PHARMACOLOGIC STRATEGIES FOR ETONOGESTREL IMPLANTS IN HIV-INFECTED WOMEN

Subtitle (descriptive): Pharmacokinetic and pharmacodynamic evaluation of etonogestrel dose escalation with efavirenz-based antiretroviral therapy in HIV-infected Ugandan women

Area:	HIV
Type:	Phase II

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Document History

Document	Version Date	Summary of Changes
Version 1.1	3 Nov 2017	
Version 2.0		Responses to NDA comments with the following additions: -Appendix 1 (WHO Medical Eligibility Criteria for IUDs and Implants) -Clarified Inclusion criteria #8 regarding menstural bleeding pattern -QRISK®2 Score, hemoglobin A1c and lipid assessment added to screening procedure -QRISK® Score added to exclusion criteria #11 -Screening window extended to 90 days to allow for IUD placement and return of regular menses -Allowance for participant re-screen -Added HIV/Family Planning Counseling added to each visits -Contraceptive Satisfaction and Condom Use Surveys removed from visits when they occur more frequently than every month -Flexibility added in the scheduling of weekly assessments for serum progesterone and cervical mucus testing -Clarified management in the case of efavirenz non-adherence or discontinuation -Clarified serious adverse event reporting requirements
Version 3.0	16 Oct 2020	Ugandan National Antiretroviral Guidance Change -Efavirenz 600 mg no longer recommended -All participants will be transitioned to either efavirenz 400 mg or dolutegravir-based antiretroviral therapy (ART) -Those participants on double-dose etonogestrel (two implants) who switch to dolutegravir-based ART will have one implant removed to return to standard dose etonogestrel -Four optional blood draws added at the time of ART switch to characterize the pharmacokinetics of efavirenz and etonogestrel after ART switch -Discontinuation of the cervical mucus collection and scoring due to futility
Version 4.0	26 May 2021	-Allows for continued participation for participants that switch from efavirenz 400mg to dolutegravir-based ART with that same study procedures as

		those who switched from efavirenz 600 mg to dolutegravir-based ART in version 3.0 -Provides counseling guidance for the removal of the copper IUD after switching to dolutegravir-based ART

Study Location and IRB of Record	**Date of Initial Approval**	**Date of Revised Protocol Approvals**
University of Pittsburgh	3 Nov 2017	
Infectious Diseases Institute; Joint Clinical Research Center IRB	5 Dec 2017	

PROTOCOL SUMMARY

Title	Pharmacokinetic and pharmacodynamic evaluation of etonogestrel dose escalation with efavirenz-based antiretroviral therapy in HIV-infected Ugandan women (DoublET)
Short Title	Evaluation of the etonogestrel implant in HIV-infected women
Protocol Number	PK-20
Phase	II
Methodology	A randomized, open-label, longitudinal pharmacodynamic study to compare frequency of ovulation between a control group of HIV-infected women on efavirenz (EFV)-based antiretroviral therapy receiving standard dose etonogestrel (ENG) implant and a treatment group receiving increased dose ENG implant. The overall goal is to assess the pharmacodynamic significance of the known drug-drug interaction between EFV and ENG and to determine if the increased dose will overcome this interaction. Overall, this study will improve long-acting reversible contraceptive treatment options for women living with HIV and prevent unintended pregnancy.
Study Duration	48 weeks; if all safety measures are met, will extend to 144 weeks
Study Center(s)	Infectious Diseases Institute; Kampala, Uganda

Objectives	*Primary objective:* To compare the rate of ovulation (by weekly endogenous progesterone at months 3, 6, and 12) when women receive two 68 mg ENG implants (dose-escalated) compared to one 68 mg ENG implant (standard dose) in combination with EFV-based ART. *Secondary objectives:* 1. To determine cervical mucus quality (by collecting weekly WHO cervical mucus scores at months 3, 6, and 12) when women receive two 68 mg ENG implants (dose-escalated) compared to one 68 mg ENG implant (standard dose) in combination with EFV-based ART. 2. To compare the PK parameters of two ENG implants (136 mg total) with combined EFV use versus the standard dose 68 mg ENG implant with no ART (historical controls in the same population using the same laboratory[1]) over 6 months of combined use. 3. To evaluate the safety and tolerability of two ENG implants with combined EFV-based ART use. 4. To describe the relationship between ENG concentrations and participant specific variables, specifically body weight, albumin, sex hormone binding globulin, pharmacogenetic polymorphisms, and ART concentrations. 5. To describe the long term feasibility and tolerability of increased dose ENG (136mg) subdermal implant use in HIV-infected women receiving EFV-based ART after weeks 96 and 144 of combined use. 6. To describe the change in EFV trough concentrations and ENG steady state concentrations after switching from EFV 600mg to either dolutegravir (DTG)- or EFV 400mg-based ART and after switching from EFV 400mg to dolutegravir (DTG)-based ART.
Number of Participants	HIV-infected women receiving EFV-based ART, n=72
Diagnosis and Main Inclusion Criteria	Consenting HIV-infected women receiving EFV-based ART for at least 3 months, who are medically eligible for the use of an ENG subdermal implant as a contraceptive method.
Study Product(s), Dose, Route, Regimen	Increased dose ENG implant (two implants, total 136mg) placed subdermally on study day 0 after baseline evaluations.

Duration of administration	Planned study duration will be at least 48 weeks if all safety measures are met, but may extend up to 144 weeks to assess long term safety The ENG implant system is approved for 3 years of use. Participants may continue to use the ENG implant as part of standard of care after the study period.
Reference therapy	For pharmacodynamic outcomes: Standard dose ENG implant (one implant, total 68mg) placed subdermally on study day 0 after baseline evaluations. For pharmacokinetic outcomes: Standard dose ENG implant without ART from a historical group of participants (N=20) from the same research site (IDI) and ENG assays performed in the same laboratory (University of Pittsburgh) followed for 6 months
Statistical Methodology	The ovulatory rate and the number of WHO mucus scores greater than 10 will be compared between the groups (standard-dose vs. dose escalated implant groups) at month 3, 6 and 12 of implant use using mixed-effects logistic regression. Between-group comparisons will evaluate changes in ENG PK parameters between the historical standard dose ENG implant without ART vs. dose-escalated ENG implant group with concurrent EFV-based ART use for 6 months. Geometric mean ENG will be compared at each time point (weeks 1, 4, 12, and 24) between the historical control group and two ENG implants (dose-escalated on EFV-based ART group using a Wilcoxon rank sum test. Drug concentrations will be summarized descriptively (geometric mean, minimum, maximum, standard deviation) by study visit. The ENG concentration-time curve will be evaluated using standard non-compartmental analysis (Phoenix, Pharsight®).

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse events
ALT	Alanine transaminase
ART	Antiretroviral therapy
AUC	Area under the concentration-time curve
CRF	Case report form
CYP	Cytochrome P450
D	Day
DAIDS	National Institute of Health Division of AIDS
DDI	drug-drug interactions
DTG	dolutegravir
EFV	efavirenz
ENG	Etonogestrel
GCP	Good Clinical Practices
GMR	Geometric mean ratio
HIV	Human Immunodeficiency Virus
HPLC	High performance liquid chromatography
IDI	Infectious Diseases Institute
IRB	Institutional Review Board
IUD	Intrauterine device
LC-MS/MS	HPLC linked to mass spectrometry
LMIC	Low and middle income country
ENG	Etonogestrel
MU-JHU	Makerere University – Johns Hopkins University Core Laboratory
NDA	National Drug Authority
NVP	Nevirapine
OCP	Oral Contraceptive Pill
PK	Pharmacokinetic
SAE	Serious Adverse Event
SMC	Safety Monitoring Committee
UNCST	Uganda National Council of Science and Technology
UNMC	University of Nebraska Medical Center
W	Week
WHO	World Health Organization

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INTRODUCTION

Family planning options including hormonal contraceptives are essential to improving womens' reproductive health. Each year, effective contraception prevents 188 million unintended pregnancies worldwide, thereby averting 1.1 million newborn and 150,000 maternal deaths, as well as preventing 112 million abortions[2,3]. While the problem is global, the burden of unintended pregnancies lies in low- and middle-income countries (LMIC) where over 222 million women face an unmet need for effective contraception[4]. This carries an even greater risk for the over 16 million HIV-infected women worldwide[5], for whom contraceptives decrease the risk of mother-to-child HIV transmission[6,7].

Despite the benefits of hormonal contraceptives, significant drug-drug interactions (DDIs) with some antiretroviral therapies (ART) represent a critical barrier to effective family planning methods for HIV-infected women. Our research team recently demonstrated that combined use of efavirenz- (EFV) based ART, the only World Health Organization (WHO)-preferred first-line ART regimen for adults living with HIV[8], with the etonogestrel (ENG)-releasing subdermal implant, also a WHO-recommended form of long-acting, reversible contraception and the easiest to insert[9], caused a 63% reduction in ENG serum concentrations in Brazilian women[10] and a 84% reduction of ENG plasma concentrations in Ugandan women[1], which in turn, jeopardized contraceptive efficacy. There are 6 case reports of etonogestrel contraceptive failures[11-13], as well as a reported pregnancy rate of 3.0 (95% CI 1·4–4·7) per 100 woman-years, in women using EFV-based ART with the ENG implant[14]. This is in significant contrast to the reported <1% pregnancy rate in women using the contraceptive implant without a coadministered interacting drug[15]. Therefore, it is of critical public health importance to identify a safe and effective treatment strategy that allows for combined use of these preferred family planning and ART strategies in HIV-infected women. This protocol investigates one practical approach to this patient care challenge.

1.1. Disease Setting/Patient Population

The public health burden of unintended pregnancies lies in LMIC where maternal mortality is highest. The magnitude of this public health burden is well illustrated in the Uganda, where approximately 800,000 women are living with HIV, 40% of pregnancies are unplanned; and 220 neonatal and 310 maternal deaths occur per 100,000 live births[16,17].

At the onset of this study, the WHO recommended EFV-containing ART as the only preferred initial regimen for HIV-1-infected adults, a recommendation recently expanded to include women of reproductive ages[8]. WHO and Uganda guidelines for ART were updated during the conduct of the trial, discussed further in section 1.4.[18]

This study will include HIV-infected women who are receiving EFV-based ART and who request female controlled contraception options for family planning at the Infectious Diseases Institute (IDI), Kampala, Uganda.

