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THE ASSOCIATION BETWEEN MATERNAL HIV AND STILLBIRTHS IN AN ERA OF UNIVERSAL ART IN PREGNANCY IN THE WESTERN CAPE, SOUTH AFRICA.

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DECLARATION

I, Elizabeth Lubinda (LBNELI006), hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.
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ABSTRACT

BACKGROUND

Annually, approximately 3 million stillbirths occur globally, with a rate of 18.4 per 1000 births. The devastating aftermath affects around 4.2 million mothers, and 75% of stillbirths are concentrated in South Asia and sub-Saharan Africa (SSA) particularly, with a rate of 32.2 per 1000 births in SSA. South Africa reported a stillbirth rate of 16 per 1000 births in 2021, despite global efforts to reduce stillbirth rates. SSA also faces the highest global HIV prevalence at 20%.

South Africa, home to 8.4 million people living with HIV, grapples with a 30% prevalence among pregnant individuals. Antiretroviral therapy (ART) coverage for pregnant individuals reached 97% in 2019, especially in the Western Cape with an HIV prevalence of 17.9% among antenatal individuals. Quality antenatal care (ANC) is crucial, with research showing a lower stillbirth rate for those receiving higher quality ANC.

The COVID-19 pandemic in 2020 introduced new challenges, potentially influencing stillbirth rates through factors like lockdowns and limited healthcare access. Pregnant individuals contracting SARS-CoV-2 faced an increased likelihood of stillbirth.

In this context, our cohort study in the Western Cape, South Africa, utilized routine health data to investigate the contemporary relationship between pregnant individuals with HIV and stillbirths in the era of universal ART during pregnancy. The study explores associations with demographic and clinical variables, including the quality of ANC.

METHODS

Utilizing data from the Western Cape Pregnancy Exposure Registry (PER) between 2017-2021, this cohort study focused on pregnant women attending ANC at Gugulethu Midwife Obstetrics Unit (GMOU) and Worcester MOU (WMOU) in South Africa. The study used integrated information from the Provincial Health Data Centre (PHDC), creating a linked database for cohort generation.

The cohort included women aged 18 or older, with known HIV status and a recorded pregnancy outcome after 20 weeks gestation. The primary outcome was stillbirth, and maternal HIV status served as the primary exposure. ANC quality, based on WHO guidelines, considered variables such as ANC timing, number of visits, and various healthcare parameters. ANC quality was

categorized using both at least 4 (old WHO guidelines) or 8 (new WHO guidelines) visits, with a good ANC quality score requiring 7 or more out of 11 Quality of ANC variables. Statistical analyses, including logistic regression, were conducted to explore associations between maternal HIV status, ANC quality, and stillbirth prevalence. The study also collected data on maternal characteristics to provide a comprehensive understanding of contributing factors.

RESULTS

The study included 15,123 participants: 4,773 women living with HIV (WLHIV) and 10,350 women without HIV. WLHIV had a median age of 28 years, while women without HIV had a median age of 31 years. The overall stillbirth rate was 15/1000 births (95% CI:13.1-16.9). Stillbirth prevalence was 1.66% for WLHIV and 1.42% for women without HIV. Women with prior diabetes exhibited a significant increase in stillbirth odds (AOR = 2.63, 95% CI: 1.06-6.52, p = 0.04). Women without HIV but with a history of diabetes had a stillbirth prevalence of 4.08%, compared to 3.80% for WLHIV. WLHIV with good-quality ANC had fewer stillbirths (4 visits: 5.06%, 8 visits: 2.53%) than women without HIV (4 visits: 11.56%, 8 visits: 5.06%). ART for ≥100 weeks among WLHIV showed a protective effect, with 47% lower stillbirth odds than ART <20 weeks (AOR = 0.53, p = 0.01) and 45% lower stillbirth odds than ART <20 weeks (AOR = 0.55, 95% CI: 0.33-0.91, p = 0.02). Despite higher stillbirth odds for WLHIV no significant association was found between maternal HIV status and stillbirths after adjustment (AOR = 1.15, 95% CI: 0.87-1.52, p = 0.34).

CONCLUSION

This study, utilizing routine program data, revealed no statistically significant difference in the prevalence of stillbirths between women living with and without HIV. Despite the lack of a statistically significant association between the quality of antenatal care (ANC) and stillbirths, the study underscores the importance of adhering to WHO recommendations and utilizing databases such as the Pregnancy Exposure Registry for evidence-based decision-making. Although the overall stillbirth rate slightly exceeded global targets, there was noticeable improvement following the universal rollout of antiretroviral therapy (ART). Notably, among women living with HIV (WLHIV), a longer duration of ART was linked to a significant reduction in the odds of stillbirth, highlighting the critical role of sustained access to ART. Despite its limitations, these findings contribute to global health objectives, particularly those

aimed at eliminating preventable newborn deaths by 2030. ART emerges as a pivotal factor in decreasing stillbirth rates among women living with HIV.

LIST OF ABBREVIATIONS

ANC: Antenatal Care

ART: Antiretroviral therapy

BMI: Body Mass Index

HIV: Human Immunodeficiency Virus

GMOU: Gugulethu Midwife Obstetric Unit

LMIC: Low- and middle-income countries

MCR: Maternity Case Record

PIPP: Perinatal Problem Identification Programme

PER: Pregnancy Exposure Registry

SES: socioeconomic status

SSA: Sub-Saharan Africa

TB: Tuberculosis

WHO: World Health Organization

WMOU: Worcester Maternity Obstetric Unit

WLHIV: Women Living with HIV

ORGANISATION OF THE DISSERTATION

The dissertation is structured into three distinct parts: Part A, Part B, and Part C.

Part A serves as the research protocol, providing an overview of the background literature, rationale for the study, objectives, research methodology, statistical analysis plan, ethical considerations, and relevant references.

Part B follows the format of a journal manuscript, adhering to the submission guidelines of the Obstetrics and Gynecology Journal (Appendix 9). This section delves into the study background, details the methods employed, presents the study results, discusses the findings, and concludes with implications drawn from the research.

Part C comprises the appendices section, housing documents related to ethical approvals and supplementary tables. This section serves as a supplementary resource supporting the comprehensive nature of the dissertation.

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PART A: RESEARCH PROTOCOL

PROTOCOL SYNOPSIS

Title	**The association between maternal HIV and stillbirths in an era of universal ART in pregnancy in the Western Cape, south Africa.**
Introduction	Despite the considerable research and policies that have been committed to reducing stillbirths, there is still an alarming number of cases being reported especially in South Asia and sub-Saharan Africa. The World Health Organisation's (WHO) definition of stillbirth is a baby born with no signs of life at/after 28 weeks gestation or with a birthweight of ≥1000g. In sub-Saharan Africa, it is estimated that 900,000 babies die *in utero* during the last twelve weeks of pregnancy and the stillbirth rate stands at 32.2 per 1000 births. In addition, the region has the highest prevalence of HIV in the world with 20% of people living with HIV. In 2019, South Africa reported 16.4 stillbirths for every 1000 births with reference to the Western Cape pregnancy exposure registry (PER), the Western Cape province stillbirths (%) was 2.2%. Another key focus area is the effect of quality of Antennal Care (ANC) on the incidence of stillbirths as recommended by the WHO 2016 recommendations for a positive pregnancy experience. With this said, there is still a gap regarding the effects of quality ANC on birth outcomes among WLHIV in an era of universal ART in pregnancy in South Africa, specifically in Cape Town. Therefore, this study seeks to assess the relationship between pregnant women living with HIV and stillbirths in the Western Cape, in an era of universal ART in pregnancy.
Aim	To determine the relationship between living with HIV during pregnancy and stillbirths in the Western Cape, South Africa in an era of universal ART in pregnancy, and to assess the associations with demographic and clinical variables, including the quality of ANC received.
Study objectives	1. To characterize women with and without stillbirths enrolled in the Western Cape Pregnancy Exposure Registry (PER) between 2017 and 2021 (5 years). 2. To compare the cumulative incidence proportion of stillbirths among pregnant women living with and without HIV in the PER between 2017 and 2021 (5 years). 3. To determine the associations between the quality of Antenatal Care (ANC) according to the World Health Organisation (WHO) criteria and stillbirths among pregnant women living with and without HIV women in the PER.

Study Design	A cohort study design will be used. The study will assess the stillbirth rate in a cohort of women living with and without HIV attending ANC between 2017 to 2021 at two sentinel sites in the Western Cape: Gugulethu Midwife Obstetrics Unit (GMOU) and Worcester MOU (WMOU).
Characteristics of population	The study population will comprise pregnant women living with and without HIV attending ANC at GMOU and WMOU from the period of 2017-2021.
Sample size	Given the sub-Saharan stillbirth rate of 32.2 per 1000 births, the ideal sample size would be about 3353 women. This study intends to enrol 23,000 women as recorded in the PER from the year 2017 to 2021. This reflects the huge amount of power the study will have given the large sample size.
Eligibility Criteria	***Inclusion Criteria*** ▪ Women aged greater or equal to 18 years old. ▪ Women enrolled in the PER with a pregnancy outcome between 01 January 2017 and 31 December 2021 ▪ Gestation age at outcome > 20 weeks. Pregnancy losses before 20 weeks gestation are considered non-viable and the definition of stillbirth is the intra-uterine demise of a viable fetus. ***Exclusion Criteria*** ▪ Women who cannot be linked to a pregnancy outcome. ▪ Women who died before pregnancy outcome ▪ Women with pregnancy losses before 20 weeks of gestation. ▪ Women under the age of 18 years
Data source	The Pregnancy Exposure Registry (PER) is the data source for this study. it is a surveillance system that monitors and captures all expectant mother's obstetric data during ANC visits at the respective primary health centres. To date, it has captured antenatal data of approximately 5000 women from the urban site and 3500 from the rural site, annually. At GMOU, women are enrolled in the PER at first attendance to ANC at the MOU. Delivery data are updated from the Maternity Case Record (MCR) after birth at the MOU or hospital. At the Worcester site, all data were entered into the PER from the MCR after delivery. The MCR is a tracking record that captures all maternal records throughout pregnancy, its major essence in this study is its ability to capture pregnancy outcomes such as live or stillbirths. Data from Worcester are available for 2018-2019.

Data collection	The study will use variables from the Pregnancy Exposure Registry (PER). The PER is managed by the Provincial Health Data Centre (PHDC) in the Western Cape Government Department of Health (WCGH) which secures and curates the data. We will request a de-identified dataset from the PHDC with the PER variables. The Antenatal Care Variables will be collected from the PER while Covid variables from the PHDC.
Data analysis	The study's statistical analysis will be done in R software. The baseline characteristics of the participants will be presented using descriptive statistics. Categorical variables will be presented as proportions and frequencies, while medians and interquartile ranges will be used to present numeric variables. Logistic regression analysis will be used to assess the odds of having the study's outcome (stillbirths) among women living with HIV compared to women not living with HIV. Univariable logistic regression models will be used to assess the significance of independent variables to the dependent variable (stillbirths). Multivariable logistic regression models will be used to control for possible confounders. Regarding the incidence of stillbirths among women living with and without HIV, the epitools function in R studio will be used to ascertain the cumulative incidence proportions . Statistical significance will be established at ≤ 0.05.
Risk and Benefit	Given the use of secondary data, the study poses minimal risk and has no direct benefit to participants. The main risk is that of loss of confidentiality; the risk is low and will be minimized. Regarding the benefits, findings from the study can inform policy as it relates to maternal and child health and healthcare services in the Western Cape.
Privacy and confidentiality	Necessary procedures will be followed to protect participants' personal information, privacy, and confidentiality, informed by the South African Protection of Personal Information (POPI) Act and the Declaration of Helsinki. A de-identified dataset will be requested from the PHDC and stored on the investigator's password-protected laptop. Therefore, all data has been anonymised and identifying information removed from the datasets where applicable. The data will be deleted from the laptop 5 years after publication. The data in the PHDC are held by the Western Cape Government in perpetuity.

BACKGROUND

A stillbirth is generally defined as no signs of fetal life before complete expulsion or extraction from its mother (1). Families affected by stillbirths are left with long-lasting sadness and often depression, an estimated number of 4.2 million mothers are living with depression associated with stillbirths (2). The World Health Assembly in 2014 agreed to a target of 12 or fewer stillbirths per 1000 birth in every country by the year 2030.

Despite most of the causes being unknown, about half of all stillbirths are diagnosed during labour (1). It is key to highlight that stillbirth rates are an important indication of the quality of care in pregnancy and childbirth and one such care is antenatal care. Findings have shown a higher association between sub-optimal antenatal care and the occurrence of stillbirths among pregnant women (1).

Despite the considerable research and policies that have been committed to reducing stillbirths, there is still an alarming number of cases being reported especially in South Asia and sub-Saharan Africa. This can be seen from the systematic review done in 2019, which indicated the slow progress being achieved in reducing the rate of stillbirths as compared to the mortality rate among children under 5 years and maternal mortality ratio (3). It is estimated that 1.9 million stillbirths occur globally on an annual basis (4) giving a global stillbirth rate of about 13.9 per 1000 births. Seventy-five percent of the total global stillbirths occur in South Asia and sub-Saharan Africa (5), with sub-Saharan Africa being the region with the highest proportion, 42% of global stillbirths (6). It is interesting to note that what the two regions have in common is that majority of the countries are categorised as *low-income* countries and have high HIV prevalence. (5).

The World Health Organization's (WHO) definition of stillbirth is a baby born with no signs of life at/after 28 weeks gestation or with a birthweight of ≥1000g (7). Others define stillbirth as a baby born with no signs of life at 24- or 20 weeks gestation or >500g (8,9). In other words, stillbirth is the death *in utero* of a *viable* fetus and the gestational age at which a fetus is considered viable depends on the resources available to manage premature neonates.

In sub-Saharan Africa, it is estimated that 900,000 babies die *in utero* during the last twelve weeks of pregnancy (10) and the stillbirth rate stands at 32.2 per 1000 births (5). In addition, the region has the highest prevalence of HIV in the world with 20% of people living with HIV (11). In 2019, South Africa reported 16.3 stillbirths for every 1000 births (12) with reference to the Western Cape pregnancy exposure registry (PER), the Western Cape province stillbirths' prevalence was 2.2% (13).

Studies done in low- and middle-income countries (LMIC) identified that the main causes of stillbirths were hypertension, bacterial infection, placenta circulatory disorders, syphilis, HIV and poor quality of antenatal care (14, 15). A review done by Andrea *et al*. highlighted an increased stillbirth risk of 1.3-2.1 times among women with obesity (16); obesity can also increase the risk of other co-morbidities associated with stillbirths e.g., hypertension, and gestational diabetes (17). In addition to this, an observational study done in Soweto, South Africa noted that the leading biomedical causes of stillbirths include, hypertension, obesity, syphilis and HIV (14). Hypertension (38%) and HIV (27%) were the leading causes in this cohort of women (14). Table 1 summarises the key factors associated with stillbirths, both maternal and fetal.

Table 1: Maternal and Fetal risk factors for stillbirth (7,15)

Maternal risk factors	**Fetal risk factors**
HIV infection Maternal syphilis Pregnancy-induced hypertension Pregnancy-associated diabetes Placental abnormalities Hypertensive Disorder Obesity	Fetal bacterial infection Placental Infection and decreased Placental function. Fetal membrane and Placental inflammation Circulatory abnormalities

Several studies have shown a strong association between stillbirths and maternal HIV status (18,19), with underlying factors such as inadequate ANC visits and poor access to ART influencing this relationship. Its key to note that South Africa is among the 15 countries with the highest HIV disease burden globally (20). Out of its total population of 61.93 million, about 8.2 million live with HIV, an estimated HIV prevalence rate of 13.7% (20). Young women comprise more of the HIV-positive populace as compared to young men (20), as evidenced by the 2021 statistical release, indicating that women (51.1%) remain more disproportionality affected than men (48.9%). This could be related to biomedical factors such as the female genital tract's large surface area as compared to men hence leading to a higher risk of HIV acquisition (21). Another reason would be the high proportion of cases linked to intimate partner violence which stands at 25% (22). What is more alarming is that majority of these women fall in the childbearing age group (23).

