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EPIC

Evaluation of **P**harmacokinetic drug-drug **I**nteractions between hormonal **C**ontraceptives and doravirine-containing ART among women living with HIV in South Africa

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LIST OF ABBREVIATIONS AND ACRONYMS

3TC	Lamivudine
CASI	Audio computer-assisted self-interviewing
AE	Adverse Events
AGYW	Adolescent girls and young women
AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral therapy
AUC	Area under the curve
BARC	Bioanalytical Research Corporation
BCEPS	Biometric Co-enrolment Prevention System
CAB	Community Advisory Board
CBC	Complete blood count
CDC	Centre of Disease Control
CHW	Community Health Workers
CLO	Community Liaison Officer
CLS	Clinical Laboratory Services
CMP	Comprehensive metabolic panel
CRF	Case report form
CRS	Clinical Research site
CYP450	Cytochrome P450
DAIDS	Division of AIDS
DDI	Drug-drug interactions
DOR	Doravirine
DMPA	Depomedroxyprogesterone acetate
DNA	Deoxyribonucleic Acid
DTG	Dolutegravir
EFV	Efavirenz
ENG	Etonogestrel
FDA	U.S. Food and Drug Administration
FTC	Emtricitabine
GCP	Good Clinical Practices
GMP	Good Manufacturing Practices
GMR	Geometric mean ratio
GPP	Good Pharmacy Practice
HBsAG	Hepatitis B surface Antigen
HBsAB	Hepatitis B surface Antibody
HB core AB	Hepatitis B core Antibody
HCP	Healthcare Professional
HHP	Hillbrow Health Precinct
HIV	Human Immunodeficiency Virus
IATA	International Air Transport Association
IM	Intramuscular
IND	Investigational drug
IRB	Institutional Review Board
IUD	Intra-uterine device
LDMS	Laboratory Data Management System
LNG	Levonorgestrel
MG	Milligrams

ML	Milliliters
MPA	Medroxyprogesterone acetate
MRC	Medical Research Council
NDoH	National Department of Health
NGO	Non-Governmental Organization
NIH	National Institute of Health
NNRTI	Non-nucleoside reverse transcriptase inhibitors
PARVI	PK study of ARVs and implants in Kenya
PEPFAR	President's Emergency Plan for AIDS Relief
PI	Principal Investigator
PID	Pelvic Inflammatory Disease
PK	Pharmacokinetic
PPE	Personal Protective Equipment
PrEP	Pre-exposure prophylaxis
RNA	Ribonucleic Acid
RC	Research Centre
RT	Reverse transcriptase
SAHPRA	South African Health Product Regulatory Agency
SAE	Serious adverse events
SAPC	South African Pharmacy Council
SC	Subcutaneous
SH	Social harms
SMC	Study Monitoring Committee
SOP	Standard Operating Procedures
SRH	Sexual and reproductive health
SUSAR	Suspected unexpected serious adverse event
TDF	Tenofovir
UNAIDS	United Nations Programme on HIV and AIDS
USAID	United States Agency for International Development
UW	University of Washington
VPD	Vaccine preventable diseases
WHO	World Health Organization
Wits RHI	Wits Reproductive Health and HIV Institute
WLHIV	Women living with HIV

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Evaluation of **P**harmacokinetic drug-drug **I**nteractions between hormonal **C**ontraceptives and doravirine-containing ART among women living with HIV in South Africa

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INVESTIGATORS SIGNATURE PAGE

Version 1.3, 12 July 2022

Institution: Wits Reproductive Health and HIV Institute

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to all applicable legal and regulatory requirements and regulations as well as ICH and SA GCP guidelines.

We, as the Co-Principal Investigators, agree to conduct this study in full accordance with the provisions of this protocol. Publication of the results of this study will be governed by Wits RHI policies.

We have read and understand the information in this protocol and will ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about the obligations incurred by their contribution to the study.

Principal Investigator:

Signature	Name:
	Title:
	Date:

Principal Investigator:

Signature	Name:
	Title:
	Date:

EPIC

Evaluation of **P**harmacokinetic drug-drug **I**nteractions between hormonal **C**ontraceptives and doravirine-containing ART among women living with HIV in South Africa

PROTOCOL SUMMARY

Short Title:	EPIC
IND Sponsor:	Merck & Co., Inc.
Funder:	Merck & Co., Inc.
Protocol Co-PIs:	Rena Patel, Thesla Palanee-Phillips, Nkosiphile Ndlovu
Study Site:	Wits Reproductive Health and HIV Institute, Research Centre Clinical Research Site
Study Design:	Observational, parallel group pharmacokinetic (PK) study
Study Population:	Women living with HIV (WLHIV) already on 1st line antiretroviral therapy (ART) and virally suppressed, 18-45 years old (inclusive)
Sample size:	Minimum of 105 participants
Study Duration:	Approximately 18-30 weeks of follow-up per participant
Study Products:	Doravirine (DOR)-containing ART tablets taken orally daily and one of the following contraceptive methods • Etonogestrel (ETG) implant • Intramuscular depo-medroxyprogesterone acetate (IM DMPA) • Subcutaneous medroxyprogesterone acetate (SC MPA) • Non-hormonal intrauterine device (IUD)
Study Regimen:	Participants who are interested in self-selecting and initiating one of the study contraceptive methods listed will be recruited for screening and eligibility assessments. If eligible and enrolled, there will be a 6-week lead-in period with daily use of oral DOR-containing ART followed by contraceptive method initiation of their choice. Study follow-up will take place every 2-4 weeks, at a minimum, for an additional 12 or 24 weeks for a total of 18 or 30 weeks of follow-up depending on the contraceptive method chosen. We will also enroll a dolutegravir (DTG) + IM DMPA group, who will be followed for 12 weeks, as the comparator group for the DOR + IM DMPA group. The comparator group for the DOR + ETG implant group will be a historical control group from a similar PK study called PARVI (**P**K study of **ARV**s and **I**mplants in Kenya) that is currently being conducted by Dr. Patel and colleagues in Kenya.[1]

Table 1: Study groups by ART regimen and contraceptive method choice

Group number	N	ART regimen and contraceptive method
Group 1	21	DOR-containing ART + initiating ETG implant
Group 2	21	DOR-containing ART + initiating IM DMPA
Group 3	21	DOR-containing ART + initiating SC MPA
Group 4	21	DOR-containing ART + initiating non-hormonal IUD
Group 5	21	DTG-containing ART + initiating IM DMPA
NDoH First line regimens: TDF + 3TC or FTC + EFV or DTG Study ART product is Delstrigo® tablet: DOR + 3TC +TDF		

Co-Primary Objectives: Pharmacokinetics

- To evaluate any associations between DOR exposure and hormonal contraceptive use in the four groups of DOR + 1) ETG implant, 2) IM DMPA, 3) SC MPA, or 4) non-hormonal IUD users by generating mean hormone concentrations at 12 weeks for IM and SC DMPA or 24 weeks for ETG implants and IUD groups; and
- To evaluate any bi-directional associations between hormonal contraceptive exposure and DOR use by generating mean DOR concentration at 24 hours ($C_{24\ hours}$) per Table 2 (see below)

Primary Endpoints

- Mean hormone concentrations at 12 or 24 weeks after contraceptive method initiation and use (for MPA and implants/IUD respectively)
- DOR concentration at 24 hours ($C_{24\ hours}$)

Table 2: DOR study and comparator groups for contraceptive hormone and antiretroviral (ARV) concentrations

DOR study group	Comparator group	
	Contraceptive Hormone concentrations	**ARV concentrations**
Group 1 DOR + ETG implant	DTG + ETG implant [primary] (historical group from PARVI) HIV-uninfected + ETG implant [secondary] (historical group from PARVI)	Group 4 DOR + non-hormonal IUD)
Group 2 DOR + IM DMPA	Group 5 DTG + IM DMPA	Group 4 DOR + non-hormonal IUD
Group 3 DOR + SC MPA	Group 2 DOR + IM DMPA	Group 4 DOR + non-hormonal IUD
DTG=dolutegravir; PARVI=**P**K study of **ARV**s and **I**mplants in Kenya		

Secondary Objectives

- To measure DOR-containing ART's efficacy, via HIV viral load <40 copies/mL, at 12-24 weeks after contraceptive initiation among women of reproductive age using hormonal and non-hormonal contraceptives.

Secondary Endpoints:

- HIV-1 viral load 12-24 weeks after contraceptive method initiation

Exploratory Objectives

- To assess safety, including side effects, satisfaction, and continuation rates of both the hormonal contraceptive method and ART;

- To qualitatively explore decision-making around ART and contraceptive method options, study experiences of ART switch, use of contraceptive method and self-administration of SC MPA; and
- To describe self-reported experiences of social harms and social benefits related to study participation.

Exploratory Endpoints
- Safety, satisfaction, and continuation rates at 12-24 weeks after contraceptive initiation;
- Participant report of acceptability, preferences and adherence; and
- Participants experiences around decision-making around ART and contraceptive options, and perceived self-reports of social harms and social benefits associated with study participation.

1.0 INTRODUCTION

1.1 Doravirine-containing antiretroviral therapy and drug-drug interactions

Doravirine (DOR)-containing antiretroviral therapy (ART) has demonstrated efficacy for those with HIV drug resistance mutations to efavirenz (EFV)[2], currently the leading ART for millions of persons living with HIV worldwide. Integrase-inhibitor containing ART, such as dolutegravir (DTG), is now the recommended 1st line ART by the World Health Organization (WHO) for use worldwide.[3] However, enthusiasm for its use among women of reproductive age was dampened by its possible association with neural tube defects, despite this signal declining over the last two years since it was first reported in 2018.[4,5] With growing drug resistance to EFV[6,7] and possible limitation to use of DTG in women of reproductive age, DOR may be the leading alternative ART recommendation for the largest group of HIV-infected individuals—women of reproductive age living in resource-limited settings, including in sub-Saharan Africa. Thus, eliciting any drug-drug interactions (DDIs) with a fuller range of hormonal contraceptives *early* is critical as the vast majority of women, including women living with HIV (WLHIV), use hormonal contraceptives at some point in their lives and these data may increase awareness of impact on contraceptive efficacy.

1.2 Efavirenz-containing ART and DDIs, and need for early studies on possible DDIs

Unintended pregnancies among WLHIV have significant consequences for HIV and maternal morbidity and vertical transmission of HIV. An estimated 40% of all pregnancies worldwide and 35% of pregnancies in Africa are unplanned.[8] Among WLHIV across sub-Saharan Africa, 35%–65% of pregnancies are considered unplanned, with up to 62% of WLHIV reporting unplanned pregnancies in South Africa.[8] However, the current evidence for the association between HIV status, ART use and unplanned pregnancy remains inconsistent.[8] Contraception reduces maternal morbidity and may be the most cost-effective tool for preventing vertical transmission of HIV by reducing rates of unintended pregnancies in the first place.[9,10] Therefore, optimizing contraceptive efficacy in combination with ART concurrently to avoid unintended pregnancies is imperative. Critical gaps exist, however, in current international and national HIV treatment guidelines regarding the concomitant use of ART and hormonal contraception. Due to concerns regarding DDIs, current HIV treatment and family planning guidelines advise using alternative or additional contraceptive methods when using certain combinations of antiretrovirals (ARVs) and hormonal contraceptives, including the combination of EFV and contraceptive implants. These guidelines are largely based on data extrapolated from various pharmacokinetic (PK) studies,[11-13] and now studies that investigate DDIs with the concomitant use of hormonal contraceptives and EFV exist.[14-17]

Some clinical data supporting the PK findings between implants and EFV is emerging. Four case reports have described WLHIV already on implants who then initiated EFV-containing ART and subsequently became pregnant.[18-21] Three out of 20 women initiating implants while on EFV-containing ART in a PK study became pregnant within the first year of implant use.[16] A retrospective review of 332 concomitant implant and ART users in eSwatini (formerly Swaziland) found 12.4% contraceptive failures among those using EFV-containing ART and none among

those using nevirapine-containing ART.[22] Finally, a three-year retrospective cohort study in Kenya conducted by Dr. Patel and colleagues examined pregnancy rates among nearly 25,000 WLHIV aged 15-45 years enrolled in PEPFAR-supported HIV facilities using various combinations of contraceptive methods and ART regimens.[23] Among implant users, the adjusted pregnancy rate was 3.3 per 100 women-years with EFV-containing ART, compared with 1.1 with nevirapine-containing ART and 1.3 with no current ART use. These data indicate that among women using implants, those using EFV-containing ART had three times higher pregnancy rates than women using nevirapine-containing ART (95% CI 1.3-4.6). These findings indicate that the potential DDI between EFV-containing ART and implants may lead to the clinical outcome of contraceptive failure and incident pregnancies, although implants still retain relatively high effectiveness compared to leading alternative contraceptive methods such as oral pills or injectables.

Despite the prior cohort data demonstrating that concomitant implant and EFV use retain relatively high effectiveness, there has been a significant gap regarding communication about these findings with patients, providers, and policy makers regarding its concomitant use in various resource-limited settings, including in South Africa.[24-26] Thus, it is imperative that a fuller profiling of potential DDIs between ARVs and hormonal contraceptive methods occur *prior* to full-scale programmatic roll out of new ARVs and contraceptive methods.

1.3 Clinical studies with DOR, regulatory approval status outside of South Africa

Doravirine is a registered drug in South Africa since August 2021. At the time of the initial submission of the protocol, it was unregistered for local use hence institutional review board, drug regulatory and import approval was required prior to shipment into South Africa. The South African Health Product Regulatory Agency (SAHPRA) was requested to approve the importation of the study product once the protocol was approved by the local IRB. On receipt of both local IRB and SAHPRA approval, the import of DOR commenced.

1.4 Clinical pharmacokinetics of DOR, mechanism of action

Doravirine is a pyridinone non-nucleoside reverse transcriptase inhibitor (NNRTI) of HIV-1 and inhibits HIV-1 replication by non-competitive inhibition of HIV-1 reverse transcriptase (RT). Doravirine does not inhibit the human cellular DNA polymerases α, ß, and mitochondrial DNA polymerase γ. The chemical name for DOR is 3-chloro-5-[[1-[(4,5-dihydro-4-methyl-5-oxo-1H-1,2,4-triazol-3-yl)methyl]-1,2-dihydro-2-oxo-4-(trifluoromethyl)-3-pyridinyl]oxy]benzonitrile. It has a molecular formula of $C_{17}H_{11}ClF_3N_5O_3$ and a molecular weight of 425.75 g/mol. It has the following structural formula:

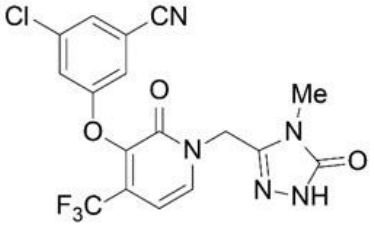


Figure 1: Structural formula of Doravirine

1.5 DOR metabolism and potential mechanisms for DDIs between hormonal contraceptives and ARVs

Concurrent use of hormonal contraceptives and ART can lead to DDIs, predominantly due to effects on liver metabolism of the therapeutics.[11,12,27] In the liver, cytochrome P450 (CYP) enzymes catalyze many important reactions, with the most significant enzyme for contraceptive metabolism being CYP3A4. Many antiretrovirals, especially NNRTIs and PIs are substrates, inhibitors, and/or inducers of CYP 450 enzymes, including CYP3A4, resulting in increases or decreases in the concentration of concomitantly administered drugs, including hormonal contraceptives.[27] Such interactions could lead to decreased contraceptive effectiveness (increasing risk of unintended pregnancy), decreased concentrations of ART effectiveness (associated with resistance and/or HIV disease progression), or increased ART or contraceptive

toxicity. Etonogestrel (ETG) and medroxyprogesterone acetate (MPA) hormones are known substrates of and metabolized by CYP3A. However, due to the limited data available on the effect of various hormonal contraceptive methods on DOR metabolism, the study will provide valuable insight regarding these DDIs.

1.6 Rationale for study design

While DOR-containing ART has been evaluated in two large clinical trials, only 16-17% of the study participants were women and only 6-10% of them were African.[2,28] In an epidemic, where the gendered majority affected by the disease are women of reproductive age living in Africa, it is imperative to conduct a trial evaluating outcomes among and specific to African women. Further underscoring the relevance of this issue is a notable data gap for DOR regarding DDIs with the most common leading hormonal contraceptive methods offered in public family planning clinics in Africa.

Dr. Patel (Co-PI) is currently conducting a study evaluating the DDIs between contraceptive implants and EFV- and DTG-containing ART in Kenya.[1] Therefore, the proposed study is well-poised to leverage this ongoing study in Kenya and efficiently address the current knowledge gaps regarding the use of DOR in women of reproductive age in South Africa. The Kenyan study, PARVI, is parallel to the proposed study with some key differences, namely:

1. A change in ART regimen did not occur in PARVI; women were continuing their current ART regimen and simply starting a contraceptive method.
2. the PARVI study team did not offer women a contraceptive method; instead, as women chose a method of interest to the study, the study staff approached the women to enrol in this study.

Otherwise, the study procedures, including the timing of study visits and sample collections are parallel in both studies.

Our intention is to study potential DDIs between DOR and the most common contraceptive methods used by WLHIV in an African context, which generally include short- (e.g., oral contraceptive pills (OCPs)/combined oral contraceptives (COCs)), intermediate (e.g., injectable) or long-acting (e.g., implants or intra-uterine device (IUD)) methods. Since the manufacturer of DOR has already conducted the industry standard PK study with DOR and a COC product, containing ethinyl estradiol and levonorgestrel,[29] which did not demonstrate any bidirectional DDI, we have chosen to exclude this method from the current study. Thus, the current EPIC study focuses on intermediate- and long-acting contraceptive methods, which have different PK profiles than daily administrated oral drugs and may be more susceptible to potential DDIs with DOR.

Participants enrolling in the study will not be randomized to groups, including contraceptive methods, of the trial, and instead participants will be given the choice to select a contraceptive method group where applicable. Those already on EFV- or DTG-containing ART and wishing to switch to DOR-containing ART will be included in the DOR groups (Groups 1-4, Table 1) and those already on DTG and wishing to remain on DTG will be included in the DTG group (Group 5, Table 1).

1.7 Justification for not randomizing women to a contraceptive method

Randomization is not essential for and rarely done in the context of PK studies. In this PK study, contraceptive method related persistence and high continuation rates are crucial for the duration of the study for the PK sampling while on ART to effectively assess DDI. The study team believes that prioritizing contraceptive method informed choice through counselling and education and making allowance for women to select a method that best suits their lifestyles and pregnancy intentions for the future will likely increase women's adherence and persistence on that self-selected method. The study investigators acknowledge the possibility that the group of women choosing one contraceptive method over another may have some fundamental differences.[30] To address this, we plan to utilize multivariate models which will help account for confounding by potential covariates, such as body mass index (BMI) or age. We do not have reasons to believe that selection of the contraceptive method by the women would bias the study in ways other than

via potential confounders. Additionally, PK studies, including this one, are powered on the variance detected in hormone concentrations within groups, which already account for variation within the group of factors such as BMI or age. Thus, this study is appropriately powered for the primary outcome to detect differences in hormone concentrations that may exist across the groups.