1.2. Background and Rationale

Long-acting reversible contraception methods, such as subdermal hormone implants, are recommended by the WHO, are widely used, and provide women with a safe and effective option for preventing pregnancy or planning birth spacing[19-21]. In addition to their very high efficacy rate,

subdermal implants offer women convenient control of their fertility without concern for frequent oral pill refills or injections. In addition, the subdermal implant insertion is quick, nearly painless and the return to fertility is almost immediate after its removal[22-24]. Contraceptive implants are the fastest growing method of contraception in sub-Saharan Africa; which includes a 9-fold increase in use from 2008 to 2012, and 9 million implants shipped to sub-Saharan Africa in 2015[25].

Despite increasing use of both EFV-based ART and subdermal hormone implants, three recent clinical studies have reported a pregnancy rate of 4.2% to 15% in women using levonorgestrel contraceptive implants while taking EFV-based ART[14,26,27]. For women using the ENG implant while on EFV-based ART reported a pregnancy rate of 3.0 (95% CI 1·4–4·7) per 100 woman-years[14]. All of these reports are in significant contrast to the reported <1% pregnancy rate in women using the contraceptive implant without a coadministered interacting drug. From these very limited data it appears that for women on EFV-based ART the ENG implant could be more effective in preventing pregnancy than the levonorgestrel implant. This could be due to the increased potency of etonogestrel compared to levonorgestrel with regards to ovulation suppression. Rice and colleagues demonstrated that only one ovulation out of 59 cycles were ovulatory with oral desogestrel and 16 ovulations out of 59 cycles for levonorgestrel[28]. Additionally, etonogestrel could be a preferred candidate for dose escalation because it the single rod system allows for easy insertion.

1.2.1. ENG Pharmacokinetics

The pharmacokinetic (PK), safety, and efficacy of the ENG implant (68mg) have been clearly established in clinical trials[22,29-32]. Following subdermal insertion into the upper arm, ENG is released from the implant into the interstitial fluids at a rate of 60-70 mcg/day at one-month post-insertion, decreasing to 40 mcg/day within one-year and to 25-30 mcg/day within three-years[22]. Serum ENG concentrations reaching peak concentrations of 1145 (±577) within one and thirteen days post-insertion and a median four days post-insertion and then slowly decline over the three years of intended use[29]. ENG is tightly protein-bound to sex hormone-binding globulin (32%) and albumin (66%)[15]. This, in addition to an inverse association between ENG concentrations and bodyweight[33], contribute to its interpatient variability. However, ENG concentrations are less variable then levonorgestrel concentrations likely due to ENG being more bound to albumin rather than sex hormone binding globulin[34].

ENG clearance and metabolism are via the cytochrome P450 (CYP) enzyme system, specifically the CYP3A4 isoenzyme, and co-administration of medications that induce or inhibit CYP3A4 are known to impact ENG concentrations[15].

1.2.2. Pharmacokinetics of ENG alone, and in combination with either NVP or EFV-based ART

Our team recently completed a 24-week PK evaluation of the ENG implant in HIV-infected women not receiving ART (control group, n=20) compared to women receiving EFV-based ART (EFV group, n=20) or nevirapine (NVP)-based ART (NVP group=20)[35]. After providing informed consent, each participant had one 68mg ENG implant (standard dose) placed subdermally at enrollment (Day 0); PK sampling for ENG plasma concentrations were performed at 1, 4, 12, and 24 weeks. As shown in **Table 1,** the EFV group showed a significant reduction in ENG

concentrations compared to the control group. The interaction was observed by week 1, and remained relatively stable throughout weeks 4-24 (**Figure 1**).

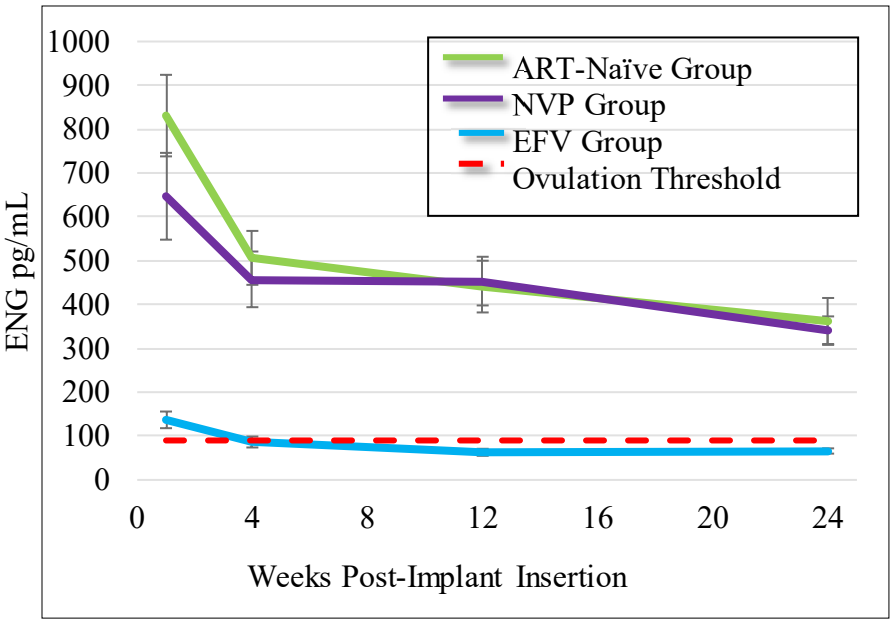
In the EFV group, ENG concentrations were significantly lower at each visit compared to the ART-naïve group [Week 24 GMR: 0.18 (0.17-0.20)]. In contrast, there were no significant differences in the ENG concentrations in the NVP group at each study visit compared to the ART-naïve group [Week 24 GMR: 0.94 (0.90-1.01)]. The ENG GM AUC_{0-24} was 11.12, 10.47, and 1.80 ng*wk/mL in the ART-naïve, NVP, and EFV groups, respectively [AUC_{0-24} GMR: NVP:ART-naïve 0.94 (0.94-0.94); EFV:ART-naïve 0.16 (0.16-0.16)]. The number of participants in the EFV group with ENG concentrations below 90 pg/mL (the reported threshold for ovulation suppression[36]) was 9 (47%), 16 (84%), and 18 (95%) at weeks 4, 12 and 24, respectively. In contrast, all participants in the ART-naïve and the NVP groups had ENG concentrations above 90 pg/mL throughout the 6 month study duration.

Table 1. Etonogestrel Plasma Concentrations over 24 weeks (pg/mL)

Weeks from Implant Insertion	ART-Naïve Group (N=20)[1]	NVP Group (N=19)[1]	EFV Group (N=19)[1]	GMR NVP:ART-Naive[2]	GMR EFV:ART-Naive[2]
1	831 (738, 924)	647 (548, 746)	137 (118, 156)	0.78 (0.74-0.81)	0.16 (0.16-0.17)
4	507 (445, 568)	457 (394, 521)	87 (74, 99)	0.90 (0.88-0.91)	0.17 (0.17-0.17)
12	441 (382,500)	453 (398, 509)	63 (55, 71)	1.03 (1.02-1.04)	0.14 (0.14-0.14)
24	362 (308, 415)	341 (310, 373)	66 (60, 72)	0.94 (0.90-1.01)	0.18 (0.17-0.20)

[1]Geometric mean with 90% confidence intervals
[2]Geometric mean ratio (GMR) with 90% confidence intervals
ART= Antiretroviral Therapy, NVP=Nevirapine, EFV=efavirenz

Figure 1. Etonogestrel (ENG) geometric mean concentrations (pg/mL) with 90% confidence intervals over 24 weeks



1.2.3. Clinical outcomes of the ENG-EFV drug-drug interaction

High quality clinical data regarding the clinical outcome of women using the contraceptive implant while on EFV-based ART are limited to retrospective secondary analyses of observational cohort studies, small prospective PK studies and 6 case reports of contraceptive failures[11-13,37]. In a PK study of the levonorgestrel implant, which was designed similarly to that described in Section 1.2.2, our team observed three (15%) unintended pregnancies among women receiving EFV-based ART with the levonorgestrel implant, all occurring between study weeks 36 and 48; no pregnancies were observed in the NVP or control groups[27]. In our subsequent PK study of the ENG implant, the women on EFV-based ART were required to use the copper intrauterine device (IUD) to avoid the life-altering event of an unplanned pregnancy; therefore we did not observe any pregnancies with the ENG implant in the EFV group[35].

There are 3 retrospective cohort studies published that explore pregnancy outcomes among women using ART and hormone implants. First, a retrospective study of 570 HIV-infected women in Swaziland reported pregnancy in 12.4% of women using the levonorgestrel implant and EFV-based ART, but no pregnancies with other ART regimens[26]. Secondly, a study combined data from three longitudinal studies and found that among women using implants, the calculated incident pregnancy rate was 6.0 vs. 1.4 pregnancies/100 women-years in women using EFV-based ART vs. no ART, respectively[38]. Finally, a three-year retrospective cohort study from Kenya examined pregnancy rates among nearly 25,000 HIV-infected women using various combinations of contraceptive methods and ART regimens. They observed a 3-fold higher pregnancy risk in implant users (either ENG or levonorgestrel-containing) receiving EFV-based ART compared to

NVP-based ART (adjusted rate ratio: 3.0 [1.3-4.6])[14]. Importantly, they also showed that among EFV-based ART users, women reporting oral and injectable contraceptive use were up to three times more likely to become pregnant than those women reporting use of implants. This retrospective study had several limitations, including self-reported use of contraceptive methods and lack of initiation or discontinuation dates for the methods. Nonetheless, it demonstrated that despite drug-drug interactions between implants and EFV, implants remain one of the most effective contraceptive methods for HIV-infected women.

Based upon the cumulative data, the WHO recently released an updated statement on the use of progestin containing implants in HIV-infected women. Given the high effectiveness of implants compared to other methods of contraception, even in the presence of a drug-drug-interaction, the WHO confirmed the 2014 consolidated HIV/contraception guidelines and advises that HIV-infected women should have the opportunity to use all types of contraception, including implants[19]. In light of this WHO recommendation, combined use of implants and EFV-based ART is certain; thus, strategies to optimize their combined use are desperately needed, specifically, strategies to improve the implant's effectiveness to <1% risk of pregnancy, as is observed in women not using an interacting co-medication.