Brocklehurst *et al*.'s (2005) systematic review and meta-analysis shows a higher risk of adverse pregnancy outcomes such as stillbirths among women living with HIV(WLHIV) compared to

women living without HIV (24, 25). The findings showed that in WLHIV stillbirths had the highest odds ratio of 3.91 (95% CI 2.65-5.77) compared to other adverse perinatal outcomes such as low birth weight and preterm delivery (26) with an odds ratio of 2.09 (1.86-2.35) and 1.83 (1.63-2.06), respectively compared to those in women living without HIV. In addition, the sensitivity analyses indicated that the association between infant mortality and HIV infection was higher in low-income countries than in high-income countries. The odds ratios of these associations were 3.72 (3.05-4.54) and 8.6 (0.53-14.11), respectively (26). Of note, these analyses were conducted before the widespread use of antiretroviral therapy (ART) in pregnancy. While ART has significantly enhanced the survival rates of mothers living with HIV, in-utero ART exposure has varying impacts on stillbirth, which differed depending on the ART regimen and the timing of ART initiation (27).

More recently, Maswime *et al*., in an analysis of South African Perinatal Problem Identification Programme (PPIP) data demonstrated an increased risk of stillbirth in in WLHIV (25/1000 births) when compared to those without HIV (22/1000 births) The difference was statistically significant (11) although the study period included years preceding the introduction of universal ART in pregnancy in South Africa in 2013 (11). Another study found that Adjusted prevalence ratios (aPR) for stillbirth were notably higher for women living with HIV (WLHIV) not on ART 1.31 (1.04: 1.66) (28). However, stillbirth rates were not elevated in WLHIV on ART initiated either preconception or during pregnancy. Conversely, Maswime *et al* found that WLHIV who did not receive any antiretrovirals had a significantly higher stillbirth rate, with a stillbirth rate (SBR) of 48 per 1000 births (11).

A 2016 cohort study in Maseru, Lesotho assessing adverse pregnancy outcomes among WLHIV who were all on ART showed higher odds of stillbirth in WLHIV as compared to those living without HIV (2.9 [1.71-3.97]) (29). Overall adverse pregnancy outcomes remained 2-3 times higher among WLHIV despite them being on ART (24). These findings underscore the critical importance of ART in reducing stillbirth rates among WLHIV, highlighting the need for timely initiation and adherence to ART regimens to improve maternal and fetal health.

The Western Cape Pregnancy Exposure Registry (PER), a sentinel surveillance database in Cape Town, South Africa that is used to detect adverse pregnancy outcomes (13) demonstrated only a slightly higher proportion of stillbirth in WLHIV using more contemporary data (13). In the Western Cape, the HIV prevalence among antenatal women is 17.9% (23,24). The term *antenatal care* (ANC) refers to all essential health care given to pregnant women (30) and it is one of the public health interventions put in place to curb adverse health outcomes such as

stillbirths (30). In Ghana, Afulani *et al.* (2016) conducted a cross-sectional study and demonstrated that the stillbirth rate was substantially lower in women who attended ANC than in those who did not: 1.5% stillbirths with ANC while those who did not attend had 5.6% stillbirths (31). Moreover, among those who attended ANC, the stillbirths among women who received low-quality ANC were 1.8% compared to 1.3% among those who received higher quality ANC and this was statistically significant (31). This finding suggests a link between the quality of ANC received by a pregnant mother and the risk of stillbirth. The study defined quality of ANC as a pregnant woman receiving at least 8 of the following antenatal services; weight, urine sample and blood sample measurements, blood pressure check, education received on signs of pregnancy complications and where to go in an event of a pregnancy complication, iron supplements, anthelminthic received and lastly tetanus vaccination (31). Another key study demonstrating the importance of ANC among WLHIV was a prospective cohort study done by Kupka *et al*. (2010) which found 50/1000 stillbirth rate among the WLHIV in Tanzania. Multivariable logistic regression demonstrated that late entry into ANC after 21 weeks gestation was the strongest predictor of stillbirth (15). In addition, the education and socio-economic status of the women was important since women with low financial power had a higher probability of not attending ANC (32). In the Soweto study, women who were living with HIV *and* were seropositive for syphilis who attended ANC did not experience any stillbirth pregnancy outcome. This highlights the role of quality ANC in limiting adverse pregnancy outcomes in WLHIV (14).

In South Africa, various studies have highlighted several benefits ANC on reducing stillbirths. According to WHO recommendations, the initial standard number of ANC visits was set to 4 visits, with the first visit preferably before 16 weeks of gestational age (18). This was reviewed in 2016 and increased to a total number of 8 visits with the first visit before 12 weeks gestational age in the 2016 WHO Recommendations on Positive Pregnancy Experience (30). South Africa was the first country to implement the new WHO-recommended ANC visits in 2017. Table 2 outlines the 2016 WHO ANC recommendations on positive pregnancy experience.

Table 2: 2016 WHO ANC Recommendations For A Positive Pregnancy Experience (30)

Recommendations	Brief description		Justification
Health systems intervention	Minimum of 8 ANC visits	The first visit is in the expectant mother's first trimester which is 12 weeks of her pregnancy. The second and third visits were (20 weeks) and (26 weeks). This would be in her second trimester. During her third trimesters, the remaining five visits will be at 30 weeks, 34weeks, 36 weeks, 38 weeks, and 40 weeks of her pregnancy.	This would enhance the utilization of ANC by the expectant mothers. The importance of an increase in the number of visits from 4 to 8, increases the monitoring sessions of the maternal and foetal wellbeing. Thus, preventing adverse pregnancy outcomes such as stillbirths. Every ANC visit comprises urine tests and blood pressure examinations.
Maternal and fetal assessment	HIV and syphilis testing	In high prevalence settings, HIV testing, and counselling is done during ANC visits. In low prevalence settings, HIV testing is integrated with syphilis testing.	The first HIV test is done during the first ANC visits and if the test result is negative, it is repeated at 30 weeks and before delivery. If the test is positive, the expectant mother is put on ART (15) Oral pre-exposure prophylaxis containing tenofovir disoproxil fumarate is offered as an additional preventive choice for pregnant women at risk of HIV infection. This intervention was introduced in Cape town in the year 2020 (PreP)
	TB Testing	In settings with high TB prevalence, screening for active TB should be considered for pregnant women as part of ANC	Screening is done at the first ANC visit. GeneXpert sputum tests are done for WLHIV.
	Ultrasound Scan	The scan assesses the baby's growth, improves detection of fetal anomalies and multiple pregnancies, reduces the induction of labour for post-term pregnancy, and improves pregnancy experience. The first scan is done at 8 weeks, then 20 weeks, 30 weeks and 35 weeks of her pregnancy (recommended)	An early ultrasound scan that is performed correctly increases the accuracy and precision of gestational age assessment, which can support the appropriate management of threatened preterm birth and post-term pregnancies.
	Glucose tests	Gestational diabetes tests	Glucose tests are done at 26weeks. This could be done earlier if you are a high-risk expectant mother e.g high BMI, 35 or older, family history of diabetes or had gestational diabetes in a previous pregnancy.
Nutritional intervention	Supplements	Provision of daily iron and folic acid supplementation with 30 to 60mg of elemental iron and 0.4 mg of folic acid.	This prevents the risk of anaemia during pregnancy.

Notes: ANC= Antenatal care, BMI=Body Mass Index, Prep= Pre-exposure prophylaxis, ART=Antiretroviral therapy, WHLIV=Women living with HIV

In 2020 a cross-sectional national survey published its findings that stated adhering to more than 4 ANC visits improved coverage of the health care services put in place for pregnant women. Therefore, it was assumed that increased ANC visits would improve overall outcomes. Stillbirths were among the adverse perinatal outcomes (33). In addition, a retrospective study done by Lavin *et al.* (2020) in Mpumalanga Province (30) on the impact of implementing the newly recommended WHO ANC visits concluded that this may be a favourable intervention to curb the alarming numbers of stillbirths in the province. The main limitation of this study was the large volume of missing data with unknown gestational age in 43.2% of reported stillbirths. In conclusion, there is still a gap regarding the effects of quality ANC on birth outcomes among WLHIV in an era of universal ART in pregnancy in South Africa, specifically in Cape Town. The studies outlined above could have been biased owing to a high percentage of data incompleteness and lack of data on confounding variables. Specifically, the impact of the quality of ANC on stillbirths in the context of HIV and ART in pregnancy has not been explored. We aim to assess the relationship between pregnant women living with HIV and stillbirths in the Western Cape, in an era of universal ART in pregnancy.

STUDY AIM AND OBJECTIVES

Aim

To determine the relationship between pregnant women living with HIV and stillbirths in the Western Cape, South Africa in an era of universal ART in pregnancy and assess the associations with demographic and clinical variables, including the quality of ANC received.

Objectives

1. To characterize women with and without stillbirths enrolled in the Western Cape Pregnancy Exposure Registry (PER) between 2017 and 2021 (5 years).
2. To compare the incidence of stillbirths among pregnant women living with and without HIV in the PER between 2017 and 2021 (5 years).
3. To determine the associations between the quality of ANC according to the WHO criteria and stillbirths among pregnant women living with and without HIV women in the PER.

METHODOLOGY

Study Design

A cohort study design will be used. The study will assess the stillbirth incidence rate in a cohort of women living with and without HIV attending ANC between 2017 to 2021 at two sentinel sites in the Western Cape: Gugulethu Midwife Obstetrics Unit (GMOU) and Worcester MOU (WMOU). This will be a secondary data analysis using data from Pregnancy Exposure Registry (PER) collected between 2017 to 2021. We will compare the incidence of stillbirths among women living with HIV and those living without HIV and the quality of ANC in terms of 2016 WHO guidelines. Our definition of stillbirth will be *in utero* death of a baby after 20 weeks of pregnancy or >500g, before or during delivery (34). HIV status will be determined from HIV testing and treatment data in the PER. Table 3 outlines the variables to be used as definitions of Quality of ANC.

Table 3: Quality of ANC variables

Quality of ANC variables
Weight check
Blood sample measurements
Urine check
Blood pressure check
Education received on signs of pregnancy complications.
Where to go in an event of a pregnancy complication
Iron supplements
Anthelminthic received.
Tetanus vaccination

Notes: An Index based tool will be used, and quality of ANC will be linked to pregnant women that have 8 or more of the above variables

Characteristics of Study Population

The study population will comprise pregnant women living with and without HIV attending ANC at GMOU and WMOU. Gugulethu is a suburb of Cape Town in the Western Cape province with a population of 98,468 people. That is relatively under-resourced with high employment rates, and an antenatal HIV prevalence rate of close to 30% (13). The GMOU is a public clinic functioning in the Nyanga Health District of the Metro Region, situated in Gugulethu. (13). Approximately 5000 women present for ANC at GMOU annually of whom

about half will deliver at the MOU and half will be referred to hospital either ante- or perinatally. GMOU refers to Mowbray Maternity Hospital (level 2) and Groote Schuur Hospital (level 3) if required.

The second sentinel site is WMOU adjacent Worcester Hospital. Worcester is a town located 120 km outside Cape Town and has a populace of approximately 230,000 who are highly dependent on seasonal agricultural work thus limiting their annual household income. As a result of this timely employment, most households are relatively poor. WMOU provides delivery services for approximately 3600 expectant mothers annually and, if required, women are referred to Worcester Hospital (district) and Tygerberg Hospital (1evel 3). Antenatal HIV prevalence stands at 16% (13). WMOU enrolled women in the PER in 2018 and 2019.

Sample size calculation

Sample size n= (p (100-p) z2 /d2

n= 2464

n= estimated sample size, p = prevalence of stillbirth according to literature, z = confidence interval, d= marginal error

Given the 16.3 per 1000 births stillbirth rate (12), the intended number of 23,000 participants from the PER will be sufficient. The population size of approximately 23,000 will be able to determine a 6% difference in the proportions of stillbirth in women living with HIV (WLHIV) and those not living with HIV at 80% power. We based our sample size calculation on the general stillbirth rate available for South Africa to ensure adequate statistical power for our analysis despite the lack of specific data on stillbirth rates among WLHIV post-universal ART.

Number of participants

Between 2017 and 2021 we estimate approximately 23,000 are recorded in the PER.

Inclusion Criteria

- Women aged greater or equal to 18 years old
- Women enrolled in the PER with a pregnancy outcome between 01 January 2017 and 31 December 2021
- Gestation age at outcome > 20 weeks. Pregnancy losses before 20 weeks gestation are considered non-viable and the definition of stillbirth is the intra-uterine demise of a viable fetus.

Exclusion Criteria

- Women who cannot be linked to a pregnancy outcome

- Women who died before pregnancy outcome
- Women with pregnancy losses before 20 weeks of gestation.
- Women under the age of 18 years

DATA SOURCE

The Pregnancy Exposure Registry (PER) is the data source for this study. As mentioned above, it is a surveillance system that monitors and captures all expectant mother's obstetric data during ANC visits at the respective primary health centres (13). To date, it has captured antenatal data of approximately 5000 women from the urban site and 3500 from the rural site, annually. The data are first entered by the midwives and doctors in the Maternity Case Record (MCR), a patient file that is given to an expectant mother during their first ANC visit which she will use during every ANC visit. It is retained at the site of delivery.

The MCR acts like a tracking record that captures all maternal records throughout pregnancy, it's worth noting that pregnancy outcomes such as live or stillbirths are captured by an attending officer in the very MCR (13). The MCR is the source document for the PER. Data clerks at the sites digitize clinical data using the routine primary care provincial electronic medical records system (PHCIS) and data are incorporated into the Western Cape Provincial Health Data Centre (PHDC) (13)

At GMOU, women are enrolled in the PER at first attendance for ANC at the MOU. Delivery data are updated from the MCR after birth at the MOU or hospital. At the Worcester site, all data were entered into the PER from the MCR after delivery.

Despite it being a key source of exposures related to pregnancy and pregnancy outcomes, the PER has a few limitations common to routine data, which include its inability to capture unmeasured confounders. Another limitation is medicines administered outside the public sector systems are not included in the registry (13).

Research Procedures and Data Collection Methods

The study will use variables from the Pregnancy Exposure Registry (PER). The PER is managed by the Provincial Health Data Centre (PHDC) in the Western Cape Government Department of Health (WCGH) which secures and curates the data. We will request a de-identified dataset from the PHDC with the PER variables presented in Table 4. These will include the outcome and potential exposure variables as well as possible confounders and effect

modifiers. Table 4 outlines the data collection source employed by the studies included in the initial analysis of the proposed study and the key variables to be retrieved from them.

Table 4: Data collection key variables

Pregnancy Exposure registry
Maternal Date of birth
Gestational age at first antenatal visit
Last menstrual period
Parity, Gravidity
Obstetric and medical history including hypertension and gestational diabetes.
Chronic medication
Height, mid-upper circumference
Weight at first ANC
Blood pressure at first ANC
Symphysis fundal height at first ANC
Alcohol use
Tobacco use
Recreational Drug use
Number of antenatal visits
TB screening
Syphilis test
Flu, tetanus injection
Iron and Folate dispensing
HIV status at first antenatal visit
Subsequent positive HIV test (seroconversion)
HIV treatment incl. regimen switches
CD4 count
Viral load
Delivery site (primary care or hospital)
Live birth
Stillbirth
Miscarriage
Termination of pregnancy
Ectopic pregnancy
Molar pregnancy
Sex, APGAR scores
Gestational age at birth
Birth weight, length, head circumference,
foot length
Neonatal/Stillbirth surface examination
Congenital abnormality
Placental histology
GMOU or WMOU
Provincial Health Data
COVID-19 test
COVID-19 wave

Notes: Stillbirth (primary outcome), HIV status (primary Exposure), Number of ANC visits (secondary exposure), Quality of care, COVID-19 and Gestation Age outcome (Covariable)

De-identified PER cohort data will be formally requested from the PHDC after UCT HREC approval. This will be securely transferred as an Excel document to the student investigator and stored on a password-protected laptop.

