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EFFECT OF MATERNAL HIV IMMUNE RECONSTITUTION INFLAMMATORY RESPONSE SYNDROME ON THE RISK OF ADVERSE PREGNANCY-FETAL OUTCOMES IN HIV-1 POSITIVE, ART NAIVE PREGNANT WOMEN OF REPRODUCTIVE AGE IN SELECTED HOSPITALS, NAIROBI, KENYA

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Abstract:
Background: Immune reconstitution inflammatory response syndrome (IRIS) is a recovery disease that may be triggered after starting ARV therapy in some individuals. The incidence of adverse pregnancy-fetal outcomes with IRIS has not been studied in Kenya among pregnant women, with focus only, on improved immune response and PMTCT after ART initiation. The indirect effect of ART, the maternal HIV - IRIS on pregnancy outcome has not been elucidated. More than 10% of the global burden of disease is due to pregnancy complications and adverse pregnancy and related birth outcomes and despite recent advances in obstetric medicine, pregnancy complications and adverse birth outcomes are a growing public health concern and economic burden on the health-care system. This has substantial burden of adverse pregnancy-fetal outcomes with prevalence of preterm birth, low birth weight, and small gestational age infants of 19.8%, 14.2%, and 12.6%, respectively, and of still birth and neonatal

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mortalityat1.9% and 0.4%, respectively. The aim of this study was to evaluate the effect of maternal HIV immune reconstitution inflammatory response syndrome on the risk of adverse pregnancy-fetal outcomes in HIV-1 positive; ART initiated pregnant women of reproductive age in selected hospitals, Nairobi, Kenya**. Methodology:** The study was conducted among 204 HIV-1 positive, ART initiated pregnant women of reproductive age in selected hospitals, Nairobi, Kenya. A prospective cohort study design was used where the subjects were recruited and followed from the end of first trimester for six and half months after they were confirmed to be HIV positive, and put on ARV treatment using a pretested data collection tool. Bivariate analyses with chi-square test to establish the association between the variables at p-value < 0.05. Logistic regression analysis was performed to identify independent outcome predictors. Adjusted relative risk at 95% confidence interval was determined. **Results:** The study indicated that, adverse pregnancy-fetal outcome cumulative incidence was 26.47% among women diagnosed with IRIS compared to 10.78% among women not diagnosed with IRIS. The incidence rate estimate was 0.012 and 0.0045 per person's week respectively with a rate ratio of 012/.0045=2.7. Women with IRIS had 2.46 times the risk of experiencing an adverse pregnancy-fetal outcome compared to those who did not [OR=3; 95%CI: 1.4-6.4; P=.004]. LBW cumulative incidence was the highest with 11 (10.8%) among IRIS exposed women and 3 (2.9%) among non-IRIS exposed women and same case with PTB 8 (7.8%) and 3 (2.9%) respectively. **Conclusion:** There was a significant relationship of maternal HIV-immune reconstitution inflammatory response syndrome diagnosis with adverse pregnancy-fetal outcomes as a result of ART initiation among HIV-1 positive, pregnant women of reproductive age. This study observes that, being diagnosed with maternal HIV-IRIS following ART initiation during pregnancy among ART naive women is associated with experiencing an adverse pregnancy outcome. This should be a concern in clinical practice as IRIS has self-resolution, it may on the other hand affect pregnancy outcome negatively. PMTCT should integrate monitoring of suspected IRIS cases using the latest defined criteria for its diagnosis in pregnant women starting ant-retroviral therapy especially in resource limited areas.