1.8 Justification of choice of contraceptive methods for the EPIC study

The study investigators have elected to include intramuscular depo-medroxyprogesterone acetate (IM DMPA), sub-cutaneous medroxyprogesterone acetate (SC MPA), the etonogestrel (ETG) implants and non-hormonal IUD for the reasons summarised below. As noted earlier, the pharmaceutical manufacturer of DOR has already conducted the industry standard PK study with DOR and a COC product, containing ethinyl estradiol and levonorgestrel,[29] therefore, the investigators have prioritized greater profiling of DOR with different, commonly used contraceptive methods over repeating a PK study with the same therapeutics, even if conducted in a different population.

1.8.1 DMPA

DMPA (150 mg of depo-medroxyprogesterone acetate (MPA)/ml IMI) is the most commonly used injectable contraceptive worldwide, and the most commonly used method of reversible injectable contraception in sub-Saharan Africa. In perfect use, DMPA is highly effective and with consistent and correct use has a 0.2% failure rate; typical use failure rates are higher (~6%).[31] Since SC MPA (104 mg of medroxyprogesterone acetate (MPA)/ml SC) was recently registered in South Africa, and can be self-administered, it may be a method suitable for community-based distribution and teaching women how to safely perform self-administration of the injectable is paramount, potentially increasing ease of contraceptive access and continuation without carrying any additional risks above what DMPA may already carry.[32]

Advantages of DMPA include its ease of administration, its ability to be used covertly, and the fact that one injection lasts for 3 months plus a 'grace period' of 4 weeks if a woman is late for her next injection. The short follow-up period for this method on the EPIC study will assure adherence to the contraceptive method as only one dose of the injectables will be required. On exit, additional doses will be offered to the participant.

Although side effects or adverse events (AEs) may be experienced by women using this method (e.g., headache, dizziness, mood changes, acne), major problems are rare. Menstrual irregularity and spotting, along with amenorrhea, are the most common side effects.[33] While frequently cited as the main reason for early discontinuation, menstrual irregularity is considered a nuisance, and is common for all progestin-only methods, and does not present a health risk for the user.

1.8.2 Contraceptive implants

Contraceptive progestin implants are thin rods inserted under the skin of a woman's arm. The most widely available implant in South Africa is currently Implanon®/Nexplanon®/Implanon NXT®, containing etonogestrel (ETG, 3-keto desogestrel). Implanon® consists of a single rod of ethylene vinyl acetate and contains 68 mg of ETG; it is manufactured by Merck and is approved for 3 years.

Implants are highly effective and user independent, with failure rates of <1% for both perfect and typical use since no user action is required after placement. Continuation rates for implants average ~90% at the end of the first year and 70% by the end of the third year.[34]

During the first year of implant use many women experience prolonged or irregular bleeding or both; in subsequent years, bleeding patterns tend to improve. As with other hormonal contraceptives, headache, minor weight increase, skin problems (such as acne), dizziness, and mood changes have been associated with use of progestin implants.[35]

1.8.3 Non-hormonal copper IUD

The NOVA T-380 non-hormonal IUD consists of a T-shaped polyethylene frame wound with copper wire, along with two monofilament threads to aid in removal of the IUD. IUDs may be left in place for up to 5 years. IUD continuation rates vary significantly and may range from 78% in a two year randomised trial in South Africa to 92% in the randomised, multicentre, open-label ECHO trial.[36-38]

Non-hormonal IUDs are extremely safe, effective, reversible, and are available worldwide, including in sub-Saharan Africa, but issues with demand, provider bias, and supplies have limited their use in most of sub-Saharan Africa.[39,40] Provider concerns about IUD use, especially in young nulliparous women, include beliefs that IUDs may increase the risk of pelvic inflammatory disease (PID) and thus tubal infertility or ectopic pregnancy. IUD use in young women and those at high risk of sexually transmitted infections (STIs) has been limited in the past by such concerns. Data suggest that IUDs do not increase the risk of PID in nulliparous women beyond a small increased risk for all women post-insertion. In a pooled analysis of the WHO clinical trials, the overall rate of PID among 22,908 IUD insertions and with 51,399 years of follow-up was 1.6/1000 woman-years (w-y) of use.[41] Additionally, IUDs do not cause tubal infertility[42] or ectopic pregnancy.[43] Even among WLHIV, PID rates with IUD insertion are low and do not vary by level of HIV disease severity.[44-46] IUDs are becoming more widely used in some African settings.[47]

Non-hormonal IUD users may experience heavier periods than they did before IUD insertion and may have more dysmenorrhea. However, data do not support a drop in haemoglobin as a result of IUD use.[36] Moreover, no other non-hormonal, highly effective, long-acting, reversible contraceptive method is available.

2.0 OBJECTIVES AND HYPOTHESES

2.1 Co-Primary Objectives: Pharmacokinetics

- To evaluate any associations between DOR exposure and hormonal contraceptive use in the four groups of DOR + 1) ETG implant, 2) IM DMPA, 3) SC MPA, or 4) non-hormonal IUD users by generating mean hormone concentrations at 12 weeks for IM and SC DMPA or 24 weeks for ETG implants and IUD groups; and
- To evaluate any bi-directional associations between hormonal contraceptive exposure and DOR use by generating mean DOR concentration at 24 hours ($C_{24\ hours}$) **per Table 2.**

Hypotheses 1:

- The mean implant hormone concentrations for DOR + ETG implant at 24 weeks after implant placement will be similar (i.e. geometric mean ratio [GMR] within 0.80 and 1.25) to the mean implant hormone concentrations for DTG + ETG implant (historical controls from Dr. Patel's current PARVI study in a similar population in Kenya). The mean MPA concentrations for DOR + IM DMPA or SC MPA at 12 weeks after DMPA/MPA administration will be similar (i.e. GMR within 0.8 and 1.25) to the mean DMPA concentrations for DTG + DMPA (contemporaneous study group).
- The mean $C_{24\ hours}$ of DOR in the ETG implant and MPA groups will be similar to the non-hormonal contraceptive method (i.e. the non-hormonal IUD) group.

2.2 Secondary Objectives

To measure DOR-containing ART's efficacy, via HIV viral load <40 copies/mL, at 12-24 weeks after contraceptive initiation among women of reproductive age using hormonal and non-hormonal contraceptives.

Hypothesis 2: The proportion of women suppressed (defined as HIV viral load <40 copies/mL) at 16-30 weeks after DOR-containing ART initiation will be similar to a contemporaneous or

historical comparison of proportion of women suppressed with non-DOR containing ART from the same study population/sample.

2.3 Exploratory Objectives

- Safety, including side effects, satisfaction, and continuation rates of both the hormonal contraceptive method and ART will be assessed; and
- To qualitatively explore decision-making around ART and contraceptive options, study experiences of ART switch and use of contraceptive method, including self-administration of SC MPA, and to describe self-reported experiences of social harms and social benefits related to study participation.

Hypotheses 3: Safety, satisfaction, and continuation rates of the various contraceptive methods will be similar to each other at 12-24 weeks after contraceptive initiation. We will gain interesting insights into women's decision-making around ART and contraceptive method options and be uniquely positioned to describe experiences of self-administration of SC MPA.

3.0 STUDY DESIGN OVERVIEW

3.1 Description of study design

This is an observational, parallel group PK study, investigating a cohort of women of reproductive age (18-45 years) living with HIV. This cohort of women will be enrolled in the study if they are already on South African standard-of-care 1st line ART, which is currently largely either EFV- or DTG-containing ART and have demonstrated viral suppression within the last three months. In addition, this group of women should not currently be on any hormonal contraceptives or received IM DMPA or SC MPA in the last two months prior to study screening but interested in initiating one of the study contraceptive method in the next 6 weeks. A total of 5 groups of women will be recruited for this study (minimum participants n=21 per group or total n=105; **Table 1**). Groups 1-4 will comprise of women switching from their current ART to DOR-containing ART, and 6 weeks after DOR initiation (for a lead-in period with DOR), the woman will be offered a choice of ETG implant, IM DMPA, SC MPA, or non-hormonal IUD. The 5th Group will comprise of women remaining on DTG containing ART and willing to initiate IM DMPA. Group 5 participants will already be on DTG-containing ART, and because they will not be switching their ART, they can initiate the IM DMPA without any lead-in periods (Figure 2).

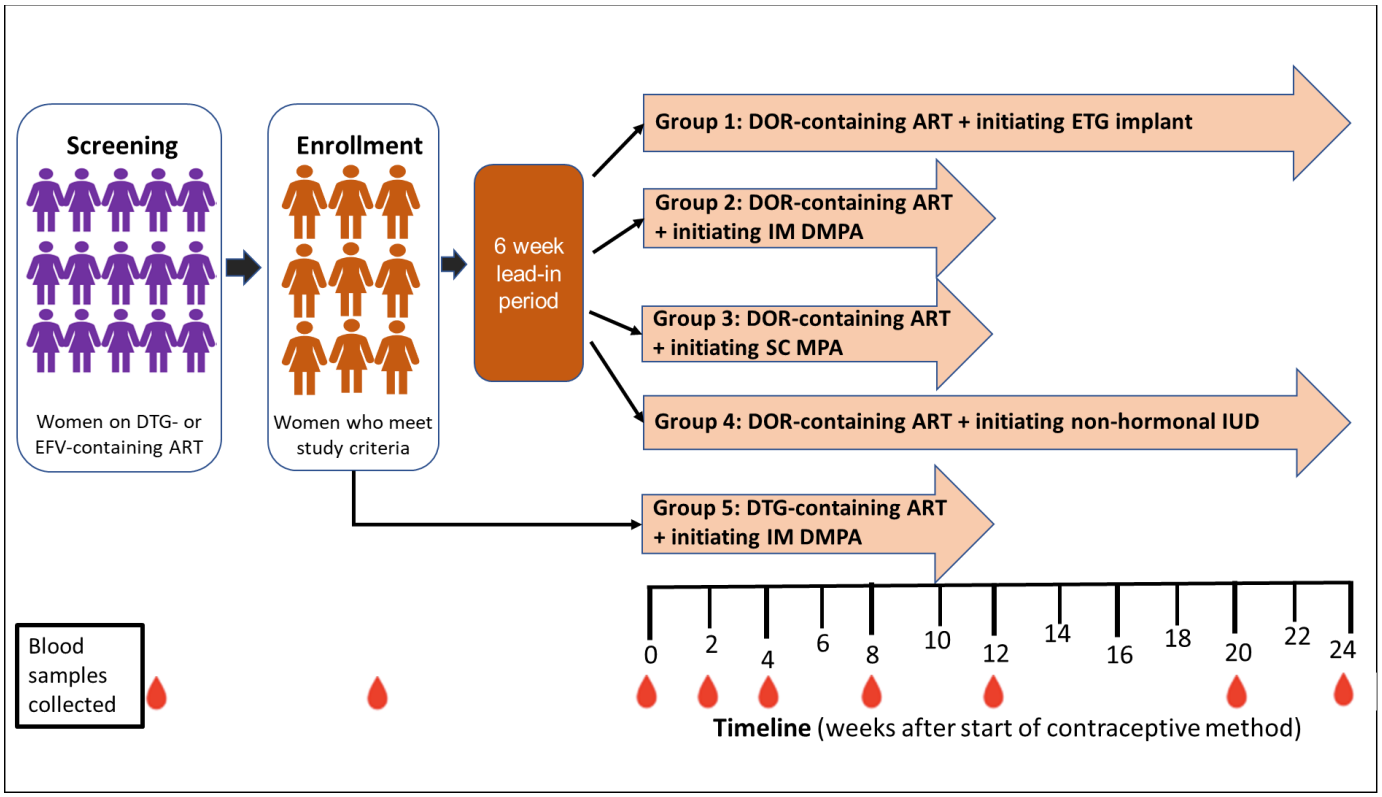


Figure: 2 EPIC study design schematics

3.2 Summary of major endpoints

The major study endpoints are PK parameters at 12 or 24 weeks after contraceptive initiation, depending on the contraceptive method.

3.3 Site

This is a single-site study conducted at the Wits-RHI Research Centre Clinical Research Site (RC CRS), part of a leading African institute focusing on research within the areas of HIV, sexual and reproductive health (SRH) and vaccine preventable diseases (VPD) and more recently COVID-19 prevention and treatment research. Wits RHI RC CRS is an NIH and Division of AIDS (DAIDS) clinical research site and are part of a NIH-supported Clinical Trials Unit. Additionally, Wits RHI is a UNAIDS, USAID, WHO and South African Medical Research Council (MRC) collaborating partner. The organization's focus ranges from investigating HIV prevention technologies and improving approaches on HIV diagnoses, care and treatment to optimizing ART and developing models of care for men and women as well as key populations and marginalized groups such as adolescent girls and young women (AGYW), sex workers, migrants and mobile populations while adhering to the principles of good participatory practice (GPP) and community engagement.

Wits RHI has a regional, national and international footprint running research projects and providing direct service delivery in various districts across the nine provinces of South Africa (SA). Their footprint across the African continent also includes research and technical assistance projects with active collaborations in Uganda, Rwanda, Kenya, Tanzania, Malawi, Mozambique, Zambia, Zimbabwe, Namibia and eSwatini. Wits RHI develops and delivers innovative, locally relevant, evidence-based solutions to improve the health and well-being of the people of South Africa, the African region and globally. Within SA, Wits RHI has a close working relationship with both the provincial and national Departments of Health (DoH) and supports the DoH as the stewards of the country's health system to strengthen the response to the HIV/AIDS and reproductive health related epidemics.

Wits RHI is especially suited to support the proposed project because of the well-established research infrastructure; well-equipped network of clinical, pharmacy, and laboratory facilities that conform to the highest local and international standards and the highly experienced clinicians, nurse counsellors with specialized adherence and motivational interviewing skills, medical laboratory scientists, pharmacists, community, behavioral and social science staff. Wits RHI has established three Community Advisory Boards (CAB) – namely the Youth, HIV Prevention and HIV Treatment CABs, to support the broad spectrum research agenda, strong collaborative relationships with local hospitals, public health clinics, and other local community resources and a proven track record of working effectively with local community leaders and residents. Key resources of the Wits RHI Research Centre RC CRS are described below. All resources and facilities are immediately available and are adequate to support the scope of work in the proposed timeframe

The Wits RHI RC CRS is a large (1.840m^2) purpose-built research clinic housed in the basement of the former University of the Witwatersrand student residence in the vulnerable inner-city urban regeneration zone known as the Hillbrow Health Precinct (HHP) in Region F, Johannesburg. The Wits RHI RC CRS provides a range of clinical, counselling and laboratory services that are fully compliant with local and international regulatory standards.

3.4 COVID-19 containment measures

The Wits RHI RC CRS will ensure that infection identification and control procedures are in place and that an adequate supply of personal protective equipment (PPE) is available as per institutional standard operating procedures (SOPs), and national and international guidelines.

4.0 STUDY POPULATION, ACCRUAL AND FOLLOW-UP

4.1 Description of study population

The study population consists of 18-45-year-old (inclusive) WLHIV currently virally suppressed on 1st line ART

4.2 Time to complete accrual

We anticipate accrual will take ~ 9-12 months from study initiation to complete, and the last participant will complete study follow-up 15-18 months after study initiation.

4.3 Expected duration of participation

Participants will be followed for the 6 weeks of oral lead-in period to ensure they tolerate the DOR -containing ART where applicable, then followed for an additional 12-24 weeks while using the contraceptive method. We anticipate following each participant for 18-30 weeks in total depending on contraceptive method.

4.4 Recruitment

Recruitment for this study will be led by the Wits RHI RC CRS community team consisting of a Community Liaison Officer (CLO) and Community Health Workers (CHWs) who have more than 10 years of experience recruiting in Hillbrow and surrounding areas and have successfully met and exceeded site accrual targets in all studies conducted since 2010. The team is well-suited to developing innovative recruitment methods and collaborating with local stakeholders to ensure that they achieve the accrual rate needed and enroll WLHIV between the ages of 18-45 years on ART who clearly comprehend the study objectives and the level of commitment required of them for the duration of the study. The team will leverage long-established recruitment strategies refined over years of clinical research implementation to initiate a multi-faceted approach to identify and timeously enroll a cohort of eligible women. Wits RHI staff will recruit participants in the City of Johannesburg (COJ) district from a variety of sources across Region F. Strategies will include, but are not limited to:

1) Identifying women who are either on EFV- or DTG-containing 1st line ART regimens through peer referrals.
2) Active recruitment by Wits RHI community health workers and community liaison officer in identifying women on ART who are interested in initiating intermediate- or long-acting contraceptive methods.
3) Recruiting eligible WLHIV from collaborating family planning or ART clinics, targeting those enrolled in HIV care and virally suppressed
    a. Recruiting from within interested WLHIV, those willing to switch to the study specified ART regimens and willing to consider initiation of one of the study contraceptive methods.
    b. Preliminary discussions with local clinics have indicated access to large numbers of WLHIV on HIV treatment but not on reliable contraception (pers comm). The study team will work with these clinics to recruit participants if interested.
4) Local research projects within Wits RHI and other health and social service providers serving the target study population.

Local IRB approved recruitment and educational materials will be used during these recruitment sessions to educate women about the study as well about the side effects and benefits associated with ART and contraceptive uptake. Interested individuals will be followed-up with a phone interview to assess their interest in participating in this study. As the study team proceeds with recruitment, they will identify strategies that are highest yielding in terms of accrual and shift focus to primarily rely on maximizing the screen:enrol ratio of participants.

Safe recruitment practices will be implemented in line with COVID-19 risk reduction practices including use of PPE and social distancing as well as informed by routine updates to guidelines in the Wits RHI COVID-19 pandemic site specific SOPs.

4.5 Inclusion criteria

For the EPIC study, participants must meet all of the following inclusion criteria to be eligible to participate in this research study:

1. Female,
2. HIV-positive,
3. Aged 18-45 years,
4. Currently on 1st line ART (namely EFV- or DTG-containing ART),
5. Have documented or confirmed viral suppression for HIV (defined as <40 copies/mL) within 3 months prior to study screening and after the start of the current ART regimen,
6. Contraception use:
   a) Not currently on reliable contraception and intending to or willing to initiate use of study hormonal/non-hormonal contraceptive methods 6 weeks after DOR lead in period (and willing to continue use for subsequent 12 to 24 weeks),
7. Able and willing to comply with all study procedural requirements,
8. Able and willing to provide informed consent for study participation in either English or Zulu,
9. Able and willing to provide adequate locator information, as defined in site SOPs,
10. Negative pregnancy test at Screening and Enrollment, and
11. At Screening and Enrollment, agrees not to participate in other research studies involving drugs, medical devices, vaginal products, or vaccines for the duration of study participation.

