TITLE: Pharmacokinetics and pharmacodynamics of the etonogestrel contraceptive implant when co-administered with efavirenz

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PI: Jennifer Robinson, MD, MPH

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1. Abstract

Women of reproductive age who are living with HIV have to navigate complex decisions regarding fertility, contraception, and managing their HIV diagnosis. One consideration for HIV-infected women who want or need to prevent pregnancy is whether the medications used to treat HIV could reduce the efficacy of a contraceptive method through drug-drug interactions. Efavirenz (EFV) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) that is an important component of first-line antiretroviral therapy worldwide. However, in addition to having a side effect profile that leads some to discontinue therapy, EFV has been associated with failures of a highly effective hormonal contraceptive, the etonogestrel (ENG) implant. A recent multi-center trial suggests that a lower EFV dose retains efficacy against HIV while reducing the incidence of side effects. We propose a pilot study to evaluate the effect of reduced dose EFV on the pharmacokinetics of the ENG implant. We will recruit 18 HIV-negative healthy women who have had the implant in place for 6 to 30 months. They will be asked to take a two-week course of reduced dose efavirenz. During these two weeks and for four additional weeks, we will monitor semi-weekly ENG concentrations, and serum, ultrasound, and cervical mucus markers of ovulation. We will also assess EFV concentration at baseline, the end of the two-week treatment course, and at the end of the study. We will derive pharmacokinetic parameters and compare concentrations across time points. Results will help determine whether the ENG implant can be used safely by HIV-positive women taking EFV, and will help to inform the design of similar larger studies with different antiretroviral medications.

2. Objectives

The primary objective of this study is to determine whether etonogestrel (ENG) pharmacokinetics in users of the ENG contraceptive implant (Nexplanon®/Implanon®) are affected by concomitant administration of a reduced dose of oral efavirenz (EFV).

Secondary objectives are:
- To determine if co-administration of reduced-dose efavirenz with the ENG contraceptive implant results in pharmacodynamic changes that suggest increased risk of ovulation and consequently decreased contraceptive efficacy.
- To determine if co-administration of reduced-dose efavirenz with the ENG contraceptive implant affects pharmacokinetic parameters of efavirenz, compared to expected levels based on historical controls.

3. Background (briefly describe pre-clinical and clinical data, current experience with procedures, drug or device, and any other relevant information to justify the research)

The hormones used in most forms of birth control, and the major classes of antiretroviral drugs, are metabolized by the same hepatic enzyme system – the P450 family, particularly CYP3A4[1]. Protease inhibitors (PI) and non-nucleoside reverse transcriptase inhibitors (NNRTI) are the classes of antiretroviral drugs (ARVs) that interact most significantly with the P450 enzymes, and individual drugs can induce or inhibit these enzymes, or both. This raises concern for interactions with contraceptive hormones that could result in decreased contraceptive efficacy. A 2011 review concluded that there may be reduced contraceptive efficacy when combined oral contraceptives (COCs) are taken simultaneously with highly-

active antiretroviral therapy (HAART), but that the efficacy of intermediate- and long-acting reversible methods (such as injectable, implantable, and intrauterine contraceptives) appears to be maintained[2].

Long-acting reversible contraceptive (LARC) methods are widely available in the US and around the world, and are highly effective in terms of both pregnancy prevention and cost. They are also safe for use by women with various medical comorbidities, including HIV[3]. Several studies have demonstrated the safety of the intrauterine device (IUD) and depot medroxyprogesterone acetate (DMPA, a 3-month injectable contraceptive) in women with HIV[4-6] . There is very limited data regarding another LARC method available in the United States and elsewhere: Nexplanon® (previously named Implanon®), an implantable rod that releases the progesterone etonogestrel (ENG) and prevents pregnancy for up to three years[7]. The implant contains 68 mg of ENG that is released slowly, maintaining a serum concentration greater than the 90 pg/ml needed for reliable ovulation suppression[8]. The package labeling for Nexplanon®/Implanon® raises concerns for potential drug interactions and decreased efficacy in HAART users; however, this is based on data regarding interactions between combined oral contraceptives (COCs) and antiretroviral drugs. There are several case reports that suggest there may be decreased contraceptive efficacy in HIV-infected women who are using the ENG implant while taking HAART[9-12]. In all six reported cases, an unintended pregnancy occurred when the implant had been in place for at least 18 months, and all women who experienced contraceptive failure were taking EFV. Two studies investigating the effects of EFV on the ENG contraceptive implant have shown large, statistically significant decreases in ENG pharmacokinetic parameters compared to women not taking EFV[13, 14]. Even more concerning are results from a similar study investigating the effects of antiretroviral regimens, including an efavirenz-based regimen, on a levonorgestrel (LNG) contraceptive implant. The investigators found not only decreased LNG concentrations in women taking EFV, but three unintended pregnancies occurred in the EFV group[15].