COVID-19

The COVID-19 pandemic can affect our study in two ways: maternal SARS-CoV-2 infection can result in stillbirth (35), and disruption of obstetric services may increase other risk factors of stillbirth. Our approach will be as follows:

- Use the peak/trough of the COVID-19 waves as a variable in the multivariable analysis (36)
- Perform a sensitivity analysis considering data from before and during the pandemic separately.

Concerning Maternal SARS-CoV-2 infection, it has been observed that pregnant women who test positive for COVID-19 are at a higher risk of placentitis which could result in a stillbirth. As this negatively affects the placenta which is the primary pathway for the fetus's nutritional and oxygen supply (35). A 2021 systematic review and meta-analysis done on the impact of COVID-19 on pregnancy outcomes concluded that there was an association between COVID-19 and stillbirths, this was shown by the summary of pooled random effects models that showed an odds ratio of 2.11 (1.14-3.90) for stillbirths (37). Despite the association indicated, the findings did not depict whether HIV increases the risk of adverse birth outcomes among women with COVID-19 (38).

DATA ANALYSIS

The study's statistical analysis will be done in R software. Baseline characteristics of the participants will be presented using descriptive statistics. Categorical variables will be presented as proportions and frequencies, while medians and interquartile ranges will be used to present numeric variables. Logistic regression analysis will be used to assess the odds of having the study's outcome (stillbirths) among women living with HIV compared to women not living with HIV. Univariable logistic regression models will be used to assess the significance of independent variables in relation to the dependent variable (stillbirths). Multivariable logistics regression models will be used to control for possible confounders. Regarding the incidence of stillbirths among women living with and without HIV, the epitools function in R studio will be used to ascertain the cumulative incidence proportions.

RISK AND BENEFITS

Since the proposed study is secondary data analysis, there will be no direct interaction with the participants, therefore, the study poses minimal risk and has no direct benefit to participants. The main risk is that of loss of confidentiality; the risk is low and will be minimized as described below. However, findings from the study can inform policy as it relates to maternal health and healthcare services in the Western Cape.

PRIVACY AND CONFIDENTIALITY

PER data are contributed automatically to the Provincial Health Data Centre (PHDC), a health information exchange managed by the Western Cape Government Department of Health and falling within its authority and protections (13). In all cases, the necessary procedures will be followed to protect participants' personal information, privacy, and confidentiality, informed by the South African Protection of Personal Information (POPI) Act and Declaration of Helsinki. A de-identified dataset will be requested from the PHDC and stored on the investigator's password-protected laptop. Therefore, all data has been anonymised and identifying information removed from the datasets where applicable. The data will be deleted from the laptop 5 years after publication of the study. The data in the PHDC are held by the Western Cape Government in perpetuity.

BALANCE OF RISK AND BENEFIT

This project represents a *sample* evaluation of health outcomes and services for a particularly vulnerable population of pregnant women in the western cape province based in the two sentinel sites "*Gugulethu and Worcester*". There are no direct benefits to individuals as this study consists of secondary data analysis using data that has already been collected. There may be indirect benefits to the field of maternal and child health as this study will provide a better understanding of the importance of the quality ANC on expectant mothers, it will also give future researchers and policymakers an overview of the effects of 2016 WHO recommendations on ANC specifically with regards to stillbirths.

INFORMED CONSENT

A waiver of informed consent has been granted for data collection in the PER. The rationale for requesting a waiver of the need for individual consent from pregnant women was as follows:

- The research is observational, part of the standard of care, and involves no additional risk.
- Every effort is made to protect the privacy and confidentiality of the women.
- The waiver does not adversely affect the rights and welfare of the women concerned, but rather, the PER may plausibly improve the quality of care provided to pregnant women.
- Obtaining individual consent from all women attending antenatal care would be too onerous for nursing staff at the sites and would therefore interfere with their routine care of women and/or undermine the viability/sustainability of the surveillance. Obtaining retrospective individual consent from all women in the study will not be possible given the size of the cohort. Women attending the MOU are advised by posters and leaflets that their routine data will be included in the PER with the option to opt out (13).

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PART B: MANUSCRIPT

The manuscript is formatted according to the author guidelines of Obstetrics & Gynecology journal (Appendix 10)

ABSTRACT

OBJECTIVES

To investigate the association between maternal Human Immunodeficiency Virus (HIV) and stillbirths in the context of universal antiretroviral therapy (ART) during pregnancy in the Western Cape, South Africa.

METHODS

Analysing data from the Western Cape Pregnancy Exposure Registry (PER) from January 2017 to December 2021, we examined 15,123 participants aged 18 or older who had documented HIV status and recorded pregnancy outcomes after 20 weeks. Exposure variables comprised maternal HIV status and Antenatal Care (ANC) quality following WHO guidelines. Descriptive and logistic regression analyses assessed stillbirth rates and odds ratios in women living with HIV (WLHIV) and without HIV. Associations with clinical, demographic variables, ANC quality, and visit frequency were also examined.

RESULTS

WLHIV, median age 31(IQR:26-35), were generally older than women without HIV (median age: 26(IQR:22-31)). Stillbirth rates were higher among WLHIV17 /1000 (95%CI: 13.34 - 20.66) births compared to women without HIV 14/ 1000 births (95% CI: 11.75 to 16.25). Maternal HIV-positive status (AOR = 1.15, 95% CI: 0.87-1.52, p = 0.34) did not show a statistically significant association with stillbirths. However, among all participants a history of prior diabetes emerged as a significant predictor in multivariable analysis (AOR = 2.63, 95% CI: 1.06-6.52, p = 0.04). Among WLHIV, longer ART duration was associated with reduced odds of stillbirth (AOR = 0.53, 95% CI: 0.33-0.93, p = 0.01 and AOR = 0.55, 95% CI: 0.33-0.93, p = 0.02). Poor-quality ANC with ≤4 or ≤8 visits showed a non-significant trend towards increased stillbirth odds (AOR = 1.34, 95% CI: 0.87-2.17, p = 0.21 and AOR = 1.61, 95% CI: 0.85-3.05, p = 0.15, respectively).

CONCLUSION

In a Western Cape cohort of pregnant participants, we found no statistically significant differences in stillbirth prevalence and adjusted odds between WLHIV and women without HIV. Longer ART duration among WLHIV was associated with reduced stillbirth odds and

incidence. Quality of ANC, as defined, did not show a significant association with stillbirth odds in adjusted analyses.

INTRODUCTION

Globally, 1.9 million stillbirths occur annually, with a rate of 13.9/1000 births (1). Defined as the birth of a lifeless baby before complete expulsion (2), stillbirths negatively impact about 4.2 million mothers (3). Sub-Saharan Africa (SSA) contributes significantly, with a stillbirth rate of 32.2/1000 births (4). In 2019, South Africa reported a stillbirth rate of 16.3 /1000 births (5), despite efforts to achieve Sustainable Development Goal 3.2 (stillbirths ≤ 12/1000 births) by 2030 (6). Major contributors in low- and middle-income countries (LMICS) include hypertension, bacterial infection, placental disorders, syphilis, HIV, and inadequate antenatal care (ANC) (7,8).

South Africa has 8.4 million people living with HIV, particularly a 30% prevalence among pregnant women (9). Studies have shown significant associations between stillbirth and maternal HIV status (10,11,12,13). Notably, the country achieved 97% coverage of antiretroviral therapy (ART) for pregnant individuals living with HIV in 2019, with the Western Cape reporting an antenatal HIV prevalence of 17.9% and ART coverage exceeding 90% (11,14).

Research emphasizes a lower stillbirth rate associates with individuals receiving good quality ANC (13,11,15,16). The World Health Organization (WHO) recommends essential ANC services, maternal and fetal clinical assessments, education on complications, and vaccinations (17).

Amid the COVID-19 pandemic, disruptions and fears may have impacted stillbirth rates indirectly by influencing ANC quality (18).

This cohort study, leveraging routine health data, explores the association between maternal HIV and stillbirths in the Western Cape, South Africa, during the era of universal ART, examining demographic and clinical variables, including ANC quality.

METHODS

Study Setting

The study utilized data from the Western Cape Pregnancy Exposure Registry (PER) between 2017 and 2021. The PER systematically captures pregnancy exposures and outcomes through routine sentinel site-based surveillance (11). Managed by the Western Cape Government Department of Health & Wellness (WCGH), the PER digitizes data elements from clinical obstetric stationary routinely collected by attending clinicians. The PER is integrated into the Provincial Health Data Centre (PHDC), a linked health information exchange synchronizing individual-level health-related electronic data throughout the province using a unique patient identifier (11). The resulting linked database allows for the generation of virtual cohorts within the PHDC. We defined a cohort including all women attending ANC at the two PER sentinel sites, Gugulethu Midwife Obstetrics Unit (GMOU) and Worcester MOU (WMOU), over the study period who were categorized by HIV status. GMOU, a public clinic in Cape Town, serves a population of 98,468, with an antenatal HIV prevalence rate of 30% (11). Annually, approximately 5,000 women seek ANC at GMOU, with half delivering at the clinic and the rest referred to hospitals. WMOU, located in the farming town of Worcester, serves around 230,000 people, and handles delivery services for approximately 3,600 expectant mothers each year. The clinic has an antenatal HIV prevalence of 16% (11).

Study Design and Population

The cohort comprised pregnant participants in the PER aged 18 years or older, with a known HIV status, and having a recorded pregnancy outcome at a gestational age exceeding 20 weeks between January 1, 2017, and December 31, 2021 (Figure 1). The period was after the launch of WHO Option B+ for prevention of vertical transmission of HIV in 2013 and the HIV Universal Test and Treat policy in 2016 in South Africa and all pregnant individuals had access to ART, many having initiated treatment before pregnancy, irrespective of CD4 count or clinical stage.

Study Variables

The primary outcome was stillbirth, defined as the intrauterine death of a baby occurring after 20 weeks gestation or weighing more than 500g (19). Maternal HIV status during pregnancy served as the primary exposure, determined through the analysis of HIV laboratory and treatment data in the Provincial Health Data Centre (PHDC). The first-line ART regimen

comprised Efavirenz, Emtricitabine, Lamivudine, Tenofovir, with Dolutegravir (DTG), being introduced in the Western Cape in 2020. The quality of ANC was evaluated based on the 2016 guidelines established by the World Health Organization (WHO) (17). These included the timing (<12 weeks gestation) and number of ANC visits (4 or 8), weight checks, HIV and syphilis testing, urine checks, blood pressure checks, the provision of iron and folate supplements, tetanus, and influenza vaccinations (17). Recognizing the potential incomplete implementation of the 2016 WHO guideline advocating for at least 8 ANC visits, we employed a two-tiered categorization of quality of ANC: one group with at least 4 visits (prior WHO recommendation) and one with at least 8 visits. A good ANC quality score was attributed to women, regardless of HIV status, who received 7 or more out of 11 Quality of ANC variables. This cutoff aligns with 67% of the WHO benchmark of 8 out of 12 variables (17).

Statistical Analysis

Statistical analyses were conducted using R software, version 1.2.5003. Descriptive statistics were employed to present characteristics at the enrolment into the PER at the first antenatal visit. Categorical variables were expressed as proportions and frequencies and assessed using the Chi-Square and Fisher tests as appropriate; medians and interquartile ranges were utilized for numeric variables and compared across groups using the two-sided Wilcoxon test.

To assess the cumulative incidence proportions of stillbirths among pregnant women living with and without HIV, the epitools package was used. Univariable logistic regression models were utilized to evaluate the significance of independent variables concerning the dependent variable (stillbirths). To control for potential confounders, we employed multivariable logistic regression models. Variables were selected a priori based on their established or theoretical relevance to stillbirth rates, drawing from existing literature and expert knowledge. The final choice of variables was made by evaluating the model fit using Bayesian Information Criterion (BIC) values, aiming for a model that best explained the variation in stillbirth rates while avoiding overfitting.

While the literature highlighted dolutegravir (DTG) as a potentially significant variable, its inclusion in our analysis was constrained by the small number of women in the dataset who were prescribed this medication. We employed the Generalized Linear Model function glm() with the logit link in R Studio to estimate the odds ratios for the selected variables. This method allowed us to assess the association between each variable and the odds of stillbirth, providing a nuanced understanding of the factors influencing stillbirth rates in our study population.

. To investigate the potential impact of COVID-19 on stillbirth rates during the study period, we conducted a sensitivity analysis considering data from before and during the pandemic separately. Statistical significance was established at ≤0.05.

Ethical Considerations

Ethical approval was obtained from the University of Cape Town Human Research Ethics Committee (reference numbers: HREC REF:689/2022 and 749/2015) and the Western Cape Department of Health (reference numbers: WC_2016RP6_286 and WC_202202_022).

RESULTS

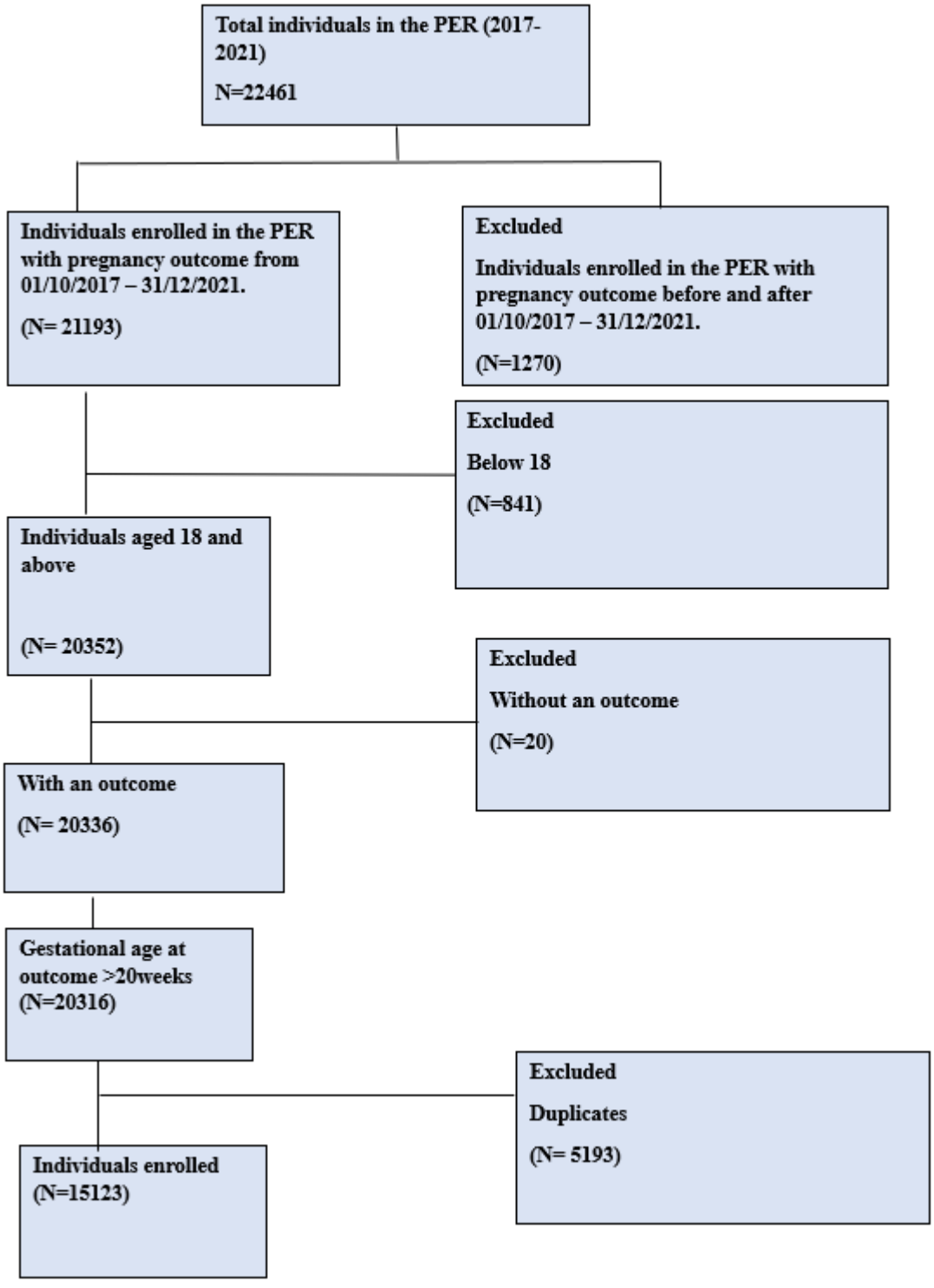

Fig 1 : Flow chart of Total participants in the Pregnancy Exposure Registry from the year 2017-2021 in the Western Cape province South Africa enrolled in the study