4.6 Exclusion criteria

Participants who present with any of the following will **not** be included in the study:

1. Currently on 2nd line, 3rd line, or salvage ART regimens,
2. Currently pregnant or intending to become pregnant within the next 6 months,
3. Currently breastfeeding or intending to breastfeed within the next 6 months,
4. Use or anticipated use of drugs for the duration of the study period known to interact with hormonal implants, DMPA/MPA, or the respective ART regimen (**Table 3**),
5. Current or planned concomitant use of other hormonal contraceptives,
6. Currently obese (BMI≥30),
7. Has any of the following laboratory abnormalities at Screening Visit:
   a) Haemoglobin abnormality Grade 2 or higher
   b) Calculated creatinine clearance less than 50 mL/min by the Schwartz Equation,
   c) Evidence of chronic Hepatitis B infection,
8. Per participant report at Screening and Enrollment, intends to do any of the following during her study participation period:
   a) relocate away from the study site
   b) travel away from the study site for a time period that would interfere with product resupply and study participation,
9. Per participant report and/or clinical evidence of any of the following:
   a) Known adverse reaction to any of the study products (ever),
   b) Participation in any other research study involving drugs, medical devices or vaccines within 60 days of enrolment,
   c) At Enrollment, as determined by the PI/designee, has any significant uncontrolled active or chronic cardiovascular, renal, liver, hematologic, neurologic, gastrointestinal, psychiatric, endocrine, respiratory, immunologic disorder, metabolic bone disease or infectious disease,
10. Has any other condition that, in the opinion of the PI/designee, would preclude informed consent, make study participation unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives.

Table 3: Prohibited concomitant medications with doravirine-containing ART

Drug name	Drug class/type
Carbamazepine	Anticonvulsants
Oxcarbazepine	Anticonvulsants
Phenobarbital	Anticonvulsants
Phenytoin	Anticonvulsants
Rifampicin	Antimycobacterials

Rifapentine	Antimycobacterials
St. John's wort (*Hypericum perforatum)*	Herbal remedy for depression and anxiety
Mitotane	Cytotoxic agent
Enzalutamide	Androgen receptor inhibitor
Lumacaftor	Cystic fibrosis transmembrane conductance regulator

4.7 Screening and enrollment

WLHIV of reproductive age will be recruited from HIV care programs in Johannesburg, South Africa and invited to screen for enrollment in this study. If a woman is interested, she will be pre-screened either in person or telephonically to determine presumptive eligibility and scheduled for an in-person screening visit at the study site. At the screening visit, she will be taken to a separate room at the facility to undergo informed, written consent and a unique study ID will be assigned to her. Following informed consent, relevant study procedures will be conducted, and specimens will be collected to assess eligibility. Once the results have been returned to the study team, which is anticipated to take between 1-48 hours, the study staff will inform the participant in-person or by phone, and if eligible or ineligible. If eligible, she will be scheduled for a return study visit for enrollment. At the time of enrollment, the participant will be provided sufficient study product (DOR-containing ART) for the lead in period if choosing to enroll in Groups 1-4. For participants in Group 5, they will proceed with receiving IM DMPA and continuing their DTG-containing ART. Participant will be considered fully enrolled when contraceptive method is chosen.

4.8 Co-enrollment guidelines

Participants may not take part in other research studies involving drugs, medical devices, products or vaccines after the Screening Visit and while taking part in the EPIC study. Exceptions to this guideline may be made for participants to co-enrol in the following types of studies at the discretion of the PI/designee:

- Participants may take part in ancillary studies approved by the PIs.
- Participants who become pregnant may take part in observational studies, including pregnancy registries through referrals to appropriate partners.

Should any participant report or should study staff discover concurrent participation in any other study after enrolling in the study, the PI/designee will consult the Senior Clinical Advisor regarding ongoing study product use and other potential safety considerations associated with co-enrolment.

4.9 Follow-up

After enrollment, the participant will return for scheduled visits up until approximately 12-24 weeks (+/- 2 weeks) after contraceptive method initiation. For participants in Groups 1-4, they will first have a lead-in period of 6 weeks to ensure they tolerate DOR-containing ART and to allow their prior ART regimen to wash out, especially if on EFV -containing ART. We are anticipating that the majority of women enrolling in this study will be on EFV-containing ART, and because EFV is a known potent inducer of CYP450 enzymes and known to influence PK parameters of both DOR and hormonal contraceptives, it is necessary to have a "washout" period for the EFV induction to decrease markedly over the next 6 weeks.[48] The participants will have these visits scheduled ahead of time, and the study staff will make a reminder text message or phone call the week and day before the appointment. Standard questionnaires, assessing safety and satisfaction, will be administered and blood and urine samples collected for various laboratory assessments at these visits.

4.10 Retention

The experience and commonly used effective strategies of the Wits RHI community team will be leveraged to ensure high retention rates among participants in the proposed study. These strategies include:

- Exclusion of participants who lack understanding of the research objectives or commitment to the research process, or who may experience personal challenges with compliance with study visits such as travel outside of the study area,
- Collection and verification of adequate participant locator information (including residential address, contact numbers and multiple alternate contacts if we are unable to make direct contact with the participant,
- Regular update and verification of locator information at every study visit along with reminders to contact the study team should details change between visits,
- Visit reminders for all enrolled participants (text message or phone call) a week before and a day prior to each scheduled study visit (Participants who do not attend a scheduled visit will receive a phone call the day after the scheduled visit and as needed until the visit is attended),
- Provision of long-distance transport (e.g. bus tickets) or additional reimbursement (with ethics approval) for participants who relocate,
- Conduct of off-site visits (with participants permission) for those who may miss a visit at a venue of their choice.

5.0 STUDY PRODUCTS

5.1 DOR-containing ART

5.1.1 Regimen

Each participant will be initiated in one of five groups, four of which contain the use of DOR 100mg oral tablet taken daily 18 or 30 weeks total (6 weeks lead in and 12-24 weeks (depending on the self-selected method of contraception) following contraceptive initiation):

Table 4: ART regimen, contraceptive method and total follow-up period per group

Group	ART regimen, contraceptive method and total follow-up period per group
Group 1	100mg DOR-containing ART + 68mg ETG implant (30 weeks)
Group 2	100mg DOR-containing ART + 150mg IM DMPA (18 weeks)
Group 3	100mg DOR -containing ART + 104mg SC MPA (18 weeks)
Group 4	100mg DOR -containing ART + 1 non-hormonal IUD device (30 weeks)
Group 5	50mg DTG -containing ART + 150mg IM DMPA (18 weeks)

5.1.2 Administration

Delstrigo® tablet (100 mg of DOR, 300 mg of lamivudine, and 300 mg of tenofovir disoproxil fumarate)

Study participants will be instructed to take one Delstrigo® oral tablet daily for the 18-30-week study period. Delstrigo® can be taken with or without food and should be taken close to the same time each day. If a participant misses a dose, the missed dose should be taken as soon as possible, unless the next dose is estimated to be due within 12 hours. If the next dose is estimated to be due within 12 hours, the missed dose must be skipped. The next dose must be taken as originally scheduled.

5.1.3 Study product formulation

Delstrigo® is a film-coated yellow, oval-shaped, tablet of dimensions 21.59 mm x 11.30 mm, debossed with the corporate logo and 776 on one side and plain on the other side. Each pill contains 100 mg of DOR, 300 mg of lamivudine, and 300 mg of tenofovir disoproxil fumarate. The tablets include the following inactive ingredients: croscarmellose sodium E468; hypromellose acetate succinate; magnesium stearate E470b; microcrystalline cellulose E460; silica, colloidal anhydrous E551; sodium stearyl fumarate. The tablets are film coated with a coating material containing the following inactive ingredients: carnauba wax E903, hypromellose E464; iron oxide yellow E172; lactose monohydrate; titanium dioxide E171; and triacetin E1518.

Delstrigo® should be optimally stored in the site pharmacy between 20°C to 25°C and kept in the original bottle. Excursions are permitted between 15°C and 30°C (59°F and 86°F). Study participants will be counselled on storage prior to receiving study drugs.

5.1.4 Supply, accountability and dispensing

5.1.4.1 Supply

Delstrigo® Merck Sharp & Dohme B.V. will oversee the manufacture of the tablet and release the tablets under Good Manufacturing Practices (GMP). Delstrigo® tablets are supplied by Merck & Co, Inc. (White House Station, New Jersey, USA).

5.1.4.2 Accountability

The Wits RHI CRS Pharmacist is required to maintain a complete record of all study products received and subsequently dispensed. All study products not dispensed must be returned to the drug donor after the study is completed or terminated unless otherwise instructed by the supplying pharmacist/study donor. All study product dispensed to a participant must be documented by the clinic staff when dispensed. Any unused study products not returned must also be documented by the clinic staff.

5.1.4.3 Study product dispensing

Study tablets are dispensed only to enrolled study participants or clinic staff on behalf of the participant, upon receipt of a written prescription from an authorized prescriber. Authorized prescribers include the PI or licensed clinicians. Dispensing takes place on the day of enrolment and at each scheduled follow-up visit. The pharmacist will dispense one bottle of 30 tablets per month. Two bottles will be provided at enrolment for the lead in period to ensure adequate supply. Any unused tablets to be returned at next scheduled visit.

During study product use, participants will receive a new supply of tablets monthly. Product will be dispensed in quantities sufficient to last until the next scheduled study visit. In the event that additional study products between visits are needed, participants will be instructed to contact the study site. If the participant is unable to attend their next scheduled visit, it is up to the discretion of the PI/designee to allow the provision of additional study product. The PI/designee will document approval of this additional dispensation

5.1.5 Discontinuation of study product

General criteria for discontinuation of study product

Participants will be temporarily/permanently discontinued from study products by the PI/designee for any of the following reasons:

- Allergic reaction to the study product (Grade 3 or above, as per DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1, July 2017 and Addendum 1, (Female Genital Grading Table for Use in Microbicide Studies; dated November 2007)
- Positive pregnancy test
- Non-therapeutic injection drug use
- Serious Adverse Event (SAE) (senior clinical advisor to be notified, and guidance to be provided)

5.2 Subcutaneous medroxyprogesterone acetate (SC MPA) or (Sayana® Press)

SC MPA was registered (registration number: 45/21.8.2/1139) in South Africa in June 2019 per the SAHPRA website. Implementation plans as part of its inclusion in the revised draft contraceptive policy related to expansion of method mix have been delayed due to COVID-19. We include available information about it below, for ease of reference. Sayana® Press is a single-dose container with 104 mg medroxyprogesterone acetate (MPA) in 0.65 mL suspension for injection. Sayana® Press is indicated for medium-long term female contraception.

5.2.1 Administration

Sayana® Press 104 mg/0.65 ml suspension for injection
Sayana® Press may be administered by a healthcare professional (HCP) or when considered appropriate by the HCP, self-injected by the patient, with medical follow-up as necessary in accordance with local clinical guidance.

Administration of Sayana® Press will be initiated under the supervision of a nurse or study clinician at the site. After comprehensive counselling and training in injection technique and schedule of administration, patients may self-inject with Sayana® Press if their HCP determines that it is appropriate and with medical follow-up as necessary.

The Sayana® Press single-dose container should be at room temperature. It must be vigorously shaken just before use to ensure that the dose being given represents a uniform suspension. The contents are completely sealed inside the reservoir of the injector. The injector must be activated before use. The activation process pierces an internal seal so that the medicine can come out through the needle when the reservoir is squeezed. The liquid does not completely fill the reservoir. There is a small bubble of air above the liquid. A dose of 104 mg of MPA is given subcutaneously (into the fatty layer just under the skin), into the front upper thigh or abdomen every 3 months (12 to 13 weeks) for the 16-28-week study period. When the injection is being given, the injector must be used with the needle downwards. This ensures that the full dose of liquid is delivered out through the needle. The medication should be injected slowly for 5-7 seconds.

5.2.2 Study product formulation

The active substance is medroxyprogesterone acetate (MPA). The pre-filled injector contains 104 mg medroxyprogesterone acetate (MPA) in 0.65 ml. The other ingredients are macrogol, methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216), sodium chloride, polysorbate 80, monobasic sodium phosphate monohydrate, disodium phosphate dodecahydrate, methionine, povidone, sodium hydroxide and/or hydrochloric acid for pH adjustment and water for injection.

Sayana® Press is a white to off-white suspension for subcutaneous injection (an injection given under the skin). It is supplied in a single-dose container in the form of a pre-filled injector. Sayana® Press is available with a pack size of one single-dose container.

5.2.3 Supply and accountability

5.2.3.1 Supply

Pfizer Manufacturing (Belgium) will oversee the manufacture of the injection and release the subcutaneous injection under Good Manufacturing Practices (GMP). Sayana® Press is supplied by Pfizer Limited (Ramsgate Road, Sandwich, Kent, CT13 9NJ, United Kingdom).

5.2.3.2 Accountability

The Wits RHI RC CRS Pharmacist is required to maintain a complete record of all study products received and subsequently dispensed. All study product dispensed to a participant must be documented by the clinic staff when dispensed. Any unused study products not returned must also be documented by the clinic.

5.2.3.3 Study product dispensing

Study injection is dispensed only to enrolled study participants or clinic staff on behalf of the participant, upon receipt of a written prescription from an authorized prescriber. An authorized prescriber includes the PI or a licensed clinician directly responsible to the PI as noted on the FDA Form 1572. Dispensing takes place on the day of Visit 3 and at each scheduled follow-up visit. The pharmacist will dispense a single dose container every 12 weeks.

During study product use, participants will receive a new injection every 12 weeks. Product will be dispensed in quantities sufficient to last until the next scheduled study visit. In the event that

additional study products between visits are needed, participants will be instructed to contact the study site. If the participant is unable to attend their next scheduled visit, it is up to the discretion of the PI/designee to allow the provision of additional study product for administration remotely off-site. The PI/designee will document approval of this additional dispensation

5.3 Intramuscular depomedroxyprogesterone acetate (IM DMPA)

5.3.1 Administration

For women choosing IM DMPA, site staff will inject the initial IM DMPA injection at Visit 3. Subsequent injections will be given every 12 weeks at the study site. Sites will assess participants who are more than 4 weeks late for their DMPA injections for pregnancy prior to administering a subsequent injection.

5.3.2 Study product formulation

Medroxyprogesterone acetate sterile aqueous suspension 150 mg per 1 ml.

5.3.3 Supply and accountability

5.3.3.1 Supply

Pfizer Manufacturing (South Africa) will oversee the manufacture of the injection and release the intramuscular injection under Good Manufacturing Practices (GMP).

5.3.3.2 Accountability

The Wits RHI RC CRS Pharmacist is required to maintain a complete record of all study products received and subsequently dispensed. All study product dispensed to a participant must be documented by the clinic staff when dispensed. Any unused study products not returned must also be documented by the clinic.

5.3.3.3 Study product dispensing

Study injection is dispensed only to enrolled study participants or clinic staff on behalf of the participant, upon receipt of a written prescription from an authorized prescriber. An authorized prescriber includes the PI or a licensed clinician directly responsible to the PI as noted on the FDA Form 1572. Dispensing takes place on the day of Visit 3. The pharmacist will dispense a single dose container.

During study product use, participants will receive a new injection every 12 weeks. Product will be dispensed in quantities sufficient to last until the next scheduled study visit. In the event that additional study products between visits are needed, participants will be instructed to contact the study site. If the participant is unable to attend their next scheduled visit, it is at the discretion of the PI/designee to allow the provision of additional study product for administration remotely off-site. The PI/designee will document approval of this additional dispensation.

5.4 ETG implant

5.4.1 Administration

For women choosing ETG implant, trained and proficient clinicians and nurses will insert the implant under the skin of her inner upper arm using standard manufacturer recommended techniques. Sites will observe women for 10 minutes after implant insertion and she will be shown how to palpate for the rod. This will occur at Visit 3. Subsequent insertion is not required as the implant is active for up to 3 years. She will be given a letter to note when it will need to be removed after the active date.

5.4.2 Study product formulation

68mg of ETG in a single ethylene vinyl acetate co-polymer rod.

5.4.3 Supply and accountability

5.4.3.1 Supply

Merck Sharp Dohme (South Africa) will oversee the manufacture of the implant and release the implant under Good Manufacturing Practices (GMP).

5.4.3.2 Accountability

The Wits RHI RC CRS Pharmacist is required to maintain a complete record of study products received and subsequently dispensed. Study product dispensed to a participant must be documented by the clinic staff when dispensed.

5.4.3.3 Study product dispensing

ETG implant will be dispensed only to enrolled study participants or clinic staff on behalf of the participant, upon receipt of a written prescription from an authorized prescriber. An authorized prescriber includes the PI or a licensed clinician directly responsible to the PI as noted on the FDA Form 1572. Dispensing takes place on the day of Visit 3 defined in the EPIC study schedule.

5.5 Non-hormonal IUD

5.5.1 Administration

For women choosing a non-hormonal IUD, trained clinicians and nurses will insert the IUD using standard insertion techniques. Study staff will observe women for 10 minutes after IUD insertion. This will occur at Visit 3. Women will be provided a letter notifying the participant when it will need to be replaced for her records. The IUD will be active for up to 5 years.

5.5.2 Study product formulation

Non-hormonal intrauterine device (NOVA T 380)

5.5.3 Supply and accountability

5.5.3.1 Supply

Bayer (Pty) Ltd will oversee the manufacture of the IUD and release the IUD under Good Manufacturing Practices (GMP).

5.5.3.2 Accountability

The Wits RHI RC CRS Pharmacist is required to maintain a complete record of study products received and subsequently dispensed. Study product dispensed to a participant must be documented by the clinic staff when dispensed.

5.5.3.3 Study product dispensing

The non-hormonal IUD will be dispensed only to enrolled study participants or clinic staff on behalf of the participant, upon receipt of a written prescription from an authorized prescriber. An authorized prescriber includes the PI or a licensed clinician on the study delegation log and as noted on the FDA Form 1572. Dispensing takes place on the day of Visit 3.

5.6 Concomitant medications and practices

Study staff will be provided with a comprehensive list of drugs known to have drug-drug interactions with the study-related medications. With the exception of those listed as prohibited in Table 3, enrolled participants may use concomitant medications during study participation. Throughout the course of the study, prescription medications, over-the-counter preparations, medications used to manage or treat AEs, vitamins and nutritional supplements, and herbal preparations will be recorded as concomitant medications on a case report form (CRF) designated for that purpose.

Interactions with other medical treatments (including oral anticoagulants) have rarely been reported, but causality has not been determined. The possibility of interactions should be borne in mind in patients receiving concurrent treatment with other drugs.

5.7 Prohibited medications

The use of additional antiretrovirals are undesired for enrollment in this study. However, ultimately, if the participant deems necessary to initiate other antiretrovirals, we may choose to terminate study participation in such cases.

