.0%), and severe newborn jaudice (0.0 % vs 1.0%)) all combined (3% vs 2%) between HIV-IRIS cases infected and HIV-IRIS non-cases group, with adjusted OR of 1.5 (95%CI: 0.25, 9.3).

Table 4.10: Specific APFOs cumulative significance with maternal-HIV-IRIS

Variable	IRIS (%)	Non-IRIS (%)	OR (95% C.I)	P –Value
APFO				
Miscarriage	3 (2.9)	2 (2.0)	1.5 (0.243 , 9.078)	0.33
LBW	11 (10.8)	3 (2.9)	3.8 (1.079 , 14.754)	**0.019**
PTB	8 (7.8)	3 (2.9)	2.8 (0.723 , 10.905)	0.067
Low APGAR	2 (2.0)	1 (1.0)	2.02 (0.180 , 22.633)	0.28
NS				
SGA				
NICA	**3 (3.0)**	**2 (2.0)**	**1.5 (0.25, 9.3) ****	
SNJ				
None	75 (73.5)	91 (89.2)		

**** Small frequency, combined with (at birth) for the P value. NS=**Neonatal Sepsis, **NICA=**New born Intesiva Care Admission, **SNJ**=Sever Neonatal Jaudice

4.16 Multiple logistic regression analysis of risk predictors for adverse pregnancy-fetal outcomes

Logistic regression was performed to evaluate the independent risk factors for adverse pregnancy-fetal outcomes. Seven (7) variables that were associated with adverse pregnancy-fetal outcomes at P<0.05 during bivariate analysis were considered in a multiple logistic regression analysis. These included: (1) woman's IRIS status, (2) separated marital status, (3) opportunistic infections, (4) HIV-RNA viral loads at baseline, (5) cluster of differentiation at baseline, (6) Mother's general health during delivery and, (7) maternal placental syndrome with a hypertensive event. After running all these factors using multiple logistic regression by specifying the 'backward conditional' progressive stepwise model with removal at P<0.05, three (3) factors were retained in the final analysis (reduced model) as presented in Table 4.11.

Among women who experienced any form of adverse pregnancy-fetal outcome, there was almost 3 times more likelyhood to have HIV-RNA viral load at baseline of above 50 copies/ml when compared to women who did not experience any form of adverse pregnancy-fetal outcome [AOR=2.7; 95%CI: 1.2-6.3; P=.017]. Maternal placental syndrome characterized by a hypertensive event was not conclusive though at the reduced model in terms of association with adverse pregnancy-fetal outcomes. This particular result is unlikely to have arisen purely by chance [AOR=0.1; 95%CI: 0.0-1.0; P = .052]. Mothers' general health during delivery was four fold more likely among women experiencing adverse pregnancy-fetal outcomes than women who did not experience adverse pregnancy-fetal outcome, [AOR= 4; 95%CI: 4.0: 1.8-9.1; P=.001]. Surprisingly, all the other predictors at full and reduced models were found to be insignificant. Again, the mother's immune reconstitution inflammatory syndrome status as the main predictor variable was found to be not associated with adverse pregnancy-fetal outcome [AOR=1.6; 95%CI: 0.4-5.8; P = .508] after controlling for significant cofounding variables during multiple regression analysis.

Table 4.11: Multiple logistic regression analysis of risk factors associated with adverse pregnancy-fetal outcomes

Variable	AOR (95% CI)	P value
Full model		
IRIS		
Yes	1.6 (0.4-5.8)	0.508
No	1.0	
Marital status		
Single	1.4 (0.5-3.6)	0.529
Married	1.0	
Separated	2.4 (0.5-11.5)	0.259
Widowed	-	1.000
Opportunistic infections		
Yes	1.8 (0.7-4.5)	0.200
No	1.0	
CD4 counts at baseline		
<350	0.5 (0.1-1.8)	0.293
>350	1.0	
HIV viral load at baseline		
> 50 copies/ml	2.8 (1.1-7.2)	0.036
< 50 copies/ml	1.0	
MPS		
Yes	0.1 (0.0-1.0)	0.048
No	1.0	
Mothers General health during delivery	3.2 (1.3-7.9)	0.014
Sick	1.0	
Not Sick		
Reduced model		
HIV viral load at baseline		
> 50 copies/ml	2.7 (1.2-6.3)	0.017
< 50 copies/ml	1.0	
MPS		
Yes	0.1 (0.0-1.0)	0.052
No	1.0	
Mothers General health during delivery	4.0 (1.8-9.1)	0.001
Sick	1.0	
Not Sick		

CHAPTER FIVE

DISCUSSION, CONCLUSIONS, AND RECOMMENDATIONS

5.1 Discussion

This current study determined the cumulative incidence, incident rate, and the predictors of adverse pregnancy-fetal outcomes as well as the effect of IRIS on adverse pregnancy-fetal outcomes and described the specific APFOs among HIV-infected ART-naive pregnant women attending Mbagathi and Kenyatta National Hospitals, with the immune reconstitution inflammatory syndrome following ART initiation within the first trimester.

5.1.1 Social-demographic, economic characteristics and adverse pregnancy-fetal outcomes among HIV positive ART initiated pregnant women

In all women studied, majority were between 20 to 45 years of age with none of the respondents being below the age of 15 years. This is consistent with KDHS 2014 findings which indicate that the reproductive age in Kenya is between 15 years to 49 years. The majority, 131 (64.2%) of the respondents were married and a proportion of 60 (29.4%) was not married. This closely correlates with KDHS 2014 survey that; six in ten (60%) women and 5 in 10 men age 15-49 are currently married or living together.

Separated women had higher odds of APFOs (P=.044). This is commensurate with studies that, specific demographic factors can affect pregnancy outcomes and complications, even with a universal healthcare system with some evidence that, for pregnancy wastage, marital status seems to be a significant fact (Kim *et al*., 2018). On parity, majority of women (47.1%) had 2-3 children followed closely by women who had a parity of 1 at 43.1% and 4-5 were at 8.8%.

Women with a parity of 6-7 were only 1 % of the total. This is consistent with the KDHS 2014 survey that most of Kenya's population of women has 2-3 children and among women with over 6 children is less than 2 %. This is consistent with KDHS, 2008/2009, and 2014 survey results indicating that, more women had conceived and given birth to at least 2 and above children. The level of was at 109 (53.4%) with secondary education and only 49 (24.0%) with tertiary education. The rest, 11.8% had a primary, and 10 % no basic education. This is somehow consistent with (KDHS, 2008/2009 and 2014) findings indicating that 7% percent of women aged 15-49 have have no education and about one-quarter of women and men have completed primary school, while 16% of women and 19% of men have completed secondary school and that 88% of women age 15-49 are literate.

As regards the religion, majority were Christians, showing the religious inclination in Nairobi and Kenya at large as per Abdullah & KDHS 2008/2009 and 2014 findings that, christianity is at 86% and muslims at about 10%. In terms of occupation, 101 (49.5%) were self-employed and about a similar proportion of them 86 (42.2%) were employed with only 16 (7.8%) being in civil service. This finding somehow inclines to Kenya employment-population ratio finding in 2016 that, 57.6% are in employment. On income source, 46 (22.5%) were housewives while majority, 142 (69.6%) had some work to generate some income, findings close to those of KDHS, 2014.

5.1.2 The composite adverse pregnancy-fetal outcome and its association with maternal HIV immune reconstitution syndrome

This study demonstrated that, maternal HIVimmune reconstitution inflammatory syndrome is a risk factor for with an adverse pregnancy fetal outcome. It has been reported that, adverse birth and pregnancy outcomes are linked to comorbidities among pregnant women receiving ART by posing a danger to pregnancy and leading to ultimate adverse maternal, birth, or pregnancy outcomes(Tsegaye & Kassa, 2018). However, after controlling for confounding factors, the association of maternal–HIV IRIS with adverse pregnancy-fetal outcomes was found to be insignificant. Hence, the finding of

this prospective cohort study supports the null hypothesis which states that "there is no significant difference in the incidence of adverse pregnancy-fetal outcomes between women with maternal HIV-IRIS and women without maternal HIV–IRIS attending the selected facilities in Kenya".

There is an evidence that HIV prevalence is higher among African women which is also replicated in Kenya (KDHS, 2016). HIV-infection among pregnant women has been linked with multiple adverse pregnancy-fetal outcomes as compared to non-infected which was due to the use of ART, as per the study done in China where adverse pregnancy outcomes were assessed by maternal HIV infection status and HIV-related factors using logistic regression analysis. The incidence of stillbirth (3.9% vs 1.1%), preterm birth (PTB) (8.9% vs 3.7%), low birth weight (LBW) (12.2% vs 3.1%) and small for gestational age (SGA) (21.3% vs 7.0%) were higher in HIV-infected women than HIV-uninfected women, with adjusted ORs of 2.77 (95%CI: 1.24-6.17), 2.37 (95%CI: 1.44-3.89), 4.20 (95%CI: 2.59-6.82) and 3.26 (95%CI: 3.26-4.64), respectively (Li *et al*., 2020).

