Impact of DTG Use During Pregnancy on Birth Outcomes of HIV-Infected Women in the Western Cape, South Africa

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Plagiarism Declaration

I, Jamie Meyer, hereby declare that the work on which this thesis 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. I authorise the University to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

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List of Abbreviations

AIDS	Acquired Immunodeficiency Syndrome
AGA	Appropriate for Gestational Age
ANC	Antenatal Care
ART	Antiretroviral Therapy
AZT	Zidovudine
BMI	Body Mass Index
CD4	Cluster of Differentiation 4
CI	Confidence Interval
DTG	Dolutegravir
EFV	Efavirenz
GA	Gestational Age
HBW	High Birthweight
HIV	Human Immunodeficiency Virus
HREC	Human Research Ethics Committee
INSTI	Integrase Strand Transfer Inhibitor
IQR	Interquartile Range
IUGR	Intrauterine Growth Restriction
IRB	Institutional Review Board
LBW	Low Birthweight
NICHD	National Institute of Child Health and Human Development
NCD	Non-Communicable disease
PTD	Preterm Delivery
SGA	Small for Gestational Age
SSA	Sub-Saharan Africa
TDF	Tenofovir Disoproxil Fumarate
TLD	Tenofovir, Lamivudine, and Dolutegravir
TOP	Termination of Pregnancy
UNAIDS	Joint United Nations Programme on HIV/AIDS
UTT	Universal Test and Treat
WNLH	Women Not Living with HIV
WLH	Women Living with HIV
WHO	World Health Organization

Part A: Literature Review

Introduction

1.3 million women living with HIV (WLH) become pregnant annually (1). South Africa faces a significant HIV burden with a prevalence of 20% in the entire population, however, this burden disproportionately effects women among whom the prevalence is 30% (2). Pregnancy is a critical time in a woman's life as it can have long-term implications for both maternal and infant health (3, 4). Furthermore, obesity is on the rise both in South Africa and globally in women of reproductive age causing public health concern (5, 6). This is further compounded in WLH on antiretroviral therapy (ART) that includes dolutegravir (DTG), as it has been implicated as an obesogen that disproportionately effects women (7).

ART has led to a drastic improvement in the quality of life for people living with HIV, by suppressing viral replication and preventing the progression into acquired immunodeficiency disease (AIDs)(8). The evolution of ART regimens for pregnant women has also been a cornerstone of HIV management by preventing perinatal mother-to-child transmission (9). Notably, significant improvements in birth outcomes of pregnant women have been seen since the shift from Option B+, which focused on initiating lifelong ART for all pregnant and breastfeeding women regardless of CD4 count, to Universal Test and Treat, which expanded this approach to all individuals living with HIV, not just pregnant women (9, 10). This HIV management strategy has improved birth outcomes as women with known HIV infection are on ART, meaning their HIV infection could be completely virally suppressed, or at least viral replication has decreased to the point of not being extremely toxic and causing problems in early pregnancy (9, 11). Effective management of HIV is important to the global sustainable goals to end the AIDS epidemic globally and in South Africa (12). Thus far the universal test and treat method of HIV management has been effective, however, there are still differences in the birth outcomes between women living with HIV (WLH) and HIV-negative women (13, 14). A further improvement in the effective management of HIV introduced in recent years is DTG. DTG is an integrase strand transfer inhibitor (INSTI), successful viral suppressant and has outperformed all other ART regimens in clinical trials with regards to efficacy, and its resistance profile (15, 16).

This literature review will delve into maternal ART use, specifically DTG, to understand its impact on birth outcomes. It is important that we study the birth outcomes, particularly in the context of South Africa where the health profile of the population is uniquely shaped by a high HIV prevalence, co-existing infectious and non-communicable disease, and other socio-economic factors (17). The aim is to collate and dissect the currently available literature on the research of adverse birth outcomes in pregnant WLH on ART, with a specific focus on DTG. Understanding the safety and potential implications of DTG use during pregnancy is necessary to optimise long-term maternal and infant health. We will explore the general implications of HIV on adverse birth outcomes, the history of ART regimens during pregnancy, comparison of DTG with other regimens, factors that influence these relationships,

particularly maternal body composition. Adverse birth outcomes pose a risk to the infant's health (18). Long-term growth and development of the infant in turn has public health implications—making it important for us to explore these outcomes in the context of DTG and the evolution of ART regimens (19). Through this literature review, we hope to identify gaps in the current literature and suggest direction for future research in order to effectively manage ART regimens in pregnant women specifically in the South African context, with the ultimate goal of providing the best health outcomes for both the mother and their children.

Adverse Pregnancy Outcomes

Definitions and Overview

Adverse pregnancy outcomes consist of a wide array of complications that can affect both the mother and the infant and have subsequent long-term implications on maternal health and infant health, growth, and development (18, 20). The adverse outcomes of particular interest in this study are;

Pregnancy loss

Pregnancy loss consists of miscarriage, stillbirth, ectopic pregnancies, and termination of pregnancy (TOP). A Stillbirth is defined as a foetal loss, after 28 weeks of gestation. Miscarriage is defined as an early foetal loss, before 28 weeks gestation. These are the cutoff standards used in South Africa and is the global standard for defining stillbirth/miscarriage. However, some higher-income countries use a lower cutoff to define stillbirth like 20/22weeks (21). This is because in high-income countries, infants born between 20 and 28 weeks of gestation have an increased likelihood of survival, which has influenced the use of lower gestational age thresholds to define stillbirth. However, in many low- and middle-income countries, including South Africa, there is a lower risk of survival before 28 weeks . Therefore, a threshold of 28 weeks' gestation is used to define stillbirth in this study, in line with context-appropriate practice and WHO guideline (22).

Preterm delivery

Preterm delivery is defined as delivery before 37 weeks of gestation. Preterm delivery can be broken down further into smaller categories that define a late preterm birth as delivery between 32 and 37 weeks of gestation, a moderately preterm birth as a delivery between 28 and 32 weeks of gestation, extremely preterm delivery if a delivery that occurs before 28 complete weeks of gestation (23). Preterm delivery places infants and an increased risk of infant mortality, as well as a number of other health conditions like brain haemorrhages, jaundice, cardiovascular complications, breathing difficulties or other complications associated with underdeveloped organs. Preterm delivery can have life-long effects

on infants as studies have shown that preterm delivery is associated with an increased risk of chronic illness, neurodevelopmental impairments, and learning difficulties (24).

According to the WHO low birthweight is defined as a birthweight less than 2500g. Which can further be classified with very low birthweight being a birthweight of less than 1500g. In South Africa these same definitions are used to define low birthweight and as such this study will apply these definitions throughout. Low birthweight is associated with similar health implications as prematurity, including an increased risk of hypothermia due to insufficient body fat and underdeveloped thermoregulation mechanisms (25, 26).

A high birthweight is defined as a birthweight greater than 4000g (macrosomia). High birthweight is associated with low blood glucose in the infant at birth, and an increased risk of developing obesity in childhood, diabetes, and other metabolic syndromes (26).

An infant with a birthweight below the 10^{th} percentile for their gestational age is defined as small for gestational age (SGA). There are a number of different conventions for defining size for gestational age. For example, the NICHD foetal growth studies in the US that developed standards for birthweights at different gestational age. These studies found that there were differences in size for gestational age between different race/ethnicity groups and such consider race in their calculations (27). The WHO also has global standards for determining size for gestational age based on growth charts made from data collected across Africa, Asia, Europe, and South America. The INTERGROWTH-21st newborn standards are based on World Health Organization (WHO) recommendations and are intended to match the WHO's child growth standards. For this study we will be utilising the INTERGROWTH-21st Project Standards as this tool was developed using the most diverse data from across 4 continents which allows the data to be more generalizable in the global context (28). SGA is an extremely worrying birth outcomes with both short- and long-term ramifications for an infants health. Short-term consequences of SGA include increased risks of hypothermia, polycythemia, and hypoglycemia. Long term consequences in infants born SGA include a risk of developing metabolic disease later in life. Reduced foetal growth has been shown to be associated with an increased risk of insulin resistance, obesity, cardiovascular disease, and type 2 diabetes mellitus (29, 30). It is possible to help SGA infants catch up through the use of hormone therapy, however, this is not always accessible. In the event an infant is not able to catch up it can lead to neurodevelopmental impairments (31).

An infant with a birthweight above the 90^{th} percentile for their gestational age is defined as large for gestational age (LGA) (32). LGA foetuses are at greater risk of birth injuries and delivery complications. The mother is placed at an elevated risk of Postpartum haemorrhage or perineal tears. LGA is also associated with low blood sugar, breathing problems and jaundice. Furthermore, infants with a large birthweight or LGA are also at an increased risk of developing type II diabetes and cardiovascular

disease in early childhood. LGA and large infant weight can also be associated with stunted neurodevelopment (33).

Factors contributing to Adverse Outcomes

The causal pathways of pregnancy losses are not well understood or studied. Early pregnancy losses i.e. miscarriages are often due to chromosomal abnormalities that would result in an unviable foetus. Other risk factors associated with an increased risk of pregnancy loss are: uterine abnormalities, thyroid disorders, exposure to infections, particularly toxoplasmosis, other diseases (syphilis, Zika virus, varicella-zoster virus), Rubella, cytomegalovirus, herpes simplex virus (TORCH) disease, including , other chronic health conditions like uncontrolled diabetes or congenital heart disease, or exposure to toxic substances like alcohol, smoking, or drugs, hormonal imbalances, malnutrition, radiation exposure, or certain medications(34, 35). While these exposures may increase the risk of pregnancy loss it is important to note that very little is known about the causal mechanism (36).

Preterm delivery can occur due to an acute event like trauma or shock(37). Infections can also be the cause of preterm delivery (38). For example, infections of the amniotic fluid or untreated urinary tract infections lead to inflammation that can cause preterm labour. There are other risk factors associated with preterm delivery like preexisting medical conditions such as diabetes or high blood pressure, exposure to substances like alcohol, smoking or illegal drugs, a shortened cervix is associated with preterm delivery(37). Preterm delivery is also associated with certain genetics. While associations have been determined between these risk factors and preterm delivery, the causal mechanism is not well understood as it isn't often studied (25).

There are two causes of a low birthweight which are preterm delivery and a growth restriction. It is possible for an infant born with a low birthweight to have had both preterm delivery and a growth restriction (39, 40). Intrauterine growth restrictions (IUGR) can be due to several factors. Maternal health has a big influence on foetal growth and so conditions like high blood pressure, diabetes, kidney disease, heart disease, lung disease, anaemia, malnutrition, infections and substance use all have an influence on the growth. Placental abnormalities, or decreased blood flow in the placenta and uterus can also cause a growth restriction. Chromosomal abnormalities of the foetus can also cause a growth restriction. Maternal age is also associated with IUGR for example mothers under 15 years are at a greater risk of growth restriction while mothers over the age of 30 are also at an increased risk of growth restriction. Multiple gestation pregnancies there is very often growth restriction, due to space which in turn leads to low birthweight (41).

Preterm delivery and low birthweight affect the infant's cognitive development and place them at an elevated risk of chronic disease later on in life like; cerebral palsy, sensory deficits, learning disabilities,

and respiratory illnesses. Complications related to preterm delivery are the leading causes of death for children aged under 5, resulting in about a million deaths worldwide in 2015. The incidence of preterm delivery is increasing (41). Low birthweight disproportionately effects developing countries (42).

HIV poses a risk to adverse birth outcomes due to its effect on the immune system leading to an increased susceptibility to infections and other complications. The inflammatory nature of the disease can impact pregnancy, inflammation during early embryonic development can impact the foetal growth and development, the effect of inflammation on the placenta can lead to nutritional deficiencies which can again stunt the growth and development of the foetus (43). Further nutritional deficiencies of WLH regularly associated with the disease can also result in improper nutrition for growth and development of the foetus (43). Poorly managed HIV can result in a higher viral load which can further affect growth and development in the foetus, similarly poorly managed HIV can trigger contractions leading to preterm delivery (34, 44, 45). As well as some ART regimens being associated with increased risk of adverse birth outcomes. Other socioeconomic factors also contribute to risk of adverse birth outcomes like access to healthcare, nutrition, stress (14, 46).

Background of Antiretroviral Therapy (ART) in Pregnancy

ART was implemented in developed countries in the mid-1990s, but not implemented in South Africa until 2002 despite the heavy burden (47). During the pre-ART era, untreated WLH had significantly increased risks of adverse birth outcomes such as preterm delivery (PTD), perinatal death, low birthweight (LBW), SGA, IUGR and chorioamnionitis compared to HIV-negative women. When ART was first introduced both globally and in South Africa ART was only given to individuals who had less than 200 CD4 cells/μL, the threshold then increased to 350 cells/μl in 2010, and 500 cells/μl in 2015 before Universal test and treat was implemented in September 2016 (48). At the time ART was initially introduced, concerns arose about its potential toxicity and its impact on birth outcomes (49). Early studies showed mixed findings with some suggesting no difference in birth outcomes between WLH taking ART vs those who remained untreated (50). However, as our knowledge of ART use during pregnancy has advanced and ART regimens have improved, we have seen improving birth outcomes of WLH taking ART during pregnancy. This has been a huge public health success as it has significantly improved the rates of mother-to-child transmission, as well as enhancing maternal and infant health outcomes overall (9, 10).

One of the most significant changes to HIV management was the shift from option B+, whereby all pregnant and breastfeeding women initiated ART regardless of their CD4 count, to UTT. UTT expanded this from pregnant women to all people living with HIV, regardless of their CD4 count. In the context of pregnancy, it has also been a huge success as it means that WLH regardless of their CD4 count are likely to be on ART before conception (51). This shift from testing and treating only pregnant women

to testing and treating the entire population has meant that there is a strong likelihood that a WLH is virally suppressed at conception and if not virally suppressed, likely to be on treatment. This decreases the impact of HIV infection on early embryonic and foetal development, improving foetal development and the pregnancy overall (52). Studies have shown associations between adverse birth outcomes and timing of initiation of ART, with women starting prior to conception or the first trimester of pregnancy having improved birth outcomes and reduced vertical transmission when compared to women initiating pregnancy in the second or third trimester (53, 54).

In 2014 UNAIDs implemented the 90-90-90 target which was the goal to reach 90% of people living with HIV to know their status, 90% of people diagnosed with HIV to receive ART and 90% of people receiving ART to have achieved viral suppression. In 2021 this has been amened to 95-95-95 strategy of which the aim is to achieve 95% coverage on all three previously mentioned targets (55). We can see the effects of universal test and treat when examining South Africa's progress toward these goals. In 2022 90% of people living with HIV knew their status, 91% of people who knew their status were on ART, and 94% of people on ART were virally suppressed. Furthermore, the countries Botswana, Eswatini, Rwanda, Tanzania, and Zimbabwe have already met these goals and a number of other Sub-Saharan African countries are close to reaching the goal (55). These are hopeful statistics and reflect a great success of public health systems (56).

As advancements have been made in ART so have the guidelines for treatment evolved. South Africa has been following the guidelines prescribed by the WHO for effective HIV management since 2002 (48). Which emphasizes early detection and treatment as well as highlighting the importance of pregnant women taking ART for the prevention of vertical transmission (57). This has included the implementation of TLD (tenofovir, lamivudine, and dolutegravir) as the standard of care since 2019 for all people living with HIV, and as such this is the current standard of care for HIV treatment in South Africa, consequently the majority of people living with HIV are now on this regimen (57). South Africa currently follows the WHO guidelines for first-, second-, and third-line regimens. The first-line ART regimen is tenofovir, disoproxil fumarate-lamivudine-dolutegravir. If a patient fails on TLD due to DTG resistance, the second-line regimen is TDF + FTC/3TC + DRV/r. Third-line regimens are tailored for an individual (57).

Currently the estimated number of people living with HIV infection globally is just under 40 million, making the prevalence 1.2%. However, this is not uniformly distributed. Sub-Saharan Africa is referred to as the world's epicentre of HIV/AIDs, with a prevalence of 9% in the adult population. Two thirds of new HIV infections occurring in sub-Saharan Africa occur in women and girls (58). The prevalence of HIV in South Africa is 20%, with a greater prevalence occurring in pregnant women in which the prevalence is 30%, particularly black South African women (2). This disproportionate distribution of HIV infection highlights the importance of interventions tailored specifically to women.

DTG Use in Pregnancy

DTG Overview

DTG entered the HIV drug landscape gaining FDA approval in 2013 (48). DTG is an integrase strand transfer inhibitor (INSTI) whose mechanism of action prevents viral integrase binding to host DNA, hence, halting the viral replication process. DTG has shown to be very effective at viral suppression in clinical trials. It has also been shown to have a good resistance profile, with very few people developing drug resistance (15, 16). For this reason, it has been upscaled and implemented as the standard of care in South Africa as per the WHO guidelines (57). This superior viral suppression is an asset with regards to reaching the 95-95-95 targets set by UNAIDS, as a more effective viral suppressor will mean a greater proportion of people living with HIV achieving viral suppression.

DTG vs Other ART Regimens

In clinical studies comparing the efficacy of DTG at viral suppression DTG has been shown to be more effective at viral suppression when compared to other regimens. For the VESTED study, a randomized control trial that enrolled ART naïve pregnant WLH comparing 3 different ART regimens found a greater proportion of virally suppressed (<200 copies/ml) women by delivery, the DTG regimens achieving 98% viral suppression, compared to the efavirenz (EFV) based regimens that achieved 91% by delivery (16). A study examining women initiating ART in third third-trimester of pregnancy found a greater proportion of viral suppression at delivery in women receiving DTG-based regimens compared to EFV-based regimens at delivery (74.2% vs 42.7%) (59). Studies also showed DTG-based regimens to have an odds of resistance decrease by 87% compared to EFV-based regimens in pregnant women (60). Furthermore, DTG has a lower incidence of unfavourable side effects, like diarrhoea, nausea, vomiting etc. DTG also has a longer half-life compared to other ART and so is only necessary to take once a day, whereas other regimens sometimes require two doses daily (61). DTG has a lower susceptibility to genetic intolerance. Furthermore, DTG has been shown to achieve viral suppression faster the EFV based regimens and is associated with an increase in CD4 t-cell count (62).

Use in Pregnant Women

Physiological changes occur during pregnancy which have a slight effect on the pharmacokinetics of DTG, it does not require an altered dose during pregnancy. The regular dose performs well and achieves viral suppression in the mothers as well as performing well in cotyledon perfusion experiments, which examine placental transfer (63).

Early studies of DTG use in pregnant women at conception in a Botswana cohort showed an increased incidence of neural tube defects 0.94% (95% CI 0.37–2.4). Thus, regimens containing DTG were initially thought to be unsafe during pregnancy (15). Analysis done since then on the same cohort of women has provided an updated association between DTG use and neural tube defects which was much lower than initially described, 0.10% (0.06–0.17) (64). Other studies examining this association have shown no association between DTG use during pregnancy and neural tube defects (65). This same study found DTG-Based regimens to be safer than EFV-based regimens as a lower proportion of women on DTG had recorded adverse birth outcomes (33% vs 35%) (60).

DTG has shown to be very effective in pregnant women, achieving viral suppression twice as fast compared to EFV based regimens (62). They also observe DTG transfer across the plasma and through breastfeeding in mothers which significantly decreases vertical transmission, this is likely due to its long half-life allowing a longer duration of action (63). Overall, DTG has shown to perform well with regards to viral suppression and reducing perinatal transmission of HIV and is a good regimen for pregnant WLH.

When examining the birth outcomes of women on DTG-based regimens compared to other regimens the current literature is relatively mixed. Some studies have shown there to be little difference in the adverse birth outcomes of women taking DTG versus EFV based regimens. However, some studies have seen improved birth outcomes in DTG based regimens compared to EFV based regimens. A study in Ethiopia found that women taking the DTG based regimen had a decreased odds of preterm birth and low birthweight compared to EFV based regimens or "other" regimens. However, this same study showed the greatest risk of neonatal death occurred in the DTG regimen group (18). Studies comparing DTG use to HIV-negative women also have slightly mixed results with some studies showing that women taking DTG are at an increased risk of stillbirth, preterm delivery, low birthweight and SGA (66, 67). With the evolution of ART regimens we have seen birth outcomes improve such that since the implementation of TLD the adverse outcomes of major concern in WLH is SGA, as the risk has not been mitigated like the other adverse birth outcomes, preterm delivery and low birthweight. SGA disproportionately effects low-and middle-income countries where they account for approximately 19.3% of live births. SGA is a risk factor for infant mortality and in low-middle income countries, 21.9% of infant deaths are attributable to SGA. If we are able to effectively manage SGA as a birth outcome it could provide up to a 10% reduction in neonatal deaths (68). These results suggest that DTG-based regimens are safe to take during pregnancy and are the favourable regimen, however, this increased risk of stillbirth and SGA could warrant further exploration, in more populations to see if this is a global phenomenon.