4. Study Procedures

a. Study design, including the sequence and timing of study procedures (distinguish research procedures from those that are part of routine care).

This will be a prospective, single arm pilot pharmacokinetic (PK) study. We will recruit 18 healthy, HIV-negative women aged 18 to 40 years who are using Nexplanon®/Implanon® for contraception and who are willing to take a reduced dose of EFV for 2 weeks. We will limit enrollment to women who have had the ENG implant in place 12 to 24 months to avoid the initial burst release of ENG after implant placement, and to target the time frame of concern based on case studies of contraceptive failures among women on HAART. Performing the study in women without HIV infection will allow us to evaluate any interactions between ENG and EFV without having to contend with the effects of other drugs that make up typical HAART regimens. A two-week course of EFV will be sufficient for EFV to reach steady-state concentration while minimizing exposure in these healthy volunteers. By using the reduced dose of EFV (400 mg daily instead of the standard 600 mg daily dose)

Over 6 weeks from study entry, we will perform twice-weekly (see visit schedule) quantitative assessments of serum ENG as well as serum hormone concentration analysis, pelvic ultrasound for markers of ovulation, and cervical mucus testing, as described below. Given the slow apparent clearance of ENG and based on previous PK studies, we estimate that sparse sampling will be adequate to assess changes in ENG clearance during EFV administration. EFV will be administered for 14 days from the beginning of the study, after collection of baseline samples for ENG concentration determination. All study procedures will take place at the Johns Hopkins Bayview Medical Center's Clinical Research Unit (CRU). All blood tests will be performed locally except for ENG concentrations, which will be performed at Columbia University

in New York City. ENG samples will be collected, frozen, and batch-shipped. The subject population will be healthy, HIV-negative women using Nexplanon®/Implanon®, with the anticipation that the findings will be applicable to HIV-infected women. There is limited data regarding the use of the etonogestrel implant in obese women. While two small studies found lower etonogestrel concentrations in obese women than normal weight women, the differences were not statistically significant[16, 17]. Overweight and obese women using the etonogestrel implant do not experience contraceptive failures more frequently than overweight or obese women using an intrauterine device[18]. We will limit enrollment to women with a BMI <30 kg/m^2 so as to limit any effect morbid obesity may have on etonogestrel concentrations. We expect that the study will take a total of 12 months to complete. A screening visit to confirm eligibility will occur prior to initiation of study visits.

Screening: Potential subjects will be identified by their treating providers as meeting basic eligibility criteria (appropriate age and currently using Nexplanon®/Implanon®). Each candidate will be informed of the study purpose and design, and will be given contact information for study personnel if she is interested in enrolling. With her permission, the potential subject's contact information will also be forwarded to study personnel, who will then contact her by phone. During a phone interview, details of the study will be discussed with her, after which she will be asked to come to the Bayview CRU for an in-person interview. During this visit, she will be asked to read and sign the approved consent form, undergo a history and physical exam, and have baseline laboratory tests performed (hematologic and metabolic panels as described in Inclusion Criteria, serum HIV, urine pregnancy test), as well as a baseline ultrasound to ensure her ovaries are detectable. Study personnel will review the results of the laboratory tests, and if all results are in the specified ranges, the subject will be contacted to schedule the start of the study protocol.