A study, investigating perinatal outcomes associated with maternal HIV and antiretroviral therapy in pregnancies with accurate gestational age in South Africa, although not directly mentioning the IRIS as presumed to occur due to HIV-ART interaction as in the current study, established that maternal HIV infection was associated with increased risk of the composite 'adverse perinatal outcome' [Odds Ratio (OR) 1.44; 95% confidence interval (CI) 1.03, 2.03],. After adjusting for confounders, maternal HIV infection remained associated with 'adverse perinatal outcome' (adjusted OR 1.47; 95% CI 1.01, 2.14) (Santosa *et al*., 2019).

A Systematic Review (Alemu, 2014), use of ART is associated with adverse birth outcomes among pregnant women in developing countries, an issue which still was not established if it was the immune responses following the ART with the debate as to the role of maternal ART as a risk factor for adverse pregnancy-fetal outcome having been

on discussion (Bisio *et al*., 2015). This compares to the current findings of this prospective cohort study especially at birth and early neonatal stage.

Subsequently, the association between maternal ART in HIV among pregnant women and pregnancy outcomes in a systematic review study on the use of antiretroviral agents in pregnant HIV-infected women was reported to increase the risk of premature delivery (Ejigu *et al*., 2019). In another study done conducted in India, HIV-infected women were more likely to have PTB, IUGR, NICU admission indicated by several APFOs and anemia (9.4%, 9.9%, 5.2%, 9%) compared to uninfected women (7.6%, 5%, 3.8%, 2%), this did not reach statistical significance (P-value =/>0.05) (Dadhwal, MD *et al*., 2017).

Neonatal intensive care unit admissions were also significantly higher in infants born to HIV-infected women with preceding opportunistic infections following ART (P-value=0.002) (Dadhwal, *et al*., 2017). Similarly, a study on the association between maternal HIV among ART-treated women and perinatal outcomes including neonatal mortality showed some positive association (OR=1.1, 95% CI 0.63-1.93) (Xiao *et al*., 2015)

In another study, women initiating ART in pregnancy was associated with higher odds of preterm delivery (AOR, 1.4; 95% CI, 1.2, 1.8), SGA (AOR, 1.5; 95% CI, 1.2, 1.9), and SB (AOR, 2.5; 95% CI, 1.6, 3.9) (Bisio *et al*., 2015). However, these studies are not directly related to this study as they were carried out either on the direct effect of HIV infection and adverse pregnancy-fetal outcomes as well as HAART with adverse pregnancy or birth outcomes without focusing on the immune reconstitution inflammatory syndrome which is purported in this study. Again, they were conducted some in diverse populations without focusing on pregnant women, some were also pregnant women who had already been initiated on ART, while others concentrated possibly on ART combination and possible adverse drug effects on pregnancy without looking into the salient concerns behind immune reconstruction following ART. Adverse pregnancy-fetal outcomes have, however, been reported more commonly in several African studies including complications of both early and late pregnancy.

HIV may be the direct cause or a marker of a complex interaction of related medical and social conditions that affect pregnancy (Sebitloane & Moodley, 2017). Moreover, there are no studies conducted on the indirect effect of ART institution among ART-naive pregnant women on the immune reconstitution response and its possible predictor of adverse pregnancy-fetal outcomes. Again, this prospective study looked at a baseline risk of adverse pregnancy-fetal outcomes as HIV infection and only focused on the exposure of interest for the adverse pregnancy-fetal outcome as maternal HIV- IRIS, a syndrome which may not be addressed during pregnancy yet it may have negative effects on pregnancy outcome.

The research findings support the fact that other factors other than maternal HIV-IRIS predict the adverse pregnancy-fetal outcomes. Maternal health during pregnancy which may be due to IRIS is associated with adverse pregnancy-fetal outcomes. Excess adverse pregnancy-fetal outcomes in HIV-infected ART-naive pregnant women is not primarily explained by the associated opportunistic infections due to IRIS but was strongly associated with HIV-RNA-loads of > 50 copies/ml at baseline, and possibly, any form of hypertensive disorder during pregnancy or maternal placental syndrome, similar to a study done in USA and Haiti (Cates *et al*., 2015) and (Bridwell *et al*., 2019) respectively.

5.1.3 Predictors for adverse pregnancy-fetal outcomes among HIV infected women on ART

Generally, maternal HIV infection is associated with increased risks of stillbirth, PTB, LBW, and SGA, even on the condition that most HIV-infected pregnant women are usually started on ARV therapy following a positive test for HIV (H. Li *et al*., 2020). HIV infection among pregnant women bears a peculiar clinical and immunological cascade owing to the immunological changes during pregnancy meant to cater for the developing fetus, as well as the possible pharmacological effects of the HAART. The combination of these two factors seemingly complicates the gestational journey as compared to women who are HIV negative and not on any ART medication (de Dieu

Anoubissi *et al*., 2019). There is also a possibility of HIV transmission from mother to child during pregnancy, labor, delivery, or breastfeeding (perinatal transmission). Perinatal HIV transmission is the most common way children are infected with HIV with possible consequence of adverse pregnancy and related birth outcomes (Armstrong-Mensah *et al*., 2020).

Hypertensive disorder during pregnancy seemingly predicted the outcome but not conclusive as a risk factor for adverse pregnancy-fetal outcomes (AOR=0.1, 95% CI: (0.0-1.0); P=.052). Similar to this finding, in a systematic review and meta-analysis study, no single test of hypertensive disorder was a strong independent predictor of an adverse pregnancy outcome. The most promising prediction was with multivariable models, especially when oxygen saturation or chest pain/dyspnea were included, just at borderline showing other inter-related clinical courses (von Dadelszen & Magee, 2016). In another cohort study, there was a mixed prediction of both protective and significant association for adverse pregnancy and birth outcomes: decreased risk of LGA (OR 0.65, 0.51-0.83), with a recommendation that; hypertensive disorder should be combined with other maternal characteristics, medical and obstetric history when calculating an individualized adjusted risk for adverse pregnancy complications. It was found that, hypertensive disorder increases the risk for stillbirth, PE, SGA, GDM, iatrogenic PTB, and elective CS and reduces the risk for LGA (Harmsen *et al*., 2017). A study done in a facility-based setting in China predicted adverse birth outcomes similarly. Precisely stillbirth, the risk decreased as gestational age increased for all women and all subtypes of hypertensive disorder and it was similar in hypertensive and normotensive women younger than 20 years of age.

In women with a hypertensive disorder, stillbirth rate was strongly influenced by socio-demographic characteristics. Moreover, a stillbirth was more likely if the woman had received few antenatal care visits, was poorly educated, was single, widowed or divorced, had a vaginal delivery, had high parity, or was older than 40 years (Xiong *et al*., 2018). Likewise, in a study conducted on 9133 singleton nulliparous pregnancies, neither blood pressure nor blood pressure and proteinuria are accurate predictors of

severe adverse maternal and perinatal outcomes with protective but borderline effect (P=0.053) (Zhang *et al*., 2001). Likewise, in another prospective study, it was noted that HIV/ART did not outrightly configure the blood pressure trajectories and adverse pregnancy and birth outcomes association but only provided more detailed insights into the relationship between a hypertensive disorder(blood pressure, PTD, and LBW for HIV-infected and uninfected women (Malaba *et al*., 2020). Seemingly, devoid of the HIV status and ART use in pregnancy, an Ethiopian study has shown that, higher incidences of adverse perinatal outcomes has occurred among women pregnancy-induced hypertension as compared to normotensive (66.4% vs 22.2%) with a higher risk of low birth weight (adjusted RR (95%CI) = 5.1(3.4,7.8)), birth asphyxia (aRR = 2.6(1.9,3.8), small for gestational age (aRR = 3.3(2.3,4.6)), preterm delivery (aRR = 5.2(3.4,7.9)), stillbirth (aRR = 3.46(1.40,8.54)), admission to neonatal intensive care unit (aRR = 5.1(3.1,8.4) and perinatal death (aRR = 3.6(1.8,7.4)) compared to normotensive pregnant women (Berhe *et al*., 2019). This tends to define the closer relationship of hypertensive disorder with adverse pregnancy-fetal outcome in this current prospective study. Another study also concluded that, chronic hypertension was associated with some specific pregnancy complications and at the same time, protective for others and that, should be combined with other maternal characteristics and medical and obstetric history when calculating an individualized adjusted risk for adverse pregnancy complications (Panaitescu *et al*., 2017). While another found that, pre-eclampsia, chronic hypertension alongside other factors were associated with low birth weight outcome (Magee *et al*., 2020), depicting the borderline nature of association in this current study findings.