Results of previous studies on ART and Adverse birth outcomes

Over the years studies assessing the birth outcomes of WLH compared to HIV-negative women have consistently showed that WLH have an increased risk of adverse birth outcomes compared to HIV-negative women. The birth outcomes are improved if a WLH is on ART, but even still we see an elevated risk of all birth outcomes. A large meta-analysis examining the results of 73 cohort studies examining birth outcomes of studies conducted from 1980 through to 2020, allowed the comparison of WLH on ART vs WLH not on ART then later studies comparing different ART regimens. Given this it also means that the ART regimens range from zidovudine (AZT) monotherapy, the first ARV through to DTG-based regimens implemented in 2019, including all WHO recommended regimens in between. WLH on ART had a 21% lower risk of preterm delivery compared to WLH not on ART. ART was associated with a 14% lower risk of low birthweight, compared to WLH not on ART. However, when comparing WLH on ART to HIV-negative women we see an increased risk of these adverse outcomes. HIV/ART exposure is associated with a 42% increased risk of preterm delivery, a 58% increased risk of low birthweight, and a 69% increased risk of SGA. These results highlight the fact that ART while protective against adverse birth outcomes, and does improve the birth outcomes of WLH, there is still an increased risk to maternal and child health, where we need to bridge the gap and improve the birth outcomes of WLH, in the global context of HIV (14).

DTG Use and Specific Birth Outcomes

Studies have shown mixed results when it comes to an association between DTG use and pregnancy loss. A study in Brazil found a greater proportion of pregnancy loss in WLH on DTG-based regimens (6%) compared to WLH on EFV based regimens (3%), however, when modelling pregnancy loss as an outcome did not find a statistically significant association. Similarly, a study in the USA found that women on DTG regimens were at a greater odds of stillbirth compared to non DTG regimens (14, 69). However, a study in Brazil found no association between DTG use during pregnancy and stillbirth (66). These same studies found there wasn't a difference in risk of stillbirth and DTG initiation, before or after conception (66, 69).

This same meta-analysis did however show that DTG use during pregnancy is associated with an increased odds in preterm delivery compared to HIV-negative women (1.45, 95% CI: 1.42, 1.28-1.57)(14). However VESTED showed that proportion of preterm delivery was in fact lower than the global average at only 6%, with the proportion of preterm delivery in South Africa being 15% an the proportion in the USA being 10%. These results suggest DTG could even be protective against preterm delivery (16).

Observed associations between DTG use a low birthweight are mixed once again. When comparing DTG use during pregnancy to EFV based regimens, WLH on DTG regimens have a lower proportion of infants born with low birthweight (16). However, when we move to compare WLH to HIV-negative

women we have mixed results. Some studies have shown an association between DTG use and low birthweight, with DTG use being associated with increased odds of low birthweight (67).

When pooling the results of a number of cohorts looking at the impact of DTG use during pregnancy on adverse birth outcomes compared to EFV we see that DTG is associated with a decreased risk of preterm delivery, SGA, and very SGA. However, they are at a greater risk of severe adverse events (60).

The TSEPAMO study looked at the occurrence of severe birth outcomes, which included very SGA (SGA <3rd percentile), and found that DTG use during pregnancy was associated with an increased risk of very SGA (70). This is cause for public health concern as we very SGA can have very serious implications for the infant. Birth outcomes are improving but this association necessitates further investigation, however, due to the large sample sizes needed to examine outcomes like this making it difficult. While the risk for SGA, and very SGA are being reduced in WLH, there is still an association being observed, and due to the serious nature and public health burden of SGA, further research into reducing the occurrence is important.

Impact of Timing of DTG Initiation

The timing of DTG initiation – whether before or during pregnancy - is likely to have an effect on in birth outcomes, however, there is limited data available of this effect. It has been indicated that initiating DTG before conception may be associated with better outcomes compared to starting it during pregnancy. A study in Ethiopia found women who initiated DTG before pregnancy had a lower risk of preterm birth compared to women who initiated DTG after pregnancy (69). A study that looked at the effect of timing of DTG initiation examined more birth outcomes found that outcomes differed by trimester of initiation, the results were as follows, for women initiating in the first trimester, 7.5% delivered preterm, for WLH initiating DTG in the second trimester, 27.3% had a preterm delivery, for women initiating DTG in their third trimester, 13.9% delivered preterm. A similar distribution is seen with regards to birthweight with 11.3% of women initiating in their first trimester delivering low birthweight infants, 28.6% of women initiating DTG in the second trimester delivering low birthweight infants, and 16.9% of women initiating in their third trimester delivering low birthweight infants. Again, we see a similar pattern in SGA, where 12.9% of women initiating DTG in their first trimester delivered SGA infants, 35% of women initiating in the second trimester delivering SG infants, and 22.5% of women initiating DTG during the third trimester delivering SGA infant (71). While these results suggest a potential pattern, this study was done shortly after DTG implementation on a small sample size and as such, further research into the effect of DTG timing on birth outcomes is necessary before we can draw any conclusions. On a more recent study of a greater sample size it has been indicated that there is no effect of timing of DTG initiation on birth outcomes (72). The effect of timing of ART initiation has been well documented but there is limited data available specifically looking at the effect of DTG initiation on birth outcomes.

Maternal Weight, BMI, and Birth Outcomes

General Overview of Maternal Weight and Birth Outcomes

Overweight and obesity are a risk factor for almost all non-communicable diseases ranging from coronary heart diseases to various different cancers. Overweight/obesity is on the rise globally and in South Africa (73). 85% of deaths due to non-communicable disease are occurring in low- and middle-income countries, where the burden of infectious diseases is also most prevalent (74). With the rise of obesity and the elevated risk of NCDs that comes with it, it is important that we examine the coexistence of these risk factors in our populations in order to understand and effectively manage the risk factors of a population.

The alarming rate of overweight/obesity in South African women should be cause for great public health concern, with 67% of women in South Africa being overweight/obese (75). In women overweight/obesity is associated with cardiovascular disease and diabetes, but furthermore, overweight/obesity is associated with the risk of several major cancers in women, particularly postmenopausal breast cancer and endometrial cancer (76). This highlights the need for changes at an individual level but also in policy, social/cultural norms, and the physical, social environment.

An increased maternal BMI and excessive gestational weight gain has been linked to elevated risk of unfavourable birth outcomes, such as preterm delivery and macrocosmic/LGA infants (77). These birth outcomes can have long term effects of the growth and development of the infant. Elevated BMI during pregnancy also places the mom at increased risk of obstetric conditions such as gestational hypertension, gestational diabetes, or pre-eclampsia/eclampsia (77). These unfavourable conditions can the have long-term implications on the mother's health. Furthermore, infants born to obese mothers or mothers who had substantial gestational weight gain are at an elevated risk of developing Type II diabetes (78).

Conversely mothers with low BMI falling into the underweight category (BMI<18.5) are also at an increased risk of preterm delivery and low birthweight/SGA infants (78). Which again can affect infant and subsequent child development and place the infant at an increased risk of mortality (44). Again, highlighting the necessity to implement interventions tailored to bringing down the prevalence of overweight/obesity in South African women, to lower the risk of adverse birth outcomes and improve maternal and infant health.

When discussing maternal BMI in the context of HIV it is important to discuss the physiological symptoms and social stigmas that surround HIV. Typically, HIV is associated with weight loss due to some side effects associated with the virus and the treatment regimens, and the bodies immune system having to work harder in general (79). So, in settings where HIV is prevalent and is associated with a

decreased body mass, it is understandable that socially this body type is less desirable, and such a larger body type would be considered ideal compared to settings in which HIV is less prevalent (80).

Interaction Between DTG and Maternal Weight

While DTG has demonstrated it's exceedingly superior efficacy in comparison to other ART regimens there are concerns of other potential side effects of this drug. DTG has also been clinically implicated as an obesogenic, however, there is limited data available on the obesogenic properties of DTG and how this affects pregnant women and their children (70, 81). The exact mechanism through which DTG causes weight gain is not well understood yet, however, studies looking at the body composition changes with DTG use, demonstrate that DTG use leads to an altered structure of fat cells. It has also been shown to affect adipose tissue which can cause weight gain. Furthermore, it is associated with an increased production in collagen types that are linked to adipocyte fibrosis and obesity. It is not yet well understood how DTG affects the metabolism in all people living with HIV, and particularly pregnant women (82).

The excess weight gain caused by DTG is is concerning as overweight/obesity is strongly associated with all-cause mortality, particularly cardiovascular diseases (70, 74). This is especially unfavourable when we are considering people living with HIV, as they are already immunocompromised and at an elevated risk of developing other non-communicable diseases (74). Furthermore, in the South African context where half of the adult population is overweight or obese, and worse in women with two thirds of South African women being overweight or obese (75). This is a public health concern as DTG has been associated with an increase in gestational weight gain (70). It is important that we examine the effect maternal weight/BMI has on the pharmacokinetics of DTG and whether it modifies the association between DTG use and birth outcomes.

Emerging research suggests that maternal weight and BMI may interact with ART, including DTG, to influence pregnancy outcomes. Some studies indicate that DTG's pharmacokinetics may be affected by maternal weight, potentially impacting drug efficacy and safety (8). For instance, overweight and obese women might experience altered drug absorption and distribution, necessitating adjustments in dosing or monitoring to ensure optimal therapeutic levels. Some evidence suggests that higher maternal BMI may exacerbate the risks associated with DTG use in pregnancy (70). However, this area remains under-explored, and more research is needed to draw definitive conclusions. Exploring the complex interplay between DTG, maternal weight, and birth outcomes is essential for developing tailored treatment protocols that account for individual patient characteristics. This approach can help optimize both maternal and neonatal health outcomes.

Gaps in the Literature and Future Directions

Current Gaps

As our knowledge and understanding has expanded and advanced drastically when it comes to understanding the effects of ART, including DTG on birth outcomes, there are still gaps to be filled in. For starters, we have yet to see the long-term health implications on maternal health of taking DTG during pregnancy and any metabolic effects that could persist into later life. Furthermore, we lack evidence on the effect of in-utero exposure to DTG and the long-term health trajectories on the infants born to WLH.

There have been several different studies globally assessing the health implications of maternal DTG use. However, more data is needed from Sub-Saharan African studies looking at the effect of DTG use during pregnancy. As the epicentre of the HIV-epidemic it is important to understand the effect of DTG in this population. Furthermore, sub-Saharan Africa has unique disease and exposure profile characterised by other infectious diseases being prevalent, and differing socioeconomic status, varying access to healthcare and an emerging obesity and noncommunicable disease burden. This is especially important in South Africa where overweight and obesity is exceptionally high in women of reproductive age.

Additionally, the interaction between DTG and maternal factors such as nutrition, co-infections, and genetic variability remains under-researched. Understanding these interactions could help tailor interventions to a specific countries needs based on their disease/risk profile.

Lastly, the differing results when it comes to DTG use and adverse birth outcomes highlight the need for greater statistical power when doing these calculations, so studies examining these associations on a larger scale could potentially give a more definitive result pertaining to whether or not DTG is associated with adverse birth outcomes.

Future Research Needs

Conducting research where we follow a cohort of individuals exposed to DTG in utero long-term will allow us to determine the long-term health implications of this exposure. These health implications could be wide-ranging, necessitating the evaluation of a variety of outcomes such as development, cognitive and physical health, and any potential late-emerging complications.

With the increasing burden of obesity and other noncommunicable diseases in the settings where HIV is most prevalent, future research needs to explore the interplay between these risk factors and HIV treatment in pregnancy in these populations. Further research into the mechanism underlying weight gain associated with DTG, particularly why this weight gain occurs disproportionately in women could help address unfavourable outcomes associated with this excess weight and improve birth outcomes.

Addressing these research gaps will contribute to the development of more comprehensive clinical guidelines and better healthcare practices for managing HIV in pregnancy, ultimately improving outcomes for both mothers and their children.

Conclusion

Summary of Findings

In summary, the management of HIV in pregnant women through ART is a critical aspect of public health, particularly in South Africa, where the prevalence of HIV is high. Dolutegravir (DTG), as a part of ART regimens, has shown promise due to its high efficacy and favourable resistance profile. So far it has had a positive impact on HIV management and has contributed towards meeting the UNAIDs targets to end the AIDS epidemic. While it appears to be the best regimen available to WLH with regards to safety and efficacy, there still appears to be an elevated risk associated with SGA and very SGA which warrants further investigation and strategy to improve. Furthermore, there are still gaps in the evidence, particularly regarding long-term outcomes and the impact of maternal factors like weight and BMI.

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Part B: Journal Manuscript

Impact of TLD on Birth Outcomes in South African women: the ORCHID cohort

Abstract

Background: The global shift to tenofovir+lamivudine+dolutegravir (TLD) has improved viral suppression in pregnant women living with HIV (WLH) but there are limited data on the combined impact of HIV and maternal body composition on birth outcomes.

Methods: We enrolled WLH on TLD and a comparison group of women not living with HIV (WNLH) seeking antenatal care at primary health facilities in Cape Town. Gestational age (GA) was determined via ultrasound by research sonographer; behavioural and demographic data were collected through questionnaires; anthropometry was through clinical examination. Birth outcome data were abstracted from medical records, including pregnancy loss (miscarriage and stillbirth), prematurity (<37weeks GA), low birthweight (LBW) (<2500g), high birthweight (>400g) and size for GA [including small- (SGA) and large-for-GA (LGA) from Intergrowth estimates. Logistic regression models assessed the association between HIV/TLD and birth outcomes adjusting for maternal age, BMI, alcohol use and education; results are reported as adjusted odds ratios (AOR).

Results: We followed 1908 women (804 WLH, 1104 HIV-; mean age 28y, median GA at enrolment, 14w; median BMI at enrolment, 31kg/m2 [IQR, 25-35]. Birth outcomes were known for 1869 women (98%) including 65 miscarriages (3.4%), 35 stillbirths (1.9%) and 1769 live births (1735 singletons). Overall rates of prematurity, LBW, HBW, SGA, HBW and LGA were 9.4%, 12%, 13%, 4% and 12%, respectively, and did not differ between WLH and HIV- women. BMI did not affect the association between HIV/TLD and any birth outcome. Independent of HIV/TLD, higher BMI was associated with reductions in prematurity, LBW and SGA.

Conclusion: These results suggest few meaningful differences in birth outcomes between WLH on TLD in this setting, where both HIV and obesity are prevalent. Maternal BMI appears to be a more significant driver of birth outcomes than HIV in this cohort.

Introduction

Antiretroviral therapy (ART) use during pregnancy has decreased vertical transmission of HIV and reduced the risk of adverse birth outcomes associated with HIV(1). ART regimens that include dolutegravir (DTG) have been upscaled and implemented as the standard of care in South Africa since 2019 as per WHO guidelines(2). Studies have shown DTG-regimens to have superior viral suppression and resistance profiles compared to other previously recommended regimens(3, 4). With the evolution and improvement of ART, there has been a corresponding improvement in birth outcomes of women on ART during pregnancy(5, 6). Despite these improvements in the risk of preterm delivery (PTD) and LBW in WLH it essential to study these and other outcomes in the context of HIV because of the complex interplay between HIV, ART and maternal and foetal health.

Overweight and obesity are increasing in prevalence, particularly in sub-Saharan Africa (SSA), reaching nearly 35% in women of childbearing age and 68% in South Africa(7, 8). This emerging public health concern is further compounded by DTG which demonstrates obesogenic properties, with studies indicating this weight gain is not uniform between men and women(9). Women are at an increased risk of weight gain when initiating DTG, highlighting the importance of studying its effect during pregnancy. This is particularly concerning because maternal overweight/obesity during pregnancy increases the risk of metabolic issues, adverse birth outcomes (miscarriage, stillbirth, PTD, LGA/macrosomia), and obstetric conditions like gestational diabetes and pre-eclampsia(10-12). Alongside this increase in overweight/obesity among women in Africa there has also been a trend of increasing macrosomia or LGA infants being born leading to an increase in childhood obesity and diseases associated with obesity, particularly diabetes and hypertension later in life(13, 14).

HIV disproportionately affects pregnant women in South Africa, comprising 30% of the population(15). This high prevalence underscores the need for targeted, safe, and effective interventions in this population. The co-existence of risk factors and their potential interplay with ART makes it important for us to study the effect of ART regimens in the South African population, to ensure we are delivering the best interventions, and tailor interventions to our population as needed. Despite both HIV and obesity being risk factors for adverse birth outcomes, little is known about the interplay of obesity and DTG use during pregnancy and their effect on birth outcomes. This analysis assessed the impact of DTG use during pregnancy on adverse birth outcomes in South African women, specifically those on TLD in a large primary healthcare-based cohort.

Methods

Study Population

The ORCHID study, a prospective cohort study examining the metabolic implications of DTG use during pregnancy on maternal and infant health in Cape Town enrolled women at the

Gugulethu Community Health Centre Midwife-Obstetric Unit. This primary healthcare facility provides comprehensive HIV/ART integrated antenatal, obstetric, and infant care. A research counsellor recruited pregnant women seeking antenatal care (ANC) at their first routine visit between 2021 and 2023.

Participants enrolled in this study were pregnant women aged 16 years or older with confirmed pregnancy based on a urine test with viable gestation <19 weeks by ultrasound. For WLH those with known HIV status had this confirmed based on medical record review and HIV antibody testing during ANC. WNLH were enrolled into the control arm. Women in both groups followed identical study procedures. HIV testing of women who tested negative at the first ANC visit occurred at subsequent study visits, all women who seroconverted during ANC were removed from this analysis. At the first ANC visit, WLH not on ART initiated TLD, and WLH on other regimens switched to TLD, consequently, all WLH in this cohort used TLD as per routine health care guidelines(16). Participants were excluded from the cohort if they were on treatment for any form of diabetes or hypertensive disorders based on self-report and/or medical record review.

Data Collection

All participants completed questionnaires at enrolment establishing maternal demographics, including maternal age and education, and medical history. Participants completed procedures measuring resting energy expenditure, body composition, including weight and height, and had an ultrasound administered by a research sonographer using standardised assessment protocols. Medical record review determined obstetric history, ART history and ART start dates for WLH. Obstetric data abstraction was done after delivery from infant Road to Health booklets and Maternity case records to determine birth outcomes. Further questionnaires were administered to collectadditional information on patients like questionnaires relating to alcohol use.

Exposure Definitions

The primary exposure of interest is HIV/DTG exposure. HIV status was determined at enrolment. DTG status was based on the timing of DTG initiation, categorised as those who initiated DTG prior to pregnancy (DTG continuers), those who switched from another ART regimen (DTG switchers), and those who initiated ART during pregnancy at enrolment (DTG Naïve). A secondary exposure explored in this analysis is maternal BMI category. Maternal BMI was calculated using maternal weight and height, measured by ORCHID research staff. Due to the distribution of maternal BMI in this cohort, the BMI categories underweight (<18.5 kg/m^2), and healthy weight (18.5-24.9 kg/m^2) have been combined, as have the categories Obese Class II (35-39.9 kg/m^2) and Obese Class III (>40 kg/m^2), such that the distribution across the four BMI categories (under/healthy weight (<24.9kg/m^2) overweight (25-29.9 kg/m^2), Obese class I (30-

34.9kg/m^2), and Obese class II/III (>35kg/m^2) is relatively even(17).

Outcomes definitions

The outcomes of interest are live birth or pregnancy loss, gestational age (GA) at delivery, birthweight, and size for GA. Pregnancy loss includes ectopic pregnancy, termination of pregnancy, miscarriage or stillbirth. Miscarriages were defined as pregnancy losses that occurred prior to 28 weeks GA, stillbirths were defined as foetal deaths that occurred after 28 weeks before or during labour(18). GA at delivery, determined by ultrasound and recorded as complete weeks is categorized as term (≥37 weeks) and PTD (<37 weeks), categorised as late preterm (34–37 weeks), moderately preterm (32–34 weeks) or very preterm (<32weeks). Birthweight, abstracted from maternal/infant records, is categorised as: high birthweight (HBW: ≥ 4000g), normal (2500-3999g), and low (<2500g). LBW is further categorized into LBW (1500-2500g) and very LBW (<1500g). Size for GA is categorised as small (SGA: <10th percentile), appropriate (AGA: 10-90th percentile), and large (LGA: >90th percentile) for GA based on INTERGROWTH-21st Project Standards(19).