Characteristics of Pregnant participants living with and without HIV Infection

A total of 15,123 participants were included in the study, with 31.56% (4,773) women living with HIV (WLHIV) and 68.44% (10,350) women living without HIV (Table 1). Significant differences were observed in age, with a median of 28 years (IQR: 23-33) for WLHIV, compared to 31 years (IQR: 26-35) for women without HIV. No significant differences were found in Body Mass Index (BMI) (WLHIV: 30.36, IQR: 25.71-35.60; without HIV: 30.09, IQR: 25.32-35.55). Gestational age at first ANC differed, with WLHIV having a median gestational age of 19.29 weeks (IQR: 13.29-25.71), compared to 18.57 weeks (IQR: 13.29-24.71) (p=0.00) for women without HIV (Appendix 1). Quality of ANC was similar in both groups with 87.55% of WLHIV and 86.99% of women without HIV receiving poor-quality ANC (4 visits) and 92.91% of WLHIV and 92.44% of women without HIV received poor-quality ANC (8 visits). (Appendix 1)

Characteristics in Pregnant Women living with and without HIV, by Pregnancy Outcome

WLHIV had a higher prevalence of stillbirth (1.66%) compared to women without HIV (1.42%), although this difference did not reach statistical significance. Notably, women without HIV with a history of diabetes had a higher prevalence of stillbirth, (4.08% versus 3.80% WLHIV). Most individuals, regardless of their HIV status, received suboptimal ANC, with 87.55% receiving poor quality ANC at 4 visits and 92.91% at 8 visits (Table 1). WLHIV who received good-quality ANC experienced fewer stillbirths compared to women without HIV who received good-quality ANC (5.06% versus 11.56%; (4 visits) and 2.53% versus 5.06%; (8 visits)) (Table 1). However, quality of ANC, regardless of the number of visits, did not demonstrate statistical significance with respect to the prevalence of stillbirth. There were no statistically significant differences between participants with and without stillbirth in terms of maternal age, gravidity, obesity, and alcohol, smoking, or drug use. A history of diabetes and hypertension were significantly associated with stillbirth in women without HIV only (Table 1).

Table 1: Comparative Analysis of Demographic, Reproductive, Antenatal, and Health Characteristics in Pregnant Women with and without HIV Infection stratified by pregnancy outcome.

Characteristic	All Women n= 15123	Living without HIV (n=10350)		p-value	Living HIV (n=4773)		p-value
		Livebirths n=10203 (98.58)	Stillbirths n=147 (1.42)		Livebirths n=4694 (98.34)	Stillbirths n= 79 (1.66)	
Age (years)				0.86			0.14
Median (IQR)	28(23-33)	26 (22-31)	26 (22-31)		31 (26-35)	30 (26-34)	
Age group (years)				0.59			0.53
18-35	12627 (83.50)	8930 (87.52)	126 (85.71)		3509 (74.56)	62 (78.48)	
35+	2496 (16.50)	1273 (12.48)	21 (14.29)		1185 (25.24)	17 (21.52)	
Gravidity				0.69			0.08
Median (IQR)	2 (1 - 3)	2 (1-3)	2 (1-3)		3 (2-3)	2 (2-3)	
Parity				0.09			0.13
Median (IQR)	1 (0 - 2)	1 (0-2)	1 (0-2)		1 (1-2)	1 (1-2)	
Obese				0.87			0.27
Yes	6165 (40.77)	4135 (40.53)	58 (39.46)		1945 (41.44)	27 (34.18)	
No	5760 (38.09)	4022 (39.42)	57 (38.78)		1653 (35.22)	28 (35.44)	
Missing	3198 (21.15)	2046 (20.05)	32 (21.77)		1096 (23.35)	24 (30.38)	
BMI (kg/m^2)				0.20			0.47
Median (IQR)	30.36 (25.71-35.60)	30.09 (25.32 – 35.49)	30.43 (26.13 – 38.64)		30.81 (26.56-35.87)	29.30 (25.97 – 34.85)	
Diabetes History				**0.01**			0.24
Yes	203 (1.34)	123 (1.21)	6 (4.08)		71 (1.51)	3 (3.80)	
No	14920 (98.66)	10080 (98.79)	141 (95.92)		4623 (98.49)	76 (96.20)	
Gestational Diabetes				0.55			1
Yes	367 (2.43)	252 (2.47)	2 (1.36)		111 (2.36)	2 (2.53)	
No	14752 (97.57)	9949 (97.51)	145 (98.64)		4581 (97.59)	77 (97.47)	
Missing	4 (0.03)	2 (0.02)	0 (0)		2 (0.04)		
Hypertension History				**0.02**			0.77
Yes	63 (0.42)	40 (0.39)	3 (2.04)		19 (0.40)	1 (1.27)	
No	15060 (99.58)	10163 (99.61)	144 (97.96)		4675 (99.60)	78 (98.73)	
Gestational Hypertension				0.98			0.78
Yes	645 (4.27)	456 (4.47)	6 (4.08)		179 (3.81)	4 (5.06)	
No	14478 (95.63)	9747 (95.53)	141 (95.92)		4515 (96.19)	75 (94.94)	
Smoking during pregnancy				0.57			0.83
Yes	767 (5.07)	519 (5.09)	8 (5.44)		236 (5.03)	43 (5.43)	
No	13584 (89.82)	9139 (89.57)	125 (1.23)		4247 (90.48)	73 (92.41)	
Missing	772 (5.10)	545 (5.34)	14 (0.14)		211 (4.50)	2 (2.53)	
Illicit Drug use during pregnancy				0.30			0.93
Yes	29 (0.19)	21 (0.21)	0 (0)		8 (0.17)	0 (0)	

No	14,303 (94.58)	9632 (94.40)	132 (89.80)		4465 (95.12)	75 (94.94)	
Missing	790 (5.22)	550 (5.39)	15 (10.20)		221 (4.71)	4 (5.06)	
Alcohol use during pregnancy				0.21			0.78
Yes	628 (4.15)	415 (4.07)	3 (2.04)		206 (4.39)	4 (5.06)	
No	13,706 (90.63)	9235 (90.51)	130 (88.44)		4268 (90.92)	73 (92.41)	
Missing	789 (5.22)	553 (5.42)	14 (9.52)		211 (4.50)	2 (2.53)	
GA at first ANC (weeks)				0.25			0.08
Median (IQR)	19 (13-25)	19 (13-25)	18 (12-23)		19 (13-26)	20 (16-28)	
Quality of ANC (at least 4 visits)				0.69			0.12
Good Quality	1883 (12.45)	1330 (13.04)	17 (11.56)		532 (11.33)	4 (5.06)	
Poor Quality	13240 (87.55)	8873 (86.96)	130 (88.44)		4162 (88.67)	75 (94.94)	
Quality of ANC (at least 8 visits)				0.41			0.12
Good Quality	1072 (7.09)	774 (7.59)	8 (5.44)		288 (6.14)	2 (2.53)	
Poor Quality	14051 (92.91)	9429 (92.41)	139 (94.56)		4406 (93.86)	77 (97.47)	
Delivery location				**<.001**			**<.001**
MOU	6388 (42.25)	4435 (43.46)	14 (9.52)		1919 (40.88)	20 (25.32)	
Level 1 hospital	271 (1.79)	220 (2.16)	2 (1.36)		48 (1.02)	1 (1.27)	
Level 2 hospital	7282 (48.15)	4893 (47.96)	84 (57.14)		2268 (48.32)	37 (46.84)	
Level 3 hospital	1162 (7.68)	646 (6.33)	47 (31.97)		448 (9.54)	21 (26.58)	
Missing	20 (0.13)	9 (0.09)			11 (0.23)		
Delivery Year				0.12			0.21
2017	1876 (12.42)	1162 (11.39)	18 (12.24)		677 (14.42)	19 (24.05)	
2018	3704 (24.49)	2527 (24.77)	39 (26.53)		1122 (23.90)	16 (20.25)	
2019	3850 (25.44)	2716 (26.62)	35 (23.81)		1083 (23.07)	16 (20.25)	
2020	3071 (20.29)	2103 (20.61)	21 (14.29)		933 (19.88)	14 (17.72)	
2021	2622 (17.36)	1695 (16.61)	34 (23.13)		879 (18.73)	14 (17.72)	

IQR=Interquartile Range; BMI=Body Mass Index; GA=Gestational Age; ANC=Antenatal Care; HIV=Human Immunodeficiency Virus

Trends in pregnancy outcomes among women living with HIV over time.

All WLHIV were on ART, with a predominant initiation or restart during pregnancy (62.60%) compared to preconception (30.40%). All stillbirths occurred among women on first-line ART. Among those exposed to efavirenz (EFV), there were fewer stillbirths 1.55% (95% CI: 1.14% - 1.96%) compared to those on dolutegravir (DTG) 2.45% (95% CI: 0.08% - 4.82%). However, when stratified by delivery year, DTG showed lower stillbirths compared to EFV, except for 2020, 0.61% (95% CI: 0.12%-1.10%) and 2021 1.84% (95% CI: 0.98%-2.70%), although the number of women on DTG was low until 2021. A longer duration of ART was associated with a lower prevalence of stillbirths as compared to ART <20 weeks. Over the years, the number of WLHIV receiving good quality antenatal care (ANC) increased. Overall, individuals who received good quality (ANC) with at least 8 visits experienced fewer stillbirths 0.69% (95% CI: 0.00%-1.63%) compared to those with good quality ANC at least 4 visits 0.75% (95% CI: 0.03%-1.47%).

Table 2: Pregnancy Outcome trends of women living with HIV stratified by delivery year.

Characteristic	All women		2017		2018	
N(%)	**Livebirths 4694 (98.34)**	**Stillbirths 79 (1.66)**	**Livebirths 677 (97.27)**	**Stillbirths 19 (2.72)**	**Livebirths 1122 (98.59)**	**Stillbirths 16 (1.41)**
Age (years)						
Median (IQR)	31 (26-35)	30 (26-34)	31 (26-35)	28 (25-31)	31 (26-35)	27 (21-33)
Duration of ART						
<20 weeks	936 (97.1)	28 (2.90)	191 (19.81)	10 (1.04)	230 (23.86)	3 (0.31)
20-40 weeks	592 (98.83)	7 (1.17)	104 (17.36)	1 (0.17)	177 (29.55)	5 (0.83)
40- <100 weeks	421 (98.83)	5 (1.17)	56 (13.15)	1 (0.23)	100 (23.47)	2 (0.47)
≥100 weeks	2476 (98.53)	37 (1.47)	277 (11.02)	7 (0.28)	547 (21.77)	5 (0.20)
Missing	269 (99.26)	2 (0.74)	49 (18.08)	0 (0)	70 (25.83)	1 (0.37)
Viral Load						
Undetectable	3297 (98.45)	52 (1.55)	462 (13.8)	11 (0.33)	783 (23.38)	12 (0.36)
Detectable	897 (98.36)	15 (1.64)	131 (14.36)	3 (0.33)	203 (22.26)	3 (0.33)
Missing	500 (97.66)	12 (2.34)	84 (16.41)	5 (0.98)	136 (26.56)	1 (0.20)
ART Initiation period						
ART Preconception	1432 (98.69)	19 (1.31)	92 (6.34)	5 (0.34)	248 (17.09)	4 (0.28)
ART Restart/During	2932 (98.13)	56 (1.87)	493 (16.50)	14 (0.47)	803 (26.87)	11 (0.37)
missing	330 (98.80)	4 (1.20)	92 (27.54)	0 (0)	71 (21.26)	1 (0.30)
ART REGIMEN n(%)						
First line	4629 (98.32)	79 (1.68)	670 (14.23)	19 (0.40)	1110 (23.58)	16 (0.34)
Second line	65 (100)	0 (0)	7 (10.77)	0 (0)	12 (18.46)	0 (0)
DTG exposed n(%)						
Yes	159 (97.55)	4 (2.45)	3 (1.84)	0 (0)	8 (4.91)	0 (0)
EFV exposed n(%)						
Yes	3547 (98.45)	56 (1.55)	603 (16.74)	18 (0.50)	1041 (28.89)	16 (0.44)
Quality of ANC (at least 4 visits)						
Good Quality	532 (99.25)	4 (0.75)	41 (7.65)	1 (0.19)	75 (13.99)	0 (0)
Poor Quality	4162 (98.23)	75 (1.77)	636 (15.01)	18 (0.42)	1047 (24.71)	16 (0.38)
At least 4 visits						
Yes	1952 (98.79)	24 (1.21)	160 (8.10)	4 (0.20)	278 (14.07)	4 (0.20)
No	2742 (98.03)	55 (1.97)	517 (18.48)	15 (0.54)	844 (30.18)	12 (0.43)
Quality of ANC (at least 8 visits)						
Good Quality	288 (99.31)	2 (0.69)	30 (10.34)	1 (0.34)	43 (14.83)	0 (0)
Poor Quality	4406 (98.28)	77 (1.72)	647 (14.43)	18 (0.40)	1079 (24.07)	16 (0.36)
At least 8 visits						
Yes	800 (98.89)	9 (1.11)	97 (11.99)	4 (0.49)	106 (13.10)	2 (0.25)
No	3894 (98.23)	70 (1.77)	580 (14.63)	15 (0.38)	1016 (25.63)	14 (0.35)

Continuation of Table 2

Characteristic	2019		2020		2021		p-value
N(%)	**Livebirths 1083 (98.54)**	**Stillbirths 16 (1.46)**	**Livebirths 933 (98.52)**	**Stillbirths 14 (1.48)**	**Livebirths 879 (98.43)**	**Stillbirths 14 (1.57)**	**0.39**
Age (years)							0.14
Median (IQR)	30 (26-35)	30 (29-34)	31 (27-35)	30 (27-37)	31 (27-35)	32 (30-35)	
Duration of ART							0.04
<20 weeks	202 (20.95)	6 (0.62)	148 (15.35)	6 (0.62)	165 (17.12)	3 (0.31)	
20-40 weeks	117 (19.53)	0 (0)	106 (17.70)	0 (0)	88 (14.69)	1 (0.17)	
40- <100 weeks	101 (23.71)	1 (0.23)	89 (20.89)	1 (0.23)	75 (17.61)	0 (0)	
≥100 weeks	598 (23.80)	9 (0.36)	543 (21.61)	6 (0.24)	513 (20.41)	10 (0.40)	
Missing	65 (23.99)	0 (0)	47 (17.34)	1 (0.37)	38 (14.02)	0 (0)	
Viral Load							0.40
Undetectable	734 (21.92)	12 (0.36)	674 (20.13)	6 (0.18)	644 (19.23)	11 (0.33)	
Detectable	199 (21.82)	3 (0.33)	188 (20.61)	3 (0.33)	176 (19.30)	3 (0.33)	
Missing	150 (29.30)	1 (0.20)	71 (13.87)	5 (0.98)	59 (11.52)	0 (0)	
ART Initiation period							0.36
ART Preconception	363 (25.02)	4 (0.28)	366 (25.22)	3 (0.21)	363 (25.02)	3 (0.21)	
ART Restart/During	651 (21.79)	12 (0.40)	516 (17.27)	10 (0.33)	470 (15.73)	9 (0.30)	
missing	69 (20.66)	0 (0)	51 (15.27)	1 (0.30)	46 (13.77)	2 (0.60)	
ART REGIMEN n(%)							0.63
First line	1065 (22.62)	16 (0.34)	917 (19.48)	14 (0.30)	867 (18.42)	14 (0.30)	
Second line	18 (27.69)	0 (0)	16 (24.62)	0 (0)	12 (18.46)	0 (0)	
DTG exposed n(%)							0.35
Yes	9 (5.52)	0 (0)	26 (15.95)	1 (0.61)	113 (69.33)	3 (1.84)	
EFV exposed n(%)							0.36
Yes	1022 (28.37)	15 (0.42)	684 (18.98)	5 (0.14)	197 (5.47)	2 (0.06)	
Quality of ANC (at least 4 visits)							0.10
Good Quality	168 (31.34)	2 (0.37)	140 (26.12)	0 (0)	108 (20.15)	1 (0.19)	
Poor Quality	915 (21.60)	14 (0.33)	793 (18.72)	14 (0.33)	771 (18.20)	13 (0.31)	
At least 4 visits							0.05
Yes	625 (31.63)	5 (0.25)	461 (23.33)	6 (0.30)	428 (21.66)	5 (0.25)	
No	458 (16.37)	11 (0.39)	472 (16.88)	8 (0.29)	451 (16.12)	9 (0.32)	
Quality of ANC (at least 8 visits)							0.24
Good Quality	87 (30)	1 (0.34)	78 (26.90)	0 (0)	50 (17.24)	0 (0)	
Poor Quality	996 (22.22)	15 (0.33)	855 (19.07)	14 (0.31)	829 (18.49)	14 (0.31)	
At least 8 visits							0.23
Yes	280 (34.61)	2 (0.25)	177 (21.88)	1 (0.12)	140 (17.31)	0 (0)	
No	803 (20.26)	14 (0.35)	756 (19.07)	13 (0.33)	739 (18.64)	14 (0.35)	

IQR=Interquartile Range; ART=Antiretroviral therapy; DTG= Dolutegravir; EFV= Efavirenz; ANC=Antenatal Care

The data percentages are presented in row statistics as this format would provide a more meaningful interpretation.