5.8 Condoms

All participants will be offered male and female condoms, which will be made available in the clinic and dispensed by clinic staff with the required levels of counselling and education related to correct use.

6.0 STUDY PROCEDURES

6.1 Overview of study procedures and evaluations

Once participants are enrolled in the study, 6 weeks after the start of DOR-containing ART (to account for a "washout/lead-in" period from the prior ART regimen), they will be ready to initiate their chosen contraceptive method, and study staff will call the participant in advance to remind them of this visit. The study team anticipates, based on national guidelines, that the majority of women screening and enrolling in this study will be on EFV-containing ART. Since EFV is a known potent inducer of CYP450 enzymes and known to influence PK parameters of both DOR and hormonal contraceptives, it would be necessary to have a "washout" period for the EFV induction to decrease markedly over the next 6 weeks.[48] The 6-week washout period has been used previously for similar PK studies when transitioning persons off of EFV- to non-EFV containing ART.[49,50] A second reason for the 6-week period without hormonal contraceptive use is to allow for a "lead-in" period so that those switching onto DOR-containing ART have some time to demonstrate tolerating the switch prior to starting the contraceptive method and regular PK sampling. After the 6-week "washout/lead-in" period, options for contraceptive methods will be offered for administration by the study staff, including ETG implants, IM DMPA, SC MPA, or non-hormonal IUD. All participants will be offered male or female condoms. For those participants wishing to have a non-hormonal IUD placed, this service will also be provided on-site. Women will have a choice of which contraceptive method they want and will not be randomized or assigned to a contraceptive method by the study team. Once a group's sample size of n=21 women enroll in the study, that group will be closed for any future enrollment; if a participant withdraws or terminates earlier than the planned terminal study visit, then enrollment in that group may be re-opened to achieve the target sample size.

Once enrolled, additional questionnaires and blood and urine samples will be taken at various time intervals for the various assessments (**Table 5**).

Table 5: Schedule of evaluations (week numbers are post contraceptive method start)

Protocol Activity	**Visit 1: Screening**	**Visit 2: Enrollment** (start of lead-in period)	**Visit 3:**	**Visit 4:**	**Visit 5:**	**Visit 6:**	**Visit 7:**	**Visit 8:** (implant /IUD)	**Visit 9:** (implant/ IUD)
Weeks (w) since DOR initiation			6w min.	8w	10w	14w	18w	26w	30w
Weeks (w) since contraception initiation			0w	2w	4w	8w	12w	20w	24w
Informed Consent	X								
Vital Signs	X	X	X	X	X	X	X	X	X
Study Registration		X	X						
Drug provision, when applicable		X	X		X	X	X	X	
Contraceptive Counselling	X	X	X	X	X	X	X	X	X

Syndromic STI assessment and management	X	X	X	X	X	X	X	X	X
Offering and provision of Hepatitis B vaccination if eligible		X*							
Laboratory									
Complete Blood Count (CBC)	X						X		X
Comprehensive Metabolic Panel (CMP)	X						X		X
HBsAg	X								
HBsAb	X								
HB core Ab	X								
Urine pregnancy test	X	X	X	X	X	X	X	X	X
HIV-1 RNA quantification (if no confirmation in medical records within the preceding 3 months)	X								
Assessment									
Review of concomitant medications	X	X	X	X	X	X	X	X	X
HIV-1 RNA quantification							X		X
Contraceptive hormonal PK assessment, via serum			X	X	X	X	X	X	X
ARV PK assessment, via plasma			X	X	X	X	X	X	X
Contraceptive & ART questionnaires (side effects and tolerability)	X		X**	X	X	X	X	X	X
Qualitative interviews, including social harms/benefits			X				X		X

*Offering and provision of Hepatitis B vaccination, if eligible, can be offered and provided at any subsequent study visit if participant declines for any reason at enrollment visit

**Visit 3 for Groups 1-4 only ART Questionnaire is completed, and for Group 5, both Contraceptive & ART questionnaires must be completed.

Women in the D/MPA groups will be followed for 12 weeks total after D/MPA administration. Women in the implant or IUD group will be followed for 24 weeks total after implant or IUD placement. Implant or IUD removals will be conducted by study staff upon request by the women, during the study. After the study ends, participants will be referred to local facilities for the implant or IUD removal and provided with detailed letters projecting out dates of viability of the methods concerned.

The study team will also enroll a DTG + DMPA group who will be followed for 12 weeks, as the comparator group for the DOR + DMPA group. The comparator groups for the DOR + implant group will be to the historical control group from PARVI study currently being conducted by Dr. Patel and colleagues in Kenya (**Figure 3**).

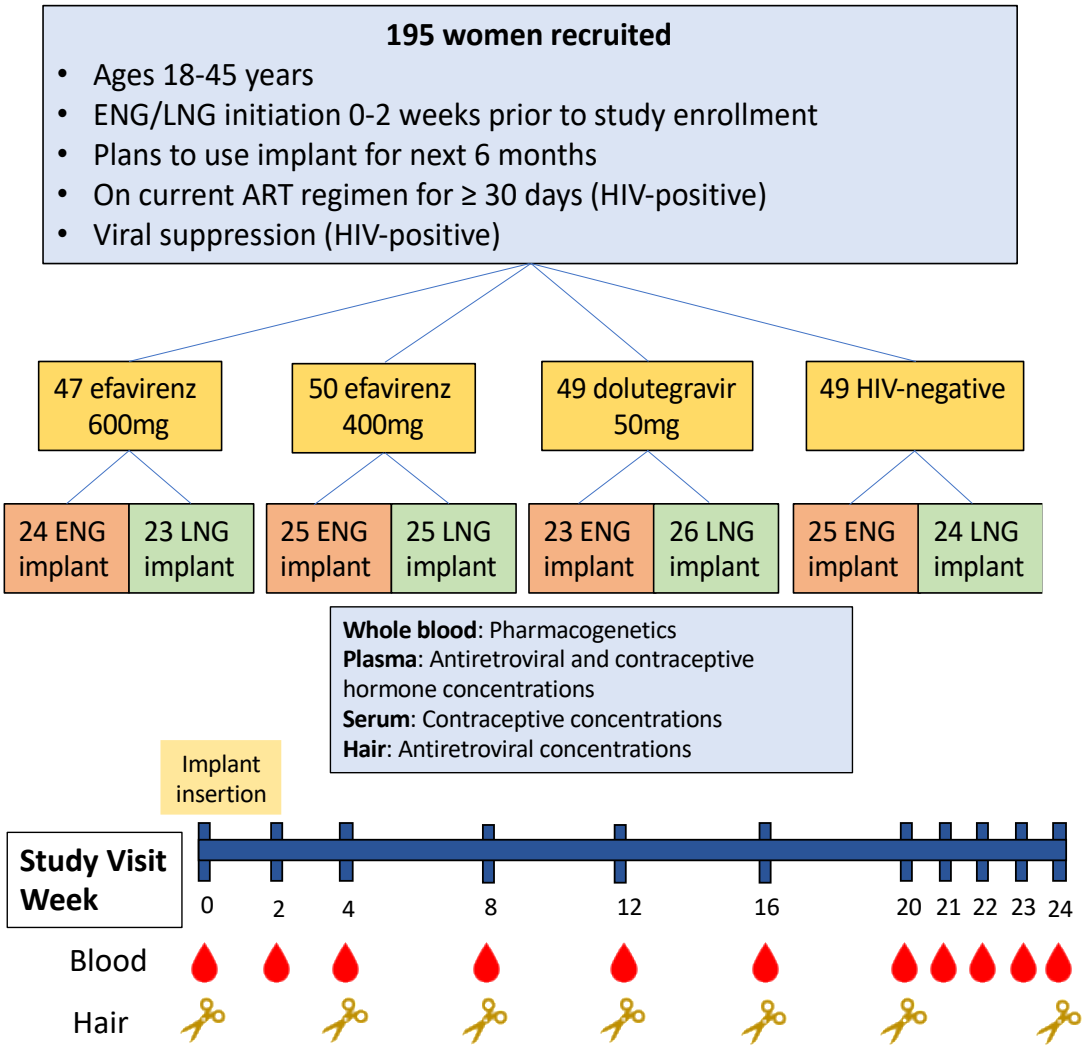


Figure 3: Schematics of PARVI study design, groups, and sample collection

6.2 Assays

Blood hormone concentrations: At each visit after study enrollment, 15-20 mL of whole blood will be collected in vacutainers containing ethylenediaminetetraacetic acid (EDTA) anticoagulant and/or in serum-separating tubes (SST) and processed within 30 minutes of collection, centrifuged at 3000 revolutions per minute for 10 minutes to separate plasma when needed, stored at -80^{0}C. Selected samples will be shipped frozen to University of Washington's (UW) International Clinical Research Center's (ICRC) repository for storage until ready for subsequent analysis, for the types of analyses where the assays or analytics are currently unavailable in-country and, therefore, cannot be conducted in South Africa, while other samples will be shipped frozen to local research laboratories for future analyses including for pharmacogenomics analysis, where the assays are currently available in South Africa. Specifically, serum samples for contraceptive hormone concentrations will be analyzed by Dr. David Erikson's laboratory at the Oregon Health and Sciences University in the USA which specializes in detection of exogenous and endogenous hormones, including implant hormones, which is currently only available in a handful of laboratories around the world. Dr. Erikson's laboratory has validated the use of liquid chromatography-heated electrospray ionization-tandem triple quadrupole mass spectrometry (LC-MS/MS) with the lower limit of quantification to 10 pg/mL for ETG.

Plasma ARV concentrations: At every visit with blood collection, we will also measure plasma trough ARV concentrations to detect any negative effects of the hormonal contraceptives on the concentrations of these ARVs. Dr. Scarsi's laboratory, the Antiviral Pharmacology Laboratory (APL) in the Center for Drug Discovery at the University of Nebraska Medical Center, will conduct this analysis. The APL is a CLIA-certified lab affiliated with the AIDS Clinical Trials Group. The

plasma samples will be analyzed using validated LC-MS/MS techniques. The LLQ in plasma for DOR is 5 ng/mL. The study investigators remain open to considering alternative, including local commercial, laboratories for analysis of ARV concentrations.

6.3 Contraceptive method related counselling

General contraceptive, and specifically method related adherence counselling is complex, however the site's study team has gained invaluable expertise on contraceptive counselling and contraceptive method delivery due to the teams participation in the ECHO trial[38]. This study included use of short, intermediate- and long-acting reversible contraceptive methods, including IM DMPA, the non-hormonal IUD and an LNG implant. The team is proficient in insertion and management of the ETG study through other prior and ongoing studies as well. The skills and lessons learned from the ECHO trial will be leveraged for use in the EPIC Study to guide participants to make informed choices related to their contraceptive method and to continue with contraceptive use beyond the life of the trial if they so choose. This counselling will support each method choice without bias.

Contraceptive counselling in the research clinic setting will include participants receiving comprehensive counselling on all contraceptive methods available in the study to enable them to make their own choice. As a research-focused clinic, the team encounters fewer limitations, such as high client volumes, as compared to public sector clinics, resulting in extra time and effort invested in the counselling process to ensure participants are well informed of the options available. The study team will adhere to, and when possible bolster, the content outlined in the National Family Planning guidelines in this research focused clinic. The site meets all the logistic, training and operational requirements related to being able to offer and manage insertion and support for use of the range of contraceptive methods. The nurses and PIs at the site have had extensive experience with contraceptive counselling and provision from former and ongoing studies.

At Screening and Enrolment visits, clinical staff will provide contraception counselling to potential study participants in the context of the study eligibility criteria related to pregnancy intentions and willingness to use an effective contraceptive method. All contraception counseling will be provided by the contraception staff in a client-centered manner and will guide and support each participant in making the best contraceptive method choice for her and in maintaining adherence to an effective method for the duration of the study at a minimum. When providing information on various contraceptive methods to study participants, the following will be provided for each method:

- Standard information in terms of:
  - administration
  - mechanism of action
  - level of effectiveness
- Information on the potential advantages and disadvantages

Contraception staff may use images from the World Health Organizations Family Planning: Guidance Global Handbook for Healthcare Providers to guide the discussions on the different contraceptive methods.[51]

At follow-up visits, participants will be provided with contraceptive method adherence counselling and side effects/AE management to maximize continuation on the chosen contraceptive method. This will be conducted in a client-centered manner by study staff. Issues discussed at the previous counselling session will be reviewed and discussed with the participant as needed. The clinic staff will assess whether the participant has any current concerns, questions, problems, or concerns with her current contraceptive method that would lead to non-adherence or intention to discontinue the method while on the study.

For participants with no concerns or problems, counselling sessions during follow-up may be brief and supportive. These sessions will also provide clear method use instructions and always reinforce key adherence messages.

For participants with concerns or problems with their current method, counselling sessions during follow-up may require more time. In some cases, only counselling and reassurance may be required to address the issues or problems. These sessions will also include discussion of the specific problems encountered and identification of potential strategies to address these issues. Some participants may experience side effects associated with use of contraception for e.g., prolonged bleeding, for which participants will be managed and treatment issued by the study clinical team. For care or issues related to contraception that falls outside the scope of the study clinic, referrals will be provided to the local health tertiary care providers within the study catchment area.

6.4 General study visits

Generally, at all study visits, components and procedures pertinent to: 1) administrative and regulatory; 2) behavioral/counseling; 3) clinical, 4) laboratory, and 5) study products/administration will be performed (more below per visit schedule). Follow-up visits will occur as per schedule with approximately 7 days before target date and approximately 7 days after target date.

A Screening Visit may take place up to 30 days prior to the Enrolment Visit. Multiple visits may be conducted to complete all required screening procedures, if necessary. Written informed consent will be obtained for all participants legally able to provide consent. For participants who do not meet the eligibility criteria, screening will be discontinued once ineligibility is determined and referrals provided to appropriate care.

NOTE: Participants who fail their first screening attempt may be re-screened at the discretion of the PI/Designee.

Visit 1 – Screening visit	
Component	**Procedures**
Administrative and Regulatory	• Obtain informed consent for screening and enrolment • Assign a unique Participant Identification (PTID) Number • Assess eligibility • Demographic information • Collect locator information • Provide reimbursement • Schedule next visit/contact
Behavioural/Counselling	• HIV ART counselling • Contraceptive counselling • Contraceptive & ART questionnaires (side effects and tolerability)
Clinical	• Medical/menstrual history • Concomitant medications • Physical exam • Vital signs • Disclosure of available test results
Laboratory – Urine	• Human chorionic gonadotropin (hCG)
Laboratory – Blood	• HIV-1 RNA quantification

	• Complete Blood Count (CBC) • Hepatitis B surface Antigen (HBsAg) • Hepatitis B surface Antibody (HBsAb) • Hepatitis B core Antibody (HBcAb) • Comprehensive Metabolic Panel (CMP), which includes creatinine clearance and hepatic function
Study Product/Supplies	• Offer male condoms • Offer Hepatitis B vaccination, if applicable

Visit 2 – Enrolment visit/ Visit 3*	
Component	**Procedures**
Administrative and Regulatory	• Re-assess and confirm eligibility • Review and update locator information • Provide reimbursement • Schedule next visit/contact
Behavioural/Counselling	• ART/Contraceptive counselling
Clinical	• Review/update medical/menstrual history • Review/update concomitant medications • Physical exam** • Vital signs • Disclosure of available test results • Collect AEs
Laboratory – Urine	• Human chorionic gonadotropin (hCG)
Study Product/Supplies	• Provision of contraception, if applicable • Provision of ART, if applicable • Provision of product use instructions • Offer male condoms

* Enrolment and Visit 3 will occur as 1 visit for participants in Group 5
**If applicable

Visit 3-6: Week 0/2/4/8	
Component	**Procedures**
Administrative and Regulatory	• Review and update locator information • Provide reimbursement • Schedule next visit/contact
Behavioural/Counselling	• ART/Contraceptive counselling • Adherence Assessment • Contraceptive & ART questionnaires (side effects and tolerability)
Clinical	• Review/update medical/menstrual history • Review/update concomitant medications • Initiation of chosen contraceptive method (Week 0 only) • Physical exam** • Vital signs • Disclosure of available test results • Collect AEs
Laboratory – Urine	• Human chorionic gonadotropin (hCG)
Laboratory – Blood	• Contraceptive hormonal PK assessment, via serum

	• ARV PK assessment, via plasma
Study Product/Supplies	• Provision of study products* • Provision of product use instructions* • Offer male condoms

**If applicable

Visit 7: Week 12	
Component	**Procedures**
Administrative and Regulatory	• Review and update locator information • Provide reimbursement • Schedule next visit/contact
Behavioural/Counselling	• ART/Contraceptive counselling • Adherence Assessment • Contraceptive & ART questionnaires (side effects and tolerability) • Qualitative interviews, including social harms/social benefit assessment^
Clinical	• Review/update medical/menstrual history • Review/update concomitant medications • Physical exam** • Vital signs • Disclosure of available test results • Collect AEs
Laboratory – Urine	• Human chorionic gonadotropin (hCG)
Laboratory – Blood	• Contraceptive hormonal PK assessment, via serum • ARV PK assessment, via plasma • Complete Blood Count (CBC)^ • Comprehensive Metabolic Panel (CMP)^ • HIV-1 RNA quantification^
Study Product/Supplies	• Provision of study products* • Provision of product use instructions* • Offer male condoms • Re-initiation of ART regimen as per NDoH guidelines^ • Linkage to care referral to local clinic for ART and contraceptive continuation^

^ DMPA groups only
** if applicable

Visit 7/8: Weeks 20 (Implant/IUD users only)	
Component	**Procedures**
Administrative and Regulatory	• Review and update locator information • Provide reimbursement • Schedule next visit/contact
Behavioural/Counselling	• ART/Contraceptive counselling • Adherence Assessment • Contraceptive & ART questionnaires (side effects and tolerability)
Clinical	• Review/update medical/menstrual history • Review/update concomitant medications • Physical exam** • Vital signs

	• Disclosure of available test results • Collect AEs
Laboratory – Urine	• Human chorionic gonadotropin (hCG)
Laboratory – Blood	• Contraceptive hormonal PK assessment, via serum • ARV PK assessment, via plasma
Study Product/Supplies	• Provision of study products* • Provision of product use instructions* • Offer male condoms

** if applicable

Visit 9: Week 24 (Implant/IUD users only)	
Component	**Procedures**
Administrative and Regulatory	• Review and update locator information • Provide reimbursement • Schedule next visit/contact
Behavioural/Counselling	• ART/Contraceptive counselling • Adherence Assessment • Contraceptive & ART questionnaires (side effects and tolerability) • Qualitative interviews, including social harms/benefit assessment
Clinical	• Review/update medical/menstrual history • Review/update concomitant medications • Physical exam** • Vital signs • Disclosure of available test results • Collect AEs
Laboratory – Urine	• Human chorionic gonadotropin (hCG)
Laboratory – Blood	• Contraceptive hormonal PK assessment, via serum • ARV PK assessment, via plasma • Complete Blood Count (CBC) • Comprehensive Metabolic Panel (CMP) • HIV-1 RNA quantification
Study Product/Supplies	• Offer male condoms • Re-initiation of ART regimen as per SA National Department of Health (NDoH) guidelines. • Linkage to care referral to local clinic for ART and contraceptive continuation

** if applicable

6.5 Interim/unscheduled visits

Interim visits may be conducted at any time during the study, for reasons such as administrative reasons (e.g., participant may have to re-schedule missed procedures), for product-related reasons, including to provide participants with a replacement tablets, or contraceptive,
at participant request, or follow-up and management of any SAEs. Such interim visits will be documented accordingly in the study records for the participant.