A woman's general health during pregnancy and at delivery is a very key area of concern on the birth outcome. Mother's general health was highly significant for adverse pregnancy-fetal outcomes in this prospective cohort study. There are mechanisms thought to account for the synergy between neonatal mortality outcome and infections during pregnancy and delivery that lead to neonatal mortality by affecting proper fetal growth and development. Regarding this, women who were defined as a 'sick' case in

this study had four times incident of adverse pregnancy-fetal outcomes compared to women who were not defined as sick within the same periods of time [OR=4; 95%CI:1.8-9.1; P=.001], which is reflective to a case-control study done in Jimma University on determinants of adverse pregnancy-fetal outcomes where; mothers who had an illness during current pregnancy had seven times to experience an adverse birth outcome than those who were not ill, AOR=7.22, 95% CI:1.65-31.58] (Yeshialem *et al*., 2017). Another similar trend with detection of a (H1N1) pdm09-specific antibodies was associated with a lower 10th percentile of birth weight, β = − 159 g (95% CI − 309, − 9), with influenza infection during pregnancy predicting a reduction of only but the birth weight of the smallest children (Laake *et al*., 2018). In another Chinese hospital-based study, maternal HBsAg carriage was associated with increased risk of pregnancy-induced hypertension [adjusted odds ratio (AOR)=2.20; 95% confidence interval (CI), 1.30-3.73], fetal distress (aOR=1.40; 95% CI, 1.09-1.78), cesarean delivery (aOR=1.70; 95% CI, 1.45-1.99), and macrosomia (aOR=1.68; 95% CI, 1.19-2.37) (Wan *et al*., 2017). This finding compares well with a study that described the prevalence of adverse pregnancy outcomes (APOs) in Chinese HIV-infected pregnant women, and examined the relationship between maternal HIV infection /HIV-related factors and APOs (H. Li *et al*., 2020). Similarly, a study under the bulletin of WHO showed a pooled estimate of neonatal mortality were 12.3%(95% CI: 9.3-16.2) among women with syphilis and 3.0%(95%CI: 2.1-4.3) among women without, for an absolute difference of 9.3% showing more risk among women with syphilis and untreated (Korenromp *et al*., 2019).

HIV-RNA viral load of >50 copies/ml at the baseline during the first trimester among the HIV positive ART-naive women was associated almost three times with adverse pregnancy-fetal outcomes as compared to HIV-RNA viral load of < 50 copies/ml. This was regarding being a risk factor for IRIS identification which was the main predictor variable for adverse pregnancy-fetal outcomes. This correlates with a USA based study on the burden of viral load which showed that the extent of HIV replication during pregnancy, as represented by plasma HIV RNA viral load, predicted an adverse pregnancy-fetal outcome; the risk of pregnancy loss for those with log10 viral load

>4.00 before pregnancy ended was 1.59 (95% confidence interval (CI): 0.99, 2.56) times as high as the risk for women whose log10 viral load was ≤1 (Cates *et al*., 2015). In a study conducted in Ethiopia, which although compared HIV positive and HIV negative women, there was a significant prevalence of low birth weight and preterm delivery among infants born to HIV-positive mothers (Kebede *et al*., 2013). This tends to explain the effect of viral loads in HIV after infection, similar to the current cohort study findings.

The study indicates that adverse pregnancy-fetal outcomes significantly associated with opportunistic infections OR= 2.3; 95%CI: (1.1-4.8); P=.013) in bivariate analysis, but it did not predict neonatal mortality outcome at the logistic regression level. This is similar to a study among Nigerian women where opportunistic infections (OR: 2.11; CI: 1.56-3.45) were to be associated with the adverse obstetric and neonatal outcome which confirmed the association of HIV, severe immunosuppression and opportunistic infection and adverse obstetric and neonatal outcome (Ezechi *et al*., 2013). Similarly, a review protocol provides evidence that chlamydia in pregnancy is associated with a small increase in the odds of multiple adverse pregnancy outcomes (Olson-Chen *et al*., 2018). This fact of opportunistic infections predicting adverse pregnancy-fetal outcomes is commensurate with the mother's general well-being at delivery in this study, which, shows a four-fold prediction rate for adverse pregnancy-fetal outcomes at logistic regression, reduced model.

5.1.4 The adverse pregnancy-fetal outcome forms and distribution among the study cohorts of pregnant women

Overall, 38 adverse pregnancy-fetal outcomes 38/204 (18.6 %) were noted. This corresponds with the existing findings in a study done in Ethiopia where a total of 580 respondents, 106(18.3%) (95%CI = 0.3–38.6%) had child-related adverse birth outcomes (Tsegaye & Kassa, 2018). Regarding the forms of adverse pregnancy-fetal outcomes experienced by women in this study, low birth weight had a higher cumulative incidence overall among 204 women of both cohorts with 14 representing (6.9%)

distributed as 11(10.8%) and 3(2.9%) in IRIS and non-IRIS respectively, followed by preterm birth with 11 cases of the overall study population distributed as 8 (7.8%) and 3 (2.9%) respectively among IRIS and non-IRIS exposed cohorts. These findings are similar to a study that established most prevalent adverse pregnancy-fetal outcomes were low birth weight, preterm birth, and stillbirth (Abdi *et al*., 2019). Similar to the current study findings, a clinical trial study in pregnant women on combined ART drugs, the investigators established a higher risk of severe adverse birth outcomes as very preterm delivery and very low birth weight being common (Sebikari *et al*., 2019). Another study similarly established that most adverse pregnancy outcomes, commonly LBW were common in HIV coupled with the obvious ART remedy (Yang *et al*., 2019), and also, LBW, < 2500 was at an average of 14 % between HIV infected and non-infected cohorts of pregnant women (Zenebe *et al*., 2020). The findings are also consistent with a report and a study that, preterm birth affects approximately 11% of births worldwide (Vogel *et al*., 2018), while LBW is estimated to be at 14.6% (uncertainty range [UR] 12.4–17.1) worldwide as a prevalence in 2015 with sub-Saharan Africa alone at 14% with approximately 15% of preterm newborns occurring before 32 weeks of gestation (Blencowe *et al*., 2019). Neonatal sepsis had an overall incidence of less than 1(0.5%) in the entire study population (204) and 1/38 (2.6%) among the experienced adverse pregnancy-fetal outcomes, of which this proportion was only among the IRIS diagnosed women. This finding is closely related to a study in Zambia which found that maternal HIV infection was associated with a reduced risk for neonatal sepsis (OR = 0.46; 95% CI, 0.23-0.93) (Kabwe *et al*., 2016), similarly, the findings reflect those of a study in South Africa where the overall incidence of neonatal sepsis was 3.9% and remained quite constant throughout the period, ranging from 0.25-0.63 (Velaphi *et al*., 2019). A Nigerian based study found the incidence of neonatal sepsis was 18.2/1000 live births (1.82%) (Medugu *et al*., 2018), close to the findings in this study but it contradicts a systematic review study that established a pooled prevalence of neonatal sepsis in East Africa as 29.65% (95% CI; 23.36–35.94) (Abate *et al*., 2020), although this was among general population unlike in specific HIV infected women in this current study. The incidence of low Apgar scores was 3/204 (1.47 %), among all women with and without

IRIS as 2 and 1 respectively. This tends to depict some findings which established that, except for Apgar scores 1 - 6, all adverse pregnancy-fetal outcomes showed worsening trends among HIV-positive mothers irrespective of IRIS exposure status. Miscarriage was noted in the entire sampled population (204) at 5 (2.5%), IRIS group with 3 (2.9%), and non-IRIS group with 2 (2%). As all these women were HIV positive regardless of IRIS status and were on ART, this finding confirms a report by the UC Davis Health department of obstetrics and gynecology (2020), that; about 2-3% of pregnancies will be lost in the second trimester, but contradicts a higher incidence of (53%) in spontaneous miscarriage in a Ugandan based study (Finocchario-Kessler *et al*., 2018), although this study was among already HIV infected women who tried to conceive, unlike the current study where the pregnant women were ART-naive and diagnosed of HIV at the first antenatal visit.

5.2 Conclusions

The conclusions of this study are based on the specific objectives and findings regarding the effect of immune reconstitution syndrome on pregnancy outcomes among HIV-infected women starting ART in public hospitals in Nairobi, Kenya. Specifically;

1. Maternal HIV-IRIS predicts the risk of adverse pregnancy and foetal outcomes, including miscarriage, low birth weight, and neonatal jaundice necessitating intensive care.
2. Generally, there is a relationship between specific social-demographic and economic factors in HIV positive ART initiated pregnant women with adverse pregnancy-fetal outcomes.
3. Along side IRIS, other modifiable covariates; hyperntesive disorders, HIV-RNA viral load of >50 copies/ml at the baseline and woman's health as being sick or ill at delivery are independently associated with experiencing an APFO.
4. IRIS diagnosis basically has an absolute risk of experiencing an APFO in ART naïve HIV positive women

5.3 Recommendations

1. Monitoring IRIS cases among pregnant women, allowing the health support team to ascertain the clinical course with a possibility of an APFO due to IRIS to those at high risk.