Cumulative incidence proportions of stillbirths among pregnant women with and without HIV in the PER between 2017 and 2021

The cumulative incidence proportions of stillbirths among pregnant individuals, both with and without HIV, were analysed over the span of five years from 2017 to 2021. Across this period, the cumulative incidence of stillbirths among WLHIV showed a slight increase compared to those without HIV. Specifically, in 2018, there was a notable decline in the incidence of stillbirths among WLHIV, dropping from 2.7% in 2017 to 1.4%, after which it plateaued (Fig 2). Conversely, there was a marked reduction in stillbirth incidence proportions (1%) among women without HIV in 2020, only to rebound in 2021 (2%).

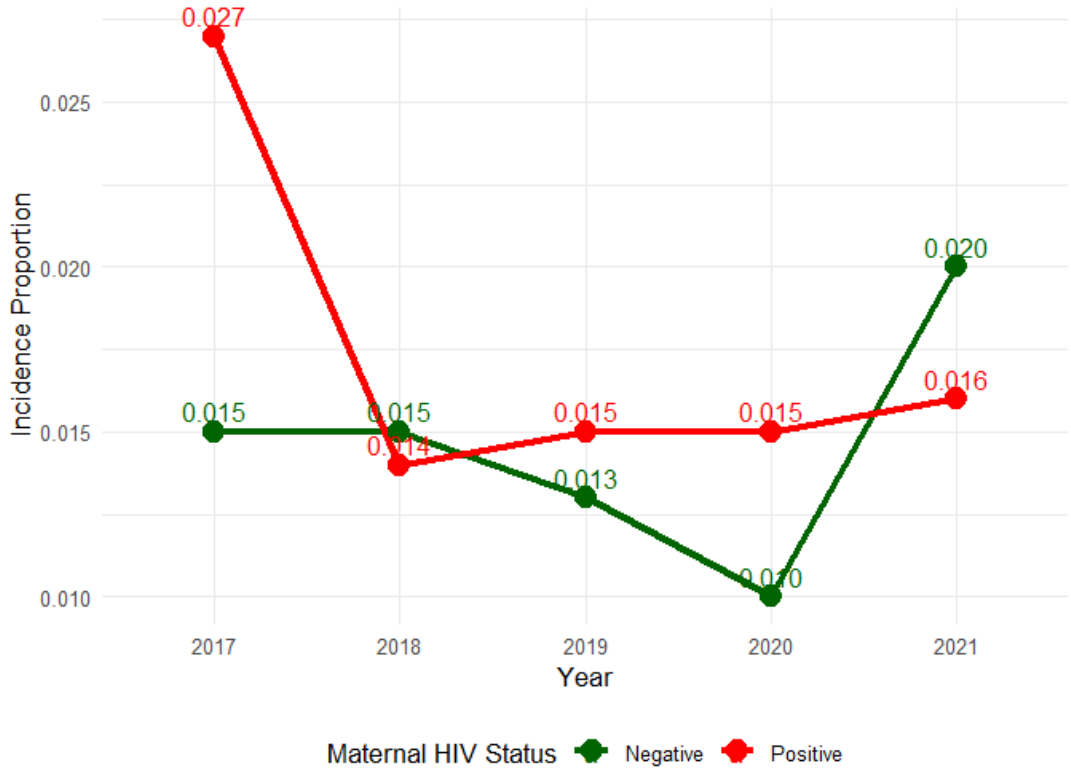

Fig 2: Cumulative Incidence proportion of Stillbirths by Maternal HIV Status Over Years

Risk factors for Stillbirths among pregnant participants living with and without HIV.

There was no statistically significant difference in stillbirth likelihood between WLHIV and women without HIV (AOR = 1.15, 95% CI: 0.87-1.52, p = 0.34) (Table 3). Analysis of poor-quality ANC with four visits indicated a non-significant trend towards increased stillbirth odds (AOR = 1.34, 95% CI: 0.87-2.17, p = 0.21), suggesting a 34% higher likelihood of stillbirth in women who received poor-quality ANC (Table 3). Similarly, poor-quality ANC with eight visits also showed a non-significant trend (AOR = 1.61, 95% CI: 0.85-3.05, p = 0.15), indicating a 61% higher likelihood of stillbirth in women who received poor-quality ANC by this definition (Appendix 3). Individuals with prior diabetes exhibited a substantial increase in stillbirth odds (AOR = 2.63, 95% CI: 1.06-6.52, p = 0.04) (Table 3) and (AOR = 2.61, 95% CI: 1.05-6.48, p = 0.04) (Appendix 3). Stillbirth odds varied across years, with 2020 initially showing significance in unadjusted analysis (OR = 0.57, 95% CI: 0.33-0.91, p = 0.02) (Table 3) but maintaining significance (AOR=0.61,95% CI:0.37-0.99, p=0.05) in adjusted analysis (Appendix 3). When stratified by maternal HIV status, a longer duration of ART demonstrated a protective effect in WLHIV. Individuals with ART duration ≥100 weeks had 47% lower odds of stillbirths (AOR = 0.53, 95% CI: 0.33-0.93, p = 0.01) compared to those with <20 weeks of ART (Table 4) and 45% lower odds of stillbirths (AOR = 0.55, 95% CI: 0.33-0.91, p = 0.02) compared to those with <20 weeks of ART (Appendix 4)

Table 3: Multivariable analysis on the risk factors of stillbirths among all participants

Predictor Variable		Unadjusted Odds Ratio (95% CI)	P-value	Adjusted Odds Ratio (95% CI)	P-value
Maternal Age group	18-35	1		1	
	35+	1.02 (0.70-1.43)	0.93	0.96 (0.66 -1.37)	0.82
Quality of ANC received (At least 4 visits)	Good quality	1		1	
	Poor quality	1.39 (0.91-2.26)	0.15	1.34 (0.87-2.17)	0.21
Maternal HIV status	HIV negative	1		1	
	HIV positive	1.17 (0.88 - 1.53)	0.27	1.15 (0.87-1.52)	0.34
Syphilis during pregnancy	Negative	1		1	
	Positive	1.03 (0.36 -2.26)	0.95	1.04 (0.42-2.54)	0.94
	Inconclusive*	1.48 (0.87 – 2.37)	0.12	1.47 (0.89-2.42)	0.13
Hypertension prior	No	1		1	
	Yes	4.53 (1.37- 11.13)	**<.001**	1.92 (0.49-7.45)	0.35
Gestational Hypertension	No	1		1	
	Yes	1.04 (0.51 – 1.87)	0.91	1.07 (0.56-2.03)	0.83
Diabetes prior	No			1	
	Yes	3.14 (1.48 – 5.87)	**<.001**	2.63 (1.06-6.52)	**0.04**
Gestational Diabetes	No	1		1	
	Yes	0.72 (0.22 – 1.71))	0.52	0.71 (0.26-1.91)	0.49
Obesity	No	1		1	
	Yes	0.93 (0.69- 1.26)	0.66	0.88 (0.65-1.20)	0.42
Year of Delivery	2017	1		1	
	2018	0.75 (0.49-1.14)	0.18	0.79 (0.50-1.125)	0.31
	2019	0.67 (0.44-1.02)	0.06	0.73 (0.46-1.17)	0.19
	2020	0.57 (0.33-0.91)	**0.02**	0.61 (0.37-1.01)	0.06
	2021	0.93 (0.60-1.43)	0.73	1 (0.63-1.58)	0.99

ANC= Antenatal Care; HIV= Human Immunodeficiency Virus; CI= Confidence Interval

* Test result that is neither definitively positive nor definitively negative for syphilis.

Table 4 : Multivariable regression of risk factors of stillbirths among women living with HIV

Predictor Variable		Unadjusted Odds Ratio (95% CI)	P-value	Adjusted Odds Ratio (95% CI)	P-value
Maternal Age group	18-35	1		1	
	35+	0.81 (0.46-1.36)	0.45	0.84 (0.46-1.43)	0.53
Quality of ANC (At least 4 visits)	Good	1		1	
	Poor	2.40 (0.99-7.86)	0.09	2.14 (0.87-7.09)	0.15
Duration of ART	<20 weeks	1		1	
	20-40 weeks	0.40 (0.99-7.89)	**0.03**	0.43 (0.17-0.96)	0.05
	40- <100 weeks	0.40 (0.16-0.86)	0.05	0.44 (0.15-1.05)	0.09
	≥100 weeks	0.50 (0.30-0.83)	**0.01**	0.53 (0.32-0.89)	**0.02**
Syphilis during pregnancy	Negative	1		1	
	Positive	1.66 (0.40-4.55)	0.39	1.74 (0.42-4.82)	0.36
	Inconclusive*	1.03 (0.31-2.52)	0.95	1.02 (0.31-2.50)	0.97
Hypertension prior	No	1		1	
	Yes	3.15 (0.17-15.49)	0.27	1.34 (0.06-15.39)	0.82
Gestational Hypertension	No	1		1	
	Yes	1.35 (0.41-3.28)	0.57	1.36 (0.41-3.36)	0.55
Diabetes prior	No	1		1	
	Yes	2.57 (0.62-7.10)	0.12	2.83 (0.45-9.59)	0.16
Gestational Diabetes	No	1		1	
	Yes	1.07 (0.17-3.46)	0.92	0.91 (0.15-2.98)	0.90
Obesity	No	1		1	
	Yes	0.82 (0.48-1.40)	0.46	0.79 (0.46-1.37)	0.40
Year of Delivery	2017	1		1	
	2018	0.51 (0.26-0.99)	0.05	0.58 (0.28-1.21)	0.14
	2019	0.53 (0.27-1.03)	0.06	0.64 (0.30-1.34)	0.23
	2020	0.53 (0.26-1.07)	0.08	0.64 (0.30-1.34)	0.24
	2021	0.57 (0.28-1.13)	0.11	0.66 (0.31-1.37)	0.27

ANC=Antenatal Care; ART=Antiretroviral therapy; CI=Confidence Interval

* Test result that is neither definitively positive nor definitively negative for syphilis.

DISCUSSION

In our study of women who were pregnant in the Western Cape using routine clinical data, we explored the association between maternal HIV and stillbirths and observed no statistically significant link. Although there was a noted increase in the odds of stillbirths among WLHIV, it did not reach statistical significance. This finding contrasts with studies in other LMIC and earlier South African research (10,12,13), which reported strong associations between maternal HIV and stillbirths. Our results align with more recent studies (20, 21) that considered confounders, involved large samples, and included women with improved access to and longer duration on ART.

The overall stillbirth rate in our study stood at 15/1000 births, slightly surpassing the WHO's Every Newborn Action Plan global target of ≤12 stillbirths/1000 births by 2030 (6). While lacking statistical significance, the stillbirth rates among women without HIV (14/1000 births) and WLHIV (17/1000 births) closely mirrored findings from a South African study, WLHIV (25/1000) and women without HIV (22/1000) (22). Notably, our overall stillbirth rate was lower than the reported rate of 20/1000 births (22), possibly attributed to the inclusion of periods preceding the universal ART rollout starting from 2010.

A noteworthy decline in stillbirths among WLHIV was observed in 2018 (incidence proportion 0.014) compared to 2017 (0.027). This could be attributed to an increase in the proportion of WLHIV on ART for more than 100 weeks in 2018. Our study indicates a significant association between the duration of ART and a reduction in the odds of stillbirth by 47% and 45%. This highlights the protective effect of prolonged ART, with over half of the WLHIV in our study being on ART for more than 100 weeks. This emphasizes the potential role of sustained ART access in mitigating the risk of stillbirth in WLHIV, aligning with findings from other studies (23).

Descriptive findings in our study demonstrated a non-significant association between the quality of ANC and stillbirths. Individuals receiving good-quality ANC with at least 8 visits experienced fewer stillbirths than those with good-quality ANC with at least 4 visits. This aligns with other studies showing an 18.4% decrease in stillbirths with more ANC visits (RR 0.82, 95% CI 0.73-0.91) (17). Highlighting adequate ANC is crucial for reducing poor pregnancy outcomes and providing a positive pregnancy experience (24).

However, our study did not find a statistically significant association between access to quality ANC and stillbirths in WLHIV or women without HIV. This might be influenced by specific

components of ANC received, with low percentages of individuals in both Quality of ANC groups (at least 4 visits and at least 8 visits) receiving good quality care.

Our study revealed a positive association between pre-pregnancy diabetes and stillbirths, aligning with findings from other studies (25). This underscores the significance of carefully evaluating comorbidities like diabetes when addressing multiple risk factors connected with stillbirths.

The incidence proportion of stillbirth differed by year and by HIV status within years. In WLHIV, the decline between 2017 and 2018 may be related to the increased proportion of individuals on ART. There was a notable decrease in the overall proportion of stillbirths in 2020, the first year of the COVID-19 pandemic and the year with the severest restrictions on movement and pressure on health services despite the sensitivity analysis showing non-significance. Stratifying by HIV status, this decrease is accounted for by women not living with HIV. Several factors may contribute to this reduction; the year 2020 stood out for having the lowest proportion of women receiving poor-quality ANC, particularly within this subgroup.

DTG for the treatment of HIV has demonstrated many clinical benefits (26, 27). DTG was introduced to first-line ART regimens in 2020 in South Africa, however there were too few individuals on DTG for us to fully assess its impact on stillbirth.

Strengths and Limitations

Our study highlights the utility of routine electronic health data in investigating a large cohort of 15,123 pregnant women, accounting for potential confounding variables. However, the study faced several limitations, including missing data, particularly in ANC components, and a limited number of individuals taking DTG. Additionally, potential unmeasured confounders introduce uncertainty into our results. Recognizing these constraints is crucial for accurate interpretation and guiding future research to address these gaps. The substantial missing data on key variables needed to assess the quality of care could have contributed to the statistically insignificant results, especially concerning those who received good-quality or poor-quality ANC.