Data collection: After successful screening, women will be asked to take 14 days of EFV in a once-nightly 400 mg regimen. We will collect blood samples for baseline ENG concentration on the day participants begin taking EFV, before the first dose (Day 1, times 0 hour, 1 hour, and 2 hours). The first dose of EFV will be taken in the evening of Day 1, and the next blood sample for ENG concentration will be drawn twelve to twenty hours after the first dose of EFV. (For example, if a participant takes her first dose of EFV at 10 PM on Day 1, she will be asked to return to the CRU between 10 AM and 6 PM on Day 2.) We will then obtain subsequent samples every 3 to 4 days (+/- 1 day) for the remainder of the two week EFV course and for 4 additional weeks (through Week 6 of study participation). This is a total of 14 outpatient visits, including screening. All serum samples will be analyzed for concentrations of ENG, which will be used to derive the ENG area under the concentration-time curve (AUC), the maximum and minimum observed serum drug concentration (C_{max}, C_{min}), and the apparent average serum concentration at steady-state (Css_{avg}) using WinNonlin®. EFV concentrations will be determined from plasma samples obtained at 2 timepoints during EFV administration, and measured using a validated LC/MS/MS assay in the Clinical Pharmacology Analytical Laboratory of the Johns Hopkins Hospital.

Table 1: Participant Visit Schedule and Timing of Study Assessments

Visit	**Screening**	**Study Entry**			**Week 1**		**Week 2**		**Week 3**		**Week 4**		**Week 5**		**Week 6**	
Day #		*1*			*2*	*7*	*11*	*14*	*18*	*21*	*25*	*28*	*32*	*35*	*39*	*42*
Serum Tests		*0 hr*	*1 hr*	*2 hr*												
ENG		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
EFV					X			X								
FSH		X			X	X	X	X	X	X	X	X	X	X	X	X
LH		X			X	X	X	X	X	X	X	X	X	X	X	X
Estradiol		X			X	X	X	X	X	X	X	X	X	X	X	X
Progesterone		X			X	X	X	X	X	X	X	X	X	X	X	X
Safety Labs	X															X
UPT	X															X
HIV	X															X
TVUS	X				X	X	X	X	X	X	X	X	X	X	X	X
CM	X				X	X	X	X	X	X	X	X	X	X	X	X

Secondary endpoints will be serum markers of ovulation (estradiol [E_2], progesterone [P], follicle stimulating hormone [FSH], and luteinizing hormone [LH]), as well as evidence of ovulation on cervical mucus exam and transvaginal ultrasound (presence and subsequent disappearance of a dominant follicle >15 mm diameter)[19]. Blood for hormone assays will be drawn at the Bayview CRU at the same time as samples for ENG and EFV. During these visits participants will also undergo a pelvic exam for cervical mucus assessment, and a pelvic ultrasound to look for ovarian follicular activity. Monitoring throughout the study will allow us to compare ovarian activity across time points through both ultrasound visualization and ovarian hormone testing (E_2 and P). Changes in cervical mucus quality secondary to the progestin activity of ENG provide secondary contraceptive effects that may be maintained even if ovulation occurs. Continued monitoring for several weeks after cessation of EFV will allow us to follow subjects for the equivalent of a normal menstrual cycle, to ascertain whether either contraceptive effect (ovulation suppression or cervical mucus quality) was altered. Urine pregnancy tests may be repeated throughout the duration of the study as needed.

Ultrasounds and venipuncture for LH, FSH, E_2 and P levels will occur in the CRU. A total of 20 mL of venous blood will be collected for each outpatient visit. FSH, LH, E_2, and P assays will be performed by the CRU at JHU. FSH and LH will be measured using the automated immunoradiometric assay (IRMA) system. Assay sensitivity of LH assays is 0.07 mIU/ml; assay sensitivity of FSH assays is 0.2 mIU/ml. P will be measured using an automated immulite chemiluminescent assay system. Assay sensitivity of the P assay is 0.05 ng/ml. E_2 will be measured via an ultra-sensitive competitive binding radioimmunoassay with sensitivity of 2.2 pg/ml. The EFV assay will be performed through the Johns Hopkins Hospital Clinical Pharmacology Analytical Lab, and will be measured via LC-MS/MS assay with a lower limit of quantification of 0.5 ng/ml.

An assay for ENG is not commercially available, but the Irving Institute for Clinical and Translational Research at the Columbia University Medical Center in New York has developed a validated assay. ENG concentrations will be measured by LC-MS/MS, and the assay has a lower limit of quantification of 50 pg/ml.