1.2.4. Relationship between ENG exposure and contraceptive effect

There are two primary mechanisms of action for contraceptive implants. First, the progestin suppresses the luteinizing hormone surge necessary for ovulation. Second, the progestin causes decreased cervical mucus formation and increases cervical mucus thickening, therefore making the mucus impenetrable to sperm. Progestin pharmacokinetics has been used as a broad marker of contraceptive effect due to easy assertainment, as compared to pharmacodynamic markers of contraceptive effectiveness. Clinical studies have shown that individual women may require differing concentations of progestins to prevent pregnancy. For example, previous studies have shown that for etonogestrel, the threshold for ovulation suppression was 90pg/mL[36], however a later study reported ovulation occuring in one woman with etonogestrel concentrations of 120pg/mL[29]. Furthermore, we reported that there was an 84% decrease in ENG exposure with 95% of women having ENG concentrations below 90pg/mL at 24 weeks of use.

In this study, we will evaluate the impact of standard dose and dose escalated ENG implant on the ovulation and cervical mucus in women on EFV-based ART, while preventing unplanned pregnancies with the placement of the copper IUD in all women. After ovulation the corpus luteum cyst secretes progesterone and measurement of serum progesterone at day 21 of the menstural cycle is commonly assessed in clinical care as a marker of ovulation. However, due to the unpredictability of ovulation during contraceptive implant use, we will collect serum enogenous progesterone weekly at specified months of use. In infertility assessment, the WHO cervical mucus score is used to evaluate the potential sperm-mucus interaction. A score of greater than 10 considered indicative of cervical mucus favoring sperm penetration[39]. By simultaneously assessing ovulation, cervical mucus and ENG plasma concentrations, we will address the knowledge gap of at what ENG concentration threshold will there be a contraceptive effect and how that threshold varies between women. Furthermore, we will be able to more accurately know the risk of pregnancy for women using the ENG implant and EFV-based ART, and whether two ENG implants (136mg – dose escalated) will improve contraceptive effectiveness for women on EFV-based ART.

1.2.5. Study rationale builds upon prior dose adjustment strategies to overcome DDIs

The premise of our study is to evaluate if the DDI between the ENG implant and EFV-based ART can be safely and adequately overcome by using an adjusted dose of the ENG implant, specifically increasing the ENG dose from 68mg to 136mg in combination with EFV-based ART. Dose adjustment is a well-accepted strategy to overcome DDIs and there are examples of this strategy being used with other medications. For example, when rifampicin, an antituberculous medication, is given concomitantly with raltegravir, an antiretroviral medication, raltegravir plasma exposure is decreased 40%; this interaction can be overcome by doubling the raltegravir standard dose, from 400mg twice daily to 800mg twice daily[40]. Additionally, a recent investigation evaluated using an increased dose of an oral contraceptive pill (OCP) containing levonorgestrel plus ethinyl estradiol to overcome the decrease in hormone PK exposure observed in obese women[41,42]. Fifteen women in this study received levonorgestrel 100mcg/day during one menstrual cycle, followed by a 50% increased levonorgestrel dose (150mcg/day) during a subsequent cycle. This dose adjustment resulted in a 42% increase in levonorgestrel AUC, with no reported adverse events (AE), demonstrating the success of dose adjustment to effectively increase exposure[43].

1.2.6. Concentrations achieved with the ENG implant are lower than what is achieved with a etonogestrel vaginal ring

As previously mentioned, the ENG implant releases variable rates of ENG over the approved 3 year duration of use (60-70 mcg/day at one-month post-insertion, 40 mcg/day within one-year and to 25-30 mcg/day within three-years). Placement of two implants (136mg total) would likely result in 140 mcg/day for only the first month, followed by 80mcg/day within one year and 50 mcg/day within 3 years. Without an interacting drug, a doubling of the dose might result in an ENG Cmax of 2400pg/mL (single dose ENG Cmax=1200pg/mL) occurring in the first 2 weeks, declining to approximately mean serum ENG concentration of 600pg/mL (300pg/mL for single dose at 6 months) and 400pg/mL at 12 month (200pg/mL for single dose at 12 months). However, in the setting of the significant drug-drug interaction with EFV, a conservative estimate reported in Brazilian women of 63% decrease in serum concentrations, therefore we anticipate that the actual ENG serum concentrations would be approximately 888pg/mL (Cmax), 222pg/mL (at 6 months) and 148pg/mL (at 12 months). In comparison, the Nuvaring® (a vaginal ring containing 11.7mg of etonogestrel and 2.7 mg of ethinyl estradiol), like the implant is 100% bioavailable and releases 120mcg/day of etonogestrel, a very similar dose to the first month placement of 2 ENG implants (136mg total). The NuvaRing® results in significantly higher serum ENG concentration than expected with 2 ENG implants and EFV-based ART: 1578 pg/mL mean serum ENG at 1 week of use[44]. Therefore, even if ENG concentrations resulting from the increased dose (136mg) of the ENG implant in the setting of a conservative estimate of the resultant ENG-EFV drug-drug interaction, ENG concentrations would still be 40% **lower** than the ENG concentrations achieved with NuvaRing® use. Given this, ENG dose related AEs are not expected in this study. However, to ensure patient safety, strict monitoring will be conducted at regular intervals for both the efficacy and safety of increased dose ENG.

AEs that were possibly related to the ENG implant in our prior study are described in **Table 2**. There were 298 reported adverse events, 297 were mild intensity (Grade 1) and one of moderate

intensity (Grade 2). The one adverse event of moderate intensity was due to menorrhagia in the NVP group. Importantly, no drug-related AE was severe or resulted in implant discontinuation.

Table 2. Cumulative Adverse Events Reported Over 24 Weeks of ENG Implant Use

Adverse Event	ART-naïve Group (n=100)	NVP Group (n=124)	EFV Group (n=74)
Menorrhagia	13 (13%)	17 (14%)	13 (17%)
Metrorrhagia	17 (17%)	12 (10%)	6 (8%)
Amenorrhea	18 (18%)	20 (16%)	14 (19%)
Headache	18 (18%)	31 (25%)	15 (20%)
Weight Gain	23 (23%)	18 (14%)	19 (26%)
Breast tenderness	3 (3%)	5 (4%)	2 (3%)
Nausea	4 (4%)	17 (14%)	2 (3%)
Implant site discomfort	4 (4%)	4 (3%)	3 (4%)
Grade 1	100	123	74
Grade 2	0	1 (menorrhagia)	0

1.2.7. Frequent interim measures of ENG efficacy and safety based on PK exposure and reported side effects

To ensure participants are not at excess risk of pregnancy, all participants will have a copper intrauterine device (IUD) placed to ensure adequate contraceptive efficacy. In addition, to ensure subjects do not receive long-term, suboptimal or supratherapeutic hormonal contraception, we will assess the futility of the ENG implant (standard and increased dose) + EFV-based ART after 24 weeks of combined use, then every 24 weeks thereafter. The first interim analysis of the ENG concentrations will occur as soon as 20 participants (at least 10 in each group) completes 24 weeks of combined ENG implant and EFV use. This assessment will be based upon lack of contraceptive effect as evidence by either ENG <90pg/mL, progesterone concentration >3ng/mL or WHO cervical mucus scores >10. See section 9.4 for the defined measures of safety monitoring, and section 9.6 for external study monitoring plans.

1.3. Intended Study Outcome and Summary

With the evidence outlined above, it is highly plausible that increasing the dose of the ENG implant to 136mg, by inserting two 68mg ENG implants, can safely and effectively overcome suboptimal ENG concentrations when combined with EFV-based ART.

Given the public health importance of preventing unplanned pregnancies in HIV-infected women, coupled with the growing use of EFV-based ART and ENG subdermal implants in this population, there is an urgent need to determine the clinical significance of the EFV-ENG interaction and to identify alternative dosing strategies for the ENG implant in women using EFV-based ART that will allow for safe and effective concomitant use of these preferred therapies. This study will determine if increasing the dose of the ENG-releasing subdermal implant effectively overcomes

the known PK interaction with EFV-based ART in a clinically meaningful way. This study will be the first to evaluate an alternate strategy for the use of the ENG implant among women receiving EFV-based ART. In doing so, we will inform and improve clinical practice by providing sound data upon which healthcare providers and policy makers can make evidence-based decision to guide the safe and effective use of ENG implants in HIV-infected women receiving EFV-based ART.

1.4 Updated Ugandan ART Guidelines in 2020: implications for study participants

In 2020, the Ugandan Ministry of Health (MoH) published new guidelines on the prevention and treatment of HIV and AIDS[45]. MoH selected first-line regimens based on reduced toxicity, pill burden, efficacy, sequencing, harmonization across populations, and lower costs based on the most recent data. Dolutegravir (DTG) is now recommended as the "anchor" ARV in the preferred first and second-line treatment regimens for all persons living with HIV. The rationale for the inclusion of DTG-based therapy recommendations include a high level of circulating resistance to NNRTIs in Uganda, DTG is more effective, better tolerated and has a higher genetic barrier to resistance. DTG has been associated with hyperglycemia, therefore persons living with HIV and that have diabetes or are at high risk of diabetes will be continued on EFV based ART. However, EFV will be given at a dose of 400 mg because this dose is non-inferior to 600 mg, is better tolerated, and can be co-administered with rifampicin-containing anti-TB treatment.

It is unclear if the reduction in the dose of EFV will have any impact on the DDI between EFV and ENG. However, there does not appear to be a clinically significant DDI between DTG and ENG based on cross-sectional data[46].

Given that the Uganda ART guidance is consistent with WHO guidance, it is anticipated that many women across the world using EFV 600mg will be transitioned to DTG- or EFV 400mg-based ART while using the ENG implant. Therefore, it is important to characterized both the ART and ENG concentrations around the time of the ART switch.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

Primary objective:
To compare the rate of ovulation (by weekly endogenous progesterone measured at months 3, 6, and 12) when women receive two 68 mg ENG implants (dose-escalated) compared to a standard dose 68 mg ENG implant in combination with EFV-based ART.