Keywords: HIV-IRIS, ART, adverse pregnancy-fetal outcome

1. Introduction

Most patients, starting ant-retro viral treatment (ART) improves immune responses to a wide range of other opportunistic pathogens. The process of ART-induced immune reconstitution commonly is not eventful. However, small percentages of patients develop inflammatory disorder in response to particular opportunistic pathogens within a few months after starting the therapy. A report by WHO & KDHS, 2009 showed that, HIV-infection among women is generally higher than men as per the latest finding in Africa based on several factors and this translates to pregnant women at large. This is associated

with negative neonatal outcomes such as neonatal mortality among women by a study done in Kenya (Kaguthi *et al.*, 2015). The overall incidence of IRIS is unknown, but is dependent on the population studied and its underlying opportunistic infections burden. The infectious pathogens most frequently associated with the syndrome have been documented. No specific treatment option exists and depends on the underlying infectious agent and its clinical presentation. A variety of mycobacterium, viral, fungal and parasitic opportunistic infections is linked with immune reconstitution inflammatory response syndrome (Naomi *et al.*, 2018). Consequently, a majority of individuals with HIV infection who achieve optimal adherence to ART will experience at least partial reversal of HIV-induced immune defects and reconstitution of the immune system (French, 2007). Mortality related with IRIS is uncommon; however, associated high morbidity contributes to burden on the health-care system (Sereti *et al.*, 2020). This has become a public health concern, as ART use has been associated with increased IRIS inform of opportunistic conditions and other non-infectious conditions. A few autoimmune and other non-infectious conditions may worsen or appear after HAART is begun; suggesting that inflammation induced by an IRIS-like syndrome is responsible. Whether such relationship represents a casual or a coincidental finding, this is unproven at present (Sharma *et al.*, 2015).

In HIV-infected pregnant women, the administration of ART during pregnancy and/or intra-partum significantly reduce the risk of mother-to-child transmission (MTCT) of HIV (Stacey *et al.*, 2015). Although the beneficial effects of ant-retro-viral (ARV) therapy for preventing mother-to-child transmission are indisputable, studies in developed and developing countries have reported conflicting findings on the association between ARV exposure and adverse birth outcomes. ART also has directly and indirectly been found to be of significant contribution to poor pregnancy outcomes (Fekadu *et al.*, 2015). WHO revealed huge evidence gaps in the potential increased risk of adverse events associated with the long-term use of ARV drugs during pregnancy and in breastfeeding mothers (WHO, 2013). IRIS is becoming a significant complication of ART in HIV-infected patients in general from resource-poor nations (Lawn & French, 2007). Various autoimmune disorders have been reported in patients with HIV infection that responds to ART (Crum *et al*, 2006). 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 (Nan Li, *et al,* 2012). Again, much of efforts have seen Infant mortality decline substantially over time in developed and developing countries despite but increasing LBW outcomes (Michael, 2013). Perinatal deaths account for 7% of the global burden of disease, with developing countries contributing about 98% of deaths (Blessmore *et al.*, 2019). Between 2018 and 2030, its 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 (Lucia *et al.*, 2019; The lancet, Global Health, 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 outcome, where studies have shown that adverse pregnancy-fetal outcome is significantly associated with HIV positive status (Ikpim *et al.,* 2016). HIV infection is associated with adverse pregnancy-fetal outcomes such as low birth weight and perinatal mortality. However, the association is conflicted with the effect of antiretroviral therapy (ART) on the pregnancy outcomes and it remains unexamined (Twabi *et al.,* 2020). 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. Having an HIV-positive status is associated with negative health outcomes, including increased risk of intrauterine infection While progress has been made towards increasing HIV-testing during pregnancy and providing antiretroviral therapy (ART) to prevent vertical mother-to-child transmission, insufficient integration of HIV services into reproductive, maternal, newborn, child and adolescent health care is a major challenge (Maternal Health Task Force, 2020). Antiretroviral therapy during pregnancy is considered the main and most effective method for reducing the vertical transmission of infection. However, there is no consensus over potential associations between antiretroviral therapy and adverse pregnancy-fetal outcomes (Fateme *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 maternal, pregnancy and birth related adverse outcomes (WHO, 2020). There is a dearth in researches evaluating the effect of maternal HIV immune reconstitution inflammatory syndrome on the risk of adverse pregnancy and related birth outcomes among HIV positive ART initiated women in selected public hospitals, Nairobi, Kenya.