6.6 Product use end visit or early termination visit

Participants will undergo the Week 12 or Week 24 procedures at the Product Use End/Early Termination Visit.

6.7 Follow-up procedures for participants who temporarily hold or permanently discontinue study product

Due to the fundamental nature of the PK study, if a participant temporarily holds or permanently discontinues the study products, including the contraceptive method, then she will undergo study termination. For all early terminations or withdrawals, the study team aim to replace the enrolment slot for the participant to enable reaching the desired sample size numbers through to the end of the follow-up period.

6.7.1 Participants who become pregnant

During the 6-week lead in period on DOR, it is essential that the participant reduce risk of pregnancy as DOR safety during pregnancy is unestablished. Participant will be counselled to present to the study site immediately for pregnancy testing if they have concerned related to an unplanned incident pregnancy.

If any participants become pregnant during the study follow-up, she will be counselled on her options and provided appropriate referrals for antenatal and other care. Pregnant participants will immediately be discontinued from DOR and terminated from the study. Any unused study products not returned at that visit will be retrieved. She will be referred to relevant healthcare providers to be switched to her prior ART regimen or another updated regimen which is the current standard of care for pregnant WLHIV per SA NDoH guidelines. Study staff will follow up with exited pregnant participants regarding ART re-initiation and pregnancy outcomes. Where possible, the site will contact participants and collect infant outcomes 1 month postpartum, based on the estimated delivery date.

Upon documentation of a positive pregnancy test, the following procedures must be performed regardless of whether or not they are scheduled to be completed:

- CBC with platelets
- Blood creatinine for creatinine clearance
- Collection of PK and biomarker specimens
- Behavioral, adherence, and product preference/acceptability assessments

Given the overall short period of follow-up for this PK study, the study investigators do not plan to re-enroll a women post-partum into the study again if she wishes to, for example, initiate a contraceptive method of interest in the study.

6.7.2 Withdrawal

Participants may voluntarily withdraw from the study at their discretion for any reason at any time during follow-up. The PI also may withdraw participants from the study to protect their safety and/or if they are unwilling or unable to comply with required study procedures. The Senior Clinical Advisor must be notified of all terminations conducted per PI discretion. Participants also may be withdrawn if the sponsors, government or regulatory authorities, or site IRBs/ECs terminate the study prior to its planned end date. Every reasonable effort will be made to complete a final evaluation of participants who withdraw or are withdrawn from the study prior to completing follow-up. Study staff members will record the reason(s) for all withdrawals in participants' study records. In the event that participants who voluntarily withdraw from the study wish to re-join the study, they may resume product use (if applicable) and follow-up through their originally scheduled study exit date, pending consultation with the Senior Clinical Advisor.

6.7.3 Study end

At the end of study follow-up or termination, participants will be switched from DOR-containing ART to either their prior ART regimen or another regimen if a more updated recommendation exists as delineated by the SA NDOH standard-of-care. Such transitions will be coordinated with the existing HIV providers and clinics.

6.8 Specimen management

Blood and urine samples will be collected from the participants per the schedule outlined in **Table 5.** The study team anticipate collecting up to 15-20 mL or approximately 2 tablespoons of whole blood, in order to process the samples for real-time laboratory testing, such as HIV-1 RNA quantification, and for storage for the required PK studies. Samples will be centrifuged at 3000 revolutions per minute (RPM) for 10 minutes to separate plasma. Plasma or serum aliquots will be stored at -80^0 C on-site at Wits RHI RC CRS All samples for hormone and ARV concentration analyses will later be shipped frozen in batches to UW ICRC's repository for storage, from which it will then be sent to appropriate laboratories for subsequent analysis. Such shipment of samples from South Africa to the USA are necessary, as detailed above, due to currently unavailable laboratory assays or analytics in-country for certain analyses.

6.9 Biohazards containment

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate infectious disease, blood and physiological samples management procedures will be implemented. Safety precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study as recommended by the U.S. CDC, International Air Transport Association (IATA) and NIH guidelines. All biological specimens will be transported using packaging mandated by US Code of Federal Regulations (CFR) 42 Part 72. All dangerous goods materials, including diagnostic specimens and infectious substances, must be transported according to instructions detailed in the IATA Dangerous Goods Regulations. Biohazard waste will be contained according to institutional, transportation/carrier, and all other applicable regulations and destroyed appropriately.

6.10 Qualitative interviews

The study team will apply qualitative research methodology to conduct in-depth interviews (IDIs) with a subset of participants enrolled in the EPIC study at Visit 3 and study exit. The study team plans to enroll ~ 4-5 women from Groups 1-4 (total n=16-20 women) to better understand: 1) their experiences in switching from their current ART regimen to one containing DOR 2) their experiences with their contraceptive method of choice, and understand user experiences between IM DMPA vs. SC MPA, including potential use of self-injectable Sayana Press®.

Figure 4: Domains of the socio-ecological model

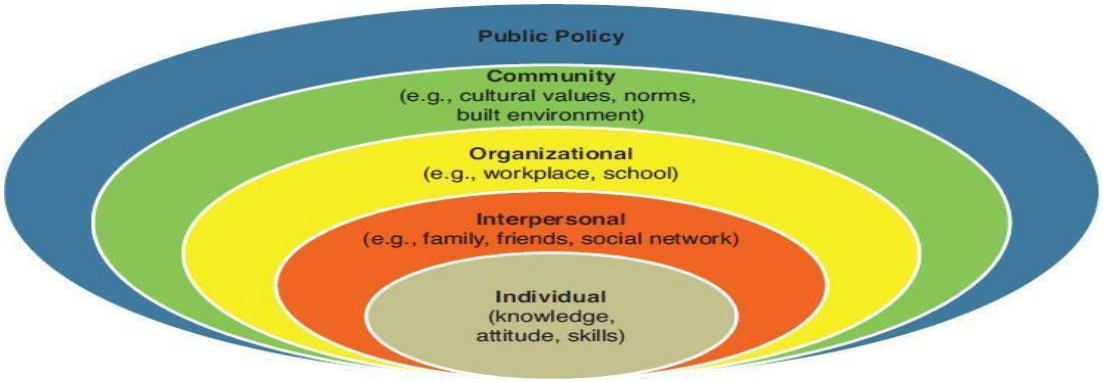


Table 6. Domains and example preliminary questions to query in IDIs with WLHIV enrolled	
Domains	Sample questions
Individual	How do you feel about your experiences with ART /contraceptive method to date?
Interpersonal	How has your partner, family, your circle of friends, or others influenced your use of ART/contraceptive method and your adherence to it?
Community	What do you think would be helpful to have in your community to support your and other young women's use of ART/contraceptive methods? Who do you think could be most helpful for this?

Organizational	What influence does your school, work, or clinic have on your use of your use of ART/contraceptive method? If it's a positive influence, how could this be amplified? If the influence is negative, how could this be reduced?
Public policy	How do you think the SA government could incorporate ways to support young women with their assessment of DOR for HIV treatment?

Using the socioecological model (**Figure 4**),[52] the team aims to explore influences, from individual, interpersonal, clinic, to structural/societal level, on both ART and contraceptive method use. Specifically, the interview guide covers the following domains: 1) knowledge and health literacy around ARVs, 2) priorities for and experiences in switches of ARVs, and 3) contraceptive use, decision-making, and experiences within study, including for SC MPA. An initial interview guide is included in **Appendix 1**, which will be iteratively modified as needed once the team begins piloting and conducting interviews. The IDIs will be conducted by trained, local interviewers in English or Zulu, digitally audio-recorded, and transcribed and translated into English. Another bilingual member of the study staff will verify accuracy of the translations against the audio files. The interviews will last for 30-60 minutes, and will be conducted serially, twice with the first time being at study enrollment and a second time at study exit (either visit Week 12 or Week 24 depending on contraceptive method type/group). Ultimately, the total number of interviews will be guided by saturation of themes.

7.0 CLINICAL DATA SAFETY REVIEW

7.1 Internal advisory committee

The study investigators have established an internal advisory committee to periodically review data on study implementation, including metrics on participant safety. The committee includes experts working in the fields of ART implementation and contraceptive use, including the lead investigators and 2 independent individuals/researchers from South Africa and the United States. The committee will meet quarterly via Skype/Zoom with the study investigators and will be governed by a charter that is agreed on by all members. Advisory committee members will be required to provide suggestions about the conduct of research and its implications for health policy in South Africa. Reports from all reviews and advisory committee recommendations will be provided for submission to overseeing IRBs/ECs.

A multi-tiered safety review process will be followed for the duration of this study. The study site investigators are the first category of this tiered system and are responsible for the initial evaluation and reporting of safety information at the participant level, and for alerting the Senior Clinical Advisor/Lead Investigator if unexpected concerns arise.

During the trial, the Senior Clinical Advisor/Lead Investigator will review safety reports and conduct calls with the local study team to review the data as appropriate.

The internal advisory committee has study oversight and is required to review participant safety data as no DSMB is planned for this study.

7.2 Adverse events definitions and reporting requirements

7.2.1 Adverse events (AE)

An AE is defined as any untoward medical occurrence in a clinical research participant administered an investigational product and which does not necessarily have a causal relationship with the investigational product. As such, an AE may be an unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of an investigational product, whether or not considered related to the product. This definition is applied to all study groups and is applied beginning at

the time of enrollment. The term “investigational products” for this study refers to use of DOR and DDIs with hormone contraception use.

Study participants will be provided instructions for contacting the study site to report any untoward medical occurrences they may experience. In cases of potentially life-threatening events, participants will be instructed to seek immediate emergency care. Where feasible and deemed medically appropriate, participants will be encouraged to seek evaluation at their local hospital. With appropriate permission of the participant, whenever possible, records from all non-study medical providers related to untoward medical occurrences will be obtained and required data elements will be recorded on study CRFs. All participants reporting an untoward medical occurrence will be followed clinically until the occurrence resolves (returns to baseline) or stabilizes while enrolled in the study. Post-exit, appropriate referrals will be provided at the discretion of the study clinician for ongoing care.

Study site staff will document all AEs reported by or observed in enrolled study participants in source documents regardless of severity and presumed relationship to study product.

Study staff will also report on CRFs the following subset of AEs reported by or observed in enrolled participants:

- All genital, genitourinary, and reproductive system AEs, including STIs
- All AEs of severity Grade 2 or higher
- All Serious AEs
- All AEs that result in permanent discontinuation of study product use
- All lab test abnormalities specified in the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, corrected Version 2.1, July 2017 and Addendum 1, (Female Genital Grading Table for Use in Microbicide Studies, dated November 2007), that are not otherwise associated with a reported clinical AE
- AEs that do not meet the above-listed criteria but do meet expedited reporting requirements per Section 7.4 below; this includes all congenital anomalies identified in the fetuses and/or infants of study participants

AE severity and laboratory tests will be graded per the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0, July 2017 and Addendum 1, (Female Genital Grading Table for Use in Microbicide Studies; dated November 2007), except that asymptomatic BV and asymptomatic candidiasis will not be reportable AEs. In cases where a genital AE is covered in both tables, the Female Genital Grading Table will be the grading scale utilized. In addition, changes in genital bleeding or irregular bleeding judged to be related to contraceptive use (hormonal or non-hormonal) will considered an AE unless it is known at baseline as a pre-existing condition. For those AEs requiring re-assessment, if the AE has not resolved or stabilized at the time of re-assessment, study staff will continue to re-assess the participant at least once per month while the study is ongoing or at the discretion of the PI/designee.

For any serious AEs (SAEs) or SUSAR (Suspected unexpected serious adverse event) that are continuing at a participant’s study exit visit, the PI/designee must establish a clinically appropriate follow-up plan for the AE. At a minimum, the SAE/SUSAR must be re-assessed by study staff 30 days after the participant’s study exit visit; additional evaluations also may take place at the discretion of the PI/designee. The same approach must be taken for any AEs that are found to have increased in severity at the study exit visit. After the study has ended, all AEs requiring re-assessment will be re-assessed at the discretion of the PI/designee. The Senior Clinical Advisor may advise study staff as to whether any additional follow-up may be indicated on a case by case basis. For AEs that are re-assessed after study exit for any reason, information on the status of the AE at the time of re-assessment will be recorded in source documents only — no updates should be made to AE Log CRFs based on the re-assessments.

7.2.2 Serious adverse events

SAEs will be recorded on the RedCap database and defined as AEs occurring at any dose/group that:

- Results in death
- Grade 3 or higher AEs
- AEs resulting in DOR discontinuation
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event that may not result in death, be immediately life-threatening, or require hospitalization but may jeopardize the participant or require intervention to prevent one of the outcomes listed in the definition above.

7.2.3 Adverse event relationship to study product

Relatedness is an assessment made by a study clinician of whether or not the event is related to the study agent. Degrees of relatedness will be categorized according to current DAIDS-approved guidelines. The relationship categories that will be used for this study are:

- *Related:* There is a reasonable possibility that the AE may be related to the study agent
- *Not Related:* There is not a reasonable possibility that the AE is related to the study agent

7.3 Adverse event reporting

For each study participant, AE reporting will be conducted throughout the scheduled duration of follow-up, i.e., from the time of Enrollment through study exit or termination. All AEs must be reported on the Study AE Tracking Log.

The following AEs must be reported on the Study AE CRF form within REDCap:

- All potentially DOR related AEs
- All AEs of severity grade 3 or higher
- All SAEs
- All AEs that result in permanent discontinuation of DOR use

All SAEs must be reported on the Study SAE CRF form within REDCap.

7.3.1 Grading severity of events

The grading of severity of events and the reporting period will be the same as for all AEs. The most current DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1, July 2017 and the Female Genital Grading Table for Use in Microbicide Studies (Addendum 1, dated November 2007), will be used.

7.4 SUSAR reporting period

The SUSAR reporting period for this study begins once the participant is enrolled and continues up through the participant's final study visit (Visit 7 or 9, depending on the Group). After the protocol-defined AE reporting period, unless otherwise noted, only suspected, unexpected serious adverse reactions (SUSARs) will be reported if the study staff become aware of the events on a passive basis (from publicly available information).

7.5 Social harms reporting

Although study sites will make every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the study could become known to others and that social harms may result. For example, participants could be treated unfairly, or could have problems being accepted by their families, partners and/or communities. Social harms that are judged by the PI/designee to be serious or unexpected will be reported to the Senior Clinical Advisor and responsible site IRBs/ECs according to their individual requirements. In the event that a participant reports social harm, every effort will be made by study staff to provide appropriate care and counseling to the participant, and/or referral to appropriate resources for the safety of the participant as needed. While maintaining participant confidentiality, study sites may engage their community advisory boards (CABs) in exploring the social context surrounding instances of social harm. All SHs must be reported on the Study SH CRF.

7.6 Regulatory requirements

Information on all reported CRFs will be included in reports to SAHPRA and other applicable government and regulatory authorities. Site Co-PI designees will submit AE information in accordance with local regulatory agencies' or other local authorities' requirements. Site PIs designees also will submit AE information and any other relevant safety information to their IRBs/ECs in accordance with IRB/ECs requirements.

8.0 CLINICAL MANAGEMENT

Guidelines for clinical management and temporary product hold/permanent discontinuation of study product are outlined in this section. In general, the PI/designee has the discretion to hold study product temporarily at any time if s/he feels that continued product use would be harmful to the participant or interfere with treatment deemed clinically necessary. Unless otherwise specified below, the PI/designee should immediately consult the Senior Clinical Advisor for further guidance on resuming study product, continuing the hold temporarily, or progressing to permanent discontinuation of study product. The PI/designee will document all temporary product holds and permanent discontinuations on applicable CRFs.

8.1 Grading system

The DAIDS AE severity grading is described in the Adverse Events Section.

8.2 Dose modification instructions

No dose modifications will be undertaken in this study.

8.3 General criteria for temporary/permanent discontinuation of study product

Participants will be permanently discontinued from study product (containing 100mg DOR) use by the PI/designee for any of the following reasons:

- Allergic reaction to the study product*
- Non-therapeutic injection drug use

**In the event of an allergic reaction (Grade 3 or above), participants will be permanently discontinued from study product use.*

A participant will be permanently discontinued from study product for any of the following reasons:

- Pregnancy
- Breastfeeding.
- Participant is unable or unwilling to comply with required study procedures, or otherwise might be put at undue risk to their safety and well-being by continuing product use, according to the judgment of the PI/designee. The PI/designee must consult the Senior Clinical Advisor on all temporary product holds instituted for this reason for further guidance on resuming product use, continuing the temporary hold, or progressing to permanent discontinuation. If product use is temporarily held/permanently discontinued for this reason, but the underlying reason for the temporary hold later resolves, the PI/designee should consult the Senior Clinical Advisor to resume product use at that time.

8.3.1 Temporary product hold/permanent discontinuation in response to observed adverse events

<u>Grade 1 or 2</u>

In general, a participant who develops a Grade 1 or 2 AE not specifically addressed below, regardless of relatedness to study product, may continue product use.

<u>Grade 3</u>

Participants who develop a Grade 3 AE that is not specifically addressed below and is judged by the PI/designee to be not related to study product may continue product use.

In general, for participants who develop a Grade 3 AE not specifically addressed below, judged by the PI/designee to be related to study product, and unless otherwise decided in consultation with the Senior Clinical Advisor, the PI/designee should:

- Temporarily hold the study product.
- Re-evaluate the participant at least weekly for up to 2 weeks.
- Resume study product if improvement to ≤ Grade 2 is documented within 2 weeks.
- Consult the Senior Clinical Advisor regarding further study product management if improvement to severity ≤ Grade 2 cannot be documented within 2 weeks.

If product use is resumed and the same Grade 3 AE deemed related to study product recurs at any time, the PI/designee must temporarily hold study product and consult the Senior Clinical Advisor within 24 hours of awareness for further guidance on continuing the temporary hold or progressing to permanent discontinuation of the study product.

Grade 4
Participants who develop a Grade 4 AE (regardless of relationship to study product) should have the study product held. The PI/designee must consult the Senior Clinical Advisor and continue the temporary product hold until a recommendation is obtained from the Senior Clinical Advisor.