Transvaginal ultrasound (TVUS) will be performed using high-resolution machines (Sonosite Edge, SonoSite, Inc., Bothell, WA) in our clinic to monitor follicular development. Follicular diameter will be calculated by averaging the mean of the length and width in both the sagittal and transverse plane. Follicles measuring $\geq$ 10 mm will be considered dominant preovulatory follicles, and only follicles measuring $\geq$10 mm will be recorded[20]. Ovulation will be defined as the disappearance of a follicle $\geq$ 15 mm in diameter that was observed the visit before. We will collect cervical mucus using an endocervical aspirator, and evaluate the sample for consistency, ferning, Spinnbarkeit, and cellularity. Each variable will be scored on a 0 to 3 point scale according to WHO guidelines. A total score of 9 to 12 will indicate mucus conditions favorable to sperm penetration[21].

Recruitment: Subjects will be recruited from the general gynecology office in JHOC and practices affiliated with JHBMC. We will recruit patients known to be using Nexplanon®/Implanon®. Written notices advertising the study will be placed in the gynecology offices as well as in other affiliated primary care offices. We will also place advertising notices throughout Johns Hopkins institutions including the School of Nursing and the School of Public Health.

b. Study duration and number of study visits required of research participants.

We anticipate that the study will take 12 months to complete. Participants will be enrolled for a total of 6 weeks (2 weeks taking EFV, and 4 weeks additional follow-up), during which time they will complete 14 visits including a screening visit. After enrollment, visits will occur twice weekly.

c. Blinding, including justification for blinding or not blinding the trial, if applicable.

Not applicable in this pilot pharmacokinetic study

d. Justification of why participants will not receive routine care or will have current therapy stopped.

Not applicable.

e. Justification for inclusion of a placebo or non-treatment group.

Not applicable.

f. Definition of treatment failure or participant removal criteria.

Treatment failure is not applicable to this study as efavirenz is being given to healthy volunteers and not part of an HIV treatment regimen. A participant will be removed from the study under the following circumstances:
- She misses more than three study visits
- She becomes pregnant
- She experiences a serious adverse event
- She requests to stop the study

g. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.

If a participant leaves the study prior to its completion, there will be no effect on her general medical care. At the conclusion of the study, participants will not receive any additional study medications and will return to their routine care providers for ongoing care as needed.

5. Inclusion/Exclusion Criteria

Inclusion Criteria:
- Healthy women aged 18-40 years who have a Nexplanon®/Implanon® in place that is palpable on exam, had the device placed between 12 and 24 months prior to enrollment, and can provide documentation of when the implant was placed
- Able to speak and read English
- Documented HIV-negative status within 30 days of enrollment
- BMI between 18.5 and 29.9 kg/m^2
- Willingness to take a two-week course of reduced-dose efavirenz
- Willingness to comply with study visit schedule (as described below), including blood sampling, transvaginal ultrasounds, and cervical mucus assessment
- Negative urine hCG pregnancy test at study entry
- Normal laboratory values within 30 days of study entry, as specified below:
    - White blood cell count ≥ 4500 and ≤ 11000 cells/mm^3
    - Platelet count $\geq 100{,}000$ platelets/mm^3

  - Hemoglobin ≥ 8.0 g/dL
  - International normalized ratio (INR) ≤ 1.8
  - Aspartate transaminase (SGOT) and alanine aminotransferase (SGPT) ≤ 3 times the upper limit of normal (ULN) (upper limit of normal)
  - Creatinine ≤ 1.5 x ULN
  - Serum amylase ≤ 1.5 x ULN
  - Total bilirubin ≤ 2.0 x ULN
- Agree to use an additional reliable method of contraception while participating in the study. Acceptable methods include:
  - Abstinence
  - Condoms (male or female) with or without spermicide
  - Pre-existing sterilization of subject or her male partner
- Willingness to abstain from alcohol consumption during the study period
- Willingness to abstain from any grapefruit product or supplement for the duration of the study.

Exclusion Criteria:
- Breastfeeding
- Hypersensitivity to efavirenz
- History of seizure disorder
- History of significant psychiatric illness
- Initiated, discontinued, or changed doses of drugs that are CYP3A4 inducers or inhibitors within 30 days of study entry.