Statistical analysis

Statistical analysis for this study was done using R (Version 4.3.3). Maternal demographic data was summarised using median and interquartile range for continuous variables and proportions to describe categorical data. For this analysis we focused on three main exposure categories; WLH versus WNLH; A comparison of the effect across BMI categories, Among WLH, DTG naïve and DTG switchers versus DTG continuers. Birth outcomes were evaluated using proportions. Among live singleton births associations between exposure and outcomes PTD, LBW, HBW, SGA and LGA were determined using multivariate logistic regression models. Confounders were identified a priori and based on confounders identified in previous literature. Confounders included maternal age, maternal education, maternal BMI at enrolment, maternal alcohol use since conception, and for WLH HIV RNA viral load (copies/L) at enrolment(20, 21). Model fit was assessed using Akaike's Information Criterion and Bayesian Information Criterion. Results were presented as odds ratios, 95% confidence intervals and p-values.

Ethical Approval

The ORCHID study followed a protocol reviewed and approved by the University of Cape Town HREC, Columbia University, and Ann & Robert H. Lurie Children's Hospital of Chicago/Northwestern University IRBs(22). At enrolment, all participants completed informed consent forms in the participants' home language (isiXhosa, Afrikaans, or English). Informed consent included access to clinical records to obtain birth outcome data for this analysis. Ethical approval for this analysis followed a protocol reviewed and approved by the University of Cape Town HREC (Approval 955/2024).

Results

Table 1: Characteristics of ORCHID 1908 participants at their first ANC visit by HIV status.

Characteristic	**Overall**, N = 1,908[1]	**Negative**, N = 1,104[1]	**Positive**, N = 804[1]
Maternal Age, years	28.0 (23.9, 32.5)	26.5 (22.9, 30.9)	30.0 (25.6, 34.5)
Education Level			
Any Basic Education	43 (2%)	17 (2%)	26 (3%)
Any Highschool	1705 (90%)	973 (89%)	732 (92%)
Any Postsecondary Education	143 (8%)	101 (9%)	42 (5%)
Unknown	17	13	4
Weight (kg)	74 (62, 89)	75 (63, 89)	73 (62, 88)
Unknown	5	3	2
Height (cm)	159.5 (155.5, 163.6)	159.3 (155.5, 163.5)	159.6 (155.5, 163.7)
Unknown	5	3	2
BMI (kg/m^2)			
Under/Healthy weight	502 (26%)	269 (24%)	233 (29%)
Overweight	519 (27%)	304 (28%)	215 (27%)
Obese class 1	446 (23%)	256 (23%)	190 (24%)
Obese class 2&3	436 (23%)	272 (25%)	164 (20%)
Unknown	5	3	2
Gestation at A1b (weeks)			
Median (IQR)	13.9 (10.9, 16.6)	13.9 (10.7, 16.3)	14.0 (10.9, 16.9)
<13 weeks	774 (41%)	448 (41%)	326 (40%)
≥13 weeks	1134 (51%)	656 (50%)	478 (53%)
Gravidity			
Primigravida	605 (32%)	443 (40%)	163 (20%)
Multigravida	1,302 (68%)	661 (60%)	641 (80%)
Previous pregnancy loss	313 (22%)	176 (22%)	137 (22%)
Alcohol Use			
Yes	325 (17%)	180 (16%)	145 (18%)
No	1583 (83%)	924 (84%)	659 (88%)
Smoking (ever)			
Yes	196 (10%)	106 (10%)	90 (11%)
No	1712 (90%)	998 (90%)	714 (89%)
Drug Use			
Yes	26 (1%)	14 (1%)	12 (1.5%)
No	1882 (99%)	1090 (99%)	792 (98.5%)
CD4 cell count at A1, (cells/ml)			
=<200			58 (7%)
200-350			138 (18%)
350-500			179 (23%)
>500			403 (52%)
Unknown			26
HIV RNA viral load at A1 (copies/L)			
<50			583 (78%)
<1000			106 (14%)
>1000			63 (8%)
Unknown			52
DTG initiation			
DTG continuer			590 (73%)
DTG Naïve			92 (11%)
DTG Switcher			122 (15%)

[1] Median (IQR); n (%)

The ORCHID study enrolled 1920 women, comprised of 1104 and 804 WLH. 12 women seroconverted during pregnancy and were removed from this analysis. Table 1 shows baseline demographic and clinical characteristics for the participants overall and

by HIV status. This cohort had an average maternal age of 28 years overall. WLH were older, median age 30 (IQR: 25.6–34.5) vs 26.5 (IQR: 22.9–30.9), less educated (post-secondary: 5% vs 9%), weighed less median weight 73kg (IQR: 62–88) vs 75kg (IQR: 63–89), had a greater proportion of under/healthy weight (29% vs 25%), alcohol use (18% vs 16%), smoking (11% vs 10%), and used drugs (1.5% vs 1%) compared to WNLH. Birth outcomes were known for 1869 participants (98%). There is no difference in proportion for known outcomes, live births or pregnancy losses between WLH and WNLH. More twins occurred among WLH (3%) compared to WNLH (1%). Miscarriages occurred more in (3.8%) and stillbirths occurred more in WLH (2.4%)(Supplementary Table 1).

Table 2 shows the birth outcomes for 1731 singleton live births stratified by HIV status and BMI category. Four observations are missing due to missing BMI data.

Gestational Age

Term deliveries (≥37 weeks) were consistent across BMI categories. Among , proportions ranged from 89% to 91%, and among WLH, from 88% to 92%. PTD was slightly higher in the under/healthy weight category (11% WNLH, 12% WLH) than in higher BMI groups. The lowest PTD rates were in Obese Class 1 (7% WNLH, 8% WLH). Most PTD cases were late preterm (34–37 weeks), with similar trends across BMI categories. Logistic regression models found no association between PTD and DTG (OR: 1.08, 95% CI:0.77-1.49). Higher BMI categories were associated with decreased odds of PTD, particularly in Obese class II/III where odds of PTD decreased by 41% compared to under/healthy weight (Table 3).

Birthweight

Table 2: Birth Outcomes by HIV status and BMI category

		HIV Negative					HIV Positive				
Outcome	**Overall**, N = 1,731[1]	**Overall**, N = 1007[1]	**Under/ Healthy weight, N = 245**[1]	**Overweight, N = 278**[1]	**Obese class 1, N = 235**[1]	**Obese class 2&3, N = 249**[1]	**Overall**, N = 724[1]	**Under/ Healthy weight, N = 212**[1]	**Overweight, N = 196**[1]	**Obese class 1, N = 170**[1]	**Obese class 2&3, N = 146**[1]
Gestational Age (weeks)											
Term (⩾37)	1,562 (91%)	909 (91%)	217 (89%)	217 (89%)	250 (91%)	223 (90%)	653 (90%)	186 (88%)	179 (91%)	157 (92%)	131 (90%)
Preterm Delivery (Any,<37)	162 (9%)	91 (9%)	28 (11%)	24 (9%)	15 (7%)	24 (10%)	71 (10%)	26 (12%)	17 (9%)	13 (8%)	15 (10%)
Late preterm (34-37)	104 (6.0%)	57 (6%)	17 (7%)	15 (6%)	7 (3%)	18 (7%)	47 (6.5%)	17 (8%)	12 (6%)	7 (4%)	11 (8%)
Moderately preterm (32-34)	25 (1%)	16 (1%)	5 (2%)	3 (1%)	6 (3%)	2 (1%)	9 (1.2%)	3 (1%)	2 (1%)	2 (1%)	2 (1%)
Very preterm (<32)	33 (2%)	18 (2%)	6 (2%)	6 (2%)	2 (1%)	4 (2%)	15 (2.1%)	6 (3%)	3 (2%)	4 (2%)	2 (1%)
Unknown	7	7	0	4	1	2	0	0	0	0	0
Birthweight, g											
Median (IQR)	3,110 (568)	3200 (2840, 3490)	3075 (2720, 3360)	3100 (2770, 3445)	3240 (2883, 3508)	3350 (3044, 3664)	3100 (2778, 3420)	2980 (2655, 3240)	3080 (2790, 3410)	3260 (2905, 3495)	3270 (2870, 3610)
High birthweight (>4000)	66 (4%)	39 (4%)	5 (2%)	8 (3%)	7 (3%)	19 (8%)	27 (4%)	3 (1%)	7 (4%)	7 (4%)	10 (7%)
Normal Birthweight (≥2500)	1,409 (84%)	817 (85%)	197 (83%)	221 (85%)	198 (88%)	201 (83%)	592 (83%)	164 (80%)	163 (85%)	147 (88%)	118 (81%)
Low Birthweight (any) (<2500)	201 (12%)	109 (11%)	36 (15%)	30 (12%)	21 (9%)	22 (9%)	92 (13%)	40 (19%)	22 (11%)	13 (8%)	17 (12%)
Low birthweight (1500-2500)	177 (11%)	92 (9%)	32 (13%)	25 (10%)	17 (7%)	18 (7%)	85 (12%)	37 (18%)	21 (10.5%)	11 (7%)	16 (11%)
Very low birthweight (<2500)	24 (1%)	17 (2%)	4 (2%)	5 (2%)	4 (2%)	4 (2%)	7 (1%)	3 (1%)	1 (0.5%)	2 (1%)	1 (1%)
Unknown	55	42	7	19	9	7	13	5	4	3	1
Wight Z-score	-0.23 (1.10)	-0.19 (1.09)	-0.46 (0.92)	-0.40 (1.04)	-0.10 (1.07)	0.21 (1.17)	-0.29 (1.11)	-0.66 (1.03)	-0.31 (1.05)	-0.11 (1.10)	0.08 (1.15)
	185 (12%)	58	12	24	11	11	26	9	9	5	3
Size for gestational age (centile)											
>90th (LGA)	148 (9%)	88 (9%)	8 (3.4%)	11 (4.3%)	23 (10%)	46 (19%)	60 (9%)	9 (4%)	16 (9%)	12 (7%)	23 (16%)
10-90th (AGA)	1224 (78%)	711 (75%)	177 (76%)	187 (74%)	173 (77%)	174 (73%)	513 (73%)	134 (66%)	140 (75%)	135 (82%)	104 (73%)
<10th (SGA)	275 (17%)	150 (16%)	48 (21%)	56 (22%)	28 (13%)	18 (8%)	125 (18%)	60 (30%)	31 (17%)	18 (11%)	16 (11%)
Unknown	84	58	12	24	11	11	26	9	9	5	3

[1] Mean (SD); n (%)

Median birthweight increased with higher BMI across both HIV statuses. Among , median birthweight ranged from 3,075g (under/healthy weight) to 3,350g (Obese Class II/III). Similarly, in WLH, median birthweight increased from 2,980g (under/healthy weight) to 3,270g (Obese Class II/III).

HBW occurred similarly between HIV groups with both groups having a proportion of 4% overall. HBW increased with rising maternal BMI, from 2% among WNLH women and 1% among WLH in the underweight/healthy weight category, to 8% and 7% respectively in the obese class II/III category. Logistic regression models found no association between DTG and HBW (OR: 0.91, 95%CI: 0.54-1.53), but did find an increased odds of HBW among Obese Class II/III women (OR: 4.18, 95% CI: 1.92-10.13)(Table 3).

LBW (<2,500 g) was more common among under/healthy weight (15% WNLH, 19% WLH) and less common in women in higher BMI categories. Logistic regression models found no association between DTG use and LBW (OR 1.17; 95%CI: 0.87-1.57). However, higher BMI categories were associated with decreased odds of LBW in by 33% in overweight, 51% obese class I, and 43% obese class II/III compared to under/healthy weight (Table 3).

SGA

Overall, there was a greater prevalence of SGA in WLH (18%) than WNLH (16%). The prevalence of SGA was higher in under/healthy weight (21% WNLH, 30% WLH). SGA rates declined with increasing BMI, with lowest proportion observed in Obese Class II/III (8% WNLH, 11% WLH). Examining the weight

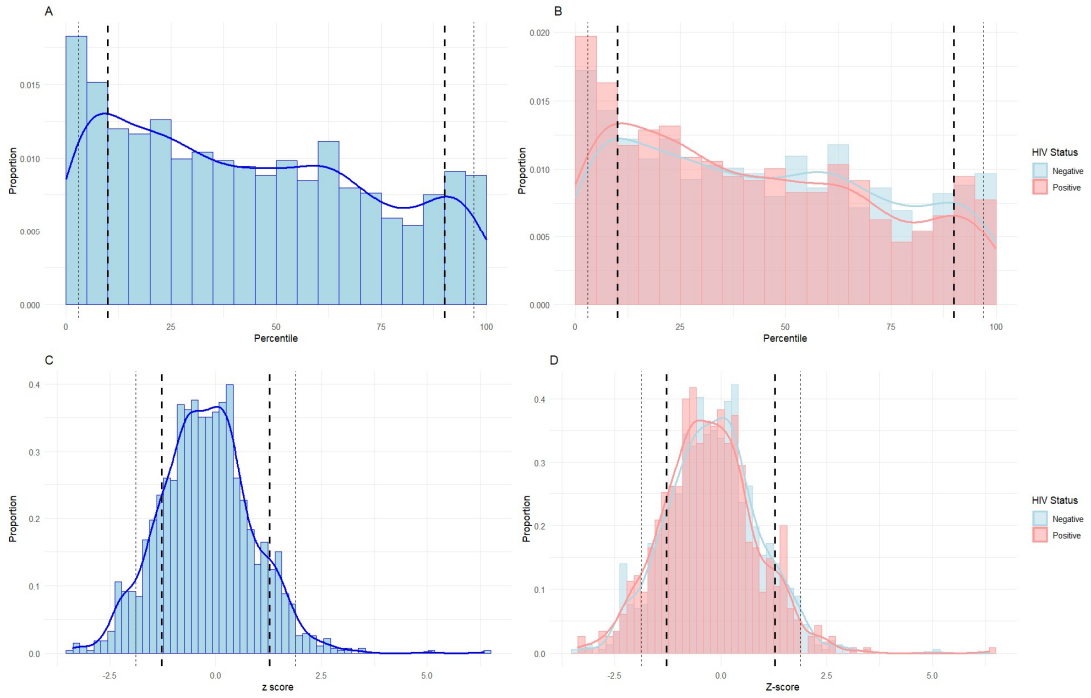

Figure 1: Histogram describing birthweight (a) centiles overall, (b) centiles by HIV status, (c) z-scores overall, and (d) z-scores by HIV status

centile and z-scores we see a relatively normal distribution overall and by HIV status. However, we see a greater proportion of infants born to WLH in the lower 10 percentile (Figure 1b). The distribution of the z-scores demonstrates that the mean birthweight was greater in than WLH. A greater proportion of very SGA (<3rd percentile) occurred in WLH compared to WNLH. The mean birthweight z-score was below 0 for both WLH and WNLH; meaning mean birthweight in this cohort was lower than the global average, but even lower in WLH. This demonstrates the birthweights in this cohort were lower than average in the global context. Logistic regression models found no association between DTG use and SGA (OR: 1.18, 95% CI:0.91-1.52). Higher BMI categories were associated with a decreased odds of SGA, in all BMI categories compared to under/healthy weight (Table 3).

LGA

LGA became more prevalent with increasing BMI. LGA prevalence was the same across HIV status (9%) but differed in distribution by BMI. LGA occurred 4% WLH vs 3% in under/healthy weight, 9% WLH vs 4% in overweight, 7% WLH vs 10% in obese class I, and 16% WLH vs 19% in obese class II/III. Logistic regression models found no association between DTG use and LGA (OR: 0.92, 95% CI:0.65-1.30). Higher BMI categories were associated with an increased odds of LGA, by 2.03-fold in Obese class I and 4.57-fold in obese class II/III compared to under/healthy weight (Table 3).

Table 3: Model results describing the odds of adverse birth outcomes

	PTD				LBW				HBW				SGA				LGA			
	Unadjusted		Adjusted Results		Unadjusted Results		Adjusted Results		Unadjusted Results		Adjusted Results		Unadjusted Results		Adjusted Results		Unadjusted Results		Adjusted Results	
Variable	OR 95% CI	p-Value	OR 95% CI	p-Value	OR 95% CI	p-Value	OR 95% CI	p-Value	OR 95% CI	p-Value	OR 95% CI	p-Value	OR 95% CI	p-Value	OR 95% CI	p-Value	OR 95% CI	p-Value	OR 95% CI	p-Value
HIV +	1.08 (0.77-1.49)	0.663	1.13 (0.80-1.59)	0.489	1.17 (0.87-1.57)	0.292	1.11 (0.81-1.51)	0.524	0.94 (0.56-1.54)	0.805	0.95 (055-1.59)	0.837	1.18 (0.91-1.52)	0.222	1.11 (0.84-1.47)	0.471	0.92 (0.65-1.30)	0.643	0.88 (0.60-1.26)	0.485
BMI category																				
Under/Healthy	Ref.		Ref.		Ref.		Ref.		Ref.		Ref.		Ref.		Ref.		Ref.		Ref.	
Overweight	0.71 (0.45-1.09)	0.122	0.72 (0.46-1.11)	0.143	0.63 (0.43-0.92)	0.018	0.67 (0.45-0.99)	0.045	1.88 (0.81–4.71)	0.154	1.80 (0.77-4.54)	0.189	0.75 (0.54-1.03)	0.073	0.82 (0.59-1.14)	0.232	1.61 (0.87-3.05)	0.135	1.45 (0.78-2.77)	0.243
Obese class 1	0.56 (0.34-0.89)	0.016	0.59 (0.36-0.96)	0.038	0.46 (0.30-0.70)	<0.001	0.49 (0.31-0.77)	0.002	2.02 (0.85-5.10)	0.118	1.89 (0.73-4.86)	0.165	0.41 (0.28-0.59)	<0.001	0.45 (0.30-0.66)	<0.001	2.44 (1.36-4.52)	0.003	2.03 (1.11-3.82)	0.024
Obese Class 2&3	0.82 (0.53-1.27)	0.524	0.86 (0.54-1.36)	0.525	0.54 (0.36-0.82)	0.004	0.57 (0.37-0.88)	0.011	4.42 (2.09-10.49)	<0.001	4.18 (1.92-10.13)	0.001	0.30 (0.19-0.45)	<0.001	0.32 (0.20-0.48)	<0.001	5.45 (3.22-9.74)	<0.001	4.57 (2.64-8.29)	<0.001
Maternal age	0.98 (0.96-1.01)	0.279	0.99 (0.96-1.02)	0.530	0.99 (0.96-1.01)	0.320	1.00 (0.97-1.02)	0.839	1.03 (0.99-1.08)	0.097	1.02 (0.97-1.06)	0.503	0.98 (0.96-1.00)	0.068	1.00 (0.97-1.02)	0.746	1.06 (1.03-1.09)	<0.001	1.04 (1.01-1.07)	0.014
Alcohol Use	1.21 (0.80-1.79)	0.351	1.18 (0.77-1.75)	0.435	1.80 (1.28-2.52)	0.001	1.72 (1.21-2.42)	0.002	0.81 (0.39-1.54)	0.551	0.83 (0.39-1.59)	0.596	2.02 (1.49-2.72)	<0.001	1.99 (1.45-2.70)	<0.001	0.79 (0.48-1.24)	0.328	0.84 (0.50-1.33)	0.470
Education																				
Any Basic Education	Ref.		Ref.		Ref.		Ref.		Ref.		Ref.		Ref.		Ref.		Ref.		Ref.	
Any Highschool	1.86 (0.56-11.50)	0.398	1.89 (0.57-11.75)	0.386	0.74 (0.33-1.98)	0.503	0.74 (0.32-2.01)	0.515	0.72 (0.21-4.47)	0.650	0.73 (0.21-4.62)	0.675	0.54 (0.27-1.19)	0.104	0.52 (0.25-1.16)	0.088	1.11 (0.39-4.66)	0.861	1.22 (0.42-5.20)	0.752
Any Postsecondary Education	1.60 (0.41-10.68)	0.551	1.69 (0.42-11.33)	0.508	0.40 (0.13-1.27)	0.105	0.43 (0.14-1.38)	0.139	0.73 (0.15-5.24)	0.713	0.76 (0.15-5.60)	0.757	0.46 (0.19-1.14)	0.083	0.46 (0.19-1.18)	0.098	1.10 (0.32-5.08)	0.885	1.28 (0.36-6.07)	0.721

OR = Odds Ratio. CI = Confidence Interval. Ref. = Reference category

Overall Table 2 shows that a higher BMI was associated with improved birth outcomes, such as lower PTD and SGA, and higher birthweights. These trends were consistent across both WNLH and WLH, although proportions were slightly higher among WLH, particularly in lower BMI categories. Associations between DTG use and adverse birth outcomes were unaffected by maternal BMI despite maternal BMI being overall rates of preterm delivery (PTD) are similar across the four groups; however, very preterm deliveries occur most frequently among DTG-naïve women. (Supplementary Figure1a). LBW occurs similarly across all groups (Supplementary Figure1b). The proportion of SGA, AGA, and LGA occurred similarly across DTG initiation groups (Supplementary Figure 1c). Multivariate logistic regression models showed no

Table 4: Model results describing the adjusted odds of preterm delivery, low birthweight, SGA and LGA

	Preterm Delivery		Low Birthweight		SGA		LGA	
DTG Initiation	AOR (95% CI)	p-value	AOR (95% CI)	p-value	AOR (95% CI)	p-value	AOR (95% CI)	p-value
DTG Continuer	Ref.		Ref.		Ref.		Ref.	
DTG Switcher	1.60 (0.81 – 3.04)	0.159	1.29 (0.68-2.35)	0.421	1.11 (0.59-2.03)	0.733	1.49 (0.62-3.24)	0.342
DTG Naive	1.20 (0.48 – 2.77)	0.680	0.59 (0.22-1.42)	0.270	1.02 (0.45-2.18)	0.961	0.81 (0.18-2.63)	0.751
HIV RNA viral load at A1 (copies/L)								
<50	Ref.		Ref.		Ref.		Ref.	
<1000	0.38 (0.14 – 0.91)	0.043	0.58 (0.25-1.21)	0.168	0.96 (0.49-1.83)	0.915	0.85 (0.31–2.02)	0.728
>1000	1.49 (0.66 – 3.22)	0.319	1.44 (0.64-3.08)	0.366	1.18 (0.52-2.54)	0.684	0.22 (0.01-1.16)	0.154
BMI category								
Under/Healthy	Ref.		Ref.		Ref		Ref.	
Overweight	0.83 (0.44 – 1.53)	0.550	0.74 (0.43-1.28)	0.289	0.56 (0.33 – 0.94)	0.030	1.72 (0.73-4.23)	0.222
Obese class 1	0.63 (0.31 – 1.24)	0.193	0.40 (0.20-0.74)	0.005	0.30 (0.16-0.59)	<0.001	1.47 (0.60-3.73)	0.407
Obese Class 2&3	0.99 (0.50 – 1.90)	0.976	0.64 (0.34-1.16)	0.149	0.32 (0.16-0.59)	<0.001	2.80 (1.22-6.85)	0.018
Maternal Age (years)	0.97 (0.93 – 1.01)	0.193	1.01 (0.97-1.05)	0.567	1.01 (0.98-1.05)	0.548	1.04 (0.99-1.09)	0.135
Alcohol Use	Na	na	2.24 (1.36–3.62)	0.001	2.46 (1.52-3.96)	<0.001	0.71 (0.29-1.55)	0.430

OR = Odds Ratio. CI = Confidence Interval. Ref. = Reference category

independently associated with adverse birth outcomes. These results demonstrate that the major driver of adverse birth outcomes in this cohort is likely maternal BMI rather than maternal HIV/ART status.