2. Public health should consider specific social-demographic and economic factors as relates to; HIVimmune reconstitution inflammatory syndrome and possible risk factors for adverse pregnancy-fetal outcomes, without over-looking them.

3. Intensify public health support systems that address modifiable risk factors such as hypertensive disorders, Plasma HIV-RNA viral loads post ART initiation and associated infections in women

4. After ART initiation, the pregnant women should be closely monitored for signs and symptoms associated with IRIS

5.3.1 Recommendations for Further Research

This study observed and noted some important gaps which merit further research:

1. Research on explicit specific immunological biomarkers of immune reconstitution response syndrome to further elucidate their predictive nature on APFOs in HIV infected women.
2. Further research to ascertain the association of a specific adverse pregnancy **a**nd related complications, other than a composite outcome of APFO, with maternal HIV-immune reconstitution inflammatory syndrome.

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APPENDICES

Appedix 1: Analysis Process Dummy Tables

Descriptive Statistics

	Respondent Characteristics	Number(n)	Percentage (%)
1	**Age**		
2	**Parity**		
3	**Education**		
4	**Gestational age**		
5	**Etc…….**		

Relative risk (incidence ratio) of adverse pregnancy-fetal Outcomes and maternal HIV immune reconstitution syndrome among the IRIS and Non-IRIS cases

IRIS CASE	Adverse pregnancy-fetal outcome	No Adverse pregnancy-fetal outcome	Total	Cumulative incidence
YES	**A**	**b**	**a+b**	**a/a+b**
NO	**C**	**d**	**c+d**	**c/c+d**
TOTAL				

Risk Ratio=a/a+b **divided by** c/c+d**.**

Adverse pregnancy-fetal outcomes and maternal HIV immune reconstitution syndrome (Main independent variable) with other confounding factors

Outcomes	overall N=266	IRIS diagnosed N=133	NON-IRIS diagnosed N=133	C.I (95%)	P-Value
a) APFO					
1.Neonatal Mortality					
2. LBW					
3. PTB					
4. Etc……					

b)Other confounders …
c)

Table 1 [Table 3.6]: Dummy: Multiple Logistic regression analysis (full and reduced modelling) of IRIS and other predisposing factors of APFOs [confounding and effect modification]

Variables	**AOR**	**95% C.I**	**P-Value**
		LOWER UPPER	
Full Model			
IRIS			
1. X			
2. Y			
3. Z			
4. ETC….			
Reduced Model			
1.Z			
2.Y			
ETC…..			

Appendix II: Chart on data collection at every single visit during follow-up

Timing-(Duration)	Phase 1 **At initial visit**	Phase 2 **At 3 months**	Phase 3 **At 6 months**	Phase 4 **At 9 months**	Phase 5 **2-weeks after delivery**
	Enrollment	*Recruitment (10-12 weeks)*	*Follow-up (First Visit) (Second Trimester)*	*Follow-up (Second Visit) (Third Trimester)*	*Delivery and post-partum period*
Data Collection tool	(Feasibility assessment) Screening data collection forms is to collect individual initial level information	IRIS event Identification to obtain the arms of the cohorts	Pretested instrument	Pretested instrument	Data collection instrument as per report from specialist
Parameter/ Information gathered	Social demographic characteristics & HIV-status (The maternal Characteristics)	-ART medication -HIV-Viral Load -CD4-Counts - Opportunistic Infections IRIS defined Event (*the defining indicator for exposed and non-exposed women*)	-ART Compliance -Any adverse fetal outcome as per the data collection instrument	-ART Compliance -Any adverse pregnancy-fetal outcome as per the data collection instrument	Any adverse fetal-pregnancy outcome
Data Collectors(concerned study personnel)	Principal Investigator and a medical specialist				-Principal Investigator - HIV interested Pediatrician or his/her report

Appendix III: General Information Abstraction Tool

DATA **ABSTRACTION TOOL** FOR OBTAINING INFORMATION FROM SUBJECTS ON FOLLOW-UP				
STUDY TITLE **Institutions and Investigators**				
(Investigator) P.I-- JOHN K. MUTHUKA	**Institution** JKUAT		**Contact** +254724274843	
Section I: Basic Information(*social demographic***)-Pregnant woman –first trimester**				
No	**Information**	**Coding categories**		**Skip to**
	Serial number – **[Subject identity code]**			
	Data collector's name and signature			
	Date of retrieval	Day: _____		
		Month:_____		
		Year: _____		
	Maternal Age	Year: _____		
	Location/address	Nairobi	1	
		Outside Nairobi	2	
	Education level	No formal education	1	
		Primary	2	
		Secondary	3	
		Higher/university	4	
		Not recorded	00	
	Occupation	Unemployed	1	
		Civil servant	2	
		Self-employed	3	
		Other (specify)_____	44	
	Religion	Christian	1	
		Muslim	2	
		Buddhist	3	
		Hindu	4	
		Traditional	5	
		Other (specify):_____	44	
		No religion	6	
		No response	99	
	Marital status	Single	1	
		Married	2	
		Separated	3	
		Windowed	4	
		Not recorded	00	
	Income source	Employed	1	
		Self employed	2	

		House wife	3	
		Not recorded	00	

Section II: Information related to maternal health (during pregnancy) and/or at birth, (Predictor variable - **maternal HIV-IRIS) Status**, Clinical factors (*Prepartum, Intrapartum and Postpartum*) , *Laboratory characteristics*, Obstetrical history, antenatal care and attendance, and Mothers' behavior during Pregnancy

No	**Questions /Statement**	**Coding categories**		**Skip to**
1.	**EXPOSURE** (Maternal HIV-IRIS)	Present **(a)***paradoxical***(b)***Un-masking*	1	
		Absence	2	
2	**Moderating Variables**			
	a)HIV/AIDS STATUS	CD4 Count Plasma HIV-RNA Concentration CDC-HIV Classification(clinical)		
	b) ARV Use Categories	Any use? ARV Therapy Duration (*Treatment or prophylaxis*)		
	c) Prophylaxis during Pregnancy	ISONIAZID/Other TB Drugs TMP-SMX		
	d) Maternal Substance Abuse	Alcohol Other Drugs		
	e) Maternal Placental Syndrome Hypertensive Disorders.....1 (Pre-*eclampsia, PIH*) Placental Abruption.....2 Placental Infarction.....3 Any-Other-Related conditions.....4			
	f)Any referral	1-YES 2-NO, If YES; Surgery Endocrine Gynecology Other		
	Maternal anemia	**1-YES**		
		2-NO		
	Caesarean section delivery	**1-YES**		

		2-NO		
	Gestational diabetes	**1-YES**		
		2-NO		
	Maternal Body Mass index (BMI).			
	Mothers General health during delivery	Sick	1	
		Not Sick	2	
		Not	3	
.	Any-other Maternal infections/conditions/co morbidities e.g.-Malaria	Yes	1	
		No	2	**
		Not	00	
	Obstetrical Interventions**	Stress test	1	
		Amniocentesis	2	
		Tocolysis	3	
	Smoking During Pregnancy	Not	00	
		Yes	1	
		No	2	
	Alcohol During Pregnancy	Not	00	
		Yes	1	
		No	2	
	Rhesus factor	Not	00	
		Positive	1	
		Negative	2	**
	Parity	1	1	
		2-3	2	
		4-5	3	
		6-7	4	
		>8	5	
	Any previous Adverse Infant Outcome	Not	00	
		Yes	1	
		No	2	
	Antenatal care and attendance	Not	00	
		Yes	1	**
		No	2	
	If yes, how many visitations	Not	00	
		One	1	
		Two	2	
		Three	3	
		Four	4	
		Not	00	

Section III. Adverse-fetal/pregnancy Information among pregnant women from first trimester through delivery to postpartum

	Date of Birth			
	Health Status at birth	Sick	1	
		Not Sick	2	
		Not	00	

Section IV. <u>The outcome</u>

PRETERM BIRTH	Yes	1	
	NO	2	
	UNKNOWN	3	
		4	

<u>Any other relevant information suitable for the study</u>

1.

2.

3.

4.