3. Material and Methods

The present study was conducted at Kenyatta National and Mbagathi Hospitals both located in Nairobi County, Kenya. The study design was a prospective cohort and the subjects were recruited and followed from the end of first trimester for six and half months after they were confirmed to be HIV positive, and put on ARV treatment with a defined case of HIV-IRIS as exposed cohort and non-HIV –IRIS as the non- exposed cohort, immediately after the first trimester. A total of 204 subjects of both cohorts were included in the final analysis following subsequent elimination process at an equal ratio to the unexposed cohort (1:1). A pretested data questionnaire abstraction tool was used. Matching by age and parity among pregnant women infected with HIV and confirmed of the status by test at least in the first trimester was performed. These protocols were designed to describe the characteristics of enrolled pregnant women, use of ARV regimens, and adverse pregnancy-fetal outcomes. The pregnant women were followed

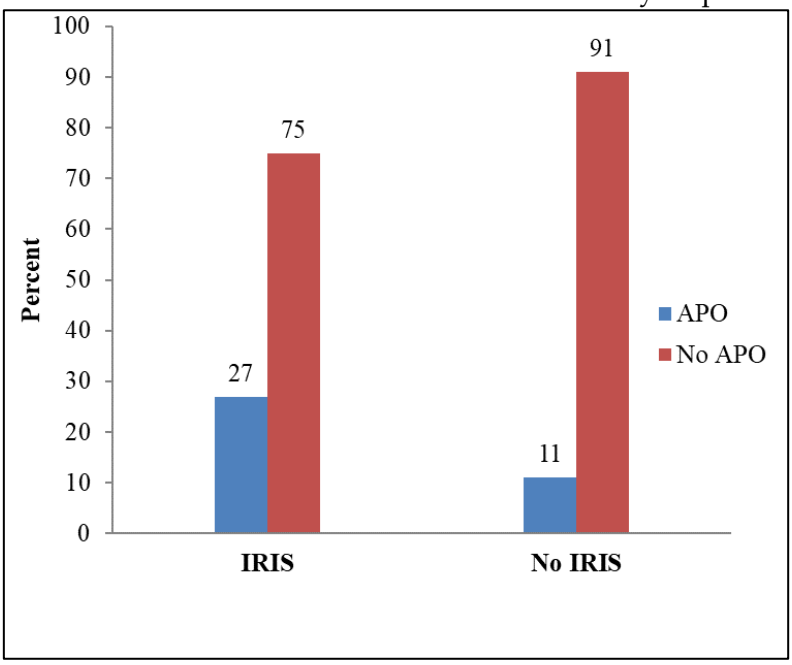
after confirmation of IRIS exposure status and meeting the inclusion criteria, until postpartum through delivery stage. Pre testing of the abstraction tool was done by the principal investigator and the research assistants during the pilot study. The information abstraction tool was uniform for both groups with coded values to conceal identity, majorly focusing on the primary outcome variable with link to maternal HIV immune reconstitution inflammatory syndrome response status and potential confounders. The data collected was analyzed using SPSS version 25.0. Chi-square test was used to establish the association between the dependent and independent variables and the level of statistical significance was set at p-value < 0.05. Multiple logistic regression analyses were performed to adjust for confounding. Adjusted Odds ratio (AOR) with corresponding 95% confidence interval was estimated. The approval to carry on with the research was sought from KNH/UoN- ERC and permission for the selected facilities' entry and data collection was sought accordingly.