Timing of DTG initiation

Supplementary figure 1 shows a comparison of adverse birth outcomes by DTG initiation compared to WNLH. This figure shows that association between DTG initiation and any adverse birth outcomes (Table 4). Similarly, these models show us the higher BMI categories are protective against LBW and SGA, while maternal alcohol use since conception over doubled the odds for LBW and SGA.

Discussion

This study investigated the impact of maternal DTG use and BMI on birth outcomes in South

African women accessing ANC at primary health care facilities. We found there is no significant associations between DTG use during pregnancy and adverse birth outcomes PTD, LBW, HBW, SGA, and LGA compared to WNLH. Our findings show that the current standard of care regimen is safe during pregnancy, however, maternal BMI is a major driver of adverse birth outcomes, indicating a need for targeted efforts toward reaching and maintaining a healthy BMI in women of reproductive age.

Similar proportions of PTD occurring regardless of HIV status are reassuring for two reasons. Since the implementation of DTG, we have seen the improved incidence of PTD in women that take DTG-based regimens compared to previous regimens(4, 6). Our results suggest little difference in PTD between women taking DTG and . Furthermore, the incidence of PTD across all countries part of the WHO is 10%, we observed a similar prevalence in our cohort (9%)(23), suggesting perhaps even lower risk of PTD in women taking DTG. These results are encouraging as PTD is the biggest risk factor for infant mortality(24). The greatest proportion of very PTD occurred in DTG naïve individuals. DTG naïve women initiated DTG at study enrolment and this cohort had a median gestation of 14 weeks at enrolment. Inflammation associated with HIV infection as well as immune activation can affect placental function. Disruption of placental functions linked to very preterm delivery(25, 26).

We found no significant difference in the occurrence of LBW in WLH compared to WNLH. Pregnant women on DTG-based regimens have a decreased risk of delivering LBW infants compared to previous regimens, results that show few differences across HIV status are encouraging(4, 6). LBW occurred at a slightly higher proportion (12%) compared to the average 10% we usually see in SSA(27). The mean birthweight for both WLH and WNLH is a z-score indicating the mean birthweight in this cohort is lower than the global average, with WLH having a slightly lower mean birthweight compared to WNLH. Given the distribution of BMI, as well as low PTD in this cohort this LBW could be because of other factors like poor maternal nutrition, nutrient deficiencies or socioeconomic factors causing stress/exposure to toxins(28-30). Further research into the cause of LBW in South Africa should be done so we can identify the cause and tailor interventions appropriately. The timing of DTG initiation had no impact on birthweight.

This cohort had a lower prevalence of HBW than expected of SSA where prevalence of HBW is approximately 8%, we had a prevalence of 4% overall and in each HIV group. This could be expected given the previously discussed lower than average birthweight(31). While it could be considered good as this should be indicative of a decreased risk of childhood obesity and linked diseases in this cohort, given the elevated maternal BMI in this cohort we would expect a greater proportion of HBW, so this lower proportion

could be again indicative of poor maternal nutrition or exposure to stress/toxins. HBW is not regularly studied as an adverse birth outcome, however, its relevance may increase with rising obesity rates, warranting comparison with future findings.

This study found no association between SGA and DTG use during pregnancy compared to WNLH, while previous studies have found this association(31, 32). Approximately three quarters of this cohort had a BMI over 25kg/m^2 which is associated with higher birthweight. This higher BMI could be masking any potential SGA effects. Examining very SGA (<3rd percentile) we see a greater proportion of these cases occur in WLH compared to WNLH similar to a study Botswana(33). This study found that the risk of very SGA was higher in women with CD4 > 500 than CD4 < 500 cells/mm^3 when baseline weight was >70 kg, but lower if baseline weight was 60 kg or less. This indicates inflammatory properties of decreased immune response is likely linked to this risk of very SGA(34). The timing of DTG initiation did not impact SGA.

This study utilised data from a large prospective cohort study in a setting where both HIV and maternal obesity are prevalent. The study design provides us detailed measures, particularly GA and maternal BMI, allowing us to control for confounding and make inferences of the source population. It is relevant as few studies have examined both DTG and maternal BMI in this population. However, this study design also resulted in some loss to follow up and missing maternal BMI and outcomes data in our cohort which could have attenuated associations. Furthermore, with the improvement of birth outcomes of women on ART we now require larger sample sizes to detect associations, our study may have been underpowered to detect these. The nature of data collection/record abstraction for the infant outcomes data leaves room for human error which could have introduced random error, potentially attenuating any association. Given the unique disease profile of South Africa the results may not be generalizable to other populations outside SSA.

Conclusion

These results suggest few meaningful differences between WLH on DTG-based regimens and . This reinforces previous studies that demonstrate DTG is a safe and efficacious regimen, indicating that the current guidelines by the WHO for DTG-based regimens to be prescribed to all people living with HIV is the best regimen, even for pregnant women. From this study we see maternal BMI seems to be a major driver for adverse birth outcomes, particularly those related to birthweight and size for gestational age, but it does not seem to alter the association between DTG use during pregnancy and adverse birth outcomes when comparing birth outcomes to suggesting efforts need to be made toward reaching and maintaining a healthy weight in women of reproductive age.

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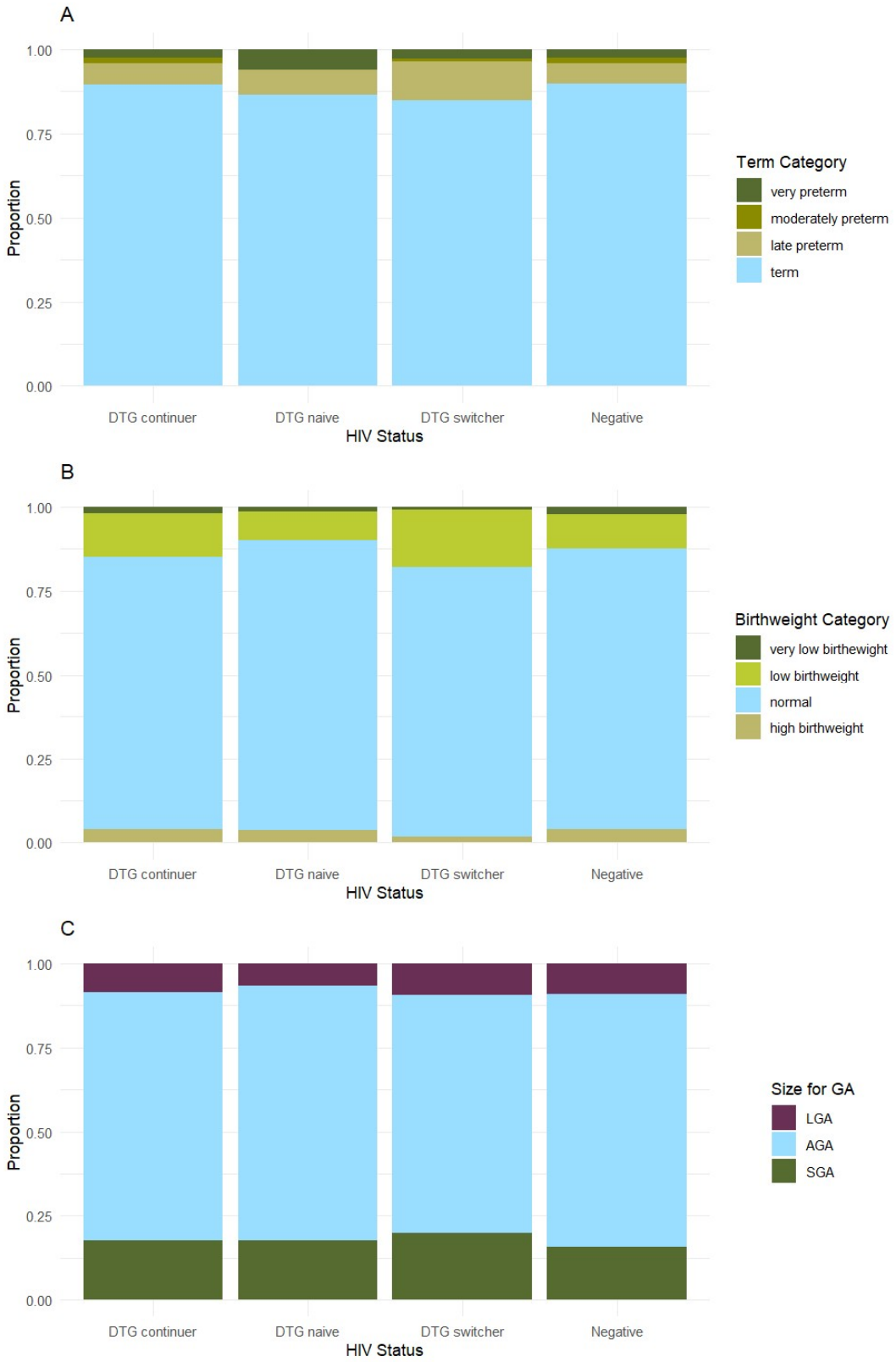
Supplementary Material

Supplementary Table 1: Table describing outcome data by HIV status

	Overall, N = 1,908[1]	**Negative**, N = 1,104[1]	**Positive**, N = 804[1]
Known outcome	**1869 (98%)**	**1080 (98%)**	**789 (98%)**
Unknown outcome	**39 (2%)**	**24 (2%)**	**15 (2%)**
Outcome			
Live Birth	1,769 (95%)	1,023 (95%)	746 (95%)
Single Live Birth	1735 (93%)	1,010 (94%)	724 (92%)
Twins	34 (2%)	13 (1%)	21 (3%)
Pregnancy Loss	100 (5.4%)	57 (5.3%)	43 (5.4%)
miscarriage	65 (3.5%)	41 (3.8%)	24 (3%)
stillbirth	35 (1.9%)	16 (1.5%)	19 (2.4%)



Supplementary Figure 1: Birth outcomes by DTG Initiation (a) Gestational age at delivery, (b) weight at delivery, (c) size for gestational age at delivery.

Part C: Policy Brief

Policy brief on dolutegravir use during pregnancy in women living with HIV

Dolutegravir (DTG) has been implemented as standard of care for all persons with HIV since 2019. The ORCHID study was conducted to determine metabolic implications of DTG use during pregnancy on maternal and infant health. We found no meaningful differences in the birth outcomes of women living with HIV (WLH) compared to HIV-negative women. However, it did find that maternal BMI seems to be a major driver of adverse birth outcomes highlighting the necessity for targeted interventions to reduce maternal obesity.

Findings

In Cape Town, South Africa, the ORCHID cohort study examines the metabolic implications of DTG use during pregnancy and postpartum on maternal and infant health. We conducted a study on the birth outcomes of the ORCHID cohort. These birth outcomes included pregnancy loss, preterm delivery, low birthweight, high birthweight, small for gestational age (SGA), and large for gestational age (LGA). This study found no significant differences in the birth outcomes of women living with HIV and HIV-negative women. Furthermore, we found that the timing of DTG initiation, whether it was before conception or after conception, also did not affect the association between DTG use during pregnancy and any of the adverse birth outcomes compared to HIV-negative women. However, in our study we did find that elevated maternal BMI is associated with elevated odds of unfavourable birth outcomes, however, maternal BMI did not have an effect the relationship between DTG use during pregnancy and adverse birth outcomes.

Implications

Few meaningful differences in birth outcomes of WLH and HIV-negative women suggest the current regimen recommended by the WHO should be continued in pregnant women. Policymakers should ensure that DTG is accessible to all pregnant women.

Maternal BMI associations with adverse birth outcomes suggest that interventions targeted toward women of reproductive age achieve and maintain a healthy weight before conception and throughout pregnancy. This should include culturally appropriate dietary and lifestyle interventions to reduce maternal obesity, especially in high-risk populations.

Recommendations

Further research into the long-term implications of DTG use during pregnancy on maternal and infant health

Targeting obesity in women of reproductive age through

- Public health education programs targeting women of reproductive age highlighting the importance of healthy weight during pregnancy
- Urban planning that supports an active lifestyle
- Tax subsidies for healthy food making them more affordable and accessible
- Nutrition counselling during antenatal care

Appendices

Research Protocol

1. Introduction

1.1 Background

World Health Organisation (WHO) recommends the use of antiretroviral therapy (ART) for all pregnant women living with HIV (WLHIV), primarily for their own health and prevention of mother-to-child transmission.[1] ART use during pregnancy has significantly aided in the prevention of mother-to-child transmission of HIV.[2,3] Untreated maternal HIV in pregnancy has been associated with increased incidence of adverse birth outcomes namely incidence of stillbirth, preterm delivery (PTD), low birthweight (LBW), and small for gestational age (SGA) compared to women not living with HIV (WNLH).[4] WLHIV on ART, particularly older regimens, have in the past been shown to be at greater risk of these adverse birth outcomes compared with WNLH.[5-7] More recent studies have shown that contemporary ART regimens are relatively safe and decrease the risk of adverse birth outcomes compared to WLHIV not taking ART.[8] In recent years, dolutegravir (DTG)-based ART regimens, namely Tenofovir, Lamivudine and DTG (TLD) has been shown to be more effective at suppressing HIV viral load.[9,10] Consequently, this regimen has been scaled up and implemented as part of the standard of care HIV treatment in South Africa as per WHO guidelines.[2,3,11,12] However, little is known about the association between DTG use during pregnancy and adverse birth outcomes.

Pregnancy is a crucial time in a woman's health and any adverse metabolic outcomes can have long-term effects on a woman's health. DTG has been shown to be obesogenic.[13,14] This is a concern in pregnancy as overweight and obesity pose further risks to pregnancy as they are associated with adverse birth outcomes such as miscarriage, stillbirth, PTD, and large for gestational age (LGA) babies among other further complications like gestational diabetes and pre-eclampsia.[15,16] Overweight/obesity also poses a risk to the metabolic health of the mother which can have long-lasting effects. These adverse metabolic effects associated with overweight/obesity can have a further impact on foetal, neonatal, and subsequent child development. [17,18]

With the development of new and improved drugs and the evolution of ART regimens, we must thoroughly investigate the effects each drug has on various health outcomes, including pregnancy and birth outcomes to ensure that the treatment the population is receiving is having the best improvement of the individuals' health while having the least possible adverse consequences. This highlights the necessity for this study as it will allow us to determine the effect of DTG a relatively new ARV on birth outcomes specifically in South Africa.

1.2 **Rationale**

South Africa as an upper middle-income country in sub-Saharan Africa is a unique disease setting in that there are very high levels of obesity particularly in women (67%) however it is also burdened with similar disease burdens as the LMIC's such as infectious diseases like HIV.[19,20] This makes it important to study the co-existence of these diseases in a population, so we can tailor interventions appropriate to the local context.

DTG use in pregnancy was previously not recommended as it was thought to have been unsafe during pregnancy as early studies had shown associations with DTG use and neural tube defects.[21] Several studies since have demonstrated that this is not the case. Some studies have shown that regimens that include DTG have similar birth outcomes to the previous efavirenz base regimen, other studies have shown that it has better birth outcomes than any other regimen and produces birth outcome results closest to WNLH.[22-24]

Obesity rates are increasing, this poses a risk to maternal and child health as maternal BMI has a significant association to pregnancy outcomes.[25,26] Maternal obesity is associated with risk to both maternal and fetal health with potential long-term consequences. Maternal obesity puts the mom at risk of gestational diabetes and preeclampsia.[27] Maternal obesity is also associated with an increased risk of stillbirth and congenital abnormalities in the child.

Children born to obese women are also at an increased risk of diabetes.[15] Obesity during pregnancy is also linked to large for gestational age babies/macrosomia babies and this can affect the development of the child. [18,28] Studies have shown that the effect of maternal BMI does seem to affect the association between maternal HIV status and adverse birth outcomes as when adjusting for age the association between HIV status and birth outcomes disappears.[4,29]

Preterm birth is a complicated outcome that is usually brought about by some sort of disruption in the process of pregnancy.[30-32] Preterm birth can be brought about via several complex pathways like infection, maternal or foetal stress, uterine overdistension, or maternal health conditions such as hypertension for example.[33] Preterm birth can influence the development of the infant, increase the risk long long-term health issues like asthma, and increase the risk of infant mortality.[33]

Low birthweight as an independent birth outcome is not particularly meaningful as an outcome alone. Low birthweight is usually caused by prematurity, growth restriction, or both.[34] SGA is also usually associated with a growth restriction.[33,35] Low birthweight/SGA are unfavourable outcomes as they have a strong association with infant mortality, they also inhibit growth and development in the child and are associated with non-communicable diseases later on in life.[36] LGA is often associated with higher maternal/BMI, large gestational weight gain, or gestational diabetes. LGA is an unfavourable birth outcome as it places the infant at an increased risk of infant mortality and a subsequent lifelong risk of obesity, type 2 diabetes and cardiovascular disease.[37] The underlying mechanisms that cause these adverse birth outcomes need to be further studied in order to be understood but some general factors associated with adverse birth outcomes include maternal health and socioeconomic status, as well as HIV/ART exposure.[32] Studies have shown that ART during pregnancy including DTG can be associated with an increased risk of pregnancy loss, preterm birth, low birthweight, and SGA.[37,38]

2. Aims and Objectives

2.1 **Aims**

To investigate the impact of maternal DTG use on adverse pregnancy and birth outcomes in South African women.

2.2 The specific objectives of this study are:

- To determine the association between DTG use and adverse pregnancy and birth outcomes (pregnancy loss, gestational age at delivery, birthweight, and size for gestational age), overall and by timing of DTG initiation (before or during pregnancy).
- To determine whether maternal BMI at enrolment modifies these associations between all outcomes.

3. Methodology

3.1 **Study Design**

This secondary analysis will involve analysing data collected from participants of the parent ORCHID study conducted at primary health care antenatal care (ANC) facilities in Cape Town. The ORCHID study was undertaken to assess the obesogenic impact of DTG use during pregnancy in WLHIV and their children. The ORCHID study was a prospective cohort study enrolling first trimester pregnant women at their first ANC) visit, with followup through to 24 months postpartum. This secondary analysis will utilize birth outcome data from this cohort to determine the association between maternal DTG use and adverse birth outcomes.