Appendix III: Distinct Data Collection Tools from Enrollment to Postpartum

DATA ABSTRACTION TOOL				
STAGE ONE: STUDY SUBJECTS ENROLLMENT				
No	**Information**	**Coding categories**		**Skip to**
	Serial number-[Subject identity code]			
	Data collector's name and signature			
	Date:	SIGN:		
	Basic Demographic Data		1	
			2	
	Maternal age			
			1	
	20-29		2	
			3	
	30-39	**NOT INDICATED**	00	
	40-49			
	WHO-HIV Staging-2016		1	
			1	
	Primary stage		2	
			3	
	Clinical stage 1		4	
	Clinical stage 2		5	
	Clinical stage 3			
	Clinical stage 5			
	Medical History	yes	1	
		No	2	
	1) Previous illnesses, if yes, state which**……**			
	2) Opportunistic infections if yes, state which**……**	yes	1	
		No	2	
	Extensive Physical exam: ***pegged on physician's report***			
			1-yes 2-no	
			1-yes2-no	

	Neurologic Skin	**others**	00	
	CD4 counts	<350 >500	1 2	
	HIV viral loads	> 50 copies/ml < 50 copies/ml	1 2	
	Full Blood Count	Abnormal-**if so, state** Normal	1 2	
	Basic Chemistry	Abnormal-**if so, state** Normal	1 2	
	TB-Screening	Signs-**reactive** No-signs-**non-reactive**	1 2	
	Any other clinical/obstetric medical related outcome during enrollment			

DATA **ABSTRACTION TOOL**				
IRIS DEVELOPMENT AND SELECTION				
No	**Information**	**Coding categories**		**Skip to**
	Serial number – **[Subject identity code]**			
	Data collector's name and signature			
	Date			
	IRIS CASE event	YES	1	
		NO	2	
	Type of iris presentation	paradoxical	1	
		exacerbated	2	
	Type of ARV Combination in ARV Naïve pregnant women	**ABC/3TC**	1	
		TDF/FTC or TDF/3TC	2	
		ATV/r plus a Preferred Two-NRTI Backbone	3	

		DRV/r plus a Preferred Two-NRTI Backbone	4	
		RAL plus a Preferred Two-NRTI Backbone	5	
	HIV viral loads	<350 >500	1 2	
	CD4 counts	> 50 copies/ml < 50 copies/ml	1 2	
	Full blood count	Abnormal-**if so, state** Normal	1 2	
	Basic blood chemistry	Abnormal-**if so, state** Normal	1 2	

DATA **ABSTRACTION TOOL**				
OUTCOME MEASUREMENTS AT 22-24 WEEKS-FOLLOW UP **& adverse infant outcome(pregnancy outcome)**				
No	**Information**	**Coding categories**		**Skip to**
	Serial number – **[Subject identity code]**			
	Data collector's name and signature			
	Date			
	IRIS-CASE event	Yes	1	
		No	2	
	Systolic/diastolic measurements	Normal	1	
		At-risk: pre-hypertension	2	
		High	3	
	Full Blood Count	Abnormal-**if so, state**	1	
		Normal	2	
	Basic blood chemistry	Abnormal-**if so, state**	1	
		Normal	2	
	HIV viral loads	<350	1	
		>500	2	
	CD4 count	> 50 copies/ml	1	
		< 50 copies/ml	2	
	ADVERSE INFANT/PREGNANCY OUTCOME			
		1-yes	1	
	Preterm birth	2-no	2	
		401–500	1	

		501–750	2	
	Birth weight	751–1000	3	
		Yes	1	
	Still birth	no	2	
			1-yes	
	Any other	…….	2-no	
DATA **ABSTRACTION TOOL**				
OUTCOME MEASUREMENTS AT 36-40 WEEKS-FOLLOW UP **& adverse infant outcome(pregnancy outcome)**				
No	**Information**	**Coding categories**		**Skip to**
	Serial number – **[Subject identity code]**			
	Data collector's name and signature			
	Date			
	IRIS-CASE event to assess	Yes	1	
		No	2	
	Systolic/diastolic measurements	Normal	1	
		At-risk: pre-hypertension	2	
		High	3	
	Full Blood Count	Abnormal-**if so, state**	1	
		Normal	2	
		Abnormal-**if so, state**	1	
	Basic blood chemistry	Normal	2	
	HIV viral loads	<350	1	
		>500	2	
		> 50 copies/ml	1	
	CD4 count	< 50 copies/ml	2	

	ADVERSE INFANT/PREGNANCY OUTCOME		1	
	Preterm birth	1-yes	1	
		2-no	2	
	Birth weight	401–500	1	
		501–750	2	
		751–1000	3	
	Still birth	Yes	1	
		no	2	
	Any other	yes	1	
		no	2	

DATA **ABSTRACTION TOOL**				
OUTCOME MEASUREMENTS AT POST-PARTUM UP [TWO WEEKS] **& adverse infant outcome(pregnancy outcome)**				
No	**Information**	**Coding categories**		**Skip to**
	Serial number – **[Subject identity code]**			
	Data collector's name and signature			
	Date			
	IRIS-CASE event to assess	Yes	1	
		No	2	
	Systolic/diastolic measurements	Normal	1	
		At-risk: pre-hypertension	2	
		High	3	
	Full Blood Count	Abnormal-**if so, state**	1	
		Normal	2	
	Basic blood chemistry	Abnormal-**if so, state**	1	
		Normal	2	
	HIV viral loads	<350	1	
		>500	2	
	CD4 count	> 50 copies/ml	1	
		< 50 copies/ml	2	
	ADVERSE INFANT/PREGNANCY OUTCOME		1	
	Neonatal mortality-early/late	1-yes	1 2	
		2-no		

	LBW, <2500G	Yes	1	
		no	2	
	Still birth	yes	1	
		no	2	
	Any other……	yes	1	
		no	2	

Appendix IV: The General Study Guide Schedule/Data Collection Tools/Questionnaire Adverse Outcome Information Assessed During Follow-Up

-Assesable ***Adverse -outcomes***		**Information: fetal-pregnancy outcome from system/ medical specialist/ etc**
-		
i.	*–Stillbirth*	death of a fetus at ≥20th weeks of gestation
ii.	*-neonatal death*	death within 30 days of life
iii.	*-preterm birth (<37 -weeks of gestation)*	gestational age
iv.	*-low birth weight (-<2500 g)*	birth weight
v.	*-macrosomia (≥4000 g)*	birth weight
vi.	*-congenital anomaly*	neonatal abnormality of chromosome and central nervous, craniofacial, cardiovascular, digestive, urogenital, skeletomuscular, and respiratory systems
vii.	*-SGA (birth weight -below the 10th -percentile for the -gestational age)*	gestational age, birth weight
viii.	***-Maternal and neonatal -confounders***	
ix.	-maternal age (y)	maternal birthday
x.	-birth year (	neonatal birthday
-		
-		
xi.	Mbagathi vs. KNH	birth region (city, county)
xii.	p-rimipara vs. multipara	Parity
xiii.	-pregnancy-related dis-	maternal anemia, diabetes, pregnancy-induced hypertension,

-Assesable ***Adverse -outcomes***		**Information: fetal-pregnancy outcome from system/ medical specialist/ etc**
	order	toxemia
xiv.	ob-stetric complication/ mothers general health	maternal fever at delivery (>38°C), meconium in the amniotic fluid, premature rupture of membrane (>12 h), placental abruption, placenta previa, massive bleeding, seizure at delivery, precipitating delivery (<3 h), breech presentation/mal-presentation, cord prolapse, prolonged labor, dysfunctional labor, fetal distress, and complications of anesthesia
xv.	<-7 vs. 7–10	Apgar score at 1 and 5 minutes
xvi.	-Cesarean section vs. v-aginal delivery	delivery mode
xvii.	Abnormal biochemistry/FBC	Any deviation from the normal scale that is usually associated with a condition or an infection due to poor balace. Eg. neutrophenia

APPENDIX-V: Informed Consent in English

-Informed Consent – ADVERSE INFANT OUTCOMES and IRIS

Stud-y title:

Adv-erse Infant Outcomes with Maternal HIV Immune Reconstitution Inflammatory Response Syn-drome among Women Attending Selected Referral Facilities in Kenya, 2018

Ins-titutions and Investigators:

R-esearcher	**Institution**	**Contact**
John Kyalo Muthuka		+254-724274843

-

I-ntroduction

-Immune reconstitution inflammatory syndrome is a restoration disease referring to a disease or -pathogen-specific inflammatory response in HIV-infected patients that may be triggered after -initiation or re-initiation of ARV therapy or change to more active ARV therapy. A paradoxical -clinical worsening of a known condition or the appearance of a new condition after initiating -therapy characterizes the syndrome. The associated risk factors / predictors/ maternal -characteristics for adverse infant outcomes with IRIS

have not been studied in Kenya among -pregnant women, with focus only on improved immunity after ART initiation. The purpose of -this study is to determine the relative risk and predictors of Adverse Infant outcome(s) with -maternal-HIV -IRIS among women and establish the composite forms of the adverse infant ou-tcomes.

Y-ou are being asked to participate in this survey because you are eligible to join the study. If you -decide to join the study, you or your health attendant will be will be asked a series of questions -regarding your socio-demographic information and HIV status, adverse infant outcomes and co-nstant review of your medical records usage.

B-efore you decide if you wish to be in this study, you need to know about any good or bad things -that could happen if you decide to join. This form tells you about the study. You can ask any q-uestions you have at any time.

Being in the study is your choice:

This consent f-orm gives you information about the study, the risks and benefits, and the process that will be e-xplained to you. Once you understand the study, and if you agree to take part, you will be aske-d to sign your name or make your mark on this form. You will be given a copy to take home.-

Before yo-u learn about the study, it is important that you know the following:

- Y-our participation in this study is entirely voluntary whether directly or indirectly

- -You may decide to withdraw from the study at any time, without facing any cons-equences

Purpose of- the study:

The purp-ose of this study is to determinewhetherimmune reconstitution inflammatory syndrome among p-regnant women may be linked to any adverse infant outcomes. Kenyatta National and Moi Te-aching and referral hospitals are being selected for this study. The study will be using semi-s-tructured data collection tool which will be obtained prospectively about IRIS and adverse infan-t outcomes.