Secondary objectives:

1. To determine cervical mucus quality (by collecting weekly WHO cervical mucus scores at months 3, 6, and 12) when women receive two 68 mg ENG implants (dose-escalated) compared to a standard dose 68 mg ENG implant in combination with EFV-based ART.

2. To compare the PK parameters of two ENG implants (136 mg total) when combined with EFV-based ART versus the standard dose 68 mg ENG implant with no ART (historical controls in the same population using the same laboratory) over 6 months of implant use.
3. To evaluate the safety and tolerability of two ENG implants (dose-escalated) in HIV-infected women receiving EFV-based ART over 12 months of combined use.
4. To describe the relationship between ENG concentrations and participant specific variables, specifically body weight, albumin, sex hormone binding globulin, pharmacogenetic polymorphisms, and EFV concentrations.
5. To describe the long term feasibility and tolerability of increased dose ENG (136mg) subdermal implant use in HIV-infected women receiving EFV-based ART after weeks 96 and 144 of combined use.
6. To describe the change in EFV trough concentrations and ENG steady state concentrations after switching from EFV 600mg to DTG- or EFV 400mg-based ART and from EFV 400mg to DTG-based ART.

2.2. Study Endpoints

Primary endpoint

1. Frequency of ovulation at months 3, 6, and 12, defined as a single serum progesterone concentration above 3ng/mL, collected at weeks 9-12 (month 3), 21-24 (month 6), and 45-48 (month 12) after implant insertion from participants on EFV-based ART using dose-escalated ENG implant (136mg) compared to standard-dose ENG implant (68mg).

Secondary endpoints

1. Frequency of WHO cervical mucus scores >10 at months 3, 6, and 12 collected at weeks 9-12 (month 3), 21-24 (month 6), and 45-48 (month 12) after implant insertion from participants on EFV-based ART using dose-escalated ENG implant (136mg) compared to standard-dose ENG implant (68mg).
2. ENG concentrations (in pg/mL) obtained at week 1, 4, 12 and 24 from participants in this study on EFV-based ART using dose-escalated ENG implant (136mg total) compared to historical controls (standard-dose ENG implant with no ART).
3. Frequency of AEs and participant satisfaction related to ENG during the study period through week 48 in women on EFV-based ART using dose-escalated ENG implant (136mg) compared to standard-dose ENG implant (68mg).
4. Differences in ENG concentrations as they relate to body weight, albumin, sex hormone binding globulin, pharmacogenetic polymorphisms, and EFV concentrations.
5. ENG concentrations, ovulatory frequency, and signs and symptoms related to hormone exposure (i.e. potential AEs) evaluated at weeks 69-72, 93-96, 117-120, and 141-144.
6. ENG and EFV concentrations at the time of ART switch to DTG- or EFV 400mg-based ART and two, four and six weeks after.

2.3. Study Hypothesis

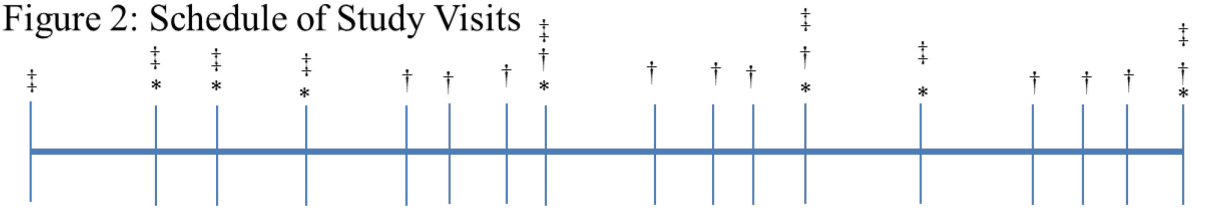
Overall, we hypothesize that the rate of ovulation in the group of women using EFV-based ART with dose-escalated ENG implants will be lower than in the group of women using EFV-based ART with a standard dose ENG implant.

3. STUDY DESIGN

This is a randomized, open-label, parallel, two-group pharmacodynamic study to compare the rate of ovulation and WHO cervical mucus scores between standard (68mg) or dose-escalated (136mg) ENG implants in 72 HIV-infected Ugandan women who are on EFV-based ART.

HIV-infected women between the ages of 18-40 years of age on EFV-based ART attending clinic at the Infectious Disease Institute will be offered study participation. All participants will be randomized to either having a dose-escalated or standard-dose implant that will inserted at study entry (Day 0) using computer generated numbers in sealed opaque envelopes. A study schema is shown in **Figure 2**.

Figure 2: Schedule of Study Visits



if safety and efficacy measures are met, extended follow=up will occur every 6 months during years 2 and 3

For the pharmacokinetic analysis of ENG, data from 20 historical control patients, comprised of Ugandan HIV-infected women receiving standard dose ENG implant will also be used in analyzed in this study. The control group will be comprised of data from our previous control group of HIV-infected women using a standard dose ENG (68mg) subdermal implant without concomitant ART (no ART, n=20) followed for 24 weeks. No additional data analysis will occur on historical participants than was performed in the original study.

4. PARTICIPANT SELECTION

The clinical study will be conducted at the IDI, Makerere University. Approximately 7,500 HIV-infected adults, 60% of whom are women, receive care at the IDI. Integrated HIV care and family planning services began in 2010. At present, EFV is used in approximately 66% of first line antiretroviral regimens at IDI. The ENG implant is registered for use in Uganda and is a desirable form of contraception among HIV-infected women at the IDI (10% of women at IDI currently use the implant).

All women receiving EFV-based ART and seeking family planning services at the IDI will receive information about this study involving the ENG implant, as well as information about all other family planning methods available to them. All family planning services at IDI are provided at no cost to the patient, including all contraceptive methods under investigation (implants and copper intrauterine device [IUD]). Condoms are provided at all visits, and will continue to be given to all participants at each study visit to prevent HIV transmission to uninfected partners. For women who are interested in the ENG implant and participation in this study, the following eligibility criteria are designed to select participants for whom protocol treatment is considered appropriate.

4.1. Inclusion Criteria

The inclusion and exclusion criteria are designed first to provide protections for research participants (informed consent, appropriateness of contraceptive choice, organ function, prevention of pregnancy, and safety of study procedures) and second to ensure the study's ability to address the stated objectives (no external drug-drug interactions and likelihood to remain on study related medications and enrolling subject that are ovulating).

Participants must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Evidence of a personally signed and dated informed consent document indicating that the participant has been informed of all pertinent aspects of the study.

2. Participants who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.
3. Women age 18 years to 40 years
4. Diagnosed with HIV infection
5. Medically eligible for the ENG subdermal implant as a contraceptive method based on the WHO Medical Eligibility Criteria for Contraceptive Use, see appendix 1[20]
6. Receiving EFV-based ART for a minimum of 3 months prior to screening
7. Must agree to have concurrent highly effective non-hormonal contraception with a copper IUD, if not previously medically sterilized.
8. Participants must report regular menses (menstrual bleeding for 4-8 days at 21 to 35 day intervals) for the preceding 2 month (intermenstral spotting is allowable).
9. Participants must have a negative urine pregnancy test at entry and report no unprotected sex since the last menstrual period or in the last two weeks.

4.2. Exclusion Criteria

Participants presenting with any of the following will not be included in the study:

1. HIV RNA > 50 copies/mL at screening visit
2. Serum hemoglobin < 10.0 g/dl
3. Elevations in serum levels of alanine transaminase (ALT) above 5 times the upper limit of normal
4. Elevations in serum creatinine above 2.5 times the upper limit of normal
5. Use of drugs known to be contraindicated with ENG or EFV within 30 days of study entry. Due to the dynamic nature of drug interactions related to ART, the study team will review all concomitant medications at screening based on the US Department of Health and Human Services drug interaction table[47] and the ENG implant product labeling[15].
6. Currently pregnant or postpartum <30 days at study entry.
7. Breastfeeding women within 6 months of delivery.
8. Use of hormonal contraception in the preceding 3 months prior to entry
9. Participants determined to be ineligible for IUD placement by the WHO Medical Eligibility Criteria for Contraceptive Use[48]
10. Patients with a history of hypersensitivity to ENG implant, undiagnosed vaginal bleeding, diagnosed or suspected sex hormone dependent neoplasia, benign or malignant liver tumor, or thromboembolic disease.
11. Presence of any active clinically significant disease or life-threatening disease that, in the investigator's opinion, would compromise the subject's safety or outcome of the study, specifically including but not limited to QRISK®2 score (calculator located at: https://qrisk.org/2017/) that predicts a greater than 10% risk of heart attack in the next 10 years, or severe depression.

5. TREATMENTS OF PARTICIPANTS

5.1. Allocation to Treatment/Group

This is a randomized, open-label, parallel, two-group pharmacodynamic study to compare standard (68mg) to dose-escalated (136mg) ENG implants in 72 HIV-infected women who are on EFV-based ART. The participants' ART will not be determined by this research protocol and HIV care will remain at the discretion of the treating clinician.

The participant's ART at enrollment will determine eligibility for the study:

- ENG subdermal implant, standard dose (68mg mg/1 rod) + EFV-based ART (control)
- ENG subdermal implant, escalated dose (136 mg/2 rods) + EFV-based ART (treatment)

At the enrollment visit, the participant will be randomized to either standard dose ENG implant or dose-escalated ENG implant.

Participants will continue their current ART as directed by their primary HIV care provider throughout the study period. No changes will occur as a result of study procedures. Participants will continue to receive HIV care and treatment through the standard IDI ART clinical treatment procedures and according to the Ugandan HIV treatment guidelines.

5.2. Drug Supplies

Active ingredients and dosage strength:	Etonogestrel 1-rod implant (68mg/rod)
Route of administration:	Subdermal placement
Dose:	Control group: 1 rod (68mg) inserted subdermally into one arm Treatment group: 2 rods (136mg) inserted subdermally; 2 rods in one arm
Duration of treatment:	Clinically approved for 3 years of use. Study participation will be complete after up to 3 years.

The study drug will be purchased from local suppliers. ENG implant is registered in Uganda. The supplier of the ENG implant will remain consistent throughout the study and will be certified through Good Manufacturing Practices or International Organization for Standardization.