3.2 **Study Setting**

The ORCHID study was conducted at the Gugulethu and Mitchells Plain Community Health Centres (CHCs) Midwife-Obstetric Units (MOU). These primary healthcare facilities provide comprehensive HIV/ART integrated antenatal, obstetric, and infant care for low-risk pregnancies. Higher-risk

pregnancies were referred to secondary (Mowbray Maternity Hospital) or tertiary (Groote Schuur Hospital) level obstetric facilities.

3.3 **Study Population and Sampling**

Women in the parent study were recruited by a research counsellor who assessed the eligibility of potential participants. Convenience sampling was used as women seeking antenatal at the MOUs were enrolled in the study. Enrolment was distributed across three main exposure categories by HIV status and DTG use:

(i) WLHIV who initiated DTG-based ART during the current pregnancy (iDTG);

(ii) WLHIV initiated DTG-based ART before pregnancy and continued DTG through pregnancy (cDTG); and

(iii) Women without HIV infection (HIV-)

The All participants enrolled in the ORCHID study who have pregnancy or birth outcomes data will be included in this secondary analysis. Additional exclusions from the parent study cohort will include women who seroconvert during pregnancy. The sample size for the ORCHID study was determined using calculations to provide the data with 77-91% power to address their aims. A post-hoc analysis will be done to determine the statistical power of our data.

3.4 **Inclusion and exclusion criteria.**

ORCHID used the following eligibility criteria:

Inclusion criteria for all women:

- Confirmed pregnancy based on urine pregnancy test with viable gestation ≤ 18 weeks and 6 days by ultrasound.
- Age 16 years or older.

- No stated intention to relocate permanently outside of Cape Town through 2 years postpartum.
- For WLHIV: Confirmed HIV infection based on medical record review and/or HIV antibody testing during antenatal care.

For WLHIV initiating DTG in pregnancy (iDTG):

- Planned initiation of TLD on the day of assessment or within 1 week thereafter, including women switching from an efavirenz-based regimen.
- For WLHIV continuing DTG in pregnancy (cDTG): Confirmed use of tenofovir 300mg + lamivudine 300mg/emtricitabine 200mg + dolutegravir 50mg (TLD) on the day of assessment.
- For WNLH: Confirmed HIV status by HIV antibody testing during antenatal care HIV- women will be assessed with ongoing HIV testing at select study visits to detect incident HIV infection; any woman seroconverting during the follow-up period will be censored.

Exclusion criteria for all women:

- In the opinion of the investigator, unable to provide informed consent due to mental or physical condition.
- In the opinion of the investigator, unable to undertake BodPod assessment due to mental (eg, active psychosis or severe claustrophobia) or physical condition (eg, weight >250 kg).
- Currently being treated for any form of diabetes mellitus or hypertensive disorder based on participant self-report and medical record review.

3.5 **Data Collection**

The data being used in this secondary analysis will be based on data collected by the ORCHID study team. ORCHID data was collected using following data sources.

3.5.1 Questionnaires

ORCHID study participants completed standardised questionnaires that included maternal demographic, and medical history questionnaires at their first

ANC visit (Appendix1-3). Participants also have their height and weight measured at enrolment as part of the procedure to establish resting energy expenditure and body composition (Appendix 4). Participants with HIV also WLHIV also underwent blood tests that established their CD4 cell count and viral load at enrolment (Appendix 5).

3.5.2 Medical Record Review

The ORCHID study performed data abstraction collecting information from both the mother's maternity case record and the infant's road to health card in order to determine birth outcomes and maternal and infant health outcomes (Appendix 6 and 7)

3.5.3 Gestational Age Measurement

To determine gestational age (GA), all participants had an ultrasound administered by a research sonographer using standardised assessment protocols. This ultrasound at enrolment was used to determine GA throughout the study and was used to calculate GA at delivery. If an ultrasound was not practical or if GA seemed implausible and the last menstrual period (LMP) was known, LMP was used to determine GA at delivery (Appendix 8).

3.6 Variables of interest

3.6.1 Exposures of interest:

This study's primary exposures of interest are HIV status and ART status. HIV status in the parent study was determined/confirmed at the participant's initial study visit via antibody testing. with HIV tests administered to WNLH at subsequent study visits to detect any instances of seroconversion. All WLHIV were on a DTG-based regimen. ART status is divided into those who initiated DTG use during pregnancy and those already taking DTG before pregnancy (cDTG).

3.6.2 Outcomes of interest:

The outcomes of interest for this study are adverse pregnancy and birth outcomes, which include

- Pregnancy loss

  These will include ectopic pregnancies, terminations of pregnancy (TOP), miscarriage (loss <28 weeks since conception) or stillbirth (born not alive ≥28 weeks since conception based on classification used for international comparisons.[28] For this study, we calculated the GA at loss by adding the time difference between the date of their enrolment ultrasound and the date of loss to their GA at the first ultrasound.

- Gestational age (GA) at delivery:

  GA at delivery will be categorized as term (≥37) and preterm delivery (<37 weeks). GA at delivery was determined by calculating the time difference between the date of delivery and adding that to the GA of the ultrasound at enrolment.

- Birthweight

  Birthweight will be categorized as: high birthweight (≥ 4000g), normal birthweight (2500-3999g), and low birthweight (<2500g). Birthweight, measured as part of routine care at delivery, was abstracted from maternal case files and/or road to health cards. Low birthweight can be further categorized into low birthweight (1500-2500g) and very low birthweight (<1500g).

- Size for gestational age:
- Size for gestational age will be categorized as small (SGA: <10th percentile), appropriate (AGA: 10-90th percentile), and large (LGA: >90th percentile) for gestational age infants based on INTERGROWTH-21st Project Standards, which pooled data from healthy pregnancies across the globe to develop certain growth standards.

Table 1: Maternal and exposure variables to be included in our analysis

Variable	Scale	Categories
Maternal Characteristics		
Age (years)	Numerical - Continuous	Quartile Category Proportions
	Categorical – ordinal	<24 25- 29 >30
Gravidity	Numerical – Discrete	Quartile category proportions
	Categorical – Binary	Primigravida Multigravida
Parity	Numerical – Discrete	Quartile category proportions
	Categorical – Ordinal	0 1 ≥2
Previous pregnancy loss	Categorical – Binary	Yes No
Weight	Numerical – Continuous	Quartile category proportions
Height	Numerical - Continuous	Quartile category proportions
	Categorical – Ordinal	<155 156- 161 >162
BMI ($kg/m^{2)}$	Numerical – Continuous	Quartile category proportions
	Categorical – Ordinal	Underweight (<18) Healthy Weight (18-25) Overweight (25-30) Obese class 1 (30-35) Obese Class 2 (35-40) Obese Class 3 (>40)
Education	Categorical – Ordinal	Basic education High school Post-secondary
Socioeconomic status	Categorical – Ordinal	Lowest Medium Highest
Smoking	Categorical – Binary	Yes No
Drug Use	Categorical – Binary	Yes No
HIV		
HIV Status	Categorical – Binary	Living with HIV

		Not living with HIV
Viral Load (copies/L)	Categorical – Ordinal	< 50 50 – 1000 > 1000
CD4 cell count (cells/ml)	Categorical – Ordinal	⩽ 200 200-350 350-500 > 500
DTG initiation timing	Categorical – Binary	Before pregnancy During pregnancy

Table 2: Infant variables to be included in our analysis

Infant variables		
Outcome	Categorical – Binary	Live Birth Pregnancy Loss
Twin	Categorical – Binary	Yes No
Gender	Categorical – Binary	Male Female
GA at birth (weeks)	Numerical – Continuous	Quartile category proportions
	Categorical – Ordinal	Term (□37-42) Preterm (<37) Post-term (□42)
Preterm delivery	Categorical – Ordinal	Late (34-37) Moderately (32-34) Very (<32)
Birthweight (grams)	Numerical – Continuous	Quartile category proportions
	Categorical – Ordinal	High > 4000 Normal (2500-4000) Low (1500-2500) Very low (<1500)
Birth length	Numerical – Continuous	Quartile category proportions
Head circumference	Numerical – Continuous	Quartile category proportions
1 min APGAR score	Numerical – Discrete	Quartile category proportions
	Categorical – Ordinal	Normal (7-10) Moderately depressed (4-6) Severely depressed (0-3)

5 min APGAR score	Numerical - Discrete	Quartile Category Proportions
	Categorical – Ordinal	Normal (7-10) Moderately depressed (4-6) Severely depressed (0-3)
Size for Gestational Age	Categorical – Ordinal	LGA (>90th percentile) AGA (10-90th percentile) SGA (<10th percentile)

Maternal variables:

All maternal variables were determined by questionnaires at ORCHID participants' initial study visit and clinical data abstraction.

Infant variables:

All infant variables were measured by clinicians at delivery and abstracted from medical files. These medical files included the maternity case record and the road to health card.

3.7 Data Management and analysis plan

3.7.1 Data monitoring and storage

The ORCHID study utilized tablets and paper forms captured on a RedCap database. The RedCap database was maintained by a data management team at UCT with restricted access, that is password protected. Participant's confidentiality was maintained through the use of unique patient identifiers. Any confidential or identifiable information recorded on paper was stored in locked cabinets. Any information not stored on RedCap was stored on passwordprotected, encrypted files.

3.7.2 Data analysis

Analyses for this study will be performed using R (Version 4.3.3). Continuous variables will be described by either the mean and standard deviations (SD) for normally distributed variables, otherwise, the median and interquartile range (IQR) will be used to summarise variables that are not normally distributed. Categorical will be described by proportions.

For the analysis of this study, we will focus on three main exposure comparisons:

(i) WLHIV versus HIV-negative

(ii) Among WLHIV, those who initiated DTG during pregnancy versus those who were already on DTG before pregnancy

(iii) A comparison of the effect across BMI categories, Underweight, Healthy weight, Overweight, Obese Class 1, Obese Class 2, and Obese Class 3.

To address our aims, we will use descriptive statistics to determine the prevalence of each adverse birth outcome, overall, and by exposure groups. In order to estimate the associations between our exposure and adverse birth outcomes we will use generalized linear modelling. The confounders identified to be used in this model are maternal age, alcohol use, education tertile and BMI category. Models used to describe associations among HIV+ women only are: DTG initiation timing, CD4 cell count and viral load at enrolment.

4. Ethical considerations

4.1 **Informed Consent**

All informed consent procedures followed a protocol approved by the University of Cape Town HREC, Columbia University, and Ann & Robert H. Lurie Children's Hospital of Chicago/Northwestern University IRBs. Before enrolment of the ORCHID study, the informed consent process was delivered in the participants' home language (isiXhosa, Afrikaans, or English) by a trained

fieldworker following a standardized script. This script detailed the purpose of the study, all study visits and procedures for the woman and child, as well as the risks and benefits that they may encounter during the study. Participants gave informed consent for data to be used in subsequent studies. This study will be seeking approval from UCT HREC for this specific analysis.

4.2 **Privacy and Confidentiality**

The ORCHID study used unique patient identification numbers to anonymize participants so that their names did not appear on any study forms. Furthermore, the ORCHID staff attended training related to confidentiality and followed specific standard operating procedures to maintain confidentiality. All patient and study-related information was kept in locked cabinets and electronic records were kept in password-protected, encrypted files. The data to be used in this analysis will contain no personal identifies, each participant will be represented by their unique patient identifier series of numbers and letters. The results of this analysis will not report on any individual results but rather compare associations between groups.

4.3 **Risk & Benefits**

There were certain risks associated with participating in the ORCHID study related to various data collection procedures, like phlebotomy. However, for this study, there is no physical risk. There is a risk of loss of confidentiality of sensitive health information, however, through data management and storage and the use of unique patient identifiers this risk should be minimal.

Participants of the ORCHID study benefitted from frequent clinical and laboratory assessments allowing for earlier identification and intervention of any health condition. There are no direct benefits to the participants for the use of their data in this study. This study will help us gain insight into the association between DTG use and birth outcomes, which will be made available to healthcare providers.

This study will provide information on the effect of DTG on adverse birth outcomes in this population and give more insight of the effect of ART use during pregnancy. Results from this study will provide further detail on the risks and benefits of using DTG during pregnancy. This will allow clinicians to prescribe better interventions tailored to an individual's needs.

4.4. Timeline and Budget

Since this study is a secondary data analysis and forms part of an MPH degree it does not require any funding.

Table 2: Proposed timeline

Activity	Deadlines
DRC Protocol Submission	24 October 2024
HREC Protocol Submission	3 November 2024
Receive Data	4 November 2024
Data Cleaning and analysis	2-20 November 2024
Manuscript write up	20 November – 4 December 2024
Manuscript Review	4 December – 18 December 2024
Editing	18 December – 14 January 2024
Submission	31 January 2025
Dissemination	March 2025

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Research Appendices

ORCHID STUDY INFORMED CONSENT FORM

STUDY TITLE: **O**besogenic o**R**igins of maternal and **C**hild metabolic **H**ealth **I**nvolving **D**olutegravir (**ORCHID**)

INTRODUCTION

You are invited to take part in a research study conducted by the University of Cape Town (South Africa) together with Columbia University (USA) and Ann & Robert H. Lurie Children's Hospital of Chicago/Northwestern University (USA). This study is being conducted at the Gugulethu and Mitchell's Plain Midwife Obstetric Units (MOUs) and is sponsored by the United States National Institutes of Health (NIH).

This study is voluntary, which means that you do not have to take part if you do not wish to. Research studies only include people who chose to take part.

The purpose of this consent form is to give you information to help you decide if you want to take part in this study. Please take your time to make a decision. If you have any questions, you may ask me now or at any point while we read over this consent form together.

WHY HAVE I BEEN CHOSEN?

You are being asked to take part in this study because you are less than or 16 weeks pregnant, at least 16 years of age, and have NOT been diagnosed with a sugar disease (diabetes) or high blood pressure disease (hypertension). This study includes women who are living with HIV, and those who do not have HIV.

WHY IS THIS STUDY BEING DONE?

Mothers and their children who have more fat in their bodies may have more health problems. The aim of the study is to learn more about the changes in body fat, food intake and nutrient (substances we get from food that are important for healthy life and growth) use during pregnancy and after delivery in women living with HIV getting antiretroviral treatment (ART) and women who are not living with HIV. This study is important, as learning about these changes will help the researchers to develop ways of helping women that may be at risk of gaining too much weight during pregnancy. The study will also help us understand how to lower their risk (and their baby's risk) of developing life-long diseases of blood sugar, blood pressure and the heart.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

We plan to enrol 1900 pregnant women, and, after delivery, their babies will also take part in the study.

HOW LONG WILL I BE IN THE STUDY?

You will be in the study during pregnancy and then both you and your baby will be followed for 2 years after the baby is born.

WHAT DO I HAVE TO DO IF I AGREE TO TAKE PART?

If you agree to take part, you will come in for up to 10 study visits, some of which may be split into two, including today's enrolment visit. After today, visits will take place about every 2 months until you deliver, within two weeks after delivering your baby and again when your baby is about 6 weeks, 3, 6, 12, 18 and 24 months old. All these study visits are separate from the usual clinic visits that you will have for your pregnancy and/or HIV care. If you would like, study visits can be timed so that they take place on the same days that you come in for your usual pregnancy and/or HIV care.
There are 4 visits that will take more than three hours and 6 that will only take one and half hours.

STUDY PROCEDURES

DURING PREGNANCY:

At all visits during pregnancy, women will be asked to do the following:

Anthropometry
We will measure your weight, height, size of your middle-upper-arm, and amount of fat under your skin (with callipers - see pictures) in the upper-arm muscle, shoulder muscle and hip bone muscle as well as blood pressure.

Questionnaires

We will ask you questions about your background, family composition, pregnancy, care you are receiving at the clinic, HIV history, past health, substance use (alcohol, smoking and drugs), food (appetite, intake, access) COVID-19, exercise, feelings about your body, sleep quality, experiences of violence, adverse childhood experiences, people you rely on, medicines/remedies you are taking and about your mood.

VISIT 1: Enrolment (A1) and VISIT 3 (A3): third trimester of pregnancy

You will be asked to not eat anything (only drink water) after 10pm the night before you come for your study visit.

Ultrasound

This test will measure the size and growth of your baby. While lying on your back, the person operating the ultrasound will put a colourless gel and scan your stomach to take measurements and images of your baby. This test will also be done to look at the amount of fat in your liver. Results from the ultrasound conducted at Visit 1 will be shared with the MOU nurses/doctors and included in your routine medical record. Results from the ultrasound conducted at Visit 3 will only be shared if there is something abnormal that the MOU nurses/doctors should be aware of for further management.

Specimen Collection

Blood sugar testing

We will do a test to measure how your body controls sugar levels in your blood in response to taking a sugary drink. The test takes 2 hours to complete. A small plastic tube will be placed into a vein in your arm and will remain in your arm for the 2 hours. We will draw blood from your arm before and after you drink a glass of sugary water. Small amounts of blood will be drawn before you drink the water and again 30, 60 and 120 minutes after you drink it.

Additional blood collection

While doing the blood sugar test, we will also draw blood for testing the amount of fat in your blood, HIV viral load and CD4 count (if you are living with HIV), markers of your immune system (part of your body that fight infections), markers of how your body uses energy, and storage for future studies.

In total, the amount of blood that will be drawn from you at these visits is 65 mL (about 4 tablespoons).

Urine collection

You will be asked to give a urine sample (10ml - about 1 tablespoon) for testing the presence of glucose and proteins, and for storage for future studies.

Nutrient use measure

This test will measure the amount of nutrients that you are using. We will ask you to rest quietly for 30 minutes. Then we will take measures of the air that you breathe in and out while resting on a bed for 30 minutes. The machine that we use to do this test is called a Q-NRG. In order to perform this test, a see-through canopy attached to a tube will be placed over your face (see picture). While wearing the canopy, you will be able to breathe normally, and the canopy will not affect your breathing or the quality of the air that you breathe in.

Body composition

We will use a special machine to measure your body composition (how much fat is in your body). The machine that we use to do this test is called a Bod Pod. This Bod Pod has a scale and a see-through chamber (see picture). We will give you special clothing (sports bra, shorts and a cap) to wear for this test. We will ask you to remove all jewellery and eyeglasses. You will be required to sit inside the Bod Pod for 3-7 minutes. We will be able to see your face through the window to make sure you are okay.

VISIT 2 (A2): second trimester of pregnancy

Specimen collection

We will draw blood for HIV testing (if you are not living with HIV) or HIV viral load (if you are living with HIV), markers of your immune system (part of your body that fight infections) and markers of how your body uses energy, and storage for future studies. In total, the amount of blood that will be drawn from you at this visit is 25 mL (about 1 and a half tablespoons).

You will be asked to give a urine sample (10ml - about 1 tablespoon) for testing the presence of glucose and proteins, and for storage for future studies.

AT DELIVERY

At delivery, usually the placenta ('afterbirth') and its cord are thrown away because your baby does not need them anymore. We will take about 20 mL of blood (about 1 tablespoon) from the placenta cord and pieces of the placenta itself. These can help us understand the health of babies while they are still in the womb before they are born. Taking these specimens does not hurt you or your baby in any way.

AFTER DELIVERY
At all visits after delivery, women and their babies will be asked to do the following:

Maternal Anthropometry
We will measure your weight, size of your middle-upper-arm, hip and waist, and amount of fat under your skin in the upper-arm muscle, shoulder muscle and hip bone muscle as well as blood pressure.

Infant Anthropometry
We will measure your baby's weight, length, head, mid-upper arm and waist (*Visit 10 only*) sizes, as well as the amount of fat under baby's skin (with callipers – see pictures) in the upper-arm muscle, shoulder muscle and hip bone muscle.

Questionnaires
We will ask you questions about care you are receiving at the clinic, substance use (alcohol, smoking and drugs), food (appetite, intake, access), COVID-19, exercise, feelings about your body, sleep quality, experiences of violence, people you rely on, menstruation, medicines/remedies you are taking and about your mood. We will also ask you questions about your baby including experience at delivery (*Visit 4 only*), baby's health, breastfeeding, childcare, medicines/remedies and any immunisations and HIV testing your baby may have gotten from the clinic.

VISIT 4 (P1): 2 weeks postnatal, VISIT 5 (P2): 6 weeks postnatal, VISIT 6 (P3): 3 months postnatal, VISIT 7 (P4): 6 months postnatal and VISIT 9 (P6): 18 months postnatal

MOTHER
Specimen collection (except for Visit 4)
We will draw blood for HIV testing (if you are not living with HIV) or HIV viral load and CD4 count (*Visit 7 only*) (if you are living with HIV), markers of your immune system (part of your body that fight infections), markers of how your body uses energy, and storage for future studies. In total, the amount of blood drawn that will be drawn from you at each of these visits is 25 mL (about 1 and a half tablespoons).

You will be asked to give a urine sample (10ml - about 1 tablespoon) for testing the presence of glucose and proteins, and for storage for future studies.

You will be asked to express some breastmilk (*Visit 5 and 6 only*, 30ml - about 2 tablespoons) for testing to understand the nutrients your baby is receiving, and for storage for future studies.