What to expect during the interview

I w-ill ask you few questions regarding HIV and ART use or actively review your records from m-edical personnel.

I-f you choose not to participate or to leave the study:

-You have the choice to not participate in this research study. If you choose not to participate in -this study or to leave the study during the interview process, you may do so freely without co-nsequences against you.

R-isks and/or discomforts:

-I do not anticipate any risks or discomforts to you during this study. You will be requested to -avail yourself for an interview at a time and place that you are most

comfortable. You may be-come worried or anxious about discussing matters of HIV related questions. Every effort will b-e made to protect your privacy and confidentiality while you are participating in the study. The interviews will take place in private.

Benefits to you:-

You may get no -direct benefit from the information you provide for this study. However, the results will be u-sed to assist in formulating policies that may initiate prevention strategies against preventable ad-verse infant outcomes in relation to IRIS in HIV infection.

Costs to you: -

There is no cost to you for -participating in this study apart from your precious time.

Your records will be priv-ate:

Every effort will be mad-e to keep the information you provide confidential. You will be only identified by a code and- personal information from the interview will not be released without your written permission-n. The information in the data collection tool cannot be identified as belonging to you. You- will not be personally identified in any publication about this study. Your records may be revie-wed by UoN-Ethics Committee.

Injury because of p-articipating in this study:

It is unlikely that a-ny form of injury could happen to you as a result of being in this study. It is important that yo-u tell the study staff if you feel that you have been irritated or damaged because of taking part in- this study.

Problems and- questions:

You will be g-iven a copy of this form to take with you or your health attendant. If you have any questions or -concerns about your rights as a research participant, please contact to:

The -Dean;

School of public Health

Jo-mo Kenyatta University of Agriculture and Technology

P.-O. Box 62200-00200; Nairobi

T-el: 254-67-52711/52181-4
-Fax: 254-67-52161

- director@itromid.jkuat.ac.ke

Your rights as a study- participant:

This research has -been approved and reviewed by the UoN-ERC. This committee has reviewed this stud-y in order to help protect participants. If you have any questions about your right as rese-arch participant you may contact to: The

secretary, UoN Ethics Review Committee on: **P-. O. Box 19676 Code 00202 NairobiTel. (254-020) 2726300-9 Ext 44355**

Your statemen-t of consent and signature:

If you have read the informed consent, or have had it read and explained to you, and you understand the information and voluntarily agree to join this study, please carefully read the statements belo-w and think about your choice before signing your name:

- I have b-een given the chance to ask any questions I may have and I am content with the answer-rs to all my questions.
- I kno-w that any information I give will be kept confidential and that I may leave this stud-y at any time.
- If I -leave or refuse to be in the study, I understand that there will be no repercussions.
- Th-e name, phone number and address of who to contact in case of an emergency has be-en told to me and has also been given to me in writing.
- I -agree to take part in this study as a volunteer, and will be given a copy of this informed c-onsent form to keep.

……-……

……..

Partic-ipant's name Participant's signature and date

……-……

……..

Int-erviewer's name Interviewers' signature and date

…-……

……..

R-esearcher's name Researcher's signature and date -

APPENDIX-VI: Informed Consent in Swahili

KIAM-BATISHO 2: RIDHAA

Ridha-a - Mabaya Infant Outcomes na kinga kurekebishwa na uchochezi ugonjwa

Utafi-ti kuhusu:

Mba-ya watoto wachanga Matokeo kwa wajawazito HIV Kinga kurekebishwa kuvimba Response Syn-drome Kati ya wanawake wanaohudhuria Baadhi Vifaa Rufaa nchini Kenya, 2018

Ta-asisi na wakaguzi:

M-tafiti	**Taasisi**	**Kuwasiliana na**
J-ohn Kyalo Muthuka	Jomo Kenyatta University of Agriculture and Technology	+254-724274843

U-tangulizi

-Kinga kurekebishwa na uchochezi ugonjwa ni ugonjwa marejesho akimaanisha ugonjwa au -maalum kwa visababishi magonjwa uvimbe wenye wagonjwa HIV ambazo zinaweza -kusababishwa baada ya kuanza au re-kuanza kwa ARV au kubadilisha kwa tiba ya kazi zaidi ya -ARV. kweli kinzani kliniki mbaya ya kujulikana hali au kuonekana ya hali mpya baada -kuanzisha tiba sifa syndrome. Kuhusishwa na hatari ya mambo / uaguzi / tabia ya mama kwa -matokeo mbaya ya watoto wachanga na IRIS si alisoma katika Kenya miongoni mwa wanawake -wajawazito, na lengo tu juu ya kuboresha kinga baada ART kufundwa. Madhumuni ya utafiti -huu ni kuamua hatari ya jamaa na predictors ya mbaya watoto wachanga matokeo (s) kwa -wajawazito na virusi vya ukimwi -IRIS katika wanawake na kuanzisha aina Composite ya -matokeo mbaya watoto wachanga. Wewe ni kuwa kuulizwa kushiriki katika utafiti huu kwa -sababu wewe ni haki ya kujiunga na masomo. Ukiamua kujiunga utafiti, wewe au afya ya -mtumishi yako itakuwa atatakiwa mfululizo wa maswali kuhusu taarifa yako ya kijamii na idadi -ya watu na hali ya VVU, matokeo mbaya ya watoto wachanga na mapitio mara

kwa mara ya -matibabu rekodi ya matumizi yako. Kabla ya kuamua kama unataka kuwa katika utafiti huu, -unahitaji kujua kuhusu mambo yoyote mema au mabaya yanayoweza kutokea ikiwa kuamua ku-jiunga. Aina hii anaelezea kuhusu utafiti. Unaweza kuuliza maswali yoyote uliyonayo wakati w-owote

-

Kuwa -katika utafiti huo ni uchaguzi wako:

Fomu- hii ya ridhaa inatoa taarifa kuhusu utafiti huu, hatari na faida, na mambo mengine ambayo utael-ezewa. Baada ya kuelezewa na kuelewa utafiti, kama utakubali kujihusisha na utafiti huu , utau-lizwa kuweka ishara ya jina lako au kufanya alama yako juu ya fomu hii. Utapewa nakala ya -kuchukua nyumbani.

K-abla ya kujifunza juu ya utafiti huu, ni muhimu kujua yafuatayo:

- -Ushiriki wako katika utafiti huu ni hiari kabisa
- Unawez-a kuamua kujiondoa katika jaribio wakati wowote, bila kukabiliwa na madhara yoyote -

Madhumuni ya utafiti:-

Madhumuni ya utafiti huu -ni kwa determinewhether kinga kurekebishwa na uchochezi ugonjwa miongoni mwa wanawake- wajawazito inaweza kuunganishwa matokeo yoyote mabaya watoto wachanga. Kenyatta Taifa- na Moi Kufundisha na hospitali ya rufaa ni kuwa kuchaguliwa kwa ajili ya utafiti huu. Utafi-ti huo utakuwa kutumia nusu muundo ukusanyaji wa data chombo ambayo itakuwa kupatik-ana kwa matazamio kuhusu IRIS na matokeo mbaya watoto wachanga.

Nini cha kutarajia wak-ati wa mahojiano:

Utaulizwa maswali mac-hache kuhusu madawa ya VVU na matokeo ya mimba au mtoto.

Ukichagua kutoshirik-i au kuondoka kwenye utafiti:

Una uhuru wa kutosh-iriki katika huu utafiti. Ukiamua kutoshiriki au kuondoka kenye utafiti wakati wa mahojiano-, unaweza kufanya hivyo kwa uhuru bila madhara dhidi yako.

Uwezekano wa Hat-ari

Sitarajii hatari yoyo-te kwako wakati wa utafiti huu. Utatarajiwa kufika kwa ajili ya mahojiano wakati na mahali -ambAPFO ni sawa na wewe. Unaweza kuwa na wasiwasi kuhusu kujadili masuala ya mada-wa ya VVU. Kila juhudi zitafanywa kulinda faragha yako na usiri wakati wewe unashiriki katik-a utafiti. Mahojiano yatafanyika kwa feraga.

Faida zinazow-eza kutokana na utafiti huu:

Kunaweza ku-wa hakuna faida ya moja kwa moja kutokana na habari utataoa kwa ajili ya utafiti huu. Hata hiv-yo, matokeo yatatumika kusaidia katika kutunga sera ambazo zinaweza kuanzisha mikakati ya -kuzuia dhidi ya matokeo mabaya ya mimba au mtoto.

Gharama:-

Hakuna ghar-ama kwako kwa ajili ya kushiriki katika utafiti huu mbali na wakati wako.