8.3.2 Other clinical findings
If the creatinine clearance is <50mL/min, study product should be held, the Senior Clinical Advisor notified, and the test repeated within one week. If a level of <50mL/min is confirmed, study product will be permanently discontinued. If either retesting cannot occur within one week or if retesting yields a result of ≥50 mL/min, the PI/designee must consult the Senior Clinical Advisor for further guidance on resuming product use.

8.4 Pregnancy
Pregnancy testing will be performed at designated study visits and participants will be encouraged to report all signs or symptoms of pregnancy to study staff. The PI/designee will counsel any participant who tests positive for pregnancy regarding possible risks to the fetus according to site SOPs. The PI/designee also will refer the participant to all applicable services; however, sites will not be responsible for paying for pregnancy-related care.

A participant who tests positive for pregnancy during the course of the study will have study product(s) discontinued and will be withdrawn from the study due to the unestablished safety of DOR during pregnancy. A participant who is pregnant at study termination will continue to be followed until the pregnancy outcome is ascertained (or if in consultation with the Senior Clinical Advisor it is determined that the pregnancy outcome cannot be ascertained). Pregnancy and infant outcomes will be reported on relevant CRFs, and outcomes meeting criteria for SUSAR reporting also will be reported on SUSAR forms. The study site will make every reasonable effort to contact participants and collect infant outcomes up to one year after delivery for those pregnancies that result in live birth.

8.5 Criteria for early termination of study participation
Participants may voluntarily withdraw from the study for any reason at any time. The PI also may withdraw participants from the study to protect their safety and/or if they are unwilling or unable to comply with required study procedures. The Senior Clinical Advisor will be notified of all terminations conducted per PI discretion. Participants also may be withdrawn if the sponsors, government or regulatory authorities, or site IRBs/ECs terminate the study prior to its planned end date. Every reasonable effort will be made to complete a final evaluation of participants who withdraw or are withdrawn from the study prior to completing follow-up. Study staff members will record the reason(s) for all withdrawals in participants' study records.

9.0 STATISTICAL CONSIDERATIONS

9.1 Analytic groups
For **primary PK objectives**, mean implant hormone concentrations will be analyzed at 24 or 12 weeks (+/- 2 weeks) after implant insertion or IM DMPA/SC MPA administration, respectively. The comparisons will be between DOR + ETG implant (Group 1) and DTG + ETG implant groups (the latter is from a historical control from one of Dr. Patel's currently ongoing study in a similar

population in Kenya; **Table 2**). A secondary analysis will make comparisons between DOR + ETG implant and no ART + ETG implant/HIV-negative groups (again, the latter is from a historical control group from one of Dr. Patel's currently ongoing study in Kenya). The mean MPA concentrations for DOR + D/MPA at 12 weeks (+/- 2 weeks) after D/MPA injection (Groups 2 and 3) will be compared to the mean MPA concentrations for DTG + DMPA group (contemporaneous study Group 5).

For **primary PK objectives**, the mean $C_{24\ hours}$ of DOR in the ETG implant and D/MPA groups will be compared to no hormonal contraceptive method group (Group 4).

For the **secondary objective**, the proportion of women suppressed (defined as HIV viral load <40 copies/mL) at 24 weeks (+/- 2 weeks) after DOR-containing ART initiation will be compared to the proportion of women suppressed with non-DOR containing ART from aggregated data shared with the study team from the respective HIV treatment clinics that our study sample is recruited from.

All exploratory analyses, including safety (including side effects), satisfaction, and continuation rates of both the hormonal contraceptive method and ART will be assessed in the cohort at 12 or 24 weeks for DMPA or implant use, respectively.

9.2 Power/sample size

For the PK sub-study, a sample size of 20 women per study arm will provide us with the ability to detect a GMR ≥20% (i.e. the FDA standard of bioequivalence bounds of 0.8-1.25) in hormonal concentrations 24 weeks after implant insertion or 12 weeks after D/MPA injection between the DOR and DTG ART groups with ≥80% power (**Table 4**). This sample size assumes a 40% coefficient of variability in hormonal levels (which is what is detected in our historical comparison group of implant users for GMR at 24 weeks; it ranges from 22-43% in DMPA users on various ART for AUC at 12 weeks in the published literature[17,53]) and one-sided type I error of 10%, which is the standard error percentage used and reported in PK studies (e.g. geometric mean with 90% confidence intervals). We have chosen to power on one-sided type I errors as only reductions in implant hormone concentrations are concerning for reduction in efficacy, and not elevations in concentrations. Another assumption is that the concentrations in the DOR groups will not vary significantly from those of the implant without DOR (which is expected given the lack of drug-drug interactions with DOR and oral contraceptives with ethinyl estradiol and levonorgestrel, per product package insert). A recent study found 53% mean difference in levonorgestrel implant concentrations at 24 weeks after implant placement between women receiving EFV 600mg versus no ART[54] so aiming to detect a difference of at least 20% is extremely conservative. Generally, we would consider reductions in mean differences that are <20-30% as not being clinically significant. Therefore, we are able to power this PK study to also show any clinically insignificant decreases with the groups. At our site in South Africa, we have extremely high retention rate (in part, due to the outreach by our community health workers and liaison), so we will sample one additional woman in each group (n=21 in each ART group) to ensure we have sufficient samples for our primary outcome at the end of the observation period.

Therefore, we anticipate enrolling and retaining a minimum of n=105 women, with n=21 participants in each of the 5 groups. We are anticipating a very conservative screening to enrollment ratio of 2:1, so may screen approximately 210 women.

Table 4. Sample size required per group to compare hormone concentrations with 80% power

	Estimated mean difference in progestin concentrations				
Inter-individual variation	*10%*	***20%***	*30%*	*40%*	*50%*

40%	89	**20**	8	4	3
50%	189	31	12	6	4
All sample size calculations assume an alpha level of 0.10 (one-sided) and 80% power					

Given the exploratory nature of study Secondary Objective, power calculations are not conducted *a priori.*

9.3 Statistical methods and analyses

For study **co-primary objectives**, the hormonal contraceptive blood samples will be analyzed using LCMS techniques[55,56]. The lower limit of quantification (LLOQ) for ETG and MPA is 20 pg/mL of plasma. To compare mean concentrations at 24 weeks after implant insertion in the DOR vs. DTG groups (**primary objective**), we will analyze the geometric mean ratios using Wilcoxon rank sum test. Similarly, to compare mean MPA concentrations at 12 weeks after D/MPA injection in the DOR vs. DTG groups (**primary objective**), we will analyze the geometric mean ratios using Wilcoxon rank sum test. Of note, for Objective 1a, for a secondary analysis, will compare mean concentrations 24 weeks after implant insertion between the DOR vs. HIV-uninfected groups. The mean $C_{24\ hours}$ of DOR in the ETG implant and D/MPA will be compared to no hormonal contraceptive method arm, and analyzed via geometric mean ratios using Wilcoxon rank sum test (**primary objective**). Potential confounders we will consider in the above analyses may include age, disease/immune status (measured via CD4 cell counts or pre-treatment HIV RNA levels, for example), co-morbidities, and weight or body mass index.

For study **secondary objective**, the proportion of women achieving viral suppression at 12-24 weeks between the DOR groups will be compared against summary data provided by the HIV treatment clinics from which the study sample will be recruited, and a two-sample t-test will be conducted if feasible. If comparator data is not feasibly obtained from the treatment clinics, we will compare the viral suppression rates in the DOR groups in our PK study against proportions with DOR- and non-DOR-containing ART reported in the published literature (e.g. from the DRIVE studies), and a two-sample t-test will be conducted if feasible. Related analyses, including the **exploratory objective** of evaluating the proportion of side effects, satisfaction, etc. will be compared similarly. Pending future funding support, we may consider future analyses, such as pharmacodynamic or pharmacogenetic analyses on existing study data. Such future analyses will be considered on a case by case basis. Of note, separate consent will be obtained from participants to consent to such future analyses.

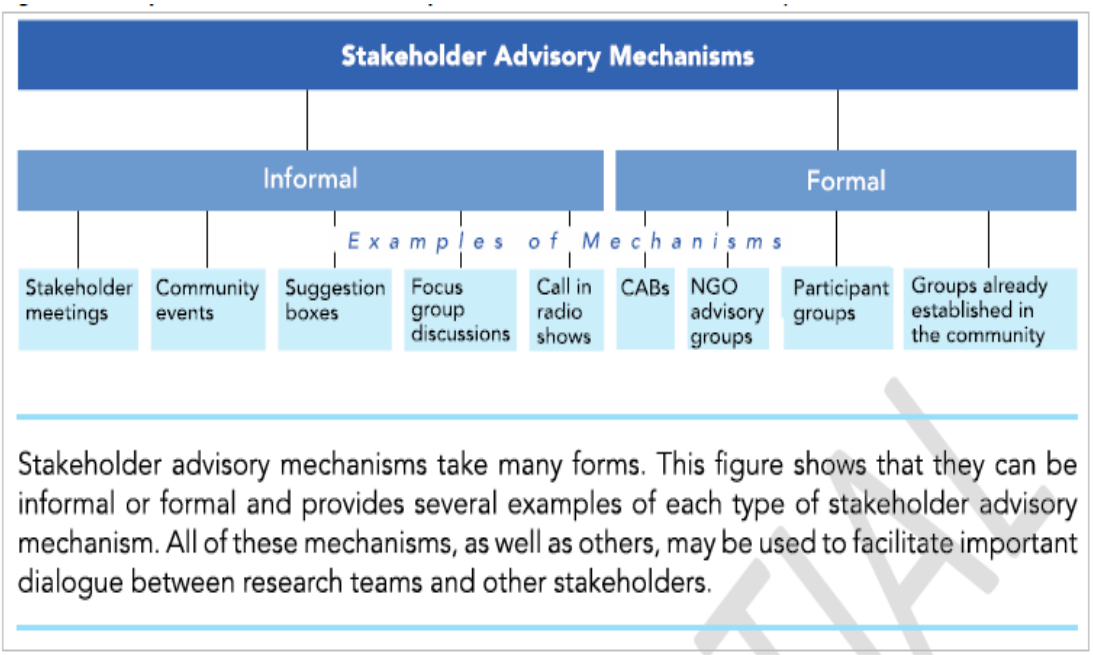
For the **exploratory objective** utilizing qualitative study methods for the IDIs, we anticipate the following. The English transcripts will be imported into Nvivo 12 for coding. We will use a combination of inductive (allowing the data to speak for itself) and deductive coding (to draw upon the respective frameworks we are relying on to build the guides). We will develop a codebook to iteratively document the codes, their definitions, and guidelines on when to use the code with example quotes. The initial, primary codes will be developed from the domains and themes queried in the interview/discussion guides. We will have 2-3 study staff independently code the transcripts, including double coding of the first few transcripts until we have confidence in the relative standard application of the codebook. After the initial round of coding, the researchers will meet to discuss their coding process, assess intercoder agreement, and resolve discrepancies through consensus. With iterative review of the transcripts, we will expand the initial codes into more detailed, secondary codes. Once the coding is complete, we will use content analysis to organize the data for further analysis.[57,58] Finally, analytic memos will be written to lift the primary and secondary codes into thematic analyses that represent a full range of perspectives, both convergent and divergent. Several measures will be taken to ensure high quality data and rigorous analysis.[59] Principles of reflexivity, such as acknowledging bias and power dynamics among the study staff, will be used when collecting and analyzing data.[60] Principles of rigor, such as exploring for discrepant data and remaining faithful to participants'

experiences, will guide our analysis.[59,61] We will describe the setting and context transparently so that readers can easily judge the transferability and trustworthiness of the findings.[58,61] We will also pursue participant validation of our interpretation of the findings by sharing the results with them through meetings held at Wits RHI, taking field notes to be included in analyses.

10.0 GOOD PARTICIPATORY PRACTICE (GPP)

The EPIC study will use the most recent edition of the GPP guidelines (2011) to guide the study's engagement with site communities and local, national, regional and global stakeholders. According to the GPP guidelines, "community stakeholders" include both individuals and groups that are ultimately representing the interests of people who would be recruited to or participate in a trial, and others locally affected by the trial. These may include trial participants, people living in the area where the research is being conducted, people in the area who are infected and affected by family planning needs, reproductive health issues and HIV, local non-governmental organizations, community groups and community-based organizations.

Good participatory practice in HIV research goes beyond having a Treatment Community Advisory Board (CAB). It involves utilizing a range of stakeholder advisory mechanisms to promote transparent, meaningful, collaborative, and mutually beneficial relationships with all levels of stakeholders (See Figure 5). The EPIC study will strive to embrace the GPP guiding principles throughout the implementation of the study. These include: respect, mutual understanding, integrity, transparency, accountability and community stakeholder autonomy.



Stakeholder Advisory Mechanisms
Informal
Formal
Examples of Mechanisms
Stakeholder meetings
Community events
Suggestion boxes
Focus group discussions
Call in radio shows
CABs
NGO advisory groups
Participant groups
Groups already established in the community
Stakeholder advisory mechanisms take many forms. This figure shows that they can be informal or formal and provides several examples of each type of stakeholder advisory mechanism. All of these mechanisms, as well as others, may be used to facilitate important dialogue between research teams and other stakeholders.

Figure 5: Examples of stakeholder advisory mechanisms from GPP guidelines, 2011

The EPIC team is committed to conducting meaningful community consultation, from protocol development and implementation to results dissemination and policy development where appropriate. To facilitate effective implementation of the GPP Guidelines, all members of the study team will be trained on the GPP Guidelines.

11.0 DATA MANAGEMENT

11.1 Data management responsibilities

The investigators have ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the case reporting forms (CRFs) and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs is true. Any corrections to entries made in the CRFs, source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry.

11.2 Source documents and access to source data/documents

To enable evaluations and/or audits, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, e.g., CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls reports) securely stored under access controlled conditions.

11.3 Quality control and assurance

During the study period, periodic monitoring may be conducted to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs is accurate. Additionally, the study site may be subject to review by the Institutional Review Board (IRB) and/or to inspection by appropriate regulatory authorities.

12.0 HUMAN SUBJECTS PROTECTIONS

12.1 Institutional review board/ethics committees

In South Africa, the protocol will be reviewed by South African Health Products Regulatory Authority (SAHPRA) and by University of the Witwatersrand, Human Research Ethics Committee (Wits HREC). In the US, the University of Washington's Institutional Review Board's Committee on Human Research will review this protocol. We will ensure that all procedures conform to South African, US, and international ethical standards regarding research involving human subjects.

12.2 Human subjects' involvement

The proposed study aims to enroll a minimum of 105 WLHIV in South Africa aged 18-45 years. Women will be followed for up to 30 weeks. No prisoners or institutionalized individuals will be included in this cohort. Eligibility criteria will include the ability to provide written informed consent.

The Wits Reproductive Health and HIV Institute (RHI) Research Centre Clinical Research Site (CRS), South Africa will be responsible for implementation of the study protocol and related activities with this cohort of young women. This responsibility includes the protection of human subjects, under the direction of the site Co-Principal Investigators (Dr. Palanee-Philips and Dr. Ndlovu+). The investigators at Wits RHI will prepare and submit the study protocol to the Wits HREC and SAHPRA for approval to ensure the rights, safety and welfare of the study participants are assured prior to implementation. The protocol will outline the plans for the implementation of the study, including recruitment, study visit procedures, and retention. Written informed consent will be obtained for prospective follow-up. Wits RHI will serve as the data center for the study and coordinate data management and the specimen repository in collaboration with University of Washington. Data obtained at the research site will be managed by a local data team, routinely entered into data management software, and transferred to the University of Washington via a secure internet connection.

Original data collection forms, including consent forms, locator forms, case report forms, notations of all contacts with the participants, and all other source documents will be stored in a secure manner at the Wits RHI RC CRS. The Wits RHI RC CRS has a secure, restricted-access space dedicated to data management and data storage and has capacity for both paper based and electronic data management. Paper case report forms (CRFs) and other support documents are stored in lockable, fire and water-resistant steel cabinets for optimal data storage. The data centre has a file sign in and sign out process to ensure aware of staff who remove and return files daily. No participants confidential identifiers will be stored within participants main file routinely. A separate file will be kept with the participants informed consent forms, locator information and copies of personal identification documents so that there is no inadvertent breach of participants personal details such as her name and personal contact information. Study staff are all Good clinical practice trained and compliant and trained on adherence to confidentiality principles.

12.3 Informed consent

Written informed consent will be obtained from each study participant prior to the conduct of screening procedures. In obtaining and documenting informed consent, the investigator and their designees will comply with applicable local regulatory requirements and will adhere to Good Clinical Practice and to the ethical principles that have their origin in the Declaration of Helsinki.

These consents will include consent for screening and enrollment as well as storage of specimens for future studies related to HIV transmission and prevention as well as contraception. Research staff at the Wits RHI CRS will administer informed consent to each participant in their preferred language (choice between English and Zulu) as per site SOPs and participants will sign the consent form indicating whether they have understood the nature of the study and the potential risks and benefits from participation. Copies of signed ICFs will be offered to the participant for her reference.

12.4 Protections against risk

We anticipate participants may face potential risks, including pregnancy and phlebotomy-related issues.

Since concomitant use of DOR is not anticipated to reduce hormonal contraceptive concentrations, the risk of contraceptive failure or pregnancy is anticipated to be low. In order to minimize the risks of pregnancy, we will counsel the women extensively on the use of dual contraceptive methods with condoms. Male or female condoms will be provided to the women on site by the study staff at no additional costs. We will also counsel the women extensively on the use of non-hormonal contraceptive methods such as IUDs. Women wishing to have these placed, will be provided to them at no additional cost.

Phlebotomy-related risks may include pain, bruising, hematoma, or phlebitis. In order to minimize any physical risks associated with phlebotomy, experienced clinical nurses will conduct the phlebotomy. Furthermore, this person will undergo additional training in phlebotomy if required. We anticipate these steps will significantly help minimize any potential physical risks associated with phlebotomy.

DOR-specific risks: Risks associated with DOR use include nausea, headaches, fatigue, diarrhea, abdominal pain, dizziness, rash, abnormal dreams, insomnia and possible somnolence. Participants will be closely monitored and managed for all potential side effects.

Risk of Adverse Reactions or Loss of Virologic Response Due to Drug Interactions: The concomitant use of DOR and certain other drugs may result in known or potentially significant drug interactions, some of which may lead to loss of therapeutic effect of DOR and possible development of resistance.

Contraceptive-specific risks: Risks associated with implant insertion or D/MPA injection include scarring, pain, bleeding and infection. Implant insertion or D/MPA injection will be performed by highly trained study staff under aseptic techniques in order to reduce these risks. Risks associated with the insertion of a non-hormonal IUD include infection, expulsion or perforation, however the risks are low. Similar common adverse reactions (>10%) have been reported for the contraceptives, and include headache, change in menstrual bleeding, weight gain, acne, breast pain and abdominal pain. Participants will be counseled to follow up with their primary care clinicians should these symptoms persist.