4. Results and Discussion

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

Figure 1 below shows that out of 102 women exposed to IRIS, 27 experienced adverse pregnancy-fetal outcomes compared to 11 among 102 women not exposed to IRIS

Figure 1: Distribution of adverse pregnancy-fetal outcomes for women with and women without maternal HIV immune reconstitution inflammatory response syndrome



4.2 Incidence of adverse pregnancy-fetal outcomes in women experiencing maternal HIV -IRIS compared to women not experiencing maternal HIV –immune reconstitution inflammatory response syndrome over the entire follow-up period (six and half months post IRIS identification

The contingency table 4.2 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. The cumulative incidence of adverse pregnancy-fetal outcomes in IRIS exposed group was therefore over double compared to that of the IRIS unexposed (comparator) group. The relative risk of experiencing an adverse pregnancy-fetal outcome was 26.47 / 10.78 = 2.46. This suggests that women with IRIS had 2.46 times the risk of experiencing adverse pregnancy-fetal outcome compared to those who did not. Exposure to IRIS contributed to adverse pregnancy-fetal outcomes [OR=3; 95%CI: 1.4-6.4; P=.004

Table 1: Cumulative incident and RR of adverse pregnancy-fetal outcome in women with maternal HIV –immune reconstitution inflammatory response syndrome as compared to women without maternal HIV –immune reconstitution inflammatory response syndrome

Variable	APO		OR (95% CI)	P value
	Yes n (%)	No 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	

4.2.1 Incidence rate estimate

The subjects were followed for duration of six and half months (26weeks) post IRIS identification and allocation, with two week post-partum period included as the last phase of follow-up. There were visits: at the end of second trimester, that is at sixth month during delivery /post partum periods with spacing of three months each visit. Since the exact time at risk could not be determined easily, each subject was allocated 50% of the duration of time at risk of adverse pregnancy-fetal outcome among the two cohorts. At the first and the last visits, the IRIS exposed and IRIS non-exposed women had the following adverse pregnancy-fetal outcomes each;

	APOs	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

4.3 Comparison and description of the composite APFOs by: maternal HIV immune reconstitution inflammatory response syndrome status; time of adverse pregnancy-fetal outcomes experience (intra-partum or at delivery/post-partum); and distribution of specific APFO forms among pregnant women

The table 2 below indicates that, at intra-partum stage, there were nine APFOs experienced; 5 (2.5%) of women experienced miscarriage and 4 (2.0%) pre-term birth (very preterm (28 to 32 weeks). Of these, 3 (2.9%) and 2 (2.0%); 3 (2.9%) and 1 (1.0%) were among IRIS diagnosed and non-IRIS diagnosed women respectively with no significant difference as relates APFO type and IRIS exposure status (p = 0.602). At delivery / post-partum stage, there were 29APFOs experienced; LBW 14 (6.9%), PTB 7 (3.4), neonatal sepsis 1 (0.5%), low Apgar score 3 (1.5), SGA 1 (0.5) AND others 3 (1.5%). Of these 29APFOs, there were; LBW 11 (10.8%). PTB 5(4.9%), neonatal Sepsis 1 (1.0%), low APGAR score 2 (2.0), SGA 0(0%), others 2 (2.0%) and LBW 3 (2.9), PTB 2 (2.0), neonatal sepsis 0(0%), low APGAR score 1 (1.0), SGA 1 (1.0%), others 1 (1.0%) were among IRIS diagnosed and non-IRIS diagnosed women respectively with no significant difference as relates APFO type and IRIS exposure status (p = 0.077). As regards overall distribution of APFOs, LBW cumulative incidence was the highest with 11 (10.8%) among IRIS exposed women and 3 (2.9%) among non-IRIS exposed women and same case with PTB 8 (7.8%) and 3 (2.9%) respectively.