Rekodi yak-o itakuwa siri:

Kila juhud-i zitafanywa kuweka habari utakazotoa siri. Hauhitaji kuandika jina lako na taarifa za kibinafsi -ambazo utatoa katika mahojiano hazitatolewa bila idhini yako

iliyoandikwa. Habari katika do-doso haiwezi kutambuliwa Kama ni yako. Habari zozote binafsi hazitatolewa katika uchapish-aji wowote kuhusu utafiti huu. Rekodi yako inaweza kupitiwa na Kamati ya Maadili Chuo K-ikuu Cha Nairobi kushirikiana na hospitali kuu ya kenyatta

Kuumi-a kwa sababu ya kushiriki katika utafiti huu:

Hakun-a uwezekano kwamba aina yoyote ya kuumia inaweza kutokea kutokana Na utafiti huu. Ni muhi-mu kumweleza wafanyakazi utafiti Kama wewe umehisi kukasirika kwa sababu ya kushiriki katik-a utafiti huu.

Ma-tatizo Na maswali:

Ut-apewa nakala ya fomu hii kuchukua Na wewe. Kama una maswali yoyote au wasiwasi juu ya h-aki zako Kama mshiriki wa utafiti, tafadhali wasiliana na:

-

The D-ean;

Shul-e ya afya ya umma

Jom-o Kenyatta University of Agriculture and Technology

P.O-. Box 62200-00200; Nairobi

Te-l: 254-67-52711/52181-4

F-ax: 254-67-52161

-director@-itromid.jkuat.ac.ke

Haki zako Kama mshiriki katika utafiti:

Utafiti huu um-epitishwa Na kupitiwa Na KNH-UON-ERC. Kamati hii imepitia huu utafiti Ili kusaidia kuli-nda haki za washiriki. Kama una maswali yoyote kuhusu haki yako Kama mshiriki wa- utafiti unaweza kuwasiliana Na: The secretary, **P. O. Box 19676 Code 00202Nairo-biTel. (254-020) 2726300-9 Ext 44355**

Kauli yako- ya ridhaa Na saini:

Kama um-esoma ridhaa, au Kama imesomwa Na ukaelezewa, Na umeelewa habari Na hiari Na umekuba-li kujiunga Na utafiti huu, tafadhali kusoma Kwa makini maelezo ya hapa chini kabla ya kusaini -jina lako:

- -Nimepewa nafasi ya kuuliza maswali yoyote Na Nina uhakika kuhusu majibu ambayo ni-mepeana.
- N-ajua kwamba taarifa yoyote nimetoa itakuwa siri Na kwamba Mimi ninaweza kuondoka k-wenye utafiti huu wakati wowote.
- -Nikiamua kuondoka au kukataa kuwa katika utafiti, naelewa kwamba hakutakuwa Na m-adhara.
- J-ina, namba ya simu Na anuani ya kuwasiliana katika kesi ya dharika kuandika.

- -Mimi kukubaliana Na kuchukua sehemu katika utafiti huu Kama kujitolea, Na nimepewa -nakala ya fomu hii ya ridhaa ya kutunza.

…….-……

……..

Jina la- mhojiwa Saini ya mhojiwa Na tarehe

……-……

……..

Jin-a la mhojaji Saini ya mhojaji Na tarehe

…-……

……..

J-ina la mtafiti Saini ya mtafiti Na tarehe

APENDIX-VII: KNH-UoN Ethical Review Committee Clearance and Approval

UNIVERSITY OF NAIROBI
COLLEGE OF HEALTH SCIENCES

KNH-UON ERC

KENYATTA NATIONAL HOSPITAL

Ref: KNH-ERC/A/221

6th June, 2019

John Kyalo Muthuka
PhD Candidate
School of Public Health
College of Health Sciences (CoHES)
JKUAT

Dear John,

RESEARCH PROPOSAL: ADVERSE INFANT OUTCOME INCIDENCES AMONG WOMEN WITH VERSUS WOMEN WITHOUT MATERNAL HIV IMMUNE RECONSTITUTION INFLAMMATORY RESPONSE SYNDROME (P609/05/2018)

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH- UoN ERC) has reviewed and approved your above research proposal. The approval period is 6th June 2019 – 5th June 2020.

This approval is subject to compliance with the following requirements:

a. Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
b. All changes (amendments, deviations, violations etc.) are submitted for review and approval by KNH-UoN ERC before implementation.
c. Death and life threatening problems and serious adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH-UoN ERC within 72 hours of notification.
d. Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH- UoN ERC within 72 hours.
e. Clearance for export of biological specimens must be obtained from KNH- UoN ERC for each batch of shipment.
f. Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (Attach a comprehensive progress report to support the renewal)
g. Submission of an executive summary report within 90 days upon completion of the study. This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/ or plagiarism.

Protect to discover

For more details consult the KNH- UoN ERC website http://www.erc.uonbi.ac.ke

Yours sincerely,

PROF. M. L. CHINDIA
SECRETARY, KNH-UoN ERC

c.c. The Principal, College of Health Sciences, UoN
The Director, CS, KNH
The Chairperson, KNH- UoN ERC
The Assistant Director, Health Information, KNH
Supervisors: Prof. Yeri Kombe (KEMRI, CPHR), Prof. Anselimo Makokha (J.K.U.A.T)

APPENDIX-VIII: NACOSTI Research License and Approval Permit

REPUBLIC OF KENYA

NATIONAL COMMISSION FOR SCIENCE,TECHNOLOGY & INNOVATION

Ref No: **640222**

Date of Issue: **09/January/2020**

RESEARCH LICENSE

This is to Certify that Mr.. JOHN MUTHUKA of Jomo Kenyatta University of Agriculture and Technology, has been licensed to conduct research in Nairobi on the topic: ADVERSE INFANT OUTCOME INCIDENCES AMONG WOMEN WITH VERSUS WOMEN WITHOUT MATERNAL HIV IMMUNE RECONSTITUTION INFLAMMATORY RESPONSE SYNDROME (CASES OF SELECTED FACILITIES IN KENYA) for the period ending : 09/January/2021.

License No: **NACOSTI/P/20/1918**

640222

Applicant Identification Number

Director General
NATIONAL COMMISSION FOR SCIENCE,TECHNOLOGY & INNOVATION

Verification QR Code

NOTE: This is a computer generated License. To verify the authenticity of this document, Scan the QR Code using QR scanner application.

APPENDIX-IX: Research Authorization [Mbagathi Hospital]

NAIROBI CITY COUNTY

Tel: 2724712, 2725791, 0721 311 808
Email: mbagathihosp@gmail.com

Mbagathi Hospital
P.O. Box 20725- 00202
Nairobi

COUNTY HEALTH SERVICES

Ref: MDH/RS/1/VOL.1

30th September 2019

John Kyalo Muthuka
JKUAT

RE: RESEARCH AUTHORIZATION

This is in reference to your application for authority to carry out a research on *"Adverse infant outcomes incidences among women with versus women without maternal HIV immune reconstitution inflammatory response syndrome."*

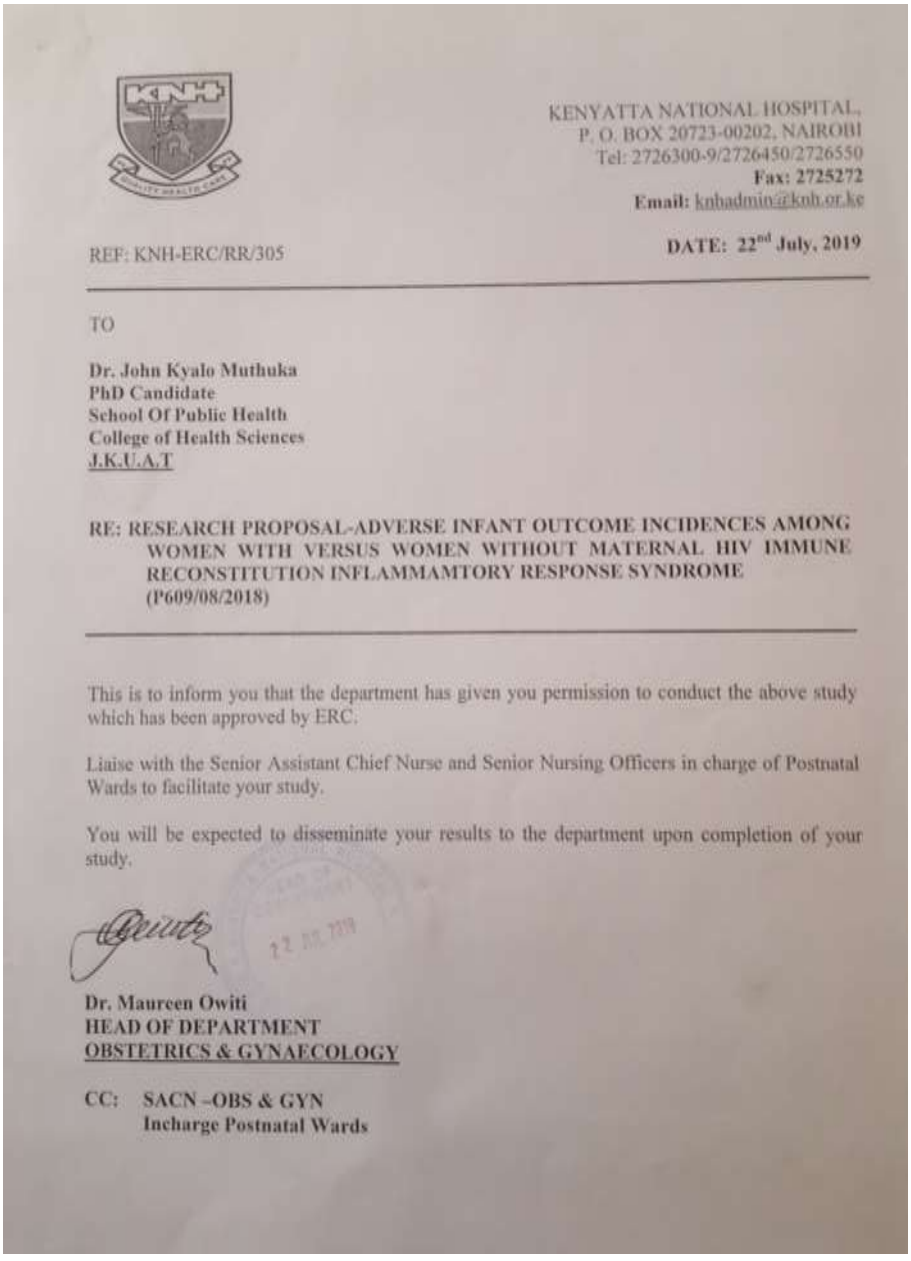
I am pleased to inform you that your request to undertake the research in the hospital has been granted.