No psychological, financial, or legal risks are anticipated with study participation. The participants will have the alternative to not participate in the studies, which carries no risks. They will be reassured that their HIV care is not in any way influenced by their participation in these studies.

12.5 Benefits

Though there are no direct anticipated benefits to the participants in these studies, findings from the studies will be shared with the participants directly, through venues determined most

appropriate by the study staff and facility leadership (e.g. through group meetings at the facilities, letters to participants, or phone calls). We also anticipate that findings from the proposed study will impact international and national HIV treatment guidelines' recommendations for concomitant ART and implant use, and study participants will be interested in participating to help determine findings for this type of impact. Optimizing concomitant ART and contraception for WLHIV is important in avoiding unintended pregnancies, which have implications for HIV-related and maternal morbidity and vertical transmission of HIV. We believe that given the large potential for impact, the potential risks of the proposed studies are minimal and, therefore, find them reasonable despite the lack of any anticipated direct benefits to the participants.

12.6 Participant privacy and confidentiality

All study procedures will be conducted in private, and every effort will be made to protect participant privacy and confidentiality to the extent possible. All study-related information will be stored securely at the Wits RHI Data Centre. All participant information will be stored in locked areas with access limited to designated study staff. All laboratory specimens, study data, and administrative forms will be identified by coded number only to maintain participant confidentiality. All records that contain names or other personal identifiers, such as locator forms and informed consent forms, will be stored securely. All electronic files of the collected data will be saved de-identified on password protected and encrypted computers. Only de-identified information will be shared and used amongst the research staff. With participant permission, remaining plasma samples after completion of our analysis may be stored at the UW ICRC repository for future studies. Use of the specimens, with de-identified information only, for future studies will be conditional on written request by investigators to the PI of the study (Dr. Rena Patel) and approval of respective IRBs to conduct the study.

12.7 Protocol registration

The protocol will be registered with the U.S. clinicaltrials.gov and the South African National Clinical Trials Register.

12.8 Compensation

Pending IRB/EC approval, participants will be compensated for time, inconvenience and expenses incurred as a consequence of their attendance to a study visit. The value of compensation is in line with standard national guidelines from Wits HREC and SAHPRA related to attendance to study visits and procedures conducted. Site specific reimbursement amounts will be specified in the site specific ICF

12.9 Study suspension or discontinuation

This study may be discontinued at any time by study sponsors, other government or regulatory authorities, or site IRBs/ECs.

13.0 PUBLICATION POLICY AND PLAN

Study findings will be disseminated to researchers through oral or written presentations at scientific conferences and through peer-reviewed journals. Full anonymity of subject's details will be maintained throughout. We will also disseminate the findings directly with the study participants, through venues determined by the study staff and facility leadership. Participants wanting to see the results of the trial can request a copy of the article from the investigators once it has been published. In South Africa, study results will be communicated to the National Department of Health (NDoH) program managers through meetings and reports and disseminated amongst Wits RHI staff. The study will be registered on Clinicaltrials.gov.

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INFORMATION SHEET (IS) AND INFORMED CONSENT

*Each participant must receive, read and understand this document **before** any study-related procedure.*

SHEET 1: Screening and Enrolment

TITLE FOR THE STUDY: EPIC- Evaluation of Pharmacokinetic drug-drug Interactions between hormonal Contraceptives and doravirine-containing ART among women living with HIV in South Africa

SPONSOR: Merck, Inc

PRINCIPAL INVESTIGATORS: Prof Thesla Palanee-Phillips and Dr Nkosiphile Ndlovu

INSTITUTION: Wits Reproductive Health and HIV Institute (Wits RHI), University of the Witwatersrand

DAY TIME AND AFTER-HOURS TELEPHONE NUMBERS: Day Tel: 011 358 5424
A/H Tel: 084 722 5877

To the potential Participant: *This consent form may contain words that you do not understand. Please ask the study doctor or the study staff to explain any words or information that you do not clearly understand. You may take home **an unsigned copy of this consent** form to think about or discuss with family or friends **before making your decision***

DATE AND START TIME OF INFORMED CONSENT DISCUSSION:

				:
DD	**MMM**	**YYYY**		**Time** *(24hr clock)*

KEY INFORMATION:

Consent is being sought for this research study and your participation is voluntary. If you decide not to take part in this study, you can still join another research study later if one is available and you qualify.

The purpose of this study is to assess any interactions between HIV treatment medications and family planning methods. You are being asked to join this study because you are already on antiretroviral therapy for HIV treatment, and study drug doravirine works like how your current antiretroviral therapy by stopping HIV from making copies of itself. But not a lot is known about interactions between doravirine and family planning methods, and that is why we are doing this study. If you decide to join the study, the duration of your participation is this study will be approximately 18-30 weeks.

Each participant will choose to be in one of five groups with 21 participants in each group. If you join one of the four doravirine groups, you will be asked to switch from your current ART to doravirine-containing ART called Delstrigo®, which is a tablet taken by mouth once a day. Six weeks after doravirine initiation, you will be offered a choice to start a family planning method contraceptive

containing hormones [implant, or injection under skin (SC MPA) or in the muscle (DMPA), and IUD]. If you are already on dolutegravir-containing ART and choose to continue using it, you will be asked to join the fifth group and remain on your dolutegravir-containing ART and start the DMPA, you will not get to pick your contraceptive for this study. For the six-week window after starting DOR, you must be on an effective form of contraception to avoid pregnancy. You will receive comprehensive counselling on all contraceptive methods available in the study as described below to enable you to make your own choice.

There are no direct benefits to participating in this study.

Risks associated with doravirine-containing ART include common side effects such as headaches, fatigue, diarrhoea, abdominal pain, dizziness, rash, abnormal dreams, insomnia (trouble sleeping) and possible somnolence (drowsiness). Rare, but more severe side effects include bone or renal toxicities. Risks associated with implant insertion or DMPA or SC MPA injection include scarring, pain, bleeding, and infection. Risks associated with implant use include prolonged or irregular bleeding or both; in subsequent years, bleeding patterns tend to improve. Risks associated with the insertion of a non-hormonal IUD include infection, expulsion (IUD being pushed out the womb) or perforation (tearing of the womb), however the risks are low. Common adverse reactions have been reported for the contraceptives, and include headache, change in menstrual bleeding, weight gain, acne, breast pain, dizziness, mood changes and abdominal pain. Some of the risks related to drawing blood include pain, bruising, hematoma, or phlebitis.

INTRODUCTION

Hello my name is _____ and I work at the Wits Reproductive Health and HIV Institute (Wits RHI) as a _____. The Wits RHI does research in reproductive health, including HIV. We have projects in many areas including Esselen Street in Hillbrow (Esselen Street Clinic and Research Centre) and Yeoville. The Wits RHI is a part of the University of Witwatersrand, Johannesburg.

The Wits RHI would like to invite you to participate in the research study called EPIC "Evaluation of Pharmacokinetic drug-drug Interactions between hormonal Contraceptives and doravirine-containing ART among women living with HIV in South Africa" which is funded by Merck, Inc. The persons in charge of this study at this clinic is Prof. Thesla Palanee-Phillips and Dr. Nkosiphile Ndlovu.

Before you decide if you want to join this study, we want you to know about it. This form gives you information about this study. The study staff will talk with you about it and answer your questions. If you would like to speak with a medical doctor or if you have medical questions, please let me know so that this can be arranged. You may choose to stop being in the study at any time. Once you read (or have read to you) this form, discuss and understand the study, and if you agree to participate, we will ask you to sign or mark this form. We will offer you a copy of this form to keep.

If you have a personal doctor, you are welcome to discuss with or inform him/her of your possible participation in this study. If you wish, I can also notify your personal doctor in this regard.

YOUR PARTICIPATION IS VOLUNTARY

If you decide not to take part in the study, you can still join another research study later, if one is available and you qualify. However, you cannot join this study if you are taking part in another study of medicines, medical devices, or vaccines. You are asked to tell the study staff about any other studies you are taking part in or thinking of taking part in.

We check for your co-enrolment in other studies by capturing your fingerprints on an electronic system called the Biometric Co-Enrolment Prevention System (BCEPS). You will need to place your fingers onto a mini screen which will enter your fingerprints onto BCEPS. This system will then check if your fingerprints are stored on the system for any other studies. Only a few members of the study team can see the information in BCEPS using a secure password. This is done at the beginning of your visit and is covered on a separate informed consent form.

PURPOSE OF THE STUDY

This research study is known as EPIC. The purpose of this study is to assess any drug interactions between Doravirine exposure and hormonal contraceptive use. The possible risks of taking the combination of contraceptives and doravirine are unknown, and that is why this study is taking place. You are being asked to join this study because you are already on antiretroviral therapy. Doravirine is not a registered medicine in South Africa however it works like how your current antiretroviral therapy works. Doravirine works by stopping HIV from making copies of itself.

WHO WILL BE IN THIS RESEARCH STUDY?

A minimum of 105 women in Johannesburg and surrounding areas, aged 18-45 years old, living with HIV, already on antiretroviral therapy (ART) and virally suppressed.

WHAT DO I HAVE TO DO IF I DECIDE TO TAKE PART IN THIS STUDY?

If you decide to join you will be in the study for approximately 18-30 weeks. Each participant will be put in one of five groups as described in the table below. We will have 21 participants in each group.

Group	Number of participants	ART regimen and contraceptive method
Group 1	21	doravirine-containing ART + initiating etonogestrel implant
Group 2	21	doravirine-containing ART + initiating Intramuscular depomedroxyprogesterone acetate (IM DMPA)
Group 3	21	doravirine-containing ART + initiating subcutaneous Medroxyprogesterone acetate (SC MPA)
Group 4	21	doravirine-containing ART + initiating non-hormonal intrauterine device
Group 5	21	dolutegravir-containing ART + initiating IM DMPA

If you join one of the four doravirine groups, you will be asked to switch from the standard of care ART to doravirine-containing ART and take the Delstrigo® tablet which contains 100 mg of Doravirine, 300 mg of Lamivudine, and 300 mg of Tenofovir Disoproxil Fumarate. Delstrigo® is a film-coated yellow, oval-shaped, tablet taken orally once a day.

Six weeks after doravirine initiation, you will be offered a choice of either etonogestrel implant, depomedroxyprogesterone acetate (DMPA), subcutaneous medroxyprogesterone acetate (SC MPA) or non-hormonal intrauterine device (IUD; which can be placed on site).

If you are already on dolutegravir-containing ART and wish to start DMPA, you will be asked to join the fifth group and remain on Dolutegravir-containing ART and start the DMPA.

You will receive comprehensive counselling on all contraceptive methods available in the study as described below to enable you to make your own choice.

- Contraceptive implants- Contraceptive progestin implants are thin rods inserted under the skin of a woman's arm. The most widely available implant in South Africa is currently Implanon/Nexplanon/Implanon NXT.
- Depot Medroxyprogesterone Acetate (DMPA), also known as Depo Provera. The DMPA injection is a hormone injection that is given in the buttocks every 3 months.
- Subcutaneous Medroxyprogesterone acetate (SC MPA) or Sayana® Press is given subcutaneously (into the fatty layer just under the skin), into the front upper thigh or abdomen every 3 months.
- Non-hormonal intrauterine device (IUD) is the T-380A copper IUD, a small T-shaped device made of plastic and copper, which a doctor or nurse places in the uterus (womb). IUDs may be left in place for up to 10 years and can be removed if needed.

DO YOU HAVE TO BE IN THIS STUDY?

You do *not* have to be in this study. You can still get the care you need from your local/public clinic even if you do not join the study. If you join today, you can change your mind at any time.

WHAT PROCEDURES WILL BE DONE FOR THIS STUDY?

Your first visit will happen today after you read (or have read to you), discuss, understand, and sign this form. The procedures done at this visit will let us know if you can join this study and will take about 4 hours. At today's visit you will complete questionnaires related to your contraceptive and ART use and we will ask you to provide a blood sample (approximately 15-20 ml or two tablespoons) to test your blood counts, kidney and liver function, HIV viral load, and a urine sample to test for pregnancy. We will test for hepatitis B and if you have the infection, you will be excluded from the study. We also will test for hepatitis B immunity and if you are not immune, we will offer you vaccination against hepatitis B infection.

If it seems like you can join, you will be asked to come back for an Enrolment visit no later than 30 days from today. After enrolment, we will ask to you to return for scheduled visits up until approximately 12-24 weeks (+/- 2 weeks) after starting your contraceptive method.

The following things may happen during your study visits:

- We will ask questions about your health and any medications you may be taking. We will also ask questions about your living situation to see if it affects your use of the study product, and about your reasons for wanting to join this study. We will collect a blood sample (approximately 15-20 ml or two tablespoons ml) to test your blood counts, ARV and hormone contraceptive levels, kidney, and liver function
- We will collect a urine sample to test for pregnancy
- At some visits, you may be asked to complete a questionnaire. You will be asked to answer some questions in private, using a computer. The study staff will show you how to use the computer to answer the questions. You will answer questions about using the

study product and other behaviours, including sexual activity, if you are sexually active, contraceptive needs and other questions that can help researchers better understand participants' experiences while in the study. Some of the questions may be sensitive. If you ever feel uncomfortable, you can choose not to answer questions at any time. You will also answer questions about what you liked and did not like about this study and about the study product.

- At some visits, we will give you a physical exam to make sure you are healthy.
- We will give you treatment for sexually transmitted and other kinds of infections if you need them.
- We will give you referrals for other services if you need them
- You may be asked to take part in a one-on-one in-depth interview that will last 30-60 minutes and be conducted twice, at the start of the study and after you complete the study. You may choose not to be interviewed. During the interviews, we may ask participants about their experiences in switching from their current ART regimen to one containing Doravirine, and about their experiences with their contraceptive method of choice, as well as experiences between the DMPA versus the subcutaneous medroxyprogesterone acetate, including self-injections. We will record the interviews (audio record). We will keep the recordings and other related things confidential and no one else other than those in the study team will have access to your answers.

It is important for you to come to every study visit. If you cannot come to the visit, please tell the study staff as soon as possible so that the visit can be rescheduled.

INTERIM/UNSCHEDULED VISITS

Study staff will discuss with you the importance of contacting the clinic as soon as you notice changes in your physical condition or when you experience health related issues. Also, it is possible that you may be asked to come to the clinic for an unscheduled visit in the event of an abnormal test result; difficulties in sample shipping, processing, or testing or to have study procedures repeated; or for other reasons. We will do this if there are abnormal test results or a mistake during the collection or the processing of your samples. We will also do this if you experience any changes in your physical condition, including symptoms of urine or sexually transmitted infections (STIs).

PREGNANCY AND BREASTFEEDING

Pregnant and breastfeeding women may not join this study. You may be able to start using the study products after your pregnancy, provided that you are not breastfeeding. The study staff will talk more with you about this after your pregnancy.

If you become pregnant during the study, you will stop using the study products and you will stop participating in the study. We will collect blood form you for testing and ask you to do an assessment with questions about your participation in this study. We will also refer you to available medical care and other services for ongoing care including any needed changes to your ART according to the local Department of Health Guidelines. The study does not pay for this care. We will contact you for information about your baby's health one month after delivery. Additionally, upon documentation of a positive pregnancy test, the following procedures will be performed regardless of whether or not the participant scheduled to be completed:

- Full blood count

- Kidney function
- Collection of blood samples for further analysis
- Behavioural adherence, and product preference/acceptability questionnaires.

RISKS AND/OR DISCOMFORTS

Risks of Blood Draws

You may feel discomfort or pain when your blood is drawn. You may feel dizzy or faint. You may have a bruise, swelling, small clot, or infection where the needle goes into your hand or arm.

Risks of study products

Side effects of doravirine-containing ART:
Common side effects include headaches, fatigue, diarrhea, abdominal pain, dizziness, rash, abnormal dreams, insomnia (trouble sleeping) and possible somnolence (drowsiness). Rare, but more severe side effects include bone or renal toxicities.

Risk of bad reactions or loss of virologic response due to drug interactions:

Using doravirine and other drugs at the same time may cause drugs to interact in powerful ways that we do not yet know about. Some of these reactions might mean that doravirine will not work for you the way it's supposed to and your body might become resistant to the drug.

Contraceptive-specific risks:
Risks associated with implant insertion or DMPA or SC MPA injection include scarring, pain, bleeding and infection. Risks associated with implant use include prolonged or irregular bleeding or both; in subsequent years, bleeding patterns tend to improve. Risks associated with the insertion of a non-hormonal IUD include infection, expulsion (IUD being pushed out the womb) or perforation (tearing of the womb), however the risks are low. Common adverse reactions have been reported for the contraceptives, and include headache, change in menstrual bleeding, weight gain, acne, breast pain, dizziness, mood changes and abdominal pain. You will receive contraception counselling.

Other Possible Risks

You may feel embarrassed and/or worried when talking about sexual activities (if you are currently sexually active) and your living situation.

We will make every effort to protect your privacy and confidentiality during the study visits. Your visits will take place in private. However, it is possible that others may learn of your participation here and, because of this, may treat you unfairly or discriminate against you. For example, you could have problems getting or keeping a job, or being accepted by your family or community. If you have any problems, study staff will talk with you and if you choose, your partner, to try to help resolve them.

BENEFITS

There are no direct benefits to participating in this study. This study cannot provide you with general medical care, but study staff will refer you to other available sources of care if needed. You will be offered free condoms, if you need them.

NEW INFORMATION

You will be told any new information learned during this study that may affect your willingness to stay in the study. For example, we will let you know if we learn that the study products may be causing bad side effects. We will also tell you when study results may be available, and how to learn about them.

WHY YOU MAY STOP TAKING THE STUDY DRUG EARLY OR BE ASKED TO LEAVE THE STUDY

You may need to leave the study early without your permission if:

- The study is cancelled by the study sponsors, the local government or regulatory agency, or the Institutional Review Board (IRB)/Ethics Committee (EC). An IRB/EC is a committee that watches over the safety and rights of study participants.
- You are not able to keep appointments.
- Other reasons that may prevent you from completing the study successfully such as pregnancy.

The study doctor will ask you to stop using the study products if you:

- Become pregnant
- Use drugs for HIV treatment beyond what the study gives you.
- Use injectable drugs for fun.
- Have a bad reaction to study product, or a study doctor decides that using study product would be bad for you.
- Are unable or unwilling to follow the study rules.

If a study doctor asks you to stop using study product, we will ask you to come in for all remaining study visits to have some of the procedures we talked about earlier.

If you are removed from the study or choose to leave, we will ask you to return the study product and to come back for one final clinic visit. If you do not have the study product with you when you come to the clinic, staff members will make every effort where possible to assist you in returning it.

ALTERNATIVES TO BEING IN THE STUDY

You may be able to join other studies here or in the community. There may be other places where you can go for family planning. We will tell you about those studies and those places if you wish.

EMERGENCY CARE AND HOSPITALISATION

If you have a medical emergency during the time you are enrolled in the study, please seek emergency care at the nearest hospital and inform the doctor treating you that you are participating in the study. That doctor is welcome to call the study staff for information. This includes the time of up to 1 month after you have completed your time in the study. Please inform the study staff of your time in the hospital as soon as possible.