CHILD
Blood collection (Visit 5 only)
We will draw blood for testing markers of your baby's immune system (part of the body that fight infections) and metabolism (process of producing energy), and storage for future studies. A maximum of 8 mL (1 and a half teaspoons) of blood will be drawn.

Body composition
This test will measure your baby's body composition (how much fat is in your baby's body). The machine that we use to do this test is called a Pea Pod. This Pea Pod has a scale and a see-through tray (see picture). To do this test, it is important that you remove all the clothing from your baby. Your baby will lie down on the Pea Pod tray and will be required to lie still in tray for 3-4 minutes. We will be able to see your baby's face through the see-through tray to make sure they are okay.

VISIT 8 (P5): 12 months postnatal and VISIT 10 (P7): 24 months postnatal
Ultrasound (Visit 10 only)
This test will examine the amount of fat in your liver.

Respiratory exchange measure
This test will measure the amount of nutrients that you are using as described above.

Specimen Collection

Blood sugar testing
We will do a test to measure how your body controls sugar levels in your blood in response to taking a sugary drink as described above.

Additional blood collection
While doing the blood sugar test, we will also draw blood for testing the amount of fat in your blood, HIV viral load and CD4 count (if you are living with HIV), markers of your immune system (part of your body that fight infections), markers of how your body uses energy, and storage for future studies.

In total, the amount of blood drawn that will be drawn from you at these visits is 65 mL (about 4 tablespoons).

Urine collection
You will be asked to give a urine sample (10ml – about 1 tablespoon) for testing the presence of glucose and proteins, and for storage for future studies.

Body composition
We will use the Bod Pod to measure your body composition (how much fat is in your body) as described above.

CHILD
Blood Collection
Blood sugar test
We will do a test to measure how your baby's body controls sugar levels in the blood. We will ask you to withhold the morning feed for your child for 4 hours on the morning of the test. As soon as you arrive, blood will be drawn from the arm of your baby and then you can feed your baby.

Additional blood collection
While doing sugar test, we will also draw blood for testing the amount of fat in your baby's blood, markers of your baby's immune system (part of their body that fight infections), metabolism (process of making energy), and storage for future studies.

For this part, a maximum of 15 mL of blood will be drawn (about 1 tablespoon).

Body composition
This test will measure your baby's body composition (how much fat is in baby's body) as described above. For visit 8, we will use the Pea Pod, and for visit 10, we will use the Bod Pod machine since your child will be too big for the Pea Pod.

Review of medical records
In addition, to your study visits, researchers involved in this study will access clinical information in your routine medical records, and the records of your baby. This information will include clinical history, past medical diagnoses, medications you are taking, laboratory results, and information about your baby's birth and health. All data that we review will be kept confidential.
We are asking permission to review this information in two ways.

1. First, we would like to look at the paper records held at the clinics or hospitals you attend.
2. Second, the Department of Health (DOH) stores all of this information centrally at the Provincial Health Data Centre. We will use your and your baby's provincial folder number (or name and date of birth) to ask for this information directly from the DOH or access this information directly from the Provincial health databases.

All data that we review will be kept confidential. Your name and your baby's name will not be recorded with these records.

Follow-up of missed visits
You will be asked to provide contact information so that we may get in touch with you during the study. Study staff will talk with you about the best way to contact you. In the event that you miss one of the scheduled study visits, a member of the study staff will contact you in order to find another day and time to complete your visit. If you repeatedly miss study visits or the staff is unable to contact you using the information that you provide, it may be necessary to visit you at home in order to reschedule the missed study visit.

CAN I STOP BEING IN THE STUDY?

Yes. You do not have to be in this study if you do not want to and are not required to give a reason. If you agree to be in the study, but later change your mind, you can drop out at any time without giving a reason and without prejudice. If you decide to drop out from the study after doing some of the procedures, we will discuss what will happen to any information or samples that you have provided. If the incomplete samples and information can usefully contribute to the study, we will ask your permission to store them and use them in our analysis. Alternatively, on your request all your information and samples will be destroyed.

You will be notified of all significant new findings during the course of the study that may impact your willingness to continue.

WHAT ARE THE POTENTIAL RISKS?

The potential risks to participants in the study include:

- ***Risk of discomfort:*** You may feel uncomfortable about some of the sensitive or personal questions you are asked. You may refuse to answer any question that you do not want to answer.
- ***Risk from collection specimens:***
  - *Risk from taking blood:* There is a risk of discomfort including pain, bruising, swelling and local infection. An experienced study nurse will perform blood collection with appropriate materials including alcohol swabs to minimise the risk of infection.
  - *Risk from taking blood while you are fasting (have not eaten since 10 PM the night before):* At those visits where you will be doing a blood sugar test, there is a slight risk that you may experience physical discomfort including hunger, dizziness and nausea. Also, after drinking a sugary drink, you may have nausea. Your child may also experience hunger and irritability due to restricted feeding on the morning of the blood sugar test. The study nurse will monitor these signs and will make sure you are comfortable with proceeding until the end of the test. At each visit when this test is complete, we will provide you with food so you can be re-energised before leaving the study site.
- ***Risk from measuring body composition:*** Sitting in the Bod Pod for 3-7 minutes may cause mild anxiety. Placing your baby in the Pea Pod for 3-4 minutes may also cause anxiety or fear. You will be present during this procedure and will be able to tell us to stop the procedure if you are worried about the level of anxiety or fear for your child. Both machines have a see-through window that allows the staff to see you or your baby at all times while inside.
- ***Risk from measuring nutrient use:*** Wearing a canopy for 30 min while resting may cause discomfort or anxiety. The canopy hood is see-through. If you experience anxiety or discomfort, it is easy and quick to take off, like a piece of clothing.
- ***Risk of contracting COVID-19:*** You may be exposed to COVID-19 while taking part in the study activities. All people attending Gugulethu CHC including patients and staff members are screened for COVID-19 symptoms prior to entering the clinic and are not allowed in if they have been exposed to a patient with Coronavirus or have a fever.
  - *Staff safety:* All staff always have their masks on and they frequently sanitise with alcohol-based hand disinfectant. Staff members have also been trained on how to disinfect surfaces (with bleach solution) including chairs, tables, phones, keyboards, and tablets before and after seeing each participant. There is a dedicated cleaner who also ensures that surfaces are cleaned frequently.
  - *Participant safety:* When you arrive in our research place, we will provide you with a disposable surgical mask if you are not wearing any mask and a hand sanitizer to disinfect your hands. Throughout the visit, you will use readily available hand sanitizer before and after entering the study room (and before/after eating/using toilets). Social distancing will be adhered to between yourself and the staff members. For follow-up visits, you will be contacted by study staff a day before your visit to check whether you have any symptoms of Covid-19, if so, you will be advised not to come for a study visit but to visit your nearest clinic for testing.
- ***Risk of loss of confidentiality:*** There is a risk of loss of confidentiality of information provided during the study, including your HIV status through conduct of interviews and by nature of taking part in the study. Other than signing this informed consent which will be locked away in a safe cabinet with restricted access only to study staff who are trained about privacy of participant information, no study forms will include your name, including forms that may reflect HIV status.

WHAT ARE THE POTENTIAL BENEFITS?

Overall, the information gained in this study may help to improve healthcare services for mothers and their babies in Cape Town, the Western Cape Province, and across South Africa.

WHAT OTHER CHOICES DO I HAVE IF I DO NOT PARTICIPATE IN THIS STUDY?

You are free to choose not to take part in the study. If you decide not to take part, it will in no way impact the care that you receive at the clinic and no one will be angry/upset at you.

WILL INFORMATION ABOUT ME BE KEPT PRIVATE?

If you agree to take part, all information collected during the study will be kept strictly private. Your name will not be put on any of your questionnaires or blood samples. Instead, you will be given a participant study number. The list linking your participant study number to any of your name information will be kept separate. The list will be destroyed within 12 months of completion of the study.

All information we collect is kept on a computer that is protected by password and only the researchers directly involved in this study will be able to see this. In addition, your name will not appear in any publication.

During the course of the study, you will receive calls from study staff members. The calls are made to remind you of upcoming appointments or to reschedule appointments. Your contact details will be kept separate from all other information provided by you.

You should also know that the University of Cape Town Human Research Ethics Committee and/or Columbia, Northwestern University's Institutional Review Boards and the Office of Research Compliance may inspect study records as a way of monitoring the study, but these reviews will only focus on the researchers and not on your responses or involvement. These people help to review research studies to protect the rights and welfare of research participants like you.

Please know that even with these procedures in place, if the study staff learns that you are at risk of hurting yourself or someone else or learn of possible child abuse and/or neglect, study staff will tell the proper authorities.

WHAT ARE THE COSTS OF TAKING PART IN THIS STUDY?

There is no cost to you for taking part in this study.

WILL I BE PAID FOR TAKING PART IN THIS STUDY?

At the end of each visit, you will be given a R200 (for 6 visits that take less than 3 hours to complete) or R300 (for 4 visits that take more than 3 hours to complete) grocery voucher plus R50 for transport, and food and drink while you are at the visit.

PLACENTA SPECIMEN:

As part of being in this study, we would like to take pieces from your baby's placenta ('afterbirth'). Often the placenta is thrown away after delivery because your baby does not need it anymore. This can help us understand the health of babies while they are still in the womb before they are born. Taking this specimen does not hurt you or your baby in any way.

Please initial below to indicate whether or not you give permission for us to take the placenta after your baby is born. You may still remain in the study, no matter which you choose.

_____ (initial) I agree to have pieces of my placenta taken as part of this research.

_____ (initial) I do **NOT** agree to have pieces of my placenta taken as part of this research.

STORAGE OF LEFT-OVER SPECIMENS FOR FUTURE USE:

If you agree, some of the remaining blood drawn from you and placenta cord, pieces of the placenta (if we have your permission to collect this), urine and breastmilk may be used for future health research. At this time, we cannot provide details of when this testing may be conducted, or exactly what tests we would like to do. However, additional testing will not be done using these stored samples without the approval of the appropriate ethics committees involved in this research.

If you agree to let us keep your samples for future research, they may be kept in a locked freezer at University of Cape Town laboratory for up to 10 years after the end of the study. Your name is never included with these samples, only the participant study number we give you (as with the rest of the information we collect for this study).

Please initial below to indicate whether or not you give permission for these samples to be used for future health research. You may still remain in the study, no matter which you choose.

_____ (initial) I agree to have the remaining blood drawn from me and placenta cord, pieces of the placenta, urine and breastmilk stored for future research.

_____ (initial) I do **NOT** agree to have the remaining blood drawn from me and placenta cord, pieces of the placenta, urine and breastmilk stored for future research.

GENETIC (DNA) TESTING:

If you agree, the extra samples could also be used for research that looks at your genes. Genes are passed to children from their birth parents. They affect how people look and how their bodies work. Differences in people's genes can help explain why some people get a disease while others do not. Your samples would only be used to look at genes related to HIV and how the body responds to ARVs (if applicable), pregnancy, body fat and the immune system.

Any genetic testing done will be reviewed and approved by the appropriate ethics committees involved in this research. The role of an ethics committee is to review the research plan and protect the rights and well-being of the people whose samples will be used. The research done with extra samples is not expected to give any information relevant to your health. Therefore, the results will not be given to the study staff or to you. The results will also not be placed in your study records.

Please initial below to indicate whether or not you give permission for genetic testing to be done in your samples for future research. You may still remain in the study, no matter which you choose.

_____ (initial) I agree to have my blood tested for genetics for future research.

_____ (initial) I do **NOT** agree to have my blood tested for genetics for future research.

FUTURE USE OF INFORMATION:

To learn new things, sometimes researchers share information they get from people enrolled in studies. The information that you give us during this study is private and will be kept in a safe and secure place. In the future there might be a chance to combine the information you give us with information from other studies. When researchers combine this information, they can learn even more about health problems.

If you agree to take part in this study, your health information will be kept by researchers so that it may be used in the future. The information that we keep will not have anything in it that can identify you like names or birthdays. It will be combined with information we collect from other people in the study. Any researcher who wants to see the information that was collected must request access to the information and be approved. If a researcher is approved, they may be able to see and use your information, along with that from many other people. They will not be able to tell that it is your information. They will only know that it is information from someone enrolled in this study.

We do not expect any direct benefits for you from any future use of your information. You may stop taking part in this study and withdraw permission for your information to be used in the future. If you choose, you may ask to have the information you give us destroyed. However, it may not be possible to withdraw or delete materials or data once they have been shared with other researchers.

Please initial below to indicate whether or not you give permission for your information to be used for future health research. You may still remain in the study, no matter which you choose.

_____ (initial) I agree to have my information used for future research.

_____ (initial) I do **NOT** agree to have my information used for future research.

USE OF LOCATOR INFORMATION FOR STUDYING NEARBY SHOPS:

As part of being in this study, we would like to use the address information that you will provide to visit you at your home so that we can take the location using the GPS device. The reason we need to locate your home with this device is so that we can investigate the type of foods that are offered by the shops that are closest to your home.

Please initial below to indicate whether or not you give permission for us to use your address information to study the nearby shops. You may still remain in the study, no matter which you choose.

_____ (initial) I agree to have my home address information used for visiting me at home to take the location using the GPS device as part of this research.

_____ (initial) I do **NOT** agree to have my home address information used for visiting me at home to take the location using the GPS device as part of this research.

WHAT IF SOMETHING GOES WRONG?

The University of Cape Town (UCT) has insurance cover for the event that research-related injury or harm results from you taking part in this research. The insurer will pay all reasonable medical expenses in accordance with the South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI) in the event of an injury or side effect resulting directly from your participation in this study. You will not be required to prove fault on the part of the University.

The University **will not be liable** for any loss, injuries and/or harm that you may sustain where the loss is caused by:

- The use of unauthorised medicine or substances during the study;
- Any injury that results from you not following the protocol requirements or the instructions that the study doctor may give you;
- Any injury that arises from inadequate action or lack of action to deal adequately with a side effect or reaction to the intervention; and/or,
- An injury that results from negligence on your part.

By agreeing to participate in this study, you do not give up your right to claim compensation for injury where you can prove negligence, in separate litigation. In particular, your right to pursue such a claim in a South African court in terms of South African law must be ensured. Note, however, that you will usually be requested to accept that payment made by the University under the SA GCP guideline 4.11 is in full settlement of the claim relating to the medical expenses.

An injury is considered study-related if, and to the extent that, it is caused by study activities. You must notify the study staff immediately of any side effects and/or injuries during the study, whether they are research-related or other related complications. UCT reserves the right not to provide compensation if, and to the extent that, your injury came about because you chose not to follow the instructions that you were given while you were taking part in the study. Your right in law to claim compensation for injury where you prove negligence is not affected. Copies of these guidelines are available on request.

WHO CAN ANSWER MY QUESTIONS ABOUT THE STUDY?

Take as long as you would like before you decide. We will answer any questions that you have now about this study, including if anything was unclear or if you need further information.

Do you have any questions?

WHO DO I CONTACT FOR ADDITIONAL INFORMATION?

If you have any questions later or any problems while taking part in this research study, you should contact:

Professor Landon Myer	Professor Elaine Abrams	Associate Professor Jennifer Jao
University of Cape Town	Columbia University	Northwestern University/ Ann & Robert H. Lurie Children's Hospital of Chicago
Tel: +27-21-406-6661 Email: landon.myer@uct.ac.za	Tel: +1-212-342-1824 Email: eja1@mail.cumc.columbia.edu	Tel: +1-312-227-4080 Email: jennifer.jao@northwestern.edu

If you have any complaints about participation in this study, or would like more information about the rules for research studies, or the rights and welfare of people who take part in this study, you may contact the following member of the University of Cape Town's, Columbia University's and Ann & Robert H. Lurie Children's Hospital of Chicago/Northwestern University's Ethics Committees:

Professor Marc Blockman	Institutional Review Board	Institutional Review Board
University of Cape Town	Columbia University	Northwestern University/ Ann & Robert H. Lurie Children's Hospital of Chicago
Tel: +27-21-406-6338	Tel: +1-212- 05-5883	Tel: +1-312-503-7110

DOCUMENTATION OF CONSENT

For participant to complete (please tick):

☐ I have read the information in this document (or it has been read to me). I have been offered a copy of this consent form. I was encouraged and given time to ask questions and all my questions about the study have been answered. I freely consent to be in this research study and know that I may withdraw at any time. My being in the study is voluntary. I understand that whether or not I participate will not affect my health care services received today, or at any time in the future.

☐ I agree that the study team can access my medical records at this hospital or another hospital if necessary for this study. My information will be kept confidential.

☐ I agree to provide contact information for myself which will be kept confidential by the study team.

☐ I agree to be called on my telephone during the course of the study.

☐ I agree to be contacted for future follow-up studies after completion of the study.

Participant Name & Surname (Please print) Participant Signature Date

For the researcher to complete:

I have discussed the proposed research with this participant and provided ample time for questions and answered all questions. In my opinion, this participant understands the risks, benefits and alternatives (including non-participation) and is capable of freely consenting to participate in this research.

Interviewer Name & Surname (Please print) Interviewer Signature Date

If this consent form is read to the participant because the participant is unable to read the form or if the participant must use a thumbprint to sign his/her name, an impartial witness not affiliated with the research or investigator must be present for the consent and sign the following statement:

I confirm that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the participant. The participant freely consented to be in the research study.

Witness Name & Surname (Please print) Witness Signature Date

Thank you! 

PWID: _ _ _ _ _ _ - _

MATERNAL DEMOGRAPHIC INFORMATION

This CRF applies to ALL enrolled ORCHID participants

Complete during Enrolment (≤14 weeks) Study Visit

Visit Date								
D	D	M	M	M	Y	Y	Y	Y

Visit Code	
A	**1a**

Sizokubuza imibuzo malunga nawe ***We are going to ask you general questions about yourself***	
1. Uzelwe Nini? *What is your date of birth?*	_____ /_____ /_____ DD MMM YYYY
2. Ulohluphi uhlanga *What population group do you belong to?*	☐ UmAfrika *African* ☐ Indiya *Indian* ☐ Umntu webala *Coloured* ☐ Umlungu *White* ☐ Olunye *Other* Cacisa *Specify:* _____
3. Uthetha oluphi ulwimi ekhaya? *What language do you speak at home?*	☐ isiXhosa ☐ isiZulu ☐ isiBhulu *Afrikaans* ☐ isiNgesi *English* ☐ Olunye *Other* Cacisa *Specify:* _____
4. Ingaba unexesha elingakanani uhlala apha esixekweni/edolophini okanye kwilali okuyo ngoku? (ukuba ingaphantsi konyaka, cacisa 0 iminyaka) *How long have you been living continuously in the city /town or village you are currently living in? (If less than one year, record "0" years)*	_____ Iminyaka *years* _____ Inyanga *months*
5. Ingaba ini isixeko, idolophi okanye ilali ohlala kuyo? *What is the name of current city, town or village of residence?*	_____
6. Ingaba uhlala apha oko okanye ungumhambeli? *Do you always live here or are you a visitor?*	☐ Oko *Always* ☐ Umtyeleli *Visitor*

Initials of interviewer: ___

7. Phambi kokuba ubelapha ubuhlala edolophini, esixekweni okanye ezilalini? *Just before you moved here, did you live in a city, in a town, or in a rural area?*	☐ iDolophu *City* ☐ iLokishi *Township* ☐ iLali *Rural area* ☐ Zange wathutha *Not moved* → **Gqithela ku Q9** ***SKIP to Q9***
8. Phambi kokuba uzohlala apha, leliphi (iphondo/ummandla/ilizwe) obuhlala kulo? *Before you moved here, which (Province/Region/State) did you live in?*	☐ Ntshona Koloni *Western Cape* ☐ Mpuma Koloni *Eastern Cape* ☐ Freyistata *Free State* ☐ Rhawutini *Gauteng* ☐ KwaZulu-Natal ☐ Limpopo ☐ Mpumalanga ☐ Mntla Koloni *Northern Cape* ☐ Mantla Ntshona *North West* ☐ Elinye ilizwe *Other country* Cacisa *Specify:* _____
9. Leliphi elona banga liphezulu oliphumeleleyo? *What is the highest level of schooling/education that you have completed?*	☐ Inqanaba: _____ *Grade* ☐ Imfundo ephezulu oyigqibileyo: cacisa ☐ Certificate *Completed Postsecondary, specify* ☐ Diploma ☐ Degree ☐ Akukho nenye *None*
10. Ukhulelwe kangaphi (kuquka noku kukhulelwa kwangoku)? *How many times have you been pregnant (including current pregnancy)?*	Inani lokukhulelwa: _____ *Number of pregnancies*
11. Bangaphi abantwana obazeleyo? *How many children have you given birth to?*	Inani labantwana: ☐ _____ ☐ Abekho *Number of children* *None* → **Ukuba awunabo abantwana, Gqithela ku Q13** ***If NONE, SKIP to Q13***
12. Bangaphi kwaba bantwana abaphilayo? *How many of these children are living?*	Inani labantwana: ☐ _____ ☐ Abekho *Number of children* *None*
13. Uyathandana ngoku? *Are you currently in a relationship?*	☐ Hayi *No* → **Phelisa** ***END*** ☐ Ewe *Yes*