On completion of the research you are expected to submit one hard copy and one soft copy of the research report / thesis to this office.

30 SEP 2019

Phillip Mibei
For: Chairman – Research Committee
Mbagathi Hospital

APPENDIX-X: Research Authorization / Study Protocal Certificate [Kenyatta National Referal Hospital]



KENYATTA NATIONAL HOSPITAL,
P. O. BOX 20723-00202, NAIROBI
Tel: 2726300-9/2726450/2726550
Fax: 2725272
Email: knhadmin@knh.or.ke

REF: KNH-ERC/RR/305

DATE: 22nd July, 2019

TO

Dr. John Kyalo Muthuka
PhD Candidate
School Of Public Health
College of Health Sciences
J.K.U.A.T

RE: RESEARCH PROPOSAL-ADVERSE INFANT OUTCOME INCIDENCES AMONG WOMEN WITH VERSUS WOMEN WITHOUT MATERNAL HIV IMMUNE RECONSTITUTION INFLAMMAMTORY RESPONSE SYNDROME (P609/08/2018)

This is to inform you that the department has given you permission to conduct the above study which has been approved by ERC.

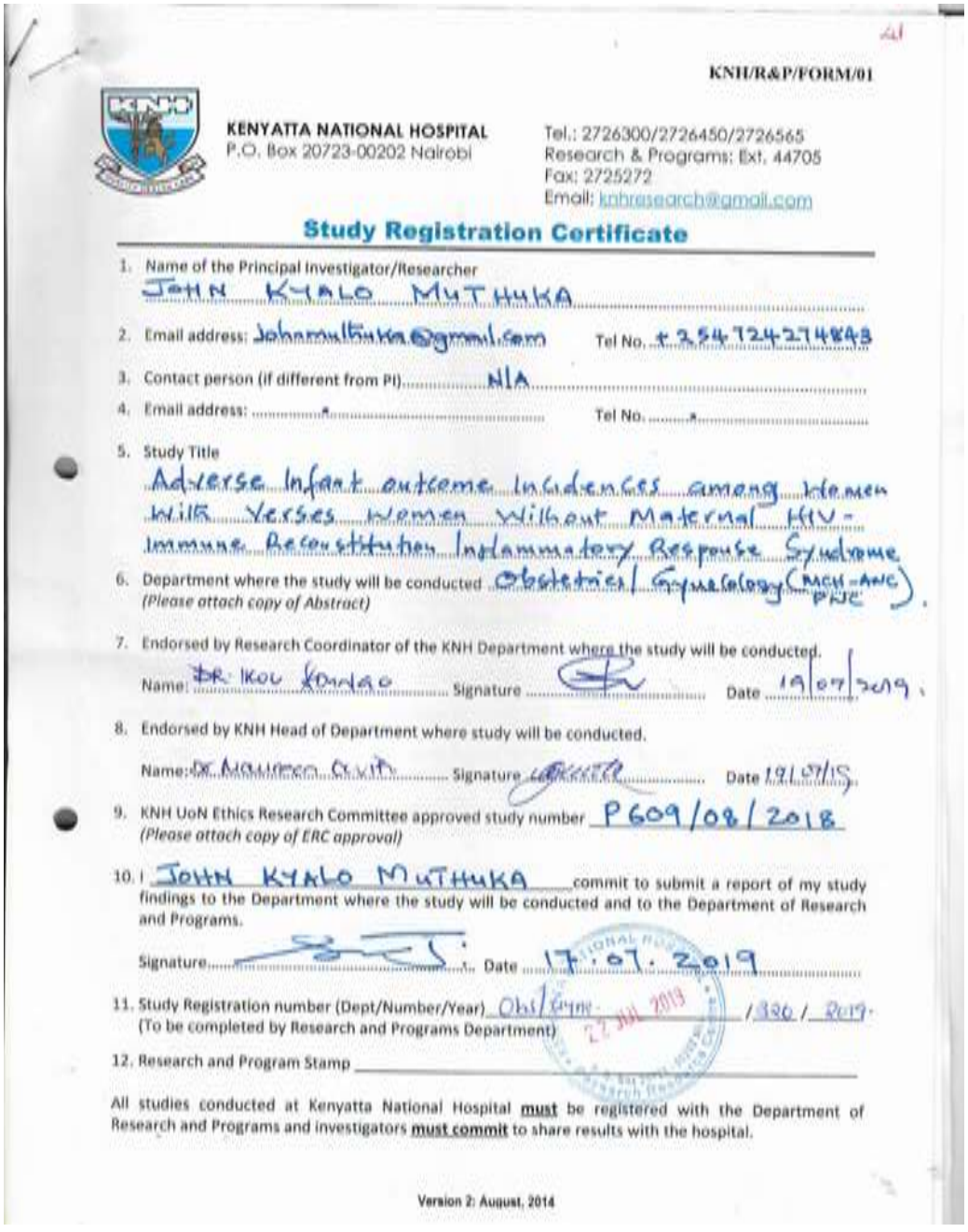
Liaise with the Senior Assistant Chief Nurse and Senior Nursing Officers in charge of Postnatal Wards to facilitate your study.

You will be expected to disseminate your results to the department upon completion of your study.

Dr. Maureen Owiti
HEAD OF DEPARTMENT
OBSTETRICS & GYNAECOLOGY

CC: SACN –OBS & GYN
Incharge Postnatal Wards

APPENDIX-XI Protocal/study registration certificate



KNH/R&P/FORM/01

KENYATTA NATIONAL HOSPITAL
P.O. Box 20723-00202 Nairobi

Tel.: 2726300/2726450/2726565
Research & Programs: Ext. 44705
Fax: 2725272
Email: knhresearch@gmail.com

Study Registration Certificate

1. Name of the Principal Investigator/Researcher
   JOHN KYALO MUTHUKA
2. Email address: Johnmuthuka@gmail.com Tel No. +254724274843
3. Contact person (if different from PI) N/A
4. Email address: * Tel No. *
5. Study Title
   Adverse Infant outcome Incidences among Women with Verses Women Without Maternal HIV-Immune Reconstitution Inflammatory Response Syndrome
6. Department where the study will be conducted Obstetrics/Gynaecology (MCH-ANC PNC)
   (Please attach copy of Abstract)
7. Endorsed by Research Coordinator of the KNH Department where the study will be conducted.
   Name: DR. IKOL KOMBO Signature Date 19/07/2019
8. Endorsed by KNH Head of Department where study will be conducted.
   Name: Dr Maureen Ovit Signature Date 19/07/19
9. KNH UoN Ethics Research Committee approved study number P609/08/2018
   (Please attach copy of ERC approval)
10. I JOHN KYALO MUTHUKA commit to submit a report of my study findings to the Department where the study will be conducted and to the Department of Research and Programs.
    Signature Date 17.07.2019
11. Study Registration number (Dept/Number/Year) Obs/Gyne/330/2019
    (To be completed by Research and Programs Department)
12. Research and Program Stamp

All studies conducted at Kenyatta National Hospital **must** be registered with the Department of Research and Programs and investigators **must commit** to share results with the hospital.

Version 2: August, 2014