COSTS TO YOU
There is no cost to you for study visits, study products, physical exams, laboratory tests or other procedures. We can give you treatments for STIs free of charge while you are in the study, or we can refer you for available treatment.

REIMBURSEMENT
You will receive R 400 for your time, inconvenience and expense to and from the clinic at each scheduled visit according to South African Health Products Regulatory Authority requirements. You may receive R 200 for any study related visits which occur in between your normally scheduled visits depending on your travel and procedures to be completed.

CONFIDENTIALITY
We will make every effort to keep your information private and confidential.

Study visits will take place in private. We will keep the information about your study visits in a secure place that only certain people can access for the purposes of this study. We will only enter your information into computers protected by passwords and will not include information that could identify you. If you are selected to participate in an in-depth interview, you can choose not to answer questions at any time. We will keep the audio recordings and materials from all interviews confidential and will only use study numbers or fake names. We store the recordings for 2 years after publication of the study results or 6 years if there is no publication.

Your personal information may be disclosed if required by law. For example, if we learn something that would immediately put you or others in danger, the study staff must take steps to keep you and others safe. This means that we have to share any information with the authorities (hospital, police, or social services) that tells us you may be in danger. For example, if you tell us that you plan to hurt or kill yourself, hurt or kill someone else, or if you tell us that someone is abusing or neglecting you.

The study staff will only use your fingerprints and personal information to verify that you are not taking part in any other research studies on BCEPS. This study will not use your name or identify you personally in any publication.

Your records may be reviewed by:
- Study sponsors and funders
- United States (US), local and international regulatory entities
- Members of the study protocol team and external advisors
- South African Health Products Regulatory Authority
- Human Research Ethics Committee, University of the Witwatersrand, an Ethics Committee is a committee that watches over the safety and rights of research participants
- National Health Research Ethics Committee (NHREC)
- Members of an Independent Data Safety Monitoring Board who review this clinical trial
- Study monitors
- Study staff

A description of this clinical trial will also be available on http://www.clinicaltrials.gov as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

The study staff will do everything they can to protect your privacy.

SPECIMEN COLLECTION

The information and/or specimens that we obtain from you for this study might be used for future studies. We may remove anything that might identify you from the information and specimens. If we do so, that information and specimens may then be used for future research studies or given to another investigator without getting additional permission from you. It is also possible that in the future we may want to use or share study information that might identify you. If we do, a review board will decide whether or not we need to get additional permission from you.

RESEARCH-RELATED INJURY

Wits RHI has obtained insurance for you in the event of study related injury or illness. A study-related injury or illness is one that occurs as a direct result of the administration of the study medicine or of study specific procedures. It is unlikely that you will be injured as a result of participating in this study. If you are injured as a result of study procedures, the Wits RHI will give you immediate necessary treatment for your injuries. You will not have to pay for this treatment. You will be told where you can get additional treatment for your injuries.

The research site or sponsor is not responsible for any loss, injuries and/or damages that are caused by any of the following things:

- Any injury that happens because you used other medicine during the study that you did not tell us about.
- Any injury that happens because you did not follow instructions given by the study doctor or nurse.
- Any injury that happens because of negligence on your part.

Merck will not cover any injuries or harms arising from study involvement, unless it is determined that the injuries or harms occurred in direct connection to manufacturing defects in study drug.

If a research related injury occurs, you have not waived any of the legal rights by signing this form.

INSURANCE AND ABPI STATEMENT

The Wits RHI through trial insurance will provide compensation for reasonable medical expenses incurred as a result of study-related injury or illness, determined according to the guidelines laid down by the **Association of the British Pharmaceutical Industry (ABPI Guidelines, Version 2014),** and **Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa (version 2006).**

Please notify the study staff immediately of any complications, side effects and/or injuries during the study and the nature of the expenses to be covered. Further detailed information on the payment of medical treatment and compensation due to injury can be obtained from me or other study staff. We have a copy of the ABPI Guidelines (version 2014) and the Insurance Certificate, should you wish to review them.

The insurance does not cover and the sponsors will not pay for:

- Medical treatment of ***other*** injuries or illnesses
- Injury caused by non-observance of the protocol

The staff working on this study is covered by the insurance as long as they:

- Comply with the applicable requirements of the study protocol
- Comply with the regulations of the South African Health Products Regulatory Authority and the University of the Witwatersrand, Human Research Ethics Committee (HREC)
- Ensure that the handling and administration of the study medication is in accordance with instructions and guidelines provided in the protocol, subsequent amendments and related documents.

This insurance is not intended to be and is not a substitute for the study staff's personal malpractice insurance.

Please note that if you have a life insurance policy you should enquire whether your insurance company requires notification of your intention to participate in a clinical study. Information to date is that it should not affect any life insurance policy taken out. Nevertheless, you are strongly advised to clarify it with the company concerned.

YOUR RIGHTS AS A RESEARCH PARTICIPANT

- Voluntary: Your participation in this study is entirely voluntary and you can refuse to participate or stop at any time without stating any reason. If you choose not to join or to leave the study, you can still join other studies you are eligible for at this clinic. If you decide to withdraw from the study, the study staff will encourage you to come to the clinic for one final visit to check on your health. Your withdrawal will not affect your access to other medical care at your local clinic. If you want the results of the study after the study is over, let the study staff members know.
- Discontinuation of study products: You must inform the study team if you wish to stop the study products as soon as possible.
- New findings: The study clinic staff will provide you with any additional information that becomes available during the study, which may affect your willingness to continue in the study.

PROBLEMS OR QUESTIONS

If you have any questions about the study, who to contact at the study site, or if you have a research related injury or any other problems related to the study, please feel free to contact the clinic staff by visiting the clinic between 08:00 to 16:30 or phoning on 011 358 5424 or after hours on 084 722 5877/ 083 797 0144. If you feel that you require more information than the clinic staff are able to give you please contact one of the people listed below:

Prof Thesla Palanee - Phillips Co-Principal Investigator Wits RHI, Research Centre No. 7 Esselen Street, Hillbrow Tel: 011 358 5471	Dr Nkosiphile Ndlovu Co-Principal Investigator Wits RHI, Research Centre No. 7 Esselen Street, Hillbrow Tel: 011 358 5424 Emergency Number: 084 722 5877

This study is conducted in accordance with the Department of Health Guidelines for the South African Good Clinical Practice: Clinical Trial Guidelines (2020) and has received ethical approval from the University of the Witwatersrand, Human Research Ethics Committee. If you want any information regarding your rights as a research participant, or complaints regarding this research study, you may contact Prof. Clement Penny, Chairperson of the University of Witwatersrand, Human Research Ethics Committee, which is an independent committee established to help protect the rights of research participants at 011 717 2301

Prof. Clement Penny Chairperson for the Committee for Human Research Ethics Committee University of the Witwatersrand Tel: 011 717 2301

If you have questions about this trial you should first discuss them with your personal/study doctor or the ethics committee (contact details as provided on this form). After you have consulted your personal/study doctor or the ethics committee and if they have not provided you with the answers to your satisfaction, you should write to the South African Health Products Regulatory Authority (SAHPRA) at:

The Chief Executive Officer South African Health Products Regulatory Authority Department of Health Private Bag X828 Pretoria 0001 E-mail: Boitumelo.Semete@sahpra.org.za Tel: 012 501 0410

ETHICAL APPROVAL OF THIS STUDY:

This study protocol has been submitted to the University of The Witwatersrand, Human Research Ethics Committee and written approval has been granted by the committee. The study has been structured in accordance with the Declaration of Helsinki (last update October 2013), which deals with the recommendations guiding doctors in biomedical research involving human subjects. A copy can be obtained from me if you wish to review it.

DATE AND TIME OF COMPLETION OF INFORMED CONSENT DISCUSSION:

DD	**MMM**	**YYYY**

:
Time *(24 hour clock)*

NOTIFICATION OF PERSONAL DOCTOR:

Please indicate whether you would like us to inform your personal doctor about your participation in this study

Please sign or place your mark/thumbprint next to the option you choose

_____ Participant's signature/mark or thumbprint	Yes, I want you to inform my personal doctor (Staff to obtain personal doctor contact details)
_____ Participant's signature/mark or Thumbprint	No, I do not want you to inform my personal doctor
_____ Participant's signature/mark or Thumbprint	I do not have a personal doctor.

AUDIO RECORDING OF INTERVIEWS SESSIONS

Please sign or place your mark/thumbprint next to the option you choose

_____ Participant's signature/mark or Thumbprint	Yes, I agree to have my interview audio recorded.
_____ Participant's signature/mark or thumbprint	No, I do not agree to have my interview audio recorded

***** If a potential participant does not agree to audio recording for the interview, she will not be able to participate in the interview.

INFORMED CONSENT:

- I hereby confirm that I have been informed by the study staff member_____*(Print full name)*, about the nature, conduct, benefits and risks of the study
- I have also received, read (or had read to me) and understood the above written information (Participant Information Sheet and Informed Consent for Screening and Enrolment) regarding the study.
- I am aware that the results of the study, including personal details regarding my ethnicity, race, sex, age, medical conditions, date of birth, initials and diagnosis will be anonymously processed into a study report.
- I may, at any stage, without prejudice, withdraw my consent and participation in the study.
- I have had sufficient opportunity to ask questions and (of my own free will) declare myself prepared to participate in the study

Signature of participant:

Signature/mark or thumbprint		Date of signature			
			DD	**MMM**	**YYYY**
Print name		Time of signature	: *(24 hour clock)*		

Signature of witness (if applicable):

Signature		Date of signature			
			DD	**MMM**	**YYYY**
Print name		Time of signature	: *(24 hour clock)*		

Signature of study staff taking consent:

Signature		Date of signature			
			DD	**MMM**	**YYYY**
Print name		Time of signature	: *(24 hour clock)*		

INFORMATION SHEET (IS) AND INFORMED CONSENT

*Each participant must receive, read and understand this document **before** any study-related procedure*

SHEET 2:	Storage and Future Testing of Specimens
TITLE FOR THE STUDY:	EPIC- Evaluation of Pharmacokinetic drug-drug Interactions between hormonal Contraceptives and doravirine- containing ART among women living with HIV in South Africa
SPONSOR:	Merck, Inc
PRINCIPAL INVESTIGATORS:	Prof. Thesla Palanee-Phillips and Dr Nkosiphile Ndlovu
INSTITUTION:	Wits Reproductive Health and HIV Institute (Wits RHI), University of the Witwatersrand
DAY TIME AND AFTER HOURS TELEPHONE NUMBERS:	Day Tel: 011 358 5424 A/H Tel: 084 722 5877

To the potential Participant: *This consent form may contain words that you do not understand. Please ask the study doctor or the study staff to explain any words or information that you do not clearly understand. You may take home **an unsigned copy of this consent** form to think about or discuss with family or friends **before making your decision.***

DATE AND START TIME OF INFORMED CONSENT DISCUSSION:

DD	**MMM**	**YYYY**

:
Time *(24hr clock)*

INTRODUCTION

While you are in the EPIC study, you agreed to have biological specimens collected and tested to check on your health or other infections. After the study is done, there may be some biological specimens left over that might be useful for future research. You are being asked to agree to the storage of these biological specimens. No additional specimens will be collected; only leftover biological specimens will be kept and used for future testing.

This consent form gives you information about the collection, storage, and use of these biological specimens and related health information for use in future studies. The study staff will talk with you about this information. Please ask study staff any questions you may have. If you would like to speak with a medical doctor or if you have medical questions, please let me know so that this can be arranged. You will be asked to sign or make your mark on this form to indicate whether you agree to have your biological specimens stored and tested in the future. You will be offered a copy of this form to keep.

HOW WILL WE USE YOUR BIOLOGICAL SPECIMENS?

We would like permission to store your biological specimens. At the moment we cannot provide exact details of what will be looked at as this is not yet known, but we give assurance that no research will be done on the specimens without the approval of the Wits Human Research Ethics Committee as well as the applicable Research Ethics Committee (REC) at the places where further testing may be done.

The future research will be related to HIV transmission and prevention as well as contraception Your biological specimens will be used to look for damage caused by infection; or your body's response to infection and drug testing. For instance, researchers may look at your blood cells and substances in your biological specimens called proteins and chemicals. Additional testing may be performed as part of specimen quality control. Some of these tests may be done outside of your country.

Only approved researchers will be able to use these specimens and health information. The researchers do not plan to contact you or your regular doctor with any results from tests done on your stored biological specimens. This is because research tests are often done using ways that are experimental, so the results do not usually help doctors manage your health. If a rare situation comes up in which the researchers decide that a test result is important for your health, the researchers will notify your study doctor and your study doctor will try to contact you. If you wish to be contacted with this type of test result, you must give the study doctor or nurse any change to your contact information. If you want your regular doctor to be told about this type of test result, you must provide the study doctor or nurse with your regular doctor's name and contact information.

Your biological specimens will not be sold or used directly to produce commercial products. Research studies wishing to use your biological specimens will be reviewed by the University of Witwatersrand Human Research Ethics Committee. The role of this committee is to protect you and other research volunteers from harm.

HOW LONG WILL WE KEEP YOUR BIOLOGICAL SPECIMENS?
Your specimens will be stored for a period of 15 years and may be shipped and/or stored outside of the country. We do not yet know the specific type of testing that will be done with these specimens. But, they may be used to check that certain laboratory tests perform correctly. Any other testing beyond that will have to be approved by the Wits Human Research Ethics Committee

HOW WILL YOUR BIOLOGICAL SPECIMENS BE STORED?
Your biological specimens will be stored at special facilities that are designed to store specimens safely and securely. Specimens will be stored by the Wits RHI laboratory or laboratories who have been contracted by Wits RHI and will be shipped at intervals to other facilities outside the country for use. The storage facilities are designed so that only approved researchers will have access to the specimens. Some employees of the storage facilities will need to have access to your specimens to store them and keep track of where they are, but these people will not have information that directly identifies you.

DOES STORAGE OF YOUR BIOLOGICAL SPECIMENS HAVE BENEFIT TO YOU?
There are no direct benefits to you. The benefit of doing research on stored biological specimens includes learning more about HIV infection.

GENETIC TESTING
Genetic testing is not currently a requirement of the protocol and your stored specimens will not be used for any genetic testing at this stage. Should the protocol team decide at a later stage to conduct a study that involves genetic testing a formal application process will be made to the Wits Human Research Ethics Committee and a separate consent will be requested from you.

WHAT ARE THE RISKS?
There are no direct risks related to storing your biological specimens.

WHAT ABOUT CONFIDENTIALITY?
To keep your information private, your biological specimens will be labeled with a code that can

only be traced back to your research clinic. Your name and other personal information will be protected by the research clinic. When researchers are given your stored biological specimens to study, they will not be given your personal information.

The results of future tests will not be included in your health records. Any publication about the results of future tests will not use your name or identify you personally. The researchers will do everything they can to protect your privacy. Every effort will be made to keep your personal information confidential. Your personal information may be disclosed if required by law. Your records may be reviewed by:

- Study sponsors and funders
- United States (US), local and international regulatory entities
- Members of the study protocol team and external advisors
- South African Health Products Regulatory Authority
- Human Research Ethics Committee, University of the Witwatersrand, an Ethics Committee is a committee that watches over the safety and rights of research participants
- National Health Research Ethics Committee (NHREC)
- Members of an Independent Data Safety Monitoring Board who review this clinical trial
- Study monitors
- Study staff

WHAT ARE YOUR RIGHTS?

Allowing your biological specimens to be stored is completely voluntary. If you decide not to have any biological specimens stored other than what is needed to complete the study, you can still remain in the study, and your leftover biological specimens will be destroyed after all of the study procedures are finished. If you decide now that your biological specimens can be stored for future research, you may change your mind at any time. However, you must inform the study staff that you no longer want your specimens used for future research. Your biological specimens will then not be used and will be destroyed but researchers will not be able to destroy specimens or information from research that is already started.

PROBLEMS OR QUESTIONS

If you have any questions about the study, who to contact at the study site, or if you have a research related injury or any other problems related to the study, please feel free to contact the clinic staff by visiting the clinic between 08:00 to 16:30 or phoning on 011 358 5424 or after hours on 084 722 5877/ 083 797 0144. If you feel that you require more information than the clinic staff are able to give you please contact one of the people listed below:

Prof. Thesla Palanee - Phillips Co-Principal Investigator Wits RHI, Research Centre No. 7 Esselen Street, Hillbrow Tel: 011 358 5471	Dr Nkosiphile Ndlovu Co-Principal Investigator Wits RHI, Research Centre No. 7 Esselen Street, Hillbrow Tel: 011 358 5424 Emergency Number: 084 722 5877

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Prof. Clement Penny Chairperson for the Committee for Human Research Ethics Committee

University of the Witwatersrand	Tel: 011 717 2301

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The Chief Executive Officer
South African Health Products Regulatory Authority
Department of Health
Private Bag X828
Pretoria
0001
E-mail: Boitumelo.Semete@sahpra.org.za
Tel: 012 501 0410

DATE AND TIME OF COMPLETION OF INFORMED CONSENT DISCUSSION:

			:
DD	**MMM**	**YYYY**	**Time** *(24 hour clock)*

INFORMED CONSENT:

- I hereby confirm that I have been informed by the study staff member_____*(PRINT FULL NAME)*, about the storage and future testing of specimens collected during my participation in the study.
- I have also received, read (or had read to me) and understood the above written information (Participant Information Sheet and Informed Consent: Storage and Future Testing of Specimens).
- I understand that my decision of whether to have my specimens stored and tested in the future will not affect my participation in the study or my medical care.
- I am aware that, if I agree to have my specimens stored and tested in the future, the results of tests on my specimens and health data, which may include personal details regarding my race, ethnicity, sex, age, medical conditions, date of birth, initials and diagnosis, will be anonymously processed into a study report.
- I may, at any stage, without prejudice, withdraw my consent for my specimens to be stored and tested in the future.
- I have had sufficient opportunity to ask questions and (of my own free will) agree to the storage of specimens for future testing.

Please sign or place your mark/thumbprint next to the option you choose

_____ Participant's signature/mark or thumbprint	I **DO** agree to allow my biological specimens and health data to be stored and used in future research studies

_____ Participant's signature/mark or thumbprint	I **DO NOT** agree to allow my biological specimens and health data to be stored and used in future research studies

Signature of participant:

Signature/mark or thumbprint		Date of signature			
			DD	**MMM**	**YYYY**
Print name		Time of signature	: *(24 hour clock)*		

Signature of witness (if applicable):

Signature		Date of signature			
			DD	**MMM**	**YYYY**
Print name		Time of signature	: *(24 hour clock)*		

Signature of study staff taking consent:

Signature		Date of signature			
			DD	**MMM**	**YYYY**
Print name		Time of signature	: *(24 hour clock)*		