5.2.1. Administration

Following completion of entry procedures (outlined below), The ENG implant systems will be placed subdermally in the upper arm by a trained clinician at the IDI clinic on study day 0. Participants will either have one implant or 2 implants placed into one arm. Placement of two rods will be performed similarly to the placement of the 2-rod levonorgestrel implant that is also commonly used in Uganda and at the Infectious Disease Institute[49]. Specifically, 2 ENG implants will be placed in one arm at a V-orientation to facilitate easy of removal.

Insertion of the implant will be according to standard procedures followed routinely in the clinic for long-acting subdermal implants, and inserted according to the product labeling. At every visit after insertion, the study team will palpate the implant sites to check for presence of the implant/s.

5.2.2. Drug Storage and Drug Accountability

The investigator will ensure that the ENG implant purchased with study grant funds will only be used in accordance with the protocol. Drug supplies will be kept in a secure, limited access storage area under the recommended storage conditions. A drug accountability log will be kept with the investigational supplies for reconciliation purposes. This should be used to record the identification of the participant to whom the investigational product was dispensed, the date and quantity of the investigational product dispensed. Storage conditions will be according to the ENG implant product labelling and individual product expiration date.

5.3. Concomitant Medication(s)

There are no restrictions to concurrent therapy, except those outlined in the exclusion criteria. Participants will be encouraged to avoid grapefruit juice, herbal or natural products during the course of the study due to the potential unknown PK interactions with those products. However, if a participant uses an herbal or natural product during the study period, she will be encouraged to report that use to study investigators. Participants' concomitant therapy will be documented at study screening and reviewed at each study visit. Any change in concomitant therapies must be recorded on the case report form (CRF).

6. STUDY PROCEDURES

Study visits will occur at screening, entry (day 0), and weeks 1, 4, 9, 10, 11, 12, 21, 22, 23, 24, 36, 45, 46, 47 and 48 for all participants. Study personnel will call participants to assess any AEs on day 3 +/- 48 h. In all participants, a single blood sample will be drawn for a serum progesterone measurement and a speculum exam will be performed for the collection of cervical mucus for the WHO cervical mucus score measurement at weeks 9, 10, 11, 12, 21, 22, 23, 24, 36, 45, 46, 47 and 48. Cervical mucus collection was discontinued on October 19th, 2020, at which time 41 participants had completed the week 48 follow-up. Additionally, in all participants, a blood sample will be drawn to measure ENG concentrations at the following study visits: day 0, and at weeks 1, 4, 12, 24, 36, and 48. Participants will also have a timed, single blood sample for EFV concentrations at: Screening, day 0, and at weeks 1, 4, 12, 24, 36, and 48. This sampling schedule, through week 48, follows the same schedule as that which was used in the historical control group.

If all safety measures are met, participants will have additional visits will be evaluated every 6 months for 4 consecutive weeks, specifically weeks 69-72, 93-96, 117-120, and 141-144.

In order to facilitate flexibility for the participant's schedule, if a participant misses the first visit among the 4 weekly consecutive visits (week 9-12, week 21-24, week 45-48, etc.), then the visit can be rescheduled to the week following when the fourth consecutive week was previous scheduled. For example, if the participant misses the week 9 visit, then they can make up that visit on week 13 within 7 days (plus or minus 24 hours) of the week 12 visit. If the participant misses both week 9 and 10 week visits, then they can make these visits on weeks 13 and 14. If the participant misses weeks 9, 10 and 11 post-insertion visits, then these visits can be made up on weeks 13, 14 and 15 post-insertion.

To improve convenience for participants, the research visits will be scheduled with concurrent clinical visits to IDI for routine HIV care, when possible. All reasonable efforts should be made to ensure that the sampling schedule falls on the outlined days or within the window defined for each study visit. All PK samples should be collected prior to ENG subdermal implant placement on day 0. Specific PK sampling considerations are as follows:

- Because EFV is dosed once daily, typically in the evening, participants should have their PK sampling performed approximately 12-14 hours after their evening dose of EFV. The study nurse will confirm the time at which the participant took the EFV dose prior to PK sampling.

Prior to all visits, the study staff will contact the participant by phone 3-7 days prior to the scheduled visit to confirm the visit time, review the ART dosing schedule, and remind the participant to remember the exact time at which the EFV dose prior to the study visit was actually taken.

Clinical information obtained during the study period as part of standard of care, such as demographics, laboratory values (as indicated in the section 6.2 below), and medication related adherence toxicities may be abstracted from the participants' medical records.

Given the known risk of HIV transmission, family planning counselling will occur at each visit, including the importance of using barrier contraception. Given the increased concerns of contraceptive failures with combined standard dose ENG implant and EFV use, we will require women to have concurrent highly effective non-hormonal contraception with a copper T380A IUD, if not already sterilized prior to study entry. The copper IUD is a T-shaped device, measuring 32 mm horizontally and 36 mm vertically with a 3 mm diameter bulb at the tip of the vertical stem. A monofilament polyethylene thread is tied through the tip, resulting in two threads to aid in detection and removal of the device. The T-frame is made of polyethylene, with barium sulfate to aid in detecting the device under x-ray. The Copper T 380A IUD has been FDA approved since 1984 for contraceptive use. It is currently approved for use up to 10 years. All IUD insertions will be performed by a trained clinician.

Following the Ugandan ART guidance change, participants already enrolled in the study will be switched to the new first line recommended therapies, either DTG- or EFV 400 mg-based ART, based on the discussion with a HIV clinician who is not affiliated with the study team. If the participant decides to remain in the study after ART switch, then they will sign an informed consent document indicating their agreement to continue study follow-up. If a participant in the double-dose ENG arm desires to remain in the study and switches from either EFV600mg or EFV400mg to DTG-based ART, then one of the contraceptive implants will be removed by a study clinician. Any participant on DTG-based ART remaining in the study may have the Copper T 380A IUD removed if she desires. It is recommended that the IUD be removed 4 weeks after the discontinuation of EFV and to avoid the risk of pregnancy due to the drug interaction between ENG and EFV and the long half-life of EFV. If the participant opts to remove the IUD prior to 4 weeks from IUD discontinuation, then the study clinician recommend that condoms be used for 4 weeks to prevent pregnancy. Participants that remain in the study will have the opportunity to participate in an additional four study visits to assess the PK of EFV and ENG after the ART

switch. Participants will sign additional consent for these additional visits if they agree to these additional visits that are described in section 6.3.2.

6.1. Screening

Each participant must sign an Informed Consent Form prior to the conduct of any screening procedures. Participants will be given the opportunity to ask any questions. Consenting patients at the IDI will be screened for eligibility.

Screening evaluations will be used to determine each candidate's eligibility for study enrollment (refer to Exclusion Criteria section 4.2, above, for detail on eligibility).

The screening visit procedures are outlined in the schedule of events (section 6.2). In addition,

- Review of eligibility criteria for enrollment (including urine pregnancy test and review of concomitant medications)
- Demographic details

The screening procedures may occur over multiple visits within 90 days prior to enrollment as necessary. The screening physical exam and laboratory examinations must occur within 30 days of enrollment. A participant may rescreen for the study at the discretion of the study investigator, but will be reassigned a new study number.

6.2. Study Period

The schedule of events is summarized in the table below:

Protocol Activity	SC	D0	D3[5]	W1[1]	W4[2]	W9[3]	W10[3]	W11[3]	W12[3]	W21[3]	W22[3]	W23[3]	W24[3]	W36[2]	W45[3]	W46[3]	W47[3]	W48[3]	Early D/C[4]
Procedures																			
Informed consent	X																		
Study registration		X																	
Medical history and physical exam	X	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A
IUD insertion (if applicable)		X																	
ENG implant placement		X																	
Height	X																		
Weight + vital signs	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assess for concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assess for AEs			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assess for ART adherence	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Contraception use questionnaire	X																		
Baseline symptoms questionnaire		X																	
Contraceptive satisfaction questionnaire				X	X				X				X	X				X	X
Condom use questionnaire	X	X		X	X				X				X	X				X	X
HIV Risk and FP counseling	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
QRISK®2 Score	X																		

Protocol Activity	SC	D0	D3[5]	W1[1]	W4[2]	W9[3]	W10[3]	W11[3]	W12[3]	W21[3]	W22[3]	W23[3]	W24[3]	W36[2]	W45[3]	W46[3]	W47[3]	W48[3]	Early D/C[4]
Laboratory																			
Pregnancy test (urine)	X	X		X	X				X				X	X				X	X
Hemoglobin	X																		
Serum Creatinine	X																		
ALT	X																		
Cholesterol/ LDL	X												X						
Glycosylated hemoglobin (HbA1c)	X												X						
HIV-RNA	X												X					X	X[6]
CD4 cell count		X																X	X[6]
SHBG		X			X								X					X	
Albumin		X			X								X					X	
EFV PK sample	X	X			X				X				X	X				X	X
ENG PK sample		X	O	X	X				X				X	X				X	X
Endogenous progesterone						X	X	X	X	X	X	X	X		X	X	X	X	X
Cervical mucus assessment[7]						X	X	X	X	X	X	X	X		X	X	X	X	X
PG sample (with optional consent)		O																	

Abbreviations: SC – Screening; X – All participants; O – Optional procedures, for consenting participants; A – As needed; D0 – Day 0, study entry; D1 – Day 1 after implant placement; D2 - Day 2 after implant placement; D3 - Day 3 after implant placement; D4 - Day 4 after implant placement; W1 – 1 week after implant placement; W4 - 4 weeks after implant placement; W9 - 9 weeks after implant placement; W12 - 12 weeks after implant placement; W21 - 21 weeks after implant placement; W24 - 24 weeks after implant placement; W36 - 36 weeks after implant placement; W48 - 48 weeks after implant placement; PG – pharmacogenomic; FP – Family Planning.

1. Visit date +/- 3 days
2. Visit date +/- 1 week
3. Visit date +/- 24 hours
4. For any participant who discontinues study procedures prior to the week 48 visit. Do not complete if the participant withdraws consent to perform study procedures.

5. Visit date +/- 48 hours.
6. Only if visit is occurring after week 24.
7. Cervical mucus assessments were stopped on October 19, 2020 due to stock outs.