Initials of interviewer: _____

14. Ungaluchaza njani uthando lwakho? *How would you describe your current relationship?*	☐ Utshatile *Married* ☐ Anditshatanga, ndiya hlalisana *Not married, living together* ☐ Nditshatile, asihlali kunye *Married, not living together* ☐ Anditshatanga, asihlali kunye *Not married, not living together* ☐ Enye *Other* Cacisa *Specify:* _____
15. Lixeshe ellingakanani unobudlelwana nalomntu? *How long have you been in a relationship with this person?*	Ixesha: Iminyaka *years* _____ *Duration in:* Inyanga *months*_____

NOTES:
Please write notes and/or any other comments here:

_____

_____

_____

_____

Signed Interviewer completing CRF: _____ Date: _____ / _____ / _____
DD MMM YYYY

Signed QC Officer: _____ Date: _____ / _____ / _____
DD MMM YYYY

Signed Study Coordinator: _____ Date: _____ / _____ / _____
DD MMM YYYY

PWID: _ _ _ _ _ _ - _ _

MATERNAL PRE-PREGNANCY AND FAMILY MEDICAL HISTORY

This CRF applies to ALL enrolled ORCHID Participants
Complete during Enrolment (≤14 weeks) Study Visit

Visit Date								
D	D	M	M	M	Y	Y	Y	Y

Visit Code	
A	1

PRE-PREGNANCY MEDICAL HISTORY

Kwezinyanga zilishumi elinesibini zidlulileyo, ingaba ubukhe waxelelwa ngugqirha okanye ngunesi ukuba unayo nayiphi na kwenye yezimeko zezigulo zilandelayo?
Before this pregnancy, *have you been told by a* ***doctor or a nurse*** *that you have ANY of the following medical conditions?*

Igama lemeko yesigulo ***Name of medical condition***	**Yafunyaniswa nini?** ***When were you diagnosed?***
1. Ntsholongwane kagawulayo *HIV* ☐ Ewe *Yes* ☐ Hayi *No* → **Ukuba HAYI Gqithela ku Q2** ***If NO Skip to Q2***	____ / ____ / _____ DD MMM YYYY
2. Isifo sephepha "TB" *Tuberculosis "TB"* ☐ Ewe *Yes* ☐ Hayi *No* → **Ukuba HAYI Gqithela ku Q3** ***If NO Skip to Q3***	____ / ____ / _____ DD MMM YYYY
3. Isifo seswekile Diabetes *"Sugar diabetes" Type 1 or Type 2* ☐ Ewe *Yes* ☐ Hayi *No* → **Ukuba HAYI Gqithela ku Q4** ***If NO Skip to Q4***	____ / ____ / _____ DD MMM YYYY
4. "Hi-Hi" *Hypertension "High Blood Pressure"* ☐ Ewe *Yes* ☐ Hayi *No* → **Ukuba HAYI Gqithela ku Q5** ***If NO Skip to Q5***	____ / ____ / _____ DD MMM YYYY
5. Isifo sentliziyo *Heart Diseases* ☐ Ewe *Yes* ☐ Hayi *No* → **Ukuba HAYI Gqithela ku Q6** ***If NO Skip to Q6***	____ / ____ / _____ DD MMM YYYY
6. *High cholesterol* ☐ Ewe *Yes* ☐ Hayi *No* → **Ukuba HAYI Gqithela ku Q7** ***If NO Skip to Q7***	____ / ____ / _____ DD MMM YYYY

7. Isifuba *Asthma* ☐ Ewe *Yes* ☐ Hayi *No* → **Ukuba HAYI Gqithela ku Q8** ***If NO Skip to Q8***	_____ / _____ / _____ DD MMM YYYY
8. Isifo sokuwa *Epilepsy* ☐ Ewe *Yes* ☐ Hayi *No* → **Ukuba HAYI Gqithela ku Q9** ***If NO Skip to Q9***	_____ / _____ / _____ DD MMM YYYY
9. Isifo samadlala *Thyroid disease* ☐ Ewe *Yes* ☐ Hayi *No* → **Ukuba HAYI Gqithela ku Q10** ***If NO Skip to Q10***	_____ / _____ / _____ DD MMM YYYY
10. Enye ingulo okanye imeko yengqondo nje "ngokucinga kakhulu", uxinizelelo, ukothuka, ixhala njalo-njalo. *Any psychological or mental conditions such as "thinking too much", depression, panic attacks, anxiety attacks etc."* **NB: Efunyaniswe ngu gqirha okanye ngunesi** ***Diagnosed by a doctor or nurse*** ☐ Ewe *Yes* ☐ Hayi *No* → **Ukuba HAYI Gqithela ku Q11** ***If NO Skip to Q11***	_____ / _____ / _____ DD MMM YYYY
11. Ezinye naziphi na imeko zesigulo *Any other medical conditions* ☐ Ewe *Yes* ☐ Hayi *No* → **Ukuba HAYI Gqithela ku Q12** ***If NO Skip to Q12***	_____ / _____ / _____ DD MMM YYYY

PREVIOUS PREGNANCY HISTORY

12. Kumatyeli okukhulelwa kwakho angaphambili, ukhe <u>wanezingxaki</u> zilandelayo? (khetha ZONKE ezifanelekileyo) *During any of your previous pregnancies, have any of the following <u>complications</u> occurred? (tick ALL that apply)*	☐ Unxinizelelo lwegazi *High blood pressure (or hypertension)* ☐ Xinizelelo lwegazi olwenzeka xa ukhulelwe lubengaphezu kweqondo elifanelekileyo kubekho neproteyini *Pre-eclampsia* ☐ Isigulo esenzeka xa ukhulelwe esinokwenza ukuba uxhuzule *Eclampsia* ☐ Ukufunyaniswa kweswekile ngexesha usakhulelweyo *Diabetes mellitus* ☐ Ukopha kakhulu ngexesha usakhulelweyo *Heavy bleeding during pregnancy* ☐ Ukopha kakhulu emva kokubeleka *Heavy bleeding during or following delivery* ☐ Ukuphazamiseka kokubeleka (umntwana angezi ngendlela efanelekileyo) *Obstructed labor (baby could not come out through the birth canal)* ☐ Ukungahambi kwegazi ngenxa yehlwili elisemithanjeni *Thromboembolism (e.g. stroke)* ☐ Akukho nanye *None* ☐ Other, Cacisa:_____ *Specify*

Initials of interviewer: ____

FAMILY MEDICAL HISTORY

Kwezinyanga zilishumi elinesibini zidlulileyo, ingaba ubukhe waxelelwa ngugqirha okanye ngunesi ukuba unayo nayiphi na kwenye yezimeko zezigulo zilandelayo?
Do you have a close blood relative (grandparent, parent, sibling or child, etc) who has ever been told by a Dr/nurse that they have any of the following conditions?

Igama lemeko yesigulo ***Name of medical condition***	***If yes, how are they related to you?***
13. Ntsholongwane kagawulayo *HIV* ☐ Ewe *Yes* ☐ Hayi *No* → **Ukuba HAYI Gqithela ku Q14** ***If NO Skip to Q14***	☐ *Grandparent* ☐ *Parent* ☐ *Sibling* ☐ *Child* ☐ Omunye, Cacisa:_____ *Other, Specify*
14. Isifo sephepha "TB" *Tuberculosis "TB"* ☐ Ewe *Yes* ☐ Hayi *No* → **Ukuba HAYI Gqithela ku Q15** ***If NO Skip to 15***	☐ *Grandparent* ☐ *Parent* ☐ *Sibling* ☐ *Child* ☐ Omunye, Cacisa:_____ *Other, Specify*
15. Isifo seswekile Diabetes *"Sugar diabetes" Type 1 or Type 2* ☐ Ewe *Yes* ☐ Hayi *No* → **Ukuba HAYI Gqithela ku Q16** ***If NO Skip to 16***	☐ *Grandparent* ☐ *Parent* ☐ *Sibling* ☐ *Child* ☐ Omunye, Cacisa:_____ *Other, Specify*
16. "Hi-Hi" *Hypertension "High Blood Pressure"* ☐ Ewe *Yes* ☐ Hayi *No* → **Ukuba HAYI Gqithela ku Q17** ***If NO Skip to Q17***	☐ *Grandparent* ☐ *Parent* ☐ *Sibling* ☐ *Child* ☐ Omunye, Cacisa:_____ *Other, Specify*
17. Isifo sentliziyo *Heart Diseases*	☐ *Grandparent* ☐ *Parent*

Initials of interviewer: ____

☐ Ewe *Yes* ☐ Hayi *No* → **Ukuba HAYI Gqithela ku Q18** ***If NO Skip to Q18***	☐ *Sibling* ☐ *Child* ☐ Omunye, Cacisa:_____ *Other, Specify*
18. *High cholesterol* ☐ Ewe *Yes* ☐ Hayi *No* → **Ukuba HAYI Gqithela ku Q19** ***If NO Skip to 19***	☐ *Grandparent* ☐ *Parent* ☐ *Sibling* ☐ *Child* ☐ Omunye, Cacisa:_____ *Other, Specify*
19. Isifuba *Asthma* ☐ Ewe *Yes* ☐ Hayi *No* → **Ukuba HAYI Gqithela ku Q20** ***If NO Skip to Q20***	☐ *Grandparent* ☐ *Parent* ☐ *Sibling* ☐ *Child* ☐ Omunye, Cacisa:_____ *Other, Specify*
20. Isifo sokuwa *Epilepsy* ☐ Ewe *Yes* ☐ Hayi *No* → **Ukuba HAYI Gqithela ku Q21** ***If NO Skip to Q21***	☐ *Grandparent* ☐ *Parent* ☐ *Sibling* ☐ *Child* ☐ Omunye, Cacisa:_____ *Other, Specify*
21. Isifo samadlala *Thyroid disease* ☐ Ewe *Yes* ☐ Hayi *No* → **Ukuba HAYI Gqithela ku Q22** ***If NO Skip to Q22***	☐ *Grandparent* ☐ *Parent* ☐ *Sibling* ☐ *Child* ☐ Omunye, Cacisa:_____ *Other, Specify*
22. Enye ingulo okanye imeko yengqondo nje "ngokucinga kakhulu", uxinizelelo, ukothuka, ixhala njalo-njalo. *Any psychological or mental conditions such as "thinking too much", depression, panic attacks, anxiety attacks etc."* **NB: Efunyaniswe ngu gqirha okanye ngunesi** ***Diagnosed by a doctor or nurse*** ☐ Ewe *Yes* ☐ Hayi *No* → **Ukuba HAYI Gqithela ku Q23** ***If NO Skip to Q23***	☐ *Grandparent* ☐ *Parent* ☐ *Sibling* ☐ *Child* ☐ Omunye, Cacisa:_____ *Other, Specify*

Initials of interviewer: ____

PWID: _ _ _ _ _ _ - _ _

23. Ezinye naziphi na imeko zesigulo *Any other medical conditions* ☐ Ewe *Yes* ☐ Hayi *No* → **Ukuba HAYI, Phelisa** ***If NO, END***	☐ *Grandparent* ☐ *Parent* ☐ *Sibling* ☐ *Child* ☐ Omunye, Cacisa:_____ *Other, Specify*

NOTES:

Please write notes and/or any other comments here:

_____

_____

_____

Signed Interviewer completing CRF: _____ Date: _____ / _____ / _____
DD MMM YYYY

Signed QC Officer: _____ Date: _____ / _____ / _____
DD MMM YYYY

Signed Study Coordinator: _____ Date: _____ / _____ / _____
DD MMM YYYY

Initials of interviewer: ____

PWID: _ _ _ _ _ _ - _ _

BOD POD ASSESSMENT FORM

This CRF applies to ALL enrolled ORCHID participants
Complete during study visit A1b, A3, P5 and P7

Visit Date									Visit Code	
D	D	M	M	M	Y	Y	Y	Y		

Umatshini we-Bod Pod ufuna ukuba ungakhange utye kwiiyure ezi-12 ezidlulileyo kwaye ungaseli amanzi kwiiyure ezi-2 ezidlulileyo. Ukuvavanya ukuba uyahlangabezana nale mfuno, siza kubuza imibuzo embalwa. *The BodPod machine requires you to not have eaten in the last 12 hours and to not have drank water in the last 2 hours. To assess whether you meet these requirements, we are going to ask you a few questions.*	
Ukhe watya okanye wasela nantoni na ukusukela ngentsimbi yeshumi ebusuku? *Have you had anything to eat or drink since 10pm last night?*	☐ Ewe *Yes* ☐ Hayi *No*
Ukhe wasela amanzi kwiiyure ezi-2 ezidlulileyo? *Have you drank water in the last 2 hours?*	☐ Ewe *Yes* ☐ Hayi *No*
Participant information	
Date of birth	_____ / _____ / _____ DD MMM YYYY
Height	___ ___ ___ . ___ cm
Weight	___ ___ ___ . ___ kg
Gestational (if pregnant)	_____ weeks + _____days ☐ Not pregnant

NB!! Before starting the Bod Pod assessment, please ask the participant to empty their bladder

TO BE COMPLETED BY INTERVIEWER	
BOD POD MACHINE	
Is the Bod Pod in good order?	☐ Yes ☐ No
THORACIC GAS VOLUME	
Has the thoracic gas volume been successfully measured?	☐ Yes ☐ Not measured
BODY COMPOSITION	
Has body composition been measured?	☐ Yes ☐ Not measured

RESULTS	
Body Mass	___ ___ ___ . ___ ___ ___ kg
Thoracic Gas Volume ~~(Predicted)~~	☐ MEASURED TGV ☐ PREDICTED TGV ___ . ___ ___ ___ L
% Fat	___ ___ . ___%
% Fat Free Mass	___ ___ . ___%
MEASURED THORACIC GAS VOLUME	
Trail 1	___ . ___ ___ ___ L
Trail 2	___ . ___ ___ ___ L
Trail 3	___ . ___ ___ ___ L
Trail 4	___ . ___ ___ ___ L
Trail 5	___ . ___ ___ ___ L
Trail 6	___ . ___ ___ ___ L
Trail 7	___ . ___ ___ ___ L
Trail 8	___ . ___ ___ ___ L
Trail 9	___ . ___ ___ ___ L
Trail 10	___ . ___ ___ ___ L

NOTES:
Please write notes and/or any other comments here:

_____

_____

_____

_____

Signed Assessor of Measurements: _____ Date: _____ / _____ / _____
DD MMM YYYY

Signed QC Officer: _____ Date: _____ / _____ / _____
DD MMM YYYY

Signed Study Coordinator: _____ Date: _____ / _____ / _____
DD MMM YYY¥

Please select hair style that most resembles the participant's hair		
 ☐1	 ☐2	 ☐3
 ☐4	 ☐5	 ☐6
 ☐7	 ☐8	 ☐9
 ☐10	 ☐11	 ☐12

PWID: _ _ _ _ _ _ - _ _

MATERNAL SPECIMEN COLLECTION FORM

This form applies to ALL enrolled ORCHID Participants
Complete during study visit A1b, A3, P5 and P7

Visit Date									Visit Code	
D	D	M	M	M	Y	Y	Y	Y		

STORE AT 4°C TEMPERATURE AFTER COLLECTION

Form Completed by: _____

Measure	Tube Type	Tube Fill Priority	Tube Size	Blood Vol needed	No. of tubes needed	Send Location	Collected	Time Collected	Collected by (initials)	Specimen ID/Bar Code
0 min (fasting) OGTT										
Plasma fasting Glucose	Fluoride	1	5ml	2ml	1	NHLS	☐ Yes ☐ No If No, give reason: _____ _____	____h ____min		Place bar coded sticker
Serum fasting Insulin, Lipid Profile, C-peptide	SST	2	5ml	4ml	1	NHLS	☐ Yes ☐ No If No, give reason: _____ _____	____h ____min		Place bar coded sticker
Storage Plasma* (Omics, cytokine etc)	EDTA	3,5	5ml	6ml	2	Epi&Bio	☐ Yes ☐ No If No, give reason: _____ _____	____h ____min		Place bar coded sticker
Storage Serum	SST	4,6	5ml	10ml	2	Epi&Bio	☐ Yes ☐ No If No, give reason: _____ _____	____h ____min		Place bar coded sticker
Storage Whole Blood	PaxGene	7	2.5m	2ml	1	Epi&Bio	☐ Yes ☐ No If No, give reason: _____ _____	____h ____min		Place bar coded sticker
30 min (post glucose loading) OGTT										
Plasma Glucose	Fluoride	1	5ml	2ml	1	NHLS	☐ Yes ☐ No If No, give reason: _____ _____	____h ____min		Place bar coded sticker
Serum Insulin & C-peptide	SST	2	5ml	4ml	1	NHLS	☐ Yes ☐ No If No, give reason: _____ _____	____h ____min		Place bar coded sticker
HIV VL Testing (HIV+ve participant only)	PPT	3	5ml	2ml	1	NHLS	☐ Yes ☐ No If No, give reason: _____ _____	____h ____min		Place bar coded sticker
CD4 Testing (HIV+ve participant only)	EDTA	4	5ml	2ml	1	NHLS	☐ Yes ☐ No If No, give reason: _____ _____	____h ____min		Place bar coded sticker

Storage Plasma	EDTA	5	5ml	4ml	1	Epi&Bio	☐ Yes ☐ No If No, give reason: _____ _____	____h ____min		Place bar coded sticker
Storage Serum	SST	6	5ml	2ml	1	Epi&Bio	☐ Yes ☐ No If No, give reason: _____ _____	____h ____min		Place bar coded sticker
60 min (post glucose loading) OGTT										
Plasma Glucose	Fluoride	1	5ml	2ml	1	NHLS	☐ Yes ☐ No If No, give reason: _____ _____	____h ____min		Place bar coded sticker
Serum Insulin & C-peptide	SST	2	5ml	4ml	1	NHLS	☐ Yes ☐ No If No, give reason: _____ _____	____h ____min		Place bar coded sticker
Storage Plasma	EDTA	3	5ml	4ml	1	Epi&Bio	☐ Yes ☐ No If No, give reason: _____ _____	____h ____min		Place bar coded sticker
Storage Serum	SST	4	5ml	2ml	1	Epi&Bio	☐ Yes ☐ No If No, give reason: _____ _____	____h ____min		Place bar coded sticker
120 min (post glucose loading) OGTT										
Plasma Glucose	Fluoride	1	5ml	2ml	1	NHLS	☐ Yes ☐ No If No, give reason: _____ _____	____h ____min		Place bar coded sticker
Serum Insulin & C-peptide	SST	2	5ml	4ml	1	NHLS	☐ Yes ☐ No If No, give reason: _____ _____	____h ____min		Place bar coded sticker
Storage Plasma	EDTA	3	5ml	3.5ml	1	NHLS	☐ Yes ☐ No If No, give reason: _____ _____	____h ____min		Place bar coded sticker
Storage Serum	SST	4	5ml	3.5ml	1	Epi&Bio	☐ Yes ☐ No If No, give reason: _____ _____	____h ____min		Place bar coded sticker
Urine sample	Falcon tube		10ml	10ml	1	Epi&Bio	☐ Yes ☐ No If No, give reason: _____ _____	____h ____min		Place bar coded sticker

NOTES:

Please write notes and/or any other comments here:

_____

_____

_____

_____

_____

Signed Nurse completing CRF: _____ Date: _____ / _____ / _____
DD MMM YYYY

Signed QC Officer: _____ Date: _____ / _____ / _____
DD MMM YYYY

Signed Study Coordinator: _____ Date: _____ / _____ / _____
DD MMM YYYY

PWID: _ _ _ _ _ _ - _ _

OBSTETRICS ABSTRACTION FORM

This form applies to ALL enrolled ORCHID Participants
Complete after delivery

Source Document	☐ Maternity Case Record ☐ Delivery Register ☐ PMTCT Register (incl PHCIS/Clinicom) ☐ Other, Please Specify: _____		
Date of Data Abstraction:	_____ / _____ / _____ DD MM YYYY	**Initials of Data Abstractor:**	
Participant Date of Birth:	_____ / _____ / _____ DD MM YYYY	**Provincial Folder Number:** specify 3 letter facility prefix; GUP or other	

Delivery Gestation Details

Estimated GA at delivery	Weeks:_____ If weeks not recorded: ☐ Term ☐ Preterm	**Delivery GA estimated by** *(Please tick all methods used)*	☐ Dates (LMP) ☐ Palpation/SFH ☐ Ultrasound Scan ☐ NR
		If USS, Amniotic fluid index	_____