Conclusion

Within a well-established HIV treatment program, encompassing women enrolled in primary care, our investigation revealed no statistically significant disparities in stillbirth prevalence and adjusted odds between WLHIV and women without HIV. Notably, a longer duration of ART among WLHIV exhibited an association with decreased adjusted odds of stillbirths. Furthermore, the quality of ANC, as defined in our study, was universally low among all

individuals and did not show a significant association with the odds of stillbirth in adjusted analyses.

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PART C: APPENDICES

Appendix 1: Comparative Analysis Characteristics in Pregnant participants living with and without HIV

Characteristic	All Women n= 15123	Women with HIV n=4773 (31.56%)	Women without HIV n=10350 (68.44%)	p-value
Age (years)				<.001
Median (IQR)	28 (23-33)	31 (26-35)	26 (22-31)	
Age group (years)				<.001
18-35	12627 (83.50)	3571 (74.82)	9056 (87.50)	
35+	2496 (16.50)	1202 (25.18)	1294 (12.50)	
Gravidity				<.001
Median (IQR)	2 (1 - 3)	3(2-3)	2 (1 - 3)	
Parity				<.001
Median (IQR)	1 (0 - 2)	1 (1 - 2)	1 (0 - 2)	
Obese				<.001
Yes	6165 (40.77)	1972 (41.31)	4193 (40.51)	
No	5760 (38.09)	1681 (35.22)	4079 (39.43)	
Missing	3198 (21.15)	1120 (23.47)	2078 (20.06)	
BMI (kg/m^2)				0.67
Median (IQR)	30.36 (25.71-35.60)	30.80 (26.56-35.84)	30.09 (25.32-35.55)	
Diabetes History				0.15
Yes	203 (1.34)	74(1.55)	129 (1.27)	
No	14920 (98.66)	4699 (98.45)	10221 (98.75)	
Gestational Diabetes				0.79
Yes	367 (2.43)	113 (2.36)	254 (2.45)	
No	14,752 (97.57)	4658 (97.60)	10094 (97.53)	
Missing	4 (0.03)	2 (0.04)	2 (0.02)	
Hypertension History				1
Yes	63 (0.42)	20 (0.42)	43 (0.42)	
No	15060 (99.58)	4753 (99.58)	10307 (99.58)	
Gestational Hypertension				0.08
Yes	645 (4.27)	183 (3.83)	462 (4.46)	
No	14,474 (95.63)	4588 (95.95)	9886 (95.59)	
Missing	4 (0.03)	2 (0.04)	2 (0.02)	
Smoking during pregnancy				0.12
Yes	767 (5.07)	240 (5.02)	527 (5.10)	
No	13584 (89.82)	4320 (90.34)	9264 (89.51)	
Missing	772 (5.10)	213 (4.45)	559 (5.39)	
Illicit Drug use during pregnancy				0.29
Yes	29 (0.19)	8 (0.17)	21 (0.20)	
No	14,303 (94.58)	4540 (94.97)	9764 (94.31)	
Missing	790 (5.22)	225 (4.71)	565 (5.48)	
Alcohol use during pregnancy				0.13
Yes	628 (4.15)	210 (4.40)	418 (4.04)	
No	13,706 (90.63)	4341 (90.95)	9365 (90.49)	
Missing	789 (5.22)	222 (4.65)	567 (5.47)	

GA at first ANC (weeks)				0.00
Median (IQR)	18.71 (13-25)	19.29(13.29-25.71)	18.57(13.29-24.71)	
Quality of ANC (at least 4 visits)				0.00
Good Quality	1883 (12.45)	536 (11.23)	1347 (13.01)	
Poor Quality	13240 (87.55)	4237 (88.77)	9003 (86.99)	
Quality of ANC (at least 8 visits)				0.00
Good Quality	1072 (7.09)	290 (6.08)	782 (7.56)	
Poor Quality	14051 (92.91)	4483 (93.92)	9568 (92.44)	
Pregnancy Outcome				0.30
Live Birth	14,897 (98.57)	4694 (98.34)	10203 (98.58)	
Still Birth	226 (1.49)	79 (1.66)	147(1.42)	
Previous Adverse Birth Outcome				0.40
Yes	2,816 (18.62)	859 (17.98)	1957 (18.92)	
No	12,033 (79.60)	3827 (80.08)	8206 (79.32)	
Missing	274 (1.81)	87 (1.82)	187 (1.81)	

IQR=Interquartile Range; BMI=Body Mass Index; GA=Gestational Age; ANC=Antenatal Care; HIV=Human Immunodeficiency Virus

Appendix 2 : Pregnancy Outcome trends of all women stratified by delivery year.

Characteristic	All women		2017		2018	
N(%)	**Livebirths 14897 (98.51)**	**Stillbirths 229 (1.54)**	**Livebirths 1839 (98.03)**	**Stillbirths 37 (1.97)**	**Livebirths 3649 (98.52)**	**Stillbirths 55 (1.48)**
Age (Years)						
Median (IQR)	28 (23-33)	27 (23-33)	28 (23-33)	25 (22-30)	27 (23 -32)	26 (22-32)
Age groups (Years)						
18-35	12439 (98.51)	188 (1.48)	1556 (12.28)	35 (0.28)	3074 (24.26)	45 (0.36)
35+	2458 (98.48)	38 (1.52)	283 (11.34)	2 (0.08)	575 (23.04)	10 (0.40)
Gravidity						
Median (IQR)	2 (1-3)	2 (1-3)	2 (1-3)	2 (1-3)	2 (1-3)	2 (1-3)
Parity						
Median (IQR)	1 (0-2)	1 (0-2)	1 (0-2)	1 (0-1)	1 (0-2)	1 (0-1)
Maternal HIV						
Positive	4,694 (98.35)	79 (1.66)	677 (14.18)	19 (0.40)	1122 (23.51)	16 (0.34)
Negative	10,203 (98.58)	147 (1.42)	1162 (11.23)	18 (0.17)	2527 (24.42)	39 (0.38)
BMI (kg/m^2)						
Median (IQR)	30.36 (25.71 – 35.60)	29.98(26.06-37.87)	30.10 (26.30 – 34.79)	29.65 (26.55-35.20)	29.62 (24.97-29.62)	27.92 (26.12-35.34)
Obesity						
Yes	6080 (98.62)	85 (1.38)	332 (5.39)	8 (0.13)	1544 (25.04)	20 (0.320
No	5675 (98.52)	85 (1.48)	312 (5.42)	8 (0.14)	1661 (28.84)	29 (0.50)
Missing	3142 (98.25)	56 (1.75)	1195 (37.37)	21 (0.66)	444 (13.88)	6 (0.19)
Diabetes History						
Yes	194(95.57)	9 (4.43)	30 (14.78)	0 (0)	50 (24.63)	4 (1.97)
No	14703 (98.55)	217 (1.45)	1809 (12.12)	37 (0.25)	3599 (24.12)	51 (0.34)
Gestational Diabetes						
Yes	363 (98.91)	4 (1.09)	48 (13.08)	1 (0.27)	97 (26.43)	0 (0)
No	14530 (98.50)	222 (1.50)	1791 (12.14)	36 (0.24)	3551 (24.07)	55 (0.37)
Missing	4 (100)	0 (0)	0 (0)	0 (0)	1 (25)	0 (0)
Pre-existing Hypertension History						
Yes	59 (93.65)	4 (6.35)	6 (9.52)	0 (0)	18 (28.57)	2 (3.17)
No	14838 (98.53)	222 (1.47)	1833 (12.17)	37 (0.25)	3631 (24.11)	53 (0.35)
Gestational Hypertension						
Yes	635 (98.45)	10 (1.55)	61 (9.46)	3 (0.47)	163 (25.27)	2 (0.31)
No	14258 (98.51)	216 (1.49)	1778 (12.28)	34 (0.23)	3486 (24.08)	53 (0.37)
Missing	4 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Smoking during pregnancy						
Yes	755 (98.44)	12 (1.56)	94 (12.26)	1 (0.13)	192 (25.03)	2 (0.26)
No	13386 (98.54)	198 (1.46)	1656 (12.19)	34 (0.25)	3266 (24.04)	48 (0.35)
Missing	756 (97.93)	16 (2.07)	89 (11.53)	2 (0.26)	291 (37.69)	5 (0.56)
Illicit Drug use during pregnancy						
Yes	29 (100)	0 (0)	2 (6.90)	0 (0)	3 (10.34)	0 (0)
No	14097 (98.55)	207 (1.45)	1745 (12.2)	34 (0.24)	3444 (24.08)	50 (0.35)
Missing	773 (97.60)	19 (2.40)	92 (11.62)	3 (0.38)	202 (25.51)	5 (0.63)
Alcohol use during pregnancy						
Yes	621 (98.89)	7 (1.11)	76 (12.1)	3 (0.48)	158 (25.16)	1 (0.16)
No	13503 (98.52)	203 (1.48)	1674 (12.21)	32 (0.23)	3299 (24.07)	49 (0.36)
Missing	773 (97.97)	16 (2.03)	89 (11.28)	2 (0.25)	192 (24.33)	5 (0.63)
GA at first ANC (weeks)						
Median (IQR)	18.71 (13-25)	18.86 (13.61-24.96)	21 (15-27)	21 (16– 26)	18 (13-25)	18 (11-23)
GA at delivery (weeks)						
Median (IQR)	39 (38-40)	33 (29-38)	39 (38-40)	33 (30-36)	38 (39-40)	33 (28-38)
Quality of ANC (at least 4 visits)						
Good Quality	1862 (98.88)	21 (1.12)	113 (6.00)	2 (0.11)	176 (9.35)	7 (0.37)
Poor Quality	13035 (98.45)	205 (1.55)	1726 (13.04)	35 (0.26)	3373 (25.48)	48 (0.36)
Quality of ANC (at least 8 visits)						
Good Quality	1062 (99.07)	10 (0.93)	81 (7.56)	1 (0.09)	163 (15.21)	4 (0.37)
Poor Quality	13835 (98.46)	216 (1.54)	1758 (12.51)	36 (0.26)	3486 (24.81)	51 (0.36)
Previous Adverse Birth Outcome						
Yes	2768 (98.30)	48 (1.70)	340 (12.07)	8 (0.28)	697 (24.75)	8 (0.28)
No	11859 (98.55)	174 (1.45)	1466 (12.18)	29 (0.24)	2881 (23.94)	45 (0.37)
Missing	270 (98.54)	4 (1.46)	33 (12.04)	0 (0)	101 (36.86)	2 (0.73)
Delivery Location						
MOU	6354 (99.47)	34 (0.53)	762 (11.93)	6 (0.09)	1646 (25.77)	5 (0.08)
Level 1 hospital	268 (98.89)	3 (1.11)	15 (5.54)	0 (0)	184 (67.90)	2 (0.74)
Level 2 hospital	7161 (98.34)	121 (1.66)	923 (12.68)	19 (0.26)	1564 (21.48)	29 (0.40)
Level 3 hospital	1094 (94.15)	68 (5.85)	137 (11.79)	12 (1.03)	252 (21.69)	19 (1.64)

IQR=Interquartile Range; BMI=Body Mass Index; GA=Gestational Age; ANC=Antenatal Care; HIV=Human Immunodeficiency Virus

The data percentages are presented in row statistics as this format would provide a more meaningful interpretation.

Continuation of Appendix 2

Characteristic	2019		2020		2021		p-value
N(%)	Livebirths 3799 (98.68)	Stillbirths 51 (1.32)	Livebirths 3036 (98.86)	Stillbirths 35 (1.14)	Livebirths 2574 (98.17)	Stillbirths 48 (1.83)	
Age (Years)							0.70
Median (IQR)	27(23-33)	28 (24-33)	28 (24-33)	28 (24-34)	28 (24-34)	30 (25-33)	
Age groups (Years)							0.97
18-35	3225 (25.45)	43 (0.34)	2496 (19.70)	26 (0.21)	2088 (16.48)	39 (0.31)	
35+	574 (23.00)	8 (0.32)	540 21.63)	9 (0.36)	486 (19.47)	9 (0.36)	
Gravidity							0.67
Median (IQR)	2 (1-3)	2 (2-3)	2 (1-3)	2 (1-3)	2 (1-3)	2 (1-3)	
Parity							0.04
Median (IQR)	1 (0-2)	1 (1-2)	1 (0-2)	1 (0-2)	1 (0-2)	1 (0-2)	
Maternal HIV							0.30
Positive	1083 (22.69)	16 (0.34)	933 (19.55)	14 (0.29)	879 (18.42)	14 (0.29)	
Negative	2716 (26.24)	35 (0.34)	2103 (20.32)	21 (0.20)	1695 (16.38)	34 (0.33)	
BMI (kg/m^2)							1
Median (IQR)	30.02 (25.21 – 35.30)	30.64 (25.08-37.87)	30.33 (25.93 – 35.80)	30.43 (26.88-37.42)	31.65 (10.82 – 37.46)	31.61 927.48-41.43)	
Obesity							0.37
Yes	1689 (27.40)	24 (0.39)	1284 (20.83)	12 (0.19)	1231 (19.97)	21 (0.34)	
No	1687 (29.29)	22 (0.38)	1214 (21.08)	11 (0.19)	801 (13.91)	15 (0.26)	
Missing	423 (13.23)	5 (0.16)	538 (16.82)	12 (0.38)	542 (16.95)	12 (0.38)	
Diabetes History							<.001
Yes	37 (18.23)	2 (0.99)	46 (22.66)	1 (0.49)	31 (15.27)	2 (0.99)	
No	3762 (25.21)	49 (0.31)	2990 (20.04)	34 (0.23)	2543 (17.04)	46 (0.31)	
Gestational Diabetes							0.67
Yes	89 (24.25)	2 (0.54)	65 (17.71)	0 (0)	64 (17.44)	1 (0.27)	
No	3708 (25.14)	49 (0.33)	2971 (20.14)	35 (0.24)	2509 (17.01)	47 (0.32)	
Missing	2 (50)	0 (0)	0 (0)	0 (0)	1 (25)	0 (0)	
Pre-existing Hypertension History							0.01
Yes	13 (20.63)	0 (0)	15 (23.81)	0 (0)	7 (11.11)	2 (3.17)	
No	3786 (25.14)	51 (0.34)	3021 (20.06)	35 (0.23)	2567 (17.05)	46 (0.31)	
Gestational Hypertension							1
Yes	154 (23.88)	1 (0.16)	137 (21.24)	1 (0.16)	120 (18.60)	3 (0.47)	
No	3645 (25.18)	50 (0.35)	2899 (20.03)	34 (0.23)	2454 (16.95)	45 (0.31)	
Missing	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	