7.3.1 Follow-up Visit

The primary comparison between these participants and the historical control group will be complete at week 48. If all safety thresholds have been met, participants in will have follow-up visits during years 2 and 3 post-implant placement to ensure long-term tolerability and PK stability of the increased ENG dose strategy in combination with EFV-based ART, as follows:

Protocol Activity	**W69[1]**	**W70[1]**	**W71[1]**	**W72[1]**	**W93[1]**	**W94[1]**	**W95[1]**	**W96[1]**	**W117[1]**	**W118[1]**	**W119[1]**	**W120[1]**	**W141[1]**	**W142[1]**	**W143[1]**	**W144[1]**
Procedures																
Medical history and PE	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A
Weight + VS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assess for concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assess for AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assess for ART adherence	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Contraceptive satisfaction questionnaire				X				X				X				X
Condom use questionnaire				X				X				X				X
HIV Risk and FP counseling	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory																
Pregnancy test (urine)				X				X				X				X
HIV-RNA				X				X				X				X
CD4 cell count								X								X
Cholesterol/ LDL								X								X
HbA1c								X								X
EFV PK sample				X				X				X				X
ENG PK sample				X				X				X				X
Endogenous progesterone	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Cervical mucus assessment[3]	X	X	X	X												

Abbreviations: X – All participants; O – Optional procedures, for consenting participants; A – As needed. If not available in clinical record, draw as part of study visit procedures; PE – physical exam; VS – vital signs.

1. Visit date +/- 24 hours
2. No discontinuation visit is required if participants choose to leave the study after week 48.
3. Cervical mucus assessments were stopped on October 19, 2020 due to stock outs.

7.3.2 Follow-up Visits after ART Switch

Participants who switch from EFV600 mg-based ART to either DTG-based ART or EFV 400mg-based ART will have an opportunity to participate in optional visits, as described in section 6. All participants that desire to remain in the study after ART switch and agree to the additional PK visits will have the following visit schedule, which can occur on their regularly scheduled visit if possible:

	Day of Switch[1]	2 Weeks[2]	4 Weeks[2]	6 Weeks[2]
EFV PK Sample	X	X	X	X
ENG PK sample	X	X	X	X
Removal of second implant[3]	X			

1. Visit date +/- 24 hours
2. Visit date +/- 7 days
3. For participants in the double dose arm who are switching to DTG-based ART

7.3.3 Participant Withdrawal

Participants may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety or behavioral reasons, or the inability of the participant to comply with the protocol required schedule of study visits or procedures.

If a participant does not return for a scheduled visit, every effort should be made to contact the participant. The participant will be contacted by telephone and if this is unsuccessful, a home visit will be arranged. In any circumstance, every effort should be made to document participant outcome, if possible. The investigator should inquire about the reason for withdrawal and follow-up with the participant regarding any unresolved AEs. Reason for withdrawal will be documented on the CRFs.

If a participant needs to switch ART to a regimen that is not based on EFV or DTG, the participant will discontinue study follow up. Participants who switch to alternative ART options will be counseled by the IDI Family Planning clinicians regarding effective contraceptive options and will have one or both ENG implants removed after this consultation.

If a participant chooses to remove the IUD before week 48, they will discontinue study follow-up. After 48 weeks, information from the study regarding the effectiveness of increasing the dose of ENG implant in combination with EFV-based ART will be available. If successful, the study will continue through week 144 and participants will have the option to remove the IUD in consultation with the IDI family planning caregivers. If the participant switches to DTG-based ART in the course of follow-up, those participants may have the IUD removed in consultation with the IDI family planning providers. Due to the long half-life of EFV, it is recommended that the IUD remain in place for 4 weeks after EFV discontinuation to avoid the risk of pregnancy. The participant may have the IUD removed sooner if desired and will be counseled to use condoms to avoid the risk of pregnancy.

If the participant desires implant and/or IUD removal upon study exit, the implant and/or IUD will be removed by a study clinician.

Participants will be considered adherent to their drug regimen if they take at least 90% of the EFV/DTG as prescribed. Non-adherence to DTG/EFV-based ART may make the study results un-interpretable, given the removal of the DDI. Subject to Institutional Review Board (IRB) approval, participants withdrawn for not adhering to study procedures may be rescheduled and/or withdrawn and replaced by the investigators.

Participants to be withdrawn prior to week 48 should be invited to attend an early discontinuation (early D/C) visit (refer to Schedule of events, Section 6.2). Participants who complete study procedures through week 24 will contribute data to the primary objective analysis. If the participant withdraws from the study and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The investigator may retain and continue to use any data collected before such withdrawal of consent.

8. ASSESSMENTS

8.3 Safety

8.3.1 Physical assessments

Full physical examinations will be performed at the screening visit and as needed during follow-up based on clinical judgment by the local investigators.

Adverse events will be assessed at each visit and documented following the procedures outlined in section 8.0.

8.3.2 Contraceptive Questionnaires

Contraception use questionnaire: Brief questionnaire (1 page) of prior contraceptive use and about the participant's rationale for desiring the use of the ENG implant. This questionnaire is completed at entry only.

Baseline symptoms questionnaire: Brief questionnaire that the participants will complete at enrolment. Questions will objectively address signs and symptoms of hormone related toxicity at baseline (prior to implant insertion).

Contraceptive satisfaction questionnaire: Brief questionnaire that the participants will complete following implant insertion, according to the Schedule of Events. Questions will objectively address signs and symptoms of hormone related toxicity, as well as the participant's satisfaction with the ENG implant as a contraceptive method.

Condom use questionnaire: Brief questionnaire that the participants will complete at baseline and according to the Schedule of Events. The condom use questionnaire will assess ongoing condom use among participants.

8.3.3 Concomitant medications and ART medication adherence

A completed medication list will be documented at screening to assess eligibility requirements (see Concomitant medications in Schedule of Events). This list will be reviewed at each study visit and any changes to concomitant medications will be documented in the CRFs.

Adherence to ART will be evaluated at all study visits and phone calls by study staff. Methods of assessment will include direct questioning of dosing schedules, missed or late doses in the past 30 days or since the last visit, using a standardized questionnaire administered and each visit. Specifically, participants will be asked to make note of the exact time at which they took their last dose of EFV prior to the study visit, which will be documented during the study visit by the study staff. Any participant found to be nonadherent to EFV will be counselled regarding the concern regarding increased ENG exposure. Any participant that completely discontinues EFV by their primary care provider or due to nonadherence will be withdrawn from the study.

8.3.4 Safety laboratory evaluations

All safety laboratory investigations (including hemoglobin, serum creatinine, glycosylated hemoglobin (HBA1c), and ALT) will be performed in real-time at the Makerere University – Johns

Hopkins (MU-JHU) core laboratory within the IDI main building, as indicated in the Schedule of Events in section 6.2. This laboratory maintains annual External Quality Assurance certification of the College of American Pathologists.

A viral load (HIV RNA) will be performed in real time at the screening visit to ensure all participants are currently virologically suppressed (per entry criteria). A viral load will be performed at regular intervals during the study period according to the schedule of events to ensure participants have remained suppressed throughout the study. Viral load measurements above 400 copies/mL will be considered AEs.

CD4 cell count will be documented at entry for all participants and then according to the schedule of events.

8.3.5 Phone calls to assess ART adherence and ENG related AEs

During the first 6 months of study participation, when ENG concentrations are expected to be highest, participants will be contacted by phone according to the schedule of events. Participants will be asked about any adverse events they may be experiencing. Adherence to ART will also be evaluated during these phone calls by study staff. Methods of assessment will include direct questioning of dosing schedules, missed or late doses in the past 30 days or since the last visit.

8.4 Pregnancy Testing

For all women interested in study participation, a urine pregnancy test will be performed at screening and entry visits, prior to enrolment. Women with positive pregnancy tests will be excluded. Enrolled women will be counseled to use a barrier contraception method (e.g. condoms) to prevent pregnancy. Enrolled women will have a urine pregnancy test at each visit (except the optional study visits on Days 1-4). Women who become pregnant during the study will be excluded from further study participation and drug treatments stopped. All pregnancy exposures will be reported to the IRB and the Uganda National Drug Authority (NDA).

8.5 Pharmacokinetics Assessments

8.5.1 Blood for PK analysis of ENG or efavirenz

Based on the study schedule of events outlined in section 6.2, one 6 mL whole blood sample will be collected to measure ENG concentrations and a second 4 mL whole blood sample will be collected to measure EFV concentrations. The maximum number of blood draws that a patient will have is 16, over the course of 3 years. EFV plasma concentrations will be analyzed at the Makerere University laboratory using previously described high performance liquid chromatography (HPLC) methods[50]. ENG will be analyzed at the University of Pittsburgh Small Biomarkers Core Laboratory using a validated, published method by HPLC linked to mass spectrometry (LC-MS/MS)[51]. This method includes evaluation for and quantification of all progestins (synthetic and endogenous). This will allow the study team to know if the study participants were using any external synthetic progestins, that could confound the study results. Additionally, this method will also quantify estradiol in the first year of the study procedures. This will evaluate the impact of the higher dose of etonogestrel evaluated on circulating endogenous progestin, therefore allowing quantitative assessment if there is any concerns regarding any adverse events related to hypoestrogenism.

All efforts will be made to obtain the PK samples at the scheduled nominal time relative to dosing (see section 6.0). If a scheduled blood sample collection cannot be completed for any reason, the missed sample time may be re-scheduled with agreement of clinical investigators.

8.5.2 Sample Handling

For each PK sample, whole blood will be obtained and collected into vacutainers containing ethylenediaminetetraacetic acid anticoagulant.

Within one hour of collection, samples will be transported by dedicated sample transport personnel from the IDI clinic to the Makerere-University Johns Hopkins University Core Laboratory. Samples will be centrifuged at 3000 revolutions per minute for 10 minutes to separate plasma. This sample is expected to yield two or three aliquots of plasma (each approximately 0.7 mL). Plasma aliquots will be stored at -70^{o} Celsius.

8.5.3 Justification for PK shipment

One aliquot of the ENG PK specimen will be shipped to the University of Pittsburgh according to the schedule outlined for safety evaluations in section 9.4 Duplicates will be retained at IDI until results from the shipped batch become available. PK samples will be assayed for ENG using a validated analytical method. Drug concentrations will be determined by high performance liquid chromatography with tandem mass spectrometry (LC-MS/MS)[51]. The IDI has a HPLC machine, however mass spectrometry equipment is expensive and not available in Uganda. Sample transfer and analysis will be governed by a material transfer agreement that will be signed between both parties. At the end of the analysis, unused samples will be discarded.