Table 2: Distribution and comparison of adverse pregnancy-fetal outcomes among women with and without maternal HIV immune reconstitution inflammatory response syndrome

Intra-partum			
Variable	**IRIS**	**Non-IRIS**	**P value**
APO			
Miscarriage	3 (2.9)	2 (2.0)	0.602
PTB	3 (2.9)	1 (1.0)	
None	96 (94.1)	99 (97.1)	
Post-partum			
Variable	**IRIS**	**Non-IRIS**	**P value**
APO			
LBW	11 (10.8)	3 (2.9)	0.077
PTB	5 (4.9)	2 (2.0)	
NS	1 (1.0)	0	
Low APGAR score	2 (2.0)	1 (1.0)	
SGA	0	1 (1.0)	
Other	2 (2.0)	1 (1.0)	
None	81 (79.4)	94 (92.2)	
Distribution of APFOs by IRIS exposure status			
Variable	**IRIS**	**Non-IRIS**	**P value**
APO			
Miscarriage	3 (2.9)	2 (2.0)	0.066
LBW	11 (10.8)	3 (2.9)	
PTB	8 (7.8)	3 (2.9)	
NS	1 (1.0)	0	

Low APGAR score	2 (2.0)	1 (1.0)	
SGA	0	1 (1.0)	
Other	2 (2.0)	1 (1.0)	
None	75 (73.5)	91 (89.2)	

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

5. Discussion

This study has demonstrated that, being diagnosed with maternal HIV immune reconstitution inflammatory response syndrome increases the incidence rate and risk of adverse pregnancy-fetal outcome in the bivariate analysis among IRIS exposed as compared to the non-IRIS exposed HIV positive ART naïve women. It has been reported that adverse birth and pregnancy outcomes are linked to co morbidities among pregnant women receiving ART therapy by posing a danger to pregnancy and leading to ultimate adverse maternal, birth or pregnancy outcomes (Fekadu *et al*, 2015). Similar to this findings although an indirect effect of ART on adverse pregnancy-fetal outcomes, in another study, among women initiating ART in pregnancy, HAART use 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) (Lynne *et al.,* 2016). The findings postulate that, HIV is associated with adverse pregnancy-fetal outcomes in several peculiar ways conforming to the findings that, HIV may be the direct cause or a marker of a complex interaction of related medical and social conditions that affect pregnancy (Sebitloane e*t al.,* 2017).

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 outcome (Berhan & Andargachew, 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 which established that, most prevalent adverse pregnancy-fetal outcomes were low birth weight, preterm birth and stillbirth (Fatemeh *et al.,* 2019). Another Lesotho based study similarly established that, LBW, < 2500 was 12.8 % in HIV infected cohort of pregnant women (Tiam *et al.,* 2019). The findings are also consistent with a report by Lara & Mary, 2019, showing that, LBW was 14·6% (uncertainty range 12·4–17·1) and pre-term birth at 10·6% (uncertainty range 9·0–12·0) with approximately 15% of preterm newborns occurring before 32 weeks of gestation. 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(Mathew, 2019). Similarly, the findings reflect those of a study done in South Africa where the overall incidence of neonatal sepsis was (incidence- 39.3/1,000 live-births) (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%) (Nubwa *et al.,* 2018),closely to the findings in this study but it contradicts a systematic review study which established a pooled prevalence of neonatal sepsis in East Africa as 29.65% (95% CI; 23.36–35.94) (Biruk *et al.,* 2019), although this was among general population unlike in specific HIV infected women in this current study. The incidence of low Apgar scores (< 7) was 3/204 (1.47.6 %), among all women with and without IRIS as 2 and 1 respectively. This tends to depict some findings which established that with the exception of 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 conforms a report by 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 *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 naïve and diagnosed of HIV at first antenatal visit.

Competing Interests Statement

Authors have declared that no competing interests exist.

About the Authors

Muthuka J. Kyalo (BSc, MPH, PGD-Biotech, Pharm-D, D. Nutr-Medicine, and PhD-Fellow) is health specialist in diverse areas. John has his interest in HIV/AIDS, Maternal, Child and Neonatal (MCNH), reproductive and adolescent health as well as neglected tropical diseases.

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