Blood Pressure Details

Any hypertension noted during <u>ANTENATAL CARE</u>? *(Systolic Over 140 and/or Diastolic Over 90)*	☐ Yes ☐ No	**Any hypertension noted during <u>LABOUR</u>?** *(Systolic Over 140 and/or Diastolic Over 90)*	☐ Yes ☐ No
Was there any hypertension medication given during <u>ANTENATAL CARE</u>?	☐ Yes ☐ No	**Was there any hypertension medication given during <u>LABOUR</u>?**	☐ Yes ☐ No
Medication name given during <u>ANTENATAL CARE</u>	☐ None ☐ Aldomet (Methyldopa) ☐ Adalat (Nifedipine) ☐ Neprosol (Dihydralazine) ☐ Labetalol ☐ Enalapril ☐ $MgSO_4$ ☐ Other _____	**Medication name given during <u>LABOUR</u>**	☐ None ☐ Aldomet (Methyldopa) ☐ Adalat (Nifedipine) ☐ Neprosol (Dihydralazine) ☐ Labetalol ☐ Enalapril ☐ $MgSO_4$ ☐ Other _____
Maximum Systolic BP (at any point in pregnancy) *Record complete measure*	_____ / _____ systolic diastolic	**Maximum Diastolic BP (at any point in pregnancy)** *Record complete measure*	_____ / _____ systolic diastolic
Date this BP was taken	____ / _____ / _____ DD MM YYYY	**Date this BP was taken**	____ / _____ / _____ DD MM YYYY

Labour Details

Delivery Date	_____ / _____ / _____ DD MMM YYYY			**Delivery time**	_____ : _____		
Fetal Heart	Present	Absent	Uncertain	**Fetal Distress**	Y	N	NR

Place of Delivery	☐ GMOU ☐ MMH ☐ GSH ☐ Other, Specify: _____	**Delivery Method**	☐ NVD ☐ Emergency C/S ☐ Elective C/S ☐ Forceps ☐ Vacuum

If C/S, Primary indication *(APH – antepartum haemorrhage)*	☐ Fetal distress ☐ Obstructed labour ☐ Twins/Triplets ☐ Pre-eclampsia /eclampsia ☐ APH ☐ Previous C/S ☐ Other, specify: _____	**If by C/S, was it performed after membrane rupture?**	☐ Yes, Duration:_____ Mins ☐ No ☐ NR

Please tick all major medical and/or obstetric conditions the mother experienced during pregnancy and/or during delivery. *(APH – antepartum haemorrhage) (PPH – postpartum haemorrhage (IUGR – intra-uterine growth retardation)*	☐ Chorio amnionitis	☐ Sepsis	☐ UTI / Pyelonephritis
	☐ IUGR	☐ Hypertension	☐ Pre-eclampsia/ eclampsia
	☐ PET/GPH/PIH	☐ Diabetes mellitus	☐ Preterm labour
	☐ APH	☐ PPH	☐ Prolonged ROM
	☐ Prolonged labour	☐ Cervical tear	☐ Perineal tear
	☐ Episiotomy	☐ None	☐ Other, specify_____
	_____		

Placental method of delivery	☐ Active ☐ Spontaneous	**Placenta**	☐ Complete ☐ Incomplete ☐ NR	Weight: _____ g

Infant Details

Infant DOB	_____ / _____ / _____ DD MMM YYYY	**Infant DOB for Twin B**	_____ / _____ / _____ DD MMM YYYY
Gender	☐ Male ☐ Female	**Gender Twin B**	☐ Male ☐ Female
Outcome	☐ Alive ☐ Stillborn ☐ NND ☐ NR	**Outcome Twin B**	☐ Alive ☐ Stillborn ☐ NND ☐ NR
Resuscitation	☐ Yes ☐ No ☐ NR	**Resuscitation Twin B**	☐ Yes ☐ No ☐ NR
Birth injuries	☐ Yes ☐ No ☐ NR	**Birth injuries**	☐ Yes ☐ No ☐ NR
Birthweight	_____ g	**Birthweight Twin B**	_____ g
Head circumference	_____ cm	**Head circumference Twin B**	_____ cm
Length	_____ cm	**Length Twin B**	_____ cm
APGAR Score	1 min: _____ 5 min: _____	**APGAR Score Twin B**	1 min: _____ 5 min: _____

Congenital Abnormalities?	☐ Yes, Specify: _____ ☐ No ☐ NR	**Congenital Abnormalities Twin B**	☐ Yes, Specify: _____ ☐ No ☐ NR
Polio Vaccine?	☐ Yes ☐ No ☐ NR	**Polio Vaccine Twin B**	☐ Yes ☐ No ☐ NR
BCG Vaccine?	☐ Yes ☐ No ☐ NR	**BCG Vaccine Twin B**	☐ Yes ☐ No ☐ NR
NVP at birth?	☐ Yes ☐ No ☐ NR ☐ NA	**Twin B NVP at birth?**	☐ Yes ☐ No ☐ NR ☐ NA
Feeding Option	☐ Breast ☐ Formula	**Feeding Option**	☐ Breast ☐ Formula
Successful initial breastfeeding	☐ Yes ☐ No ☐ NR	**Successful initial breastfeeding**	☐ Yes ☐ No ☐ NR

Discharge Summary

Family planning choice	☐ Oral contraceptive ☐ Injectable ☐ IUD ☐ Implant ☐ Tubal ligation ☐ Other: _____
Date of discharge	_____ / _____ / _____ DD MMM YYYY

Any hypertension noted during POSTNATAL CARE? *(Systolic Over 140 and/or Diastolic Over 90)*	☐ Yes ☐ No	**Medication name given during POSTNATAL CARE**	☐ None ☐ Aldomet (Methyldopa) ☐ Adalat (Nifedipine) ☐ Neprosol (Dihydralazine) ☐ Labetalol ☐ Enalapril ☐ $MgSO_4$ ☐ Other _____
Was there any hypertension medication given during POSTNATAL CARE?	☐ Yes ☐ No		
Maximum Systolic BP (at any point in pregnancy) *Record complete measure*	_____ / _____ systolic diastolic	**Maximum Diastolic BP (at any point in pregnancy)** *Record complete measure*	_____ / _____ systolic diastolic
Date this BP was taken	____ / _____ / _____ DD MM YYYY	**Date this BP was taken**	____ / _____ / _____ DD MM YYYY

Stage Period	Date	Time	Reading
BLOOD PRESSURE READINGS DURING ANTENATAL CARE			
1st ANC Visit	____ / ____ / ____ (DD / MMM / YYYY)	____ : ____ (HOUR / MIN)	____ / ____ (systolic / diastolic)
2nd ANC Visit	____ / ____ / ____ (DD / MMM / YYYY)	____ : ____ (HOUR / MIN)	____ / ____ (systolic / diastolic)
3rd ANC Visit	____ / ____ / ____ (DD / MMM / YYYY)	____ : ____ (HOUR / MIN)	____ / ____ (systolic / diastolic)
4th ANC Visit	____ / ____ / ____ (DD / MMM / YYYY)	____ : ____ (HOUR / MIN)	____ / ____ (systolic / diastolic)
5th ANC Visit	____ / ____ / ____ (DD / MMM / YYYY)	____ : ____ (HOUR / MIN)	____ / ____ (systolic / diastolic)
6th ANC Visit	____ / ____ / ____ (DD / MMM / YYYY)	____ : ____ (HOUR / MIN)	____ / ____ (systolic / diastolic)
7th ANC Visit	____ / ____ / ____ (DD / MMM / YYYY)	____ : ____ (HOUR / MIN)	____ / ____ (systolic / diastolic)
8th ANC Visit	____ / ____ / ____ (DD / MMM / YYYY)	____ : ____ (HOUR / MIN)	____ / ____ (systolic / diastolic)
Other Readings	____ / ____ / ____ (DD / MMM / YYYY)	____ : ____ (HOUR / MIN)	____ / ____ (systolic / diastolic)
	____ / ____ / ____ (DD / MMM / YYYY)	____ : ____ (HOUR / MIN)	____ / ____ (systolic / diastolic)
	____ / ____ / ____ (DD / MMM / YYYY)	____ : ____ (HOUR / MIN)	____ / ____ (systolic / diastolic)
	____ / ____ / ____ (DD / MMM / YYYY)	____ : ____ (HOUR / MIN)	____ / ____ (systolic / diastolic)

Stage Period	Date	Time	Reading
BLOOD PRESSURE READINGS DURING LABOUR			
Labour Initial	____ / ____ / ____ (DD / MMM / YYYY)	____ : ____ (HOUR / MIN)	____ / ____ (systolic / diastolic)
1st Stage	____ / ____ / ____ (DD / MMM / YYYY)	____ : ____ (HOUR / MIN)	____ / ____ (systolic / diastolic)
2nd Stage	____ / ____ / ____ (DD / MMM / YYYY)	____ : ____ (HOUR / MIN)	____ / ____ (systolic / diastolic)
3rd Stage	____ / ____ / ____ (DD / MMM / YYYY)	____ : ____ (HOUR / MIN)	____ / ____ (systolic / diastolic)
4th Stage	____ / ____ / ____ (DD / MMM / YYYY)	____ : ____ (HOUR / MIN)	____ / ____ (systolic / diastolic)
Post-delivery	____ / ____ / ____ (DD / MMM / YYYY)	____ : ____ (HOUR / MIN)	____ / ____ (systolic / diastolic)
Other Readings	____ / ____ / ____ (DD / MMM / YYYY)	____ : ____ (HOUR / MIN)	____ / ____ (systolic / diastolic)
	____ / ____ / ____ (DD / MMM / YYYY)	____ : ____ (HOUR / MIN)	____ / ____ (systolic / diastolic)
	____ / ____ / ____ (DD / MMM / YYYY)	____ : ____ (HOUR / MIN)	____ / ____ (systolic / diastolic)
	____ / ____ / ____ (DD / MMM / YYYY)	____ : ____ (HOUR / MIN)	____ / ____ (systolic / diastolic)

Notes

RTHC abstraction

PCID: _ _ _ _ _ _ - _ _

ROAD TO HEALTH CARD ABSTRACTION FORM

This CRF applies to ALL babies of ORCHID participants

To be completed once off at any visit

Completion Date								
D	D	M	M	M	Y	Y	Y	Y

Visit Code	

Infant DOB	_____ / _____ / _____ DD MMM YYYY				
Place/facility of birth	☐ GMOU ☐ MMH ☐ Mitchel's plain MOU ☐ Mitchel's plain District ☐ GSH ☐ KDH ☐ Tygerberg ☐ Hanover Park ☐ Other, specify _____				
Gestational age	_____ weeks	**Gender**	☐ Male ☐ Female		
Outcome	☐ Alive ☐ Stillborn ☐ Neonatal death ☐ Not recorded				
Resuscitation	☐ Yes ☐ No ☐ Not recorded				
Birth injuries	☐ Yes ☐ No ☐ Not recorded				
Birthweight	_____ g	**Length**	_____ cm		
Head circumference	_____ cm	**APGAR Score**	1 min: _____ 5 min: _____		
Blood Group	☐ A ☐ B ☐ O ☐ Not recorded	**Rhesus**	☐ Pos ☐ Neg ☐ NR	**RPR**	☐ Pos ☐ Neg ☐ NR
Congenital Abnormalities?	☐ Yes, Specify: _____ ☐ No ☐ Not recorded				
Polio (OPVO) Vaccine?	☐ Yes ☐ No ☐ Not recorded				
BCG Vaccine?	☐ Yes ☐ No ☐ Not recorded				
NVP at birth?	☐ Yes ☐ No ☐ Not recorded ☐ N/A (for HIV negative moms)				
Breastfeeding	☐ Yes ☐ No ☐ Unknown				

NOTES:

Please write notes and/or any other comments here:

Signed Abstractor : _____ Date: _____ / _____ / _____ DD MMM YYYY

Signed QC Officer: _____ Date: _____ / _____ / _____ DD MMM YYYY

Signed Study Coordinator: _____ Date: _____ / _____ / _____ DD MMM YYYY

PWID: _ _ _ _ _ _ - _ _

FETAL GROWTH RESULTS FORM

This CRF applies to ALL enrolled ORCHID Participants

Complete during study visit A1 and A3 Study Visits

Visit Date								
D	D	M	M	M	Y	Y	Y	Y

Visit Code	
A	**1a**

LMP	☐ Known: ____ /_____ /_____ DD MMM YYYY ☐ Not Known	**LMP EDD**	☐ Known: ____ /_____ /_____ DD MMM YYYY ☐ Not Known
U/S Gestation	_____ weeks + _____days	**U/S EDD**	☐ Known: ____ /_____ /_____ DD MMM YYYY ☐ Not Known

Technical Conditions	☐ Good ☐ Limited by_____

Foetus number	☐ Singleton ☐ Twins ☐ Multiple
Chorionicity	☐ Monochorionic ☐ Dichorionic ☐ N/A
Presentation	☐ Intrauterine ☐ Extrauterine ☐ Cephalic ☐ Breech ☐ Transverse
Foetus Heartbeat	☐ Yes ☐ No ☐ Too early to detect
Foetus Movement	☐ Yes ☐ No
Placental Position *Tick all that apply*	☐ Anterior ☐ Posterior ☐ Right ☐ Left ☐ Lateral ☐ Fundal ☐ High ☐ Low
Placenta maturity (grannum)	☐ 1 ☐ 2 ☐ 3
Placenta relation to cervical os	☐ Clear ☐ Covering _____ mm from os
Amniotic fluid	☐ Normal ☐ Decreased ☐ Increased
Stomach	☐ Seen ☐ Not seen
Bladder	☐ Seen ☐ Not seen

Initials of sonographer: ___

PWID: _ _ _ _ _ _ - _ _

FETAL BIOMETRY MEASUREMENTS	
Crown-rump length (CRL)	_____ mm ☐ Not measurable
Gestational Sac	_____ mm ☐ Not measurable
Biparietal diameter (BPD)	_____ mm ☐ Not measurable
Foetal ascites	☐ Absent ☐ Mild ☐ Moderate ☐ Severe

Sex	☐ Male ☐ Female ☐ Not Determined

CONCLUSION		
☐ Complete examination	☐ Incomplete Examination	☐ Referred Examination

NOTES:

Please write notes and/or any other comments here:

Signed Sonographer completing CRF: _____ Date: _____ / _____ / _____
DD MMM YYYY

Signed QC Officer: _____ Date: _____ / _____ / _____
DD MMM YYYY

Signed Study Coordinator: _____ Date: _____ / _____ / _____
DD MMM YYYY

Initials of sonographer: ___

Ethics Approval Letter

UNIVERSITY OF CAPE TOWN

Faculty of Health Sciences

Human Research Ethics Committee

Room 45 E-52-E-Floor- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-submissions@uct.ac.za
Website: www.health.uct.ac.za/home/human-research-ethics

11 December 2024

HREC REF: 955/2024

Prof Landon Myer
Division of Epidemiology & Biostatistics
School of Public Health-FHS
Email: Landon.myer@uct.ac.za
Student: Myrjam006@myuct.ac.za

Dear Prof Myer

PROJECT TITLE: IMPACT OF DTG USE DURING PREGNANCY ON BIRTH OUTCOMES OF HIV-INFECTED WOMEN IN THE WESTERN CAPE, SOUTH AFRICA-SUB-STUDY LINKED TO 709/2020-(MSC CANDIDATE-MS JAMIE EMMA MEYER)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

- The protocol is unclear as to the time point for the "exposure variables" to be included in the analysis. For example, which BMI is going to be included in the planned linear model? BMI at entry into the cohort at 1st ANC? BMI at time of delivery? Will change in BMI over pregnancy and association of that change with adverse outcomes be explored?
- It would be useful to see the postulated causal pathways underpinning the investigators thinking. The concern seems to be that dolutegravir is "obesogenic" and that this may lead to adverse pregnancy outcomes. It is unclear in the analysis description exactly how that will be teased out in the planned analysis. The HREC would also recommend more caution in concluding that any association identified is causal.

Approval is granted for one year until the 30 December 2025.

Please submit a progress form, using the standardised Annual Report Form (FHS016) or FHS017 if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

The HREC acknowledge that the student: Ms Jamie Emma Meyer will also be involved in this study.

Please quote HREC REF 955/2024 in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

PROFESSOR MARC BLOCKMAN
CHAIRPERSON, FACULTY OF HEALTH SCIENCES HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637. Institutional Review Board (IRB) number: IRB00001938 NHREC-registration number: REC-210208-007

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP),

National Health Research Ethics Council (2024) South African Ethics in Health Research Guidelines: Principles, Processes and Structures, 3rd ed. Department of Health of South Africa. South African Good Clinical Practice Guidelines (SA GCP 2020), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2024) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

Target Journal Author Guidelines

JAIDS: Journal of Acquired Immune Deficiency Syndromes

Online Submission and Review System

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Instructions for Authors (this page)
Reprint Ordering
Permissions Requests
Reprints

SCOPE

JAIDS: Journal of Acquired Immune Deficiency Syndromes is a peer-reviewed, multidisciplinary journal directed to an audience of physicians and researchers. The journal publishes original work in the form of Original Articles, Rapid Communications, Brief Reports, and Letters to the Editor. *JAIDS* does not publish case reports.

MANUSCRIPT SUBMISSION

A submitted manuscript must be an original contribution not previously published (except as an abstract or preliminary report), must not be under consideration for publication elsewhere, and, if accepted, must not be published elsewhere in similar form, in any language, without the consent of Lippincott Williams & Wilkins. Each person listed as an author is expected to have participated in the study to a significant extent. Although the editors and referees make every effort to ensure the validity of published manuscripts, the final responsibility rests with the authors, not with the journal, its editors, or the publisher.

All submissions will be rigorously peer-reviewed by members of the Editorial Board and by other specially qualified individuals as well. In the interests of rapid reviewing of contributions, only one of the Editors-in-Chief will, in general, make the final determination as to the acceptability of a submission, after collecting the referee's comments. Contributors may recommend specific names of reviewers from the Editorial Board, as well as other individuals they deem especially well qualified. However, the Editors-in-Chief will not be bound to follow such suggestions.

In general, the instructions for preparation of manuscripts should follow the International Committee of Medical Journal Editors (ICMJE) Uniform Requirements for Manuscripts Submitted to Biomedical Journals. In case of questions, please feel free to contact the Editorial Office of any one of the Editors-in-Chief.

Authors must submit their manuscripts to JAIDS through the Web-based tracking system: (**http://www.editorialmanager.com/jaids**)
The site contains instructions and advice on how to use the system, guidance on the creation/scanning and saving of electronic art, and supporting documentation. In addition to allowing authors to submit manuscripts on the Web, the site allows authors to follow the progression of their manuscript through the peer review process. Authors should not send hard copies of the manuscript or artwork to the editorial office. Address all inquiries regarding manuscripts not yet accepted or published to the Journal's editorial office. The editorial office will acknowledge receipt of your manuscript via e-mail.

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Epidemiology, Implementation Science, and Prevention Research

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Journal Article

1. Schambelan M, Benson CA, Carr A, et al. Management of metabolic complications associated with antiretroviral therapy for HIV-1 infection: recommendations of an International AIDS Society-USA panel. *J Acquir Immune Defic Syndr.* 2002;31:257–275.

Book Chapter

2. Wortmann RL, Bentzel CJ. Renal handling of uric acid. In: Massry SG, Glassock RJ, eds. *Massry and Glassock's Textbook of Nephrology*. Phiadelphia: Lippincott Williams & Wilkins, 2001;90–92.

Entire Book

3. Mandell GL, Mildvan D, eds. *Atlas of AIDS*. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2001.

Software

4. Epi Info [computer program]. Version 6. Atlanta: Centers for Disease Control and Prevention, 1994.

Online Journals

5. Friedman SA. Preeclampsia: a review of the role of prostaglandins. *Obstet Gynecol* [serial online]. January 1988;71:22–37. Available from: BRS Information Technologies, McLean, VA. Accessed December 15, 1990.

Database

6. CANCERNET-PDQ [database online]. Bethesda, MD: National Cancer Institute, 1996. Updated March 29, 1996.

World Wide Web

7. Panel on Clinical Practices for the Treatment of HIV Infection. Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. Department of Health and Human Services and Henry J. Kaiser Foundation, January 28, 2000. Available at: http://www.hivatis.org/guidelines/AA599.pdf.

Paper Presented at a Conference

8. Koenig L, Ellerbrock T, Pratt-Palmire M, et al. Prospective predictors of medication adherence: a study of the first six months of highly active antiretroviral therapy (HAART) using electronic monitoring [WePeB5818]. Presented at: XIV International AIDS Conference; 2002; Barcelona.

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