8.6 Other measurements

8.6.1 Patient characteristics that may influence pharmacokinetic properties

Body weight (as Kg) will be measured according to the schedule of events as ENG concentrations have been correlated with body weight. Height will be documented at screening to calculate body mass index.

Albumin and sex hormone binding globulin will be measured according to the schedule of events, as ENG binds to both serum albumin and sex hormone binding globulin. Blood samples for albumin will be processed at the MU-JHU core laboratory and samples for sex hormone binding globulin will be processed at Lancet Lab, Kampala, Uganda.

Participants will be asked to contribute a single blood sample for pharmacogenetic analysis at study entry. This will be an optional study element and participants may refuse to participate in this pharmacogenetic research and still participate in the study. Blood samples for pharmacogenetic analysis of functional polymorphisms known to influence the disposition of EFV or ENG will be processed at the IDI translational laboratory.

8.6.2 Endogenous progesterone as a measure of ovulation and cervical mucus assessment

As a laboratory marker to assess recent ovulation, endogenous progesterone will be evaluated at study visits at weeks 9, 10, 11, 12, 21, 22, 23, 24, 45, 46, 47, and 48, ideally on the same day of the week. Evaluation will continue during years 2 and 3 if safety and efficacy standards are met. Samples for measurement of endogenous progesterone will be processed at Lancet Lab, Kampala, Uganda.

In order to assess the contraceptive effect of ENG on the cervical mucus, cervical mucus samples will be collected at weeks 9, 10, 11, 12, 21, 22, 23, 24, 45, 46, 47, and 48. The collection procedure will be performed according the WHO manual for Examination and processing of human semen, 5th edition, Appendix 5 (Cervical Mucus), specifically section A5.2 (Collection and preservation of cervical mucus)[39]. The cervical mucus will be evaluated by an assessor blinded to the participant's study arm immediately after collection and scored according to section A5.3 (Evaluation of cervical mucus)[39]. Every effort will be made to have the cervical mucus assessment completed by the same assessor. A score of greater than 10 is favorable for sperm penetration indicating a lack of contraceptive effect[39]. The cervical mucus collection was discontinued on October 19th, 2020.

9. ADVERSE EVENT REPORTING

9.3 Adverse Events

All observed or volunteered AEs regardless of suspected causal relationship will be reported.

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a serious adverse event (SAE) requiring immediate notification (see section 8.5). For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality. Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator.

During each study visit the co-investigator will assess AEs that may have occurred since the previous visit. This will be done by:

- Active interrogation and collection of reported information from the participant at each study visit or phone call. Patients will be questioned specifically about study drug associated AEs and any other unanticipated AEs.
- The contraceptive satisfaction questionnaire will be administered to the participant and completed by the study nurse at each study visit after the ENG subdermal implant is placed. This will also highlight known ENG toxicities as well as family planning method satisfaction.
- Safety labs will be performed as outlined in the schedule of events.

9.4 Serious Adverse Events

An SAE is any untoward medical occurrence at any dose that:

Results in death; Is life-threatening (immediate risk of death); Requires inpatient hospitalization or prolongation of existing hospitalization; Results in persistent or

significant disability/incapacity (substantial disruption of the ability to conduct normal life functions); Results in congenital anomaly/birth defect, may require medical or surgical intervention to prevent one of the outcomes listed above.

9.5 Severity Assessment

The severity of AEs will be graded according to the National Institute of Health Division of AIDS (DAIDS) classification system for reporting adverse experiences in adults[52].

9.6 Causality Assessment

The investigator will assess causality for all AEs (serious and non-serious) and record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements. The relationship to study drug of each AE will be assessed using the following definitions:

DEFINITE: distinct temporal relationship with drug treatment. Known reaction to agent or chemical group, or predicted by known pharmacology. Event cannot be explained by participant's clinical state or other factors.

PROBABLE: reasonable temporal relationship with drug treatment. Likely to be known reaction to agent or chemical group, or predicted by known pharmacology. Event cannot easily be explained by participant's clinical state or other factors.

POSSIBLE: reasonable temporal relationship with drug treatment. Event could be explained by participant's clinical state or other factors.

UNLIKELY: poor temporal relationship with drug treatment. Event easily explained by participant's clinical state or other factors.

UNRELATED: the event occurs prior to dosing. Event or concurrent illness is due wholly to factors other than drug treatment.

9.7 Reporting Requirements

Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, expedited reporting will follow IRB, local and international regulations, as appropriate. All SAEs determined to be related to the study will be reported to IDI Scientific Review Committee, the Joint Clinical Research Centre IRB, the Uganda National Council of Science and Technology (UNCST), the Uganda National Drug Authority (NDA). All SAEs determined to be related to the study will be reported to the project and consortium PIs within 24 hours of knowing about the event and to the ethics committee, UNCST and NDA within seven days of knowing about the event. Principal Investigator shall forward to Merck's Global Safety ("Merck GS") group and to the Safety Monitoring Committee (SMC), any SAE determined to be related to the study, within two (2) business days but not longer than three (3) calendar days of receipt of learning of the information. Further relevant follow-up information will be given as soon as possible. Follow-up will continue until the event resolves.

All AEs will be tabulated and reported to the JCRC IRB in annual study reports. SAEs will be reported to IRB and the regulatory authorities within seven days from the time the study team becomes aware of the occurrence of the SAE. All AEs will be reported on the participant and study AE log. The same AE term(s) should be used consistently across all AE-related forms. AEs should be reported using concise medical terminology on the CRFs as well as on the form for collection of SAE information.

Study team AE reporting: All other AEs will be compiled weekly and submitted to the project and consortium PI. The protocol team will discuss the weekly AE reports on regularly scheduled biweekly teleconferences. The Safety and Monitoring Committee (SMC) will be identified prior to study initiation. The SMC will have the authority to suspend any study related activity at any time based on their assessment of AEs (see section 9.6).

- Any contraception related AE requiring medical management, including contraceptive failure resulting in pregnancy, will be discussed with the consultant OB/Gyne in the United States and in Uganda.
- Any HIV related AE requiring medical management would be discussed with the IDI primary care provider who is providing HIV care to the participant. Additionally, the study team HIV physician will be notified.

9.8 Post-Recruitment Illness

All participants with post-recruitment illness will be evaluated at the IDI clinic and if necessary, be referred for care at Mulago National Referral and Teaching Hospital and patients will be managed in accordance with Uganda national treatment guidelines.

10. DATA ANALYSIS/STATISTICAL METHODS

10.3 Sample Size Determination

To evaluate our primary outcome of ovulation frequency in the standard-dose ENG implant vs. the dose-escalated ENG implant groups, we estimate a desired sample size of 36 participants per group or 72 participants total and will allow for attrition of 4 participants total. This sample size is based on unpublished data from our previous study which showed an ovulation rate of 0.15/month (9 ovulations noted in 20 participants) when sampling at month 1, 3, and 6 with standard dose ENG implant with women on EFV[1]. The progesterone sampling was performed simultaneously with the ENG sampling at only one time per month, therefore ovulations were likely missed. Additionally, we assumed that with the dose-escalated ENG implant use in women on EFV that there would be only one ovulation in twenty participants within six months, or a cumulative ovulations rate of 0.017/month. The sample size of 34 per group was determined using a method published by Leon based on mixed-effects logistic regression with a two-tailed alpha level of 0.05, a power of 0.80 and assuming an intraclass correlation coefficient of 0.25[53].

Additionally, for the PK outcome, this sample size provides an estimated power of 0.80 to detect a 30% change in ENG concentrations at 6 months between the dose-escalated ENG implant + EFV-based ART and the historical control (standard-dose ENG implant without ART) using an alpha level of 0.05. This estimate is based on an mean ENG concentration of 361.54 pg/mL (SD 144.16 pg/mL) in HIV+ Ugandan women not on ART at 6 months post implant insertion (n=20)[35].

Participants found to be nonadherent to EFV by an serum EFV concentration of less than 200ng/mL will be excluded from the analysis.

10.4 Analysis of Endpoints

10.4.1 Ovulation frequency and cervical mucus assessment

Between-group comparisons will evaluate the differences in ovulatory frequency (progesterone >3ng/mL) and WHO cervical mucus scores greater than 10 (indicating lack of contraceptive effect) between the standard-dose ENG implant (68mg) control group and the dose-escalated ENG implant (136mg) treatment group. Ovulation will be assessed by weekly serum endogenous progesterone measurements after 3 months of implant use (weeks 9-12), 6 months of implant use (weeks 21-24) and 12 months of implant use (weeks 45-48). Any progesterone measurement greater than 3ng/mL will indicate that an ovulation occurred in that participant during that month and the number of participants ovulating in one month will be determined. Similarly, cervical mucus will be assess by the WHO cervical mucus score collected after 3 months of implant use (weeks 9-12), 6 months of implant use (weeks 21-24) and 12 months of implant use (weeks 45-48). Any WHO mucus score greater than 10 will indicate that the mucus is favorable for sperm penetration, or a lack of contraceptive effect. The ovulatory rate and the rate of cervical mucus scores greater than 10 will be compared between the groups (standard-dose vs. dose escalated implant groups) at months 3, 6 and 12 of implant use using mixed-effects logistic regression to account for multiple assessments in each participant over time.

10.4.2 Analysis of ENG concentrations

Between-group comparisons will evaluate changes in ENG PK parameters between the treatment group (dose-escalated ENG implant +EFV-based ART, n=36) and a historical control group (standard dose ENG implant without ART, n=20). Log transformed area under the concentration time curve of ENG will be compared between the historical control group and the double dose ENG EFV group using a student's t-test or Wilcoxon rank sum test, based on the normality of result distribution. Drug concentrations will be summarized descriptively (mean, median, minimum, maximum, standard deviation) by study visit and compared between groups using a geometric mean ratio. The ENG concentration-time curve will be pharmacokinetically modeled using Phoenix modeling software (Pharsight®). Pharmacokinetics after switch from EFV 600mg to alternative regimens (EFV 400mg or DTG), ENG PK will be described descriptively after switch.