Disallowed Drugs

Antibiotics and other anti-infectives	Artemether Atovaquone Bedaquiline Clarithromycin Lumefantrine Proguanil Rifabutin Rifampin
Anticoagulants and Antiplatelet Drugs	Apixaban Clopidogrel Rivaroxiban Ticagrelor Warfarin
Anticonvulsants	Carbamazepine Felbamate Fosphenytoin Lamotrigine Oxcarbazepine Perampanel Phenobarbital Phenytoin Topiramate
Antidepressants, Antipsychotics	Aripiprazole Bupropion Citalopram

	Clobazam Clozapine Lurasidone Mirtazapine Pimozide Quetiapine Sertraline Vilazodone Vortioxetine
Antifungals	Caspofungin Griseofulvin Itraconazole Posaconazole Voriconazole
Antihistamines	Astemizole Azelastine Cisapride Doxylamine Hydroxyzine
Antihypertensive and Cardiac Drugs	Bepridil Carvedilol Diltiazem Dofetilide Dronedarone Eplerenone Guanfacine Metyrosine Nifedipine Nisoldipine Propafenone Ranolazine Timozide
Antineoplastic Agents	Abiraterone acetate Axitinib Bortezomib Bosutinib Bretuximab vedotin Cabozantinib Crizotinib Dabrafenib Dasatinib Everolimus Ifosfamide Imatinib Lapatinib Nilotinib Paclitaxel Pazopanib Ponatinib

	Regorafenib Romidepsin Sorafenib Sunitinib Vandetanib Vemurafenib Vincristine
Cholesterol-lowering agents	Atorvastatin Lovastatin Pravastatin Simvastatin
Ergot derivatives	Dihydroergotamine Ergotamine Ergonovine Methylergonovine
Immunomodulators and immunosuppressants	Cyclosporine Mycophenolate Pomalidomide Sirolimus Tacrolimus Tocilizumab Tofacitinib
Sedative hypnotics, Sleep aid	Midazolam Quazepam Triazolam Zolpidem
Herbal products	St. John's Wort Bloodroot Chasteberry Oregano Grapefruit juice Gingko biloba
Opiate agonists and antagonists	Buprenorphine Fentanyl Methadone Tapentadol
Hypoglycemic agents	Exenatide Linagliptin Saxagliptin
Anti-Parkinson's Agents	Pramipexole Ropinirole Rotigotine
Antiemetics	Aprepitant Fosaprepitant
Antiretroviral drugs	Atazanavir Boceprevir Cobicistat Darunavir Dolutegravir

	Etraverine Fosamprenavir Indinavir Lopinavir Maraviroc Nevirapine Raltegravir Ritonavir Saquinavir Telaprevir

6. Drugs/ Substances/ Devices

a. The rationale for choosing the drug and dose or for choosing the device to be used.

Nexplanon®/Implanon® is the only contraceptive implant currently available in the United States, and is the most effective reversible contraceptive method with a failure rate of less than 0.05%[22]. As it is a progestin-only method, it is safe for use in women with a variety of medical comorbidities who are unable to take estrogen-containing methods. The World Health Organization Medical Eligibility Criteria (WHO MEC) rates Nexplanon®/Implanon® as category 1 (no restriction for use) for women with HIV/AIDS, and category 2 (advantages of use generally outweigh theoretical or proven risks) for women taking NNRTIs and PIs, due to theoretical concerns about decreased contraceptive efficacy related to drug interactions[23]. Case reports of 7 pregnancies occurring in 6 HIV-positive women taking efavirenz and Nexplanon®/Implanon® simultaneously suggest the concern about drug interactions between these two compounds may be more than theoretical[9-12]. Two recent clinical studies have demonstrated significant reductions in serum etonogestrel concentrations when women using Nexplanon® were treated for HIV infection using standard doses of efavirenz[13, 14]. Another study evaluating the concurrent use of a levonorgestrel contraceptive implant and either efavirenz- or nevirapine-based antiretroviral regimens for treatment of HIV found that women taking efavirenz experienced not only decreased levonorgestrel concentrations, but unplanned pregnancies as a result of contraceptive implant failures[15].