Smoking during pregnancy							0.87
Yes	189 (24.64)	3 (0.39)	171 (22.29)	2 (0.26)	109 (14.21)	4 (0.52)	
No	3444 (25.35)	44 (0.32)	2699 (19.87)	29 (0.21)	2321 (17.09)	43 (0.32)	
Missing	166 (21.50)	4 (0.52)	166 (21.50)	4 (0.52)	144 (18.65)	1 (0.13)	
Illicit Drug use during pregnancy							0.51
Yes	10 (34.48)	0 (0)	8 (27.59)	0 (0)	6 (20.69)	0 (0)	
No	3620 (25.31)	46 (0.32)	2862 (20.01)	31 (0.22)	2426 (16.96)	46 (0.32)	
Missing	169 (21.34)	5 (0.63)	166 (20.96)	4 (0.51)	142 (17.93)	2 (0.25)	
Alcohol use during pregnancy							0.59
Yes	154 (24.52)	1(0.16)	130 (20.70)	1 (0.16)	103 (16.40)	1 (0.16)	
No	3469 (25.31)	46 (0.34)	2735 (19.95)	30 (0.22)	2326 (16.97)	46 (0.34)	
Missing	176 (22.31)	4 (0.51)	171 (21.67)	4 (0.51)	145 (18.38)	1 (0.13)	
GA at first ANC (weeks)							0.90
Median (IQR)	18 (13-25)	19 (13-23)	18 (13- 24)	20 (16-26)	19 (13-24)	18 (14-23)	
GA at delivery (weeks)							<.001
Median (IQR)	39 (38-40)	35 (30-39)	39 (38-40)	32 (29-37)	39 (38-40)	35 (28-38)	
Quality of ANC (at least 4 visits)							0.18
Good Quality	663 (35.21)	5 (0.27)	477 (25.33	3 (0.16)	333 (17.68)	4 (0.21)	
Poor Quality	3136 (23.69)	46 (0.35)	2559 (19.33)	32 (0.24)	2241 (16.93)	44 (0.33)	
Quality of ANC (at least 8 visits)							0.15
Good Quality	394 (36.75)	2 (0.19)	271 (25.28)	1 (0.09)	153 (14.27)	2 (0.19)	
Poor Quality	3405 (24.23)	49 (0.35)	2765 (19.68)	34 (0.24)	2421 (17.23)	46 (0.33)	
Previous Adverse Birth Outcome							0.59
Yes	736 (26.14)	18 (0.64)	537 (19.07)	5 (0.18)	458 (16.26)	9 (0.32)	
No	3006 (24.98)	31 (0.26)	2441 (20.29)	30 (0.25)	2069 (17.19)	39 (0.32)	
Missing	57 (20.80)	2 (0.73)	58 (21.17)	0 (0)	47 (17.15)	0 (0)	
Delivery Location							<.001
MOU	1625 (25.44)	5 (0.08)	1307 (20.46)	13 (0.20)	1014 (15.87)	13 (0.20)	
Level 1 hospital	27 (9.96)	0 (0)	26 (9.59)	1 (0.37)	16 (5.90)	1 (0.37)	
Level 2 hospital	1871 (25.69)	30 (0.41)	1460 (20.05)	24 (0.33)	1337 (18.36)	24 (0.33)	
Level 3 hospital	267 (22.98)	16 (1.38)	231 (19.88)	10 (0.86)	207 (17.81)	10 (0.86)	
Missing	3 (20.00)		12 (80.00)				

IQR=Interquartile Range; BMI=Body Mass Index; GA=Gestational Age; ANC=Antenatal Care; HIV=Human Immunodeficiency Virus

Appendix 3: Multivariable analysis of risk factors of stillbirths among all participants

Predictor Variable		Unadjusted Odds Ratio (95% CI)	P-value	Adjusted Odds Ratio (95% CI)	P-value
Maternal Age group	18-35	1		1	
	35+	1.02 (0.70-1.43)	0.93	0.95 (0.66 -1.37)	0.77
Quality of ANC received (Atleast 8 visits)	Good quality	1		1	
	Poor quality	1.66 (0.93 - 3.36)	0.12	1.61 (0.85-3.05)	0.15
Maternal HIV status	HIV negative	1		1	
	HIV positive	1.17 (0.88 - 1.53)	0.27	1.15 (0.87-1.52)	0.34
Syphilis during pregnancy	Negative	1		1	
	Positive	1.03 (0.36 -2.26)	0.95	1.04 (0.42-2.54)	0.93
	Inconclusive*	1.48 (0.87 – 2.37)	0.12	1.46 (0.89-2.41)	0.14
Hypertension prior	No	1		1	
	Yes	4.53 (1.37- 11.13)	**<.001**	1.97 (0.51-7.66)	0.33
Gestational Hypertension	No	1		1	
	Yes	1.04 (0.51 – 1.87)	0.91	1.07 (0.56-2.20)	0.84
Diabetes prior	No			1	
	Yes	3.14 (1.48 – 5.87)	**<.001**	2.61 (1.05-6.48)	**0.04**
Gestational Diabetes	No	1		1	
	Yes	0.72 (0.22 – 1.71))	0.52	0.71 (0.26-1.91)	0.49
Obesity	No	1		1	
	Yes	0.93 (0.69- 1.26)	0.66	0.88 (0.65 -1.20)	0.42
Year of Delivery	2017	1		1	
	2018	0.75 (0.49-1.14)	0.18	0.79 (0.50-1.24)	0.30
	2019	0.67 (0.44-1.02)	0.06	0.73 (0.46-1.56)	0.18
	2020	0.57 (0.33-0.91)	**0.02**	0.61 (0.37-0.99)	**0.05**
	2021	0.93 (0.60-1.43)	0.73	1 (0.62-1.56)	0.95

ANC= Antenatal Care; HIV= Human Immunodeficiency Virus; CI= Confidence Interval

* Test result that is neither definitively positive nor definitively negative for syphilis.

Appendix 4: Multivariable analysis of Risk factors of stillbirths among Women living with HIV

Predictor Variable		Unadjusted Odds Ratio (95% CI)	P-value	Adjusted Odds Ratio (95% CI)	P-value
Maternal Age group	18-35	1			
	35+	0.81 (0.46-1.36)	0.45	0.84 (0.46-1.43)	0.53
Quality ANC (At least 8 visits)	Yes	1			
	No	2.52 (0.79-15.35)	0.20	2.30 (0.71-14.11)	0.23
Duration of ART	<20 weeks	1			
	20-40 weeks	0.40 (0.16-0.86)	**0.03**	0.42 (0.17-0.93)	0.05
	40- <100 weeks	0.40 (0.16-0.86)	0.06	0.43 (0.14-1.03)	0.09
	≥100 weeks	0.50 (0.30-0.83)	**0.01**	0.55 (0.33-0.91)	**0.02**
Syphilis during pregnancy	Negative	1			
	Positive	1.66 (0.40-4.55)	0.39	1.72 (0.41-4.77)	0.37
	Inconclusive*	1.03 (0.31-2.52)	0.95	1.02 (0.31-2.50)	0.97
Hypertension prior	No	1			
	Yes	3.15 (0.17-15.49)	0.27	1.39 (0.06-15.92)	0.80
Gestational Hypertension	No	1			
	Yes	1.35 (0.41-3.28)	0.57	1.37 (0.41-3.37)	0.55
Diabetes prior	No	1			
	Yes	2.57 (0.62-7.10)	0.12	2.75 (0.44-9.30)	0.17
Gestational Diabetes	No	1			
	Yes	1.07 (0.17-3.46)	0.92	0.91 (0.15-2.99)	0.90
Obesity	No	1			
	Yes	0.82 (0.48-1.40)	0.46	0.79 (0.46-1.36)	0.40
Year of Delivery	2017	1			
	2018	0.51 (0.26-0.99)	0.05	0.58 (0.28-1.21)	0.15
	2019	0.53 (0.27-1.03)	0.06	0.63 (0.30-1.31)	0.21
	2020	0.53 (0.26-1.07)	0.08	0.63 (0.29-1.32)	0.22
	2021	0.57 (0.28-1.13)	0.11	0.64 (0.30-1.35)	0.25

ANC= Antenatal Care; ART= Antiretroviral Therapy; CI= Confidence Interval

* Test result that is neither definitively positive nor definitively negative for syphilis.

Appendix 5: Sensitivity Analysis accounting for before and after Covid-19

Predictor Variable		Unadjusted Odds Ratio (95% CI)	P-value	Adjusted Odds Ratio (95%)	P-value
Maternal Age group	18-35	1		1	
	35+	1.02 (0.70-1.43)	0.93	0.96 (0.66 -1.37)	0.82
Quality of ANC received (Atleast 4 visits)	Good quality	1		1	
	Poor quality	1.39 (0.91-2.26)	0.15	1.34 (0.87-2.17)	0.21
Maternal HIV status	HIV negative	1		1	
	HIV positive	1.17 (0.88 - 1.53)	0.27	1.15 (0.87-1.52)	0.34
Syphilis during pregnancy	Negative	1		1	
	Positive	1.03 (0.36 -2.26)	0.95	1.04 (0.42-2.54)	0.94
	Inconclusive*	1.48 (0.87 – 2.37)	0.12	1.47 (0.89-2.42)	0.13
Hypertension prior	No	1		1	
	Yes	4.53 (1.37- 11.13)	**<.001**	1.92 (0.49-7.45)	0.35
Gestational Hypertension	No	1		1	
	Yes	1.04 (0.51 – 1.87)	0.91	1.07 (0.56-2.03)	0.83
Diabetes prior	No			1	
	Yes	3.14 (1.48 – 5.87)	**<.001**	2.63 (1.06-6.52)	**0.04**
Gestational Diabetes	No	1		1	
	Yes	0.72 (0.22 – 1.71))	0.52	0.71 (0.26-1.91)	0.49
Obesity	No	1		1	
	Yes	0.93 (0.69- 1.26)	0.66	0.88 (0.65-1.20)	0.42
Covid Period	No	1		1	
	Yes	1.03 (0.62-1.61)	0.90	1.03 (0.62-0.91)	0.91

ANC= Antenatal Care; CI= Confidence Interval

* Test result that is neither definitively positive nor definitively negative for syphilis.

Appendix 6: Sensitivity analysis accounting for before and after Covid-19

Predictor Variable		Unadjusted Odds Ratio 95% (CI)	P-value	Adjusted Odds Ratio 95% (CI)	P-value
Maternal Age group	18-35	1		1	
	35+	1.02 (0.70-1.43)	0.93	0.95 (0.66 -1.37)	0.77
Quality of ANC received (Atleast 8 visits)	Good quality	1		1	
	Poor quality	1.66 (0.93 - 3.36)	0.12	1.61 (0.85-3.05)	0.15
Maternal HIV status	HIV negative	1		1	
	HIV positive	1.17 (0.88 - 1.53)	0.27	1.15 (0.87-1.52)	0.34
Syphilis during pregnancy	Negative	1		1	
	Positive	1.03 (0.36 -2.26)	0.95	1.04 (0.42-2.54)	0.93
	Inconclusive	1.48 (0.87 – 2.37)	0.12	1.46 (0.89-2.41)	0.14
Hypertension prior	No	1		1	
	Yes	4.53 (1.37- 11.13)	**<.001**	1.97 (0.51-7.66)	0.33
Gestational Hypertension	No	1		1	
	Yes	1.04 (0.51 – 1.87)	0.91	1.07 (0.56-2.20)	0.84
Diabetes prior	No			1	
	Yes	3.14 (1.48 – 5.87)	**<.001**	2.61 (1.05-6.48)	**0.04**
Gestational Diabetes	No	1		1	
	Yes	0.72 (0.22 – 1.71))	0.52	0.71 (0.26-1.91)	0.49
Obesity	No	1		1	
	Yes	0.93 (0.69- 1.26)	0.66	0.88 (0.65 -1.20)	0.42
Covid Period	No	1	0.90	1	0.93
	Yes	1.03 (0.62-1.61)		1.02 (0.62-1.60)	

ANC= Antenatal Care; CI= Confidence Interval

Appendix 7: Antenatal Care Quality check form

SOCIODEMOGRAPHIC INFORMATION								
Maternal date of birth								
Location								
MATERNAL HEALTH ANTENATAL VISIT INFORMATION								
Gestation age at first Antenatal care visit								
Number of Antenatal care visits								
MATERNAL ANTENATAL ASSESSMENT CHECKS								
	1st visit	2nd visit	3rd visit	4th visit	5th Visit	6th Visit	7 th Visit	8 th Visit
Weight History								
MUAC								
Blood pressure								
Haemoglobin (g/ld)								
HIV INFORMATION DURING PREGNANCY								
HIV Status								
CD4 Result								
Viral load and dates at each measurement								
Pregnancy HIV test (*Tick all that apply*)								
This pregnancy								
Before this pregnancy								
ART uptake during pregnancy								
ART regimen								
AZT-FTC-EFV								
AZT-3TC-NVP								
TDF-3TC-EFV								
TDF-3TC-NVP								
PI regimen								
OTHER TESTED AND TREATED COMORDITIES DURING PREGNANCY								
Tuberculosis								
Syphilis								
Anaemia								
Hypertension								
Rhesus status								
Diabetes								
SUPPLEMENTS AND INJECTIONS								
Iron								
Folate dispensing								
Tetanus injection								
NEWBORN INFORMATION								
Sex of baby								
Was the baby stillborn								
Gestational age at birth								
What was the mode of delivery								
Weight of baby at delivery								
Abnormalities on examination								

Appendix 8: UCT- HREC approval document

HUMAN RESEARCH ETHICS COMMITTEE
08 JUL 2022
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

UNIVERSITY OF CAPE TOWN
FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938) This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	30-8-23
☐ Not approved	See attached comments		
Signature Chairperson of the HREC/ Designee		Date Signed	1/7/2022

Note: Please email this form and supporting documents (if applicable) in a combined pdf-file to hrec-enquiries@uct.ac.za.
Please clarify your plan for research-related activities during COVID-19 lockdown.
Please use the latest form found on our website:
http://www.health.uct.ac.za/fhs/research/humanethics/forms

Comments to PI from the HREC

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	08 July 2022		
HREC REF Number	749/2015	Current Ethics Approval was granted until	30 Aug 2022
Protocol title	B positive: a population-based evaluation of expanded (anti-retroviral therapy) ART access in pregnancy		
Protocol number (if applicable)	5.0		
Are there any sub-studies linked to this study?		x Yes	☐ No
If yes, could you please provide the HREC Reference number for all sub-studies? **Note:** A separate FHS016 must be submitted for each sub-study.		HREC REF: 541/2015 (separate FHS016 enclosed)	
Principal Investigator	Emma Kalk		
Department / Office Internal Mail Address	Centre for Infectious Disease Epidemiology & Research, School of Public Health & Family Medicine, 5th floor Falmouth Building, UCT FHS, Anzio Road		

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

Appendix 9: UCT- HREC approval renewal document

HUMAN RESEARCH ETHICS COMMITTEE
- 8 NOV 2023
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938) This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	30.11.2024
☐ Not approved	See attached comments		
Signature Chairperson of the HREC/ Designee		Date Signed	9/11/2023

Note: Please email this form and supporting documents (if applicable) in a combined pdf-file to hrec-enquiries@uct.ac.za.
Please clarify your plan for research-related activities during COVID-19 lockdown.
Please use the latest form found on our website: http://www.health.uct.ac.za/fhs/research/humanethics/forms

Comments to PI from the HREC

Principal Investigator to complete the following:

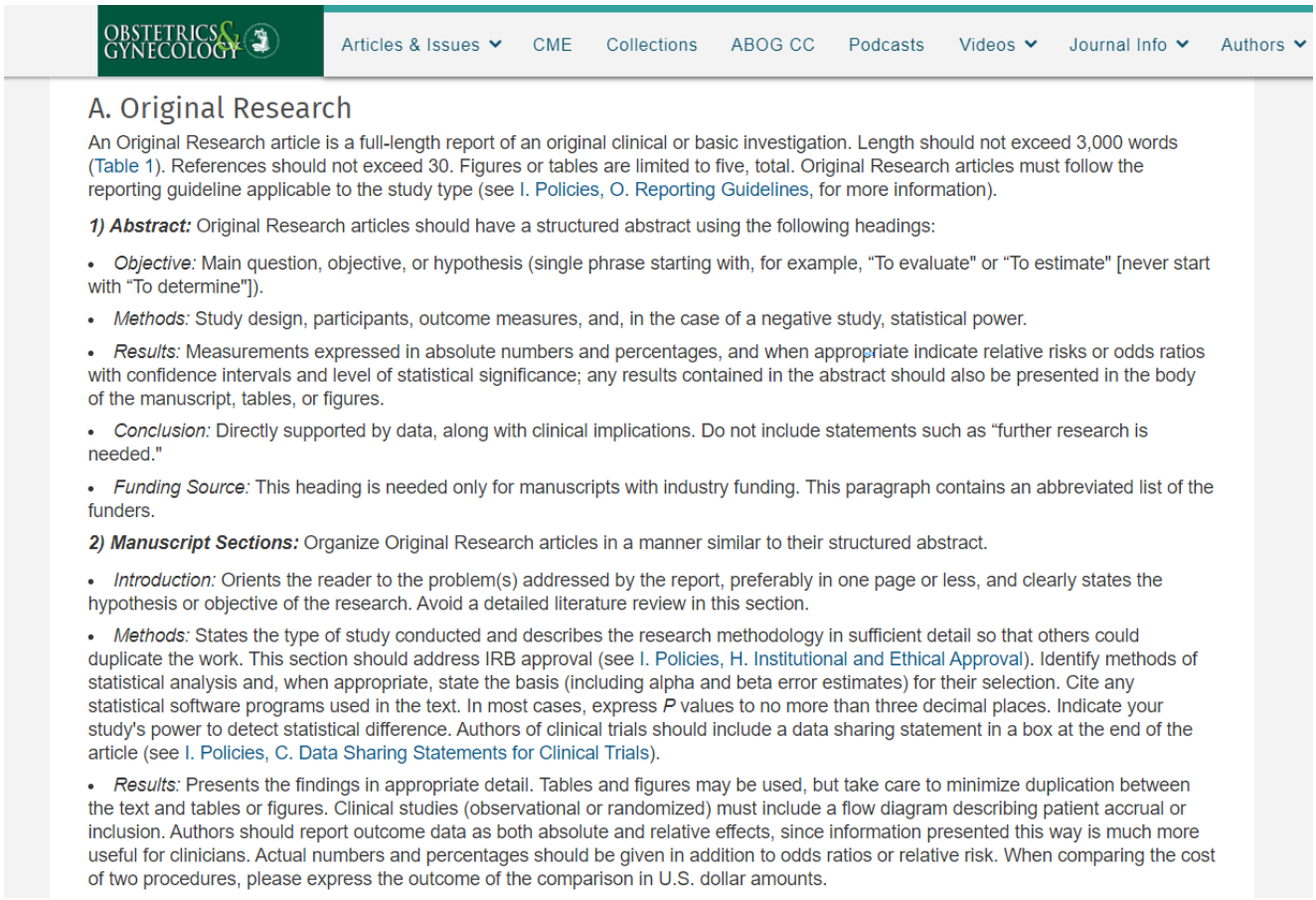
1. Protocol information

Date (when submitting this form)	08th November 2023		
HREC REF Number	689/2022	Current Ethics Approval was granted until	30th November 2023
Protocol title	**THE ASSOCIATION BETWEEN MATERNAL HIV AND STILLBIRTHS IN AN ERA OF UNIVERSAL ART IN PREGNANCY IN THE WESTERN CAPE, SOUTH AFRICA**		
Protocol number (if applicable)			

Are there any sub-studies linked to this study?	✓ Yes	☐ No
If yes, could you please provide the HREC Reference number for all sub-studies? **Note:** A separate FHS016 must be submitted for each sub-study	749/2015	

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

Appendix 10: Instructions for Authors Obstetrics & Gynecology journal



OBSTETRICS & GYNECOLOGY

Articles & Issues | CME | Collections | ABOG CC | Podcasts | Videos | Journal Info | Authors

A. Original Research

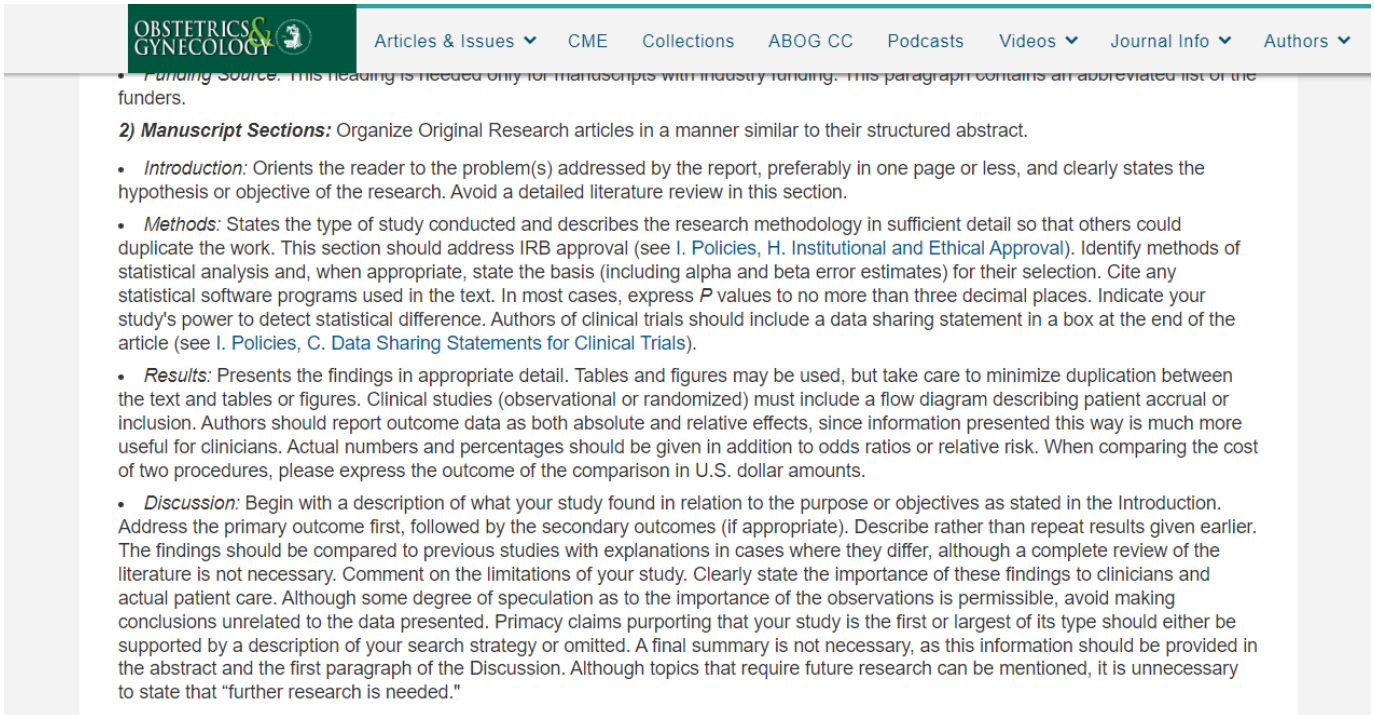
An Original Research article is a full-length report of an original clinical or basic investigation. Length should not exceed 3,000 words (Table 1). References should not exceed 30. Figures or tables are limited to five, total. Original Research articles must follow the reporting guideline applicable to the study type (see I. Policies, O. Reporting Guidelines, for more information).

1) Abstract: Original Research articles should have a structured abstract using the following headings:

- *Objective:* Main question, objective, or hypothesis (single phrase starting with, for example, "To evaluate" or "To estimate" [never start with "To determine"]).
- *Methods:* Study design, participants, outcome measures, and, in the case of a negative study, statistical power.
- *Results:* Measurements expressed in absolute numbers and percentages, and when appropriate indicate relative risks or odds ratios with confidence intervals and level of statistical significance; any results contained in the abstract should also be presented in the body of the manuscript, tables, or figures.
- *Conclusion:* Directly supported by data, along with clinical implications. Do not include statements such as "further research is needed."
- *Funding Source:* This heading is needed only for manuscripts with industry funding. This paragraph contains an abbreviated list of the funders.

2) Manuscript Sections: Organize Original Research articles in a manner similar to their structured abstract.

- *Introduction:* Orients the reader to the problem(s) addressed by the report, preferably in one page or less, and clearly states the hypothesis or objective of the research. Avoid a detailed literature review in this section.
- *Methods:* States the type of study conducted and describes the research methodology in sufficient detail so that others could duplicate the work. This section should address IRB approval (see I. Policies, H. Institutional and Ethical Approval). Identify methods of statistical analysis and, when appropriate, state the basis (including alpha and beta error estimates) for their selection. Cite any statistical software programs used in the text. In most cases, express *P* values to no more than three decimal places. Indicate your study's power to detect statistical difference. Authors of clinical trials should include a data sharing statement in a box at the end of the article (see I. Policies, C. Data Sharing Statements for Clinical Trials).
- *Results:* Presents the findings in appropriate detail. Tables and figures may be used, but take care to minimize duplication between the text and tables or figures. Clinical studies (observational or randomized) must include a flow diagram describing patient accrual or inclusion. Authors should report outcome data as both absolute and relative effects, since information presented this way is much more useful for clinicians. Actual numbers and percentages should be given in addition to odds ratios or relative risk. When comparing the cost of two procedures, please express the outcome of the comparison in U.S. dollar amounts.



OBSTETRICS & GYNECOLOGY

Articles & Issues | CME | Collections | ABOG CC | Podcasts | Videos | Journal Info | Authors

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2) Manuscript Sections: Organize Original Research articles in a manner similar to their structured abstract.

- *Introduction:* Orients the reader to the problem(s) addressed by the report, preferably in one page or less, and clearly states the hypothesis or objective of the research. Avoid a detailed literature review in this section.
- *Methods:* States the type of study conducted and describes the research methodology in sufficient detail so that others could duplicate the work. This section should address IRB approval (see I. Policies, H. Institutional and Ethical Approval). Identify methods of statistical analysis and, when appropriate, state the basis (including alpha and beta error estimates) for their selection. Cite any statistical software programs used in the text. In most cases, express *P* values to no more than three decimal places. Indicate your study's power to detect statistical difference. Authors of clinical trials should include a data sharing statement in a box at the end of the article (see I. Policies, C. Data Sharing Statements for Clinical Trials).
- *Results:* Presents the findings in appropriate detail. Tables and figures may be used, but take care to minimize duplication between the text and tables or figures. Clinical studies (observational or randomized) must include a flow diagram describing patient accrual or inclusion. Authors should report outcome data as both absolute and relative effects, since information presented this way is much more useful for clinicians. Actual numbers and percentages should be given in addition to odds ratios or relative risk. When comparing the cost of two procedures, please express the outcome of the comparison in U.S. dollar amounts.
- *Discussion:* Begin with a description of what your study found in relation to the purpose or objectives as stated in the Introduction. Address the primary outcome first, followed by the secondary outcomes (if appropriate). Describe rather than repeat results given earlier. The findings should be compared to previous studies with explanations in cases where they differ, although a complete review of the literature is not necessary. Comment on the limitations of your study. Clearly state the importance of these findings to clinicians and actual patient care. Although some degree of speculation as to the importance of the observations is permissible, avoid making conclusions unrelated to the data presented. Primacy claims purporting that your study is the first or largest of its type should either be supported by a description of your search strategy or omitted. A final summary is not necessary, as this information should be provided in the abstract and the first paragraph of the Discussion. Although topics that require future research can be mentioned, it is unnecessary to state that "further research is needed."

F. Tables

Authors are strongly encouraged to become familiar with the format of tables published in *Obstetrics & Gynecology* by reviewing recently published tables. The publisher formats wide tables so that they appear on one printed page in the published article. The journal does not print tables in "landscape" orientation, nor do we print tables across two pages. If a table is too wide for one printed page, the first column will repeat on the next page with the remaining columns. For more information on how to format your tables for the journal, see the tables checklist online at *http://edmgr.ovid.com/ong/accounts/table_checklist.pdf*.

G. Figures

At first submission, please submit your figures with their accompanying figure legends within the manuscript. If your manuscript is peer reviewed and deemed potentially acceptable for publication, you will be asked to submit your figures as individual files separate from the manuscript file in Editorial Manager. Source files, EPS or PDF files, or higher resolution TIFFs may be requested. Art that is low resolution, digitized, or downloaded from the Internet will not reproduce well. Graphs created in Microsoft Word, PowerPoint, or Excel should be submitted as .doc or .docx, .xls or .xlsx, or .ppt or .pptx files. Original, high-resolution, or editable files are needed. Unacceptable art may be redrawn or removed from the article.

H. Figure Legends

Each figure should have an accompanying legend. For purposes of the initial submission and peer review process, please include each legend with its figure on a separate page of the manuscript. A sentence or two is usually sufficient. Identify any abbreviations or symbols in the legend. In the case of photomicrographs, provide magnification and stain data.

VI. SUPPLEMENTAL DIGITAL CONTENT

Authors may submit supplemental digital content to enhance their article's text. All supplemental digital content will be reviewed by the Editors and editorial staff before posting. Supplemental digital content may include the following types of content: text documents, graphs, tables, figures, graphics, illustrations, audio, PowerPoint, and video. Content should be original and not previously published or posted elsewhere.

When submitting supplemental digital content online to Editorial Manager, the digital files should be uploaded along with your other submission items.

Supplemental digital content that comprises text, tables, or figures should be cited consecutively in the text as "Appendix 1," "Appendix 2," etc. Do not number supplemental text, figures, or tables separately—order them in the way they are cited at first mention. In addition, any references cited in appendixes should be added to a separate References list in the appendixes file. For video files, provide a legend that includes the title of the video, brief summary of the content, and the name of the creator(s). Authors should ensure that patients are not identifiable in the supplemental digital content unless they obtain written consent from the patients and document that they have obtained consent in the cover letter submitted with the manuscript. To ensure a quality experience for those viewing supplemental digital content, the journal's publisher suggests that authors submit supplemental digital files no larger than 10 MB each.

Obstetrics & Gynecology: Table Checklist

Use the checklist below as a guide when preparing tables for submission to *Obstetrics & Gynecology*.

Formatting and Placement

- ☐ Group tables at the end of the manuscript; do not intersperse within the text.
- ☐ Create tables using the table function in word processing software. Do not use tabs and spaces to create columns.
- ☐ Do not use gray shading or any other colors of shading inside the tables.
- ☐ Information should be sufficiently detailed to allow the table to be understood by itself.
- ☐ Report demographic information in tabular form. Do not use a table for data that can be described adequately in two or three sentences in the text.
- ☐ All columns should be labeled with a column heading, including the first column.
- ☐ Do not use different headings mid-table. There should be one set of headings across the top that apply to the whole table.
- ☐ Do not use brand names in tables.
- ☐ List racial and ethnic categories in alphabetical order instead of order by majority. Use "None of the above" instead of "Other."

Numbering

- ☐ Each table should numbered using the Arabic system and identified by a clear and concise title at the top.
- ☐ Do not use numbering such as 1a, 1b, 1c, etc.; use 1, 2, 3, instead.
- ☐ Tables should be cited in order of first mention in the text.

Numbering

- Each table should numbered using the Arabic system and identified by a clear and concise title at the top.
- Do not use numbering such as 1a, 1b, 1c, etc.; use 1, 2, 3, instead.
- Tables should be cited in order of first mention in the text.

Formatting the Data

- Standard deviations are indicated by use of the plus/minus sign (ie, "6.3±2.1"); standard deviations should not appear in parentheses (ie, "6.3 (2.1)").
- The two numbers in a confidence interval should be separated by a hyphen (-) or en dash (–), not a comma.
- Groupings of ranges should not exclude numbers. That is, a range is two numbers on either side of an en dash (ie, 1.0–10.0).

Table Footnotes

- All abbreviations must be defined in order of appearance going across the heading row and then in each subsequent row (rather than in alphabetical order). If "NA" is used to mean "not applicable" or "not available," be sure to define it.
- Tables taken from other publications should include the original citation in the footnote. Provide a copy of the original article where the information was taken with your manuscript.
- The Green Journal uses these symbols in this order: *, †, ‡, §, ||, ¶, #, **, ††, ‡‡. No other symbols may be used). If there are more than 10 footnotes, use all letters (instead of symbols). The order of footnote symbols is determined by order of appearance in the table: First in the title, then in the heading row, and then going across each row from left to right (rather than down each column).

Explaining the Data

- Be sure the data in your tables are defined, either in the column headings (only if the data are the same in the entire column) or in the footnote (if the data are different throughout). In the table footnote, state, "Data are…"
- Column totals should be verified and percentages should add up to 100% (if they do not, specify a reason).