10.4.3 Analysis of EFV concentrations

Within group comparisons will evaluate changes in EFV concentrations from prior to the ENG implant insertion. Mean EFV concentrations will be compared at each time point within both the single ENG implant group and the double dose implant group using a paired student's t-test or Wilcoxon signed-rank test, based on the normality of result distribution. Drug concentrations will be summarized descriptively (mean, median, minimum, maximum, standard deviation) by study visit and used to assess the relationship between ENG and EFV exposure.

10.5 Analysis of Other Endpoints

Additional data will be compared between the single ENG implant group vs. the two ENG implants group in the current study all on EFV-based ART using standard methods of student's t-test or

nonparametric tests for two group comparisons of continuous variables, as appropriate, and chi-square or Fisher's exact test for discrete data.

10.6 Safety Analysis

ENG efficacy and safety based on PK exposure: To mitigate the risk for any unexpected ENG dose-related AEs related to supratherapeutic ENG concentrations, any ENG concentration that is 1.5-fold higher than the control group's geometric mean ENG level (**Table 1**) will be reported to the study's key personnel and the SMC chair within 1 week of detection. Current AE reports for that participant will simultaneously be provided for SMC review. This strategy employs an abundance of caution, given that a 1.5-fold higher ENG concentration from the implant is still significantly lower than ENG exposure from the etonogestrel vaginal ring (NuvaRing®)[44].

To ensure subjects do not receive long-term, suboptimal hormonal contraception, we will also assess futility of increased dose ENG implant and EFV-based ART throughout the study period. Absence of contraceptive effect will be determined by reviewing all ENG plasma concentrations, serum progesterone measurements, and WHO cervical mucus score assessments. The criteria for determining absence of contraceptive effect will be agreed upon by the SMC and the safety team, but will include lack of contraceptive effect as evidence by ENG <90pg/mL, progesterone concentration >3ng/mL and/or WHO cervical mucus scores >10.

All safety and AE data will be descriptively summarized by severity, incidence and number of patients affected.

10.7 Interim Analysis

The first PK analysis of the ENG concentrations will occur as soon as 20 participants (at least 10 in each group) completes 24 weeks of combined use ENG and EFV use, and will continue every 6 months or sooner if a grade 3 or 4 study medication-related adverse event occurs or if there is significant concern of lack of contraceptive effect as evidenced by the serum progesterone concentrations and the WHO cervical mucus scores. SMC in conjunction with the study team will review all available PK/PD outcomes and safety data and will determine if either arm should be stopped. These recommendations will be based on 2 different criteria:

1) Safety - all the adverse events and the contraceptive satisfaction survey will be reviewed. If one arm has a Grade 3 or 4 adverse events that are deemed related to the study medication, then consideration will be made to stopping the trial.

2) Absence of contraceptive effect – all available ENG, progesterone and cervical mucus data will be reviewed. The criteria for determining absence of contraceptive effect will be agreed upon by the SMC and the safety team, but will include lack of contraceptive effect as evidence by ENG <90pg/mL, progesterone concentration >3ng/mL and/or WHO cervical mucus scores >10 occurring within the same participant during the same month.

At the same time points as the PK interim analyses, study AEs and endogenous progesterone levels will be summarized for simultaneous review by the SMC to inform their study decision. As described in section 9.4, any supratherapeutic ENG concentration will be reported to the study's key personnel and the SMC chair within 1 week of detection.

10.8 Data Safety and Monitoring Committee

The SMC will include professionals who have no conflict with serving on the SMC. The SMC will include medical professionals with expertise in the design, conduct and analysis of PK studies, HIV clinical care and research, and/or obstetrics and gynecology and family planning. The SMC will convene either in person, or via teleconference at the following times:

- Prior to the study opening to enrollment:
  - Review the research protocol, informed consent, and ethics approvals.
  - Make recommendations about the readiness to open the study
- Within 2 weeks after 20 participants (at least 10 in each group) complete 24 weeks of combined use ENG and EFV use:
  - Assess if the ENG PK, serum progesterone, and WHO cervical mucus score results indicate excess risk of pregnancy or toxicity in study subjects
  - Review all study related AEs or subject concerns
  - Make recommendations about continuation or conclusion of the study
- Every 6 months during follow-up:
  - Assess if the ENG PK, serum progesterone, and WHO cervical mucus score results indicate excess risk of pregnancy or toxicity in study subjects
  - Review all study related AEs or subject concerns
  - Make recommendations about continuation or conclusion of the study at week 48
- Annually, the SMC will perform the following activities:
  - Review the research protocol and any changes that occurred over the year
  - Review all study related AEs or subject concerns
  - Assess study progress, including enrollment, data quality, risk vs. benefit, and any interim or final study results
  - Evaluate if there have been scientific or therapeutic developments that impact the conduct of the study
  - Make recommendations about continuation or conclusion of the study
- Ad hoc: any time there is a Grade 3 or 4 adverse event related to the study medication or as the SCM chair, project or consortium PI deems necessary

11. QUALITY CONTROL AND QUALITY ASSURANCE

During study conduct 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 participant to review by the IRB and/or to inspection by appropriate regulatory authorities.

12. DATA HANDLING/RECORD RETENTION

12.3 Case Report Forms (CRF)/Electronic Data Record

A CRF is required and should be completed for each included participant. The investigator has ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the 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.

12.4 Record Retention

To enable evaluations and/or audits, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, eg, 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 (eg, letters, meeting minutes, telephone calls reports).
Investigator records will be kept in accordance with current UNCST and the NDA guidelines.

12.5 Confidentiality

Clinical data will be entered into a study specific database by designated staff on a regular basis from completed CRF. CRFs and other source documents will be kept in locked cabinets. Data will be entered on a regular basis to ensure that it is up to date. The database will be on a password protected, secure PC, as will the PK database that will be received by the laboratories. Access to database will be given to authorized personnel only (members of the immediate study team) and a log of authorized personnel will be stored in the trial master file. Hard copies of CRFs and trial documents will be kept in locked cabinets. No participant identifying information will be disclosed in any publication or at any conference activities arising from the study.

12.6 Missing Data

All efforts will be made to collect required data at each study visit within one month after the study visit. Any remaining missing clinical data will be considered 'missing' during statistical analysis.

13. ETHICS

13.3 Institutional Review Board (IRB)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents from the IRB. All correspondence with the IRB should be retained in the regulatory or trial master file. Copies of IRB approvals should be filed with other study documents.

13.4 Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Participants and the Declaration of Helsinki. In addition, the study will be conducted in accordance with the protocol, GCP guidelines, and applicable local regulatory requirements and laws.

13.5 Participant Information and Consent

All parties will ensure protection of participant personal data and will not include participant names on any forms, reports, publications, or in any other disclosures, except where required by laws.

The informed consent document used in this study, and any changes made during the course of the study, must be prospectively approved by the IRB.

The investigator, or a person designated by the investigator, will obtain written informed consent from each participant or the participant's legal representative before any study-specific activity is performed. The investigator will retain the original of each participant's signed consent document.

13.6 Risks and benefits

Risks of study participation include risk of infection or hemorrhage at the site of venipuncture or cannulation, and the risk of loss of confidentiality. The study will take all reasonable steps to minimize or eliminate these risks.

Changes to ART or HIV care and treatment are not planned during the study period, therefore we don't expect additional ART related toxicities. The risk of AEs associated with the use of ENG implants exists, though because the increased dose of ENG given in combination with EFV is expected to be similar to the ENG exposure in a normal population, it is not expected to be higher in this study as compared to standard use of the implant. ENG implant may have the following side effects:

Physical: There may be slight pain, discomfort, redness or swelling associated with the subdermal ENG implant insertion. Some of the more common AEs include menstrual irregularities (increased or decreased menstrual flow, spotting, irregularity and amenorrhea), weight gain, headache, depression or mood changes, nausea, nervousness, and dizziness.

Psychological: Participants may experience psychological risks if pregnancy were to occur during the study period, as this would be unintended.

The copper IUD may have the following side effects:
Physical: Changes in the bleeding patterns (especially in the first 3-6 months) including heavier menstrual bleeding, irregular bleeding, or uterine cramping.
Adverse Events: The risk of AEs associated with the use of copper IUDs exist, though is not expected to be in higher in this study as compared to standard use of copper IUD. Some of the rare AEs include: infection, uterine perforation, IUD expulsion, difficult IUD removal, and pregnancy, including ectopic pregnancy.

Benefits: Evidence is accumulating that subjects using an ENG implant while on EFV-based ART have suboptimal ENG drug concentrations, which may lead to increased risk of unintended pregnancies. Participating in the proposed research study will allow subjects to receive *increased* dose ENG implants to possibly overcome this drug interaction, with the goal to achieve ENG PK exposure similar to normal dose ENG without EFV-based ART. Although we do not expect an increased rate of toxicity with the increased dose ENG implant, we have implemented a rigorous safety monitoring plan to allow early identification of safety concerns should they occur. Importantly, this strategy may improve the contraceptive safety and efficacy for women receiving EFV-based ART.

The potential benefit of the proposed research to participants, as well as others, include providing new data regarding the potential interaction between ENG implants and ART. Based on study findings, we will be able to inform changes in clinical practice to offer guidance on the safe dose and duration of concomitant use of EFV-based ART and ENG implants, thereby reducing risk of unintended pregnancy for HIV-infected women receiving these therapies and improving women's health. The study will also monitor the HIV-RNA (viral load) and CD4 cell count as an assessment of HIV disease throughout the study period.

14. DEFINITION OF END OF TRIAL

This study is complete when participants have completed follow up to week 144, unless the trial is suspended prior to week 144.

15. PUBLICATION OF STUDY RESULTS

Study findings will be disseminated to researchers through oral or written presentations at scientific conferences and through peer-reviewed journals. Full anonymity of participant's details will be maintained throughout. 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 Uganda, study results will be communicated to Ministry of Health program managers through meetings and reports. Study summaries will be communicated to health workers in Uganda through the AIDS Treatment Information Centre newsletter, which is published by the IDI and distributed to all health workers in the public and not-for profit sectors in Uganda. The study will be registered on Clinicaltrials.gov.

16. FUNDING

This proposal is funded by the Merck Investigator Studies Program. No fault insurance will be procured to cover any study related adverse event that occurs during the study.

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