Accumulating evidence suggests a significant effect of efavirenz on systemic concentrations of etonogestrel when the two medications are taken together. Published studies have focused on changes in serum concentrations of etonogestrel and serum progesterone concentrations as a marker of ovulation, but they have not evaluated the other ways the etonogestrel implant likely prevents pregnancy (i.e. changes in endometrium and cervical mucus). It remains unclear whether a lower dose of efavirenz will lead to a similar decrease in etongestrel concentrations. We propose this study to formally evaluate the interactions that may exist between these two drugs. Among the antiretroviral drugs that could affect the activity of ENG, we selected EFV for this study because of the case reports mentioned above as well as its widespread use as part of first-line antiretroviral regimens. We will use a lower dose than that currently used in clinical practice (400 mg orally each night, instead of the standard dose of 600 mg).

b. Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed.

This pilot study is being conducted to determine if reduced-dose EFV decreases the efficacy of ENG delivered by the contraceptive implant to the point where HIV-positive women taking reduced-dose EFV

who are also relying on this contraceptive are at increased risk of unintended pregnancy. The use of EFV in this protocol is therefore off-label in that EFV will be given to HIV-uninfected women. EFV is indicated only for use in combination with other antiretroviral drugs in the treatment of HIV. Consequently, it would be very difficult to isolate the effects of EFV on ENG in women taking combination antiretroviral therapy due to the potential other drug interactions that may be present.

EFV was chosen for this study because it is the backbone of one of the preferred antiretroviral regimens recommended by the NIH[24]. As such, it is commonly taken by women of reproductive age. There is some concern that EFV increases the risk of neural-tube defects when exposure occurs during the first 5-6 weeks of pregnancy[21]. For this reason, it is particularly important to avoid unintended pregnancy in women taking EFV. Determining whether the ENG implant retains its high level of contraceptive efficacy in women taking EFV is important so that HIV-positive women and their healthcare providers can make the most informed decisions regarding antiretroviral regimens and contraception.

The dose of EFV that is used in clinical practice is 600 mg given orally once per day, typically at bedtime, and it is generally well tolerated[25]. Recent data suggest that a lower daily dose of EFV (400 mg) is as effective as the standard 600 mg dose in suppressing HIV, with lower incidence of drug-related side effects. As the criteria for starting ART continue to broaden, there is considerable concern about the costs of providing treatment to more individuals, and reducing the accepted dose of EFV is one strategy to make ART available to as many people as possible[26].

Certain drugs are contraindicated or not recommended for use with EFV, including ergot derivatives, benzodiazepines, calcium channel blockers, cisapride, pimozide, and St. John's wort. Women taking these drugs will be excluded from the study due to potential adverse drug interactions. While the 400 mg daily dose of EFV has been associated with a lower incidence of drug-related adverse events, participants will be informed of potential adverse reactions to EFV prior to enrolling in the study, and will be counseled regarding when and how to inform study personnel of any potential adverse reactions. The adverse reactions that have been identified in studies comparing EFV-based antiretroviral regimens to control regimens include:

- Psychiatric symptoms: depression (19% with EFV-based regimen vs. 16% with control), anxiety (13% vs. 9%), nervousness (7% vs. 2%)
- Nervous system symptoms: dizziness, insomnia, impaired concentration, somnolence, abnormal dreaming, euphoria, confusion, agitation, amnesia, hallucinations, stupor, abnormal thinking, depersonalization. Mild symptoms occurred in 33.3% of patients taking EFV compared to 15.6% of patients in control groups; moderate symptoms occurred in 17.4% of patients taking EFV compared to 7.7% of controls; and severe symptoms occurred in 2% of patients taking EFV compared to 1.3% of controls.
- Rash: 26% of patients taking EFV developed a rash compared to 17% of patients in control groups. A grade 4 rash (erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, necrosis requiring surgery, exfoliative dermatitis) was seen in 0.1% of patients treated with EFV and no patients in control groups. Rashes usually occur during the first two weeks of treatment, and are mild-to-moderate maculopapular skin eruptions. The rash typically resolves within one month in patients who continue EFV.
- Hepatotoxicity: it is recommended that liver enzymes be evaluated before and during treatment with EFV, as EFV can cause elevated liver enzymes even in patients without underlying hepatic disease.
- Convulsions: Convulsions have been noted in patients treated with EFV, typically in the setting of a known seizure disorder.
- Lipid elevations: EFV can lead to increased concentrations of total cholesterol and triglycerides. Some HIV-uninfected volunteers who received EFV were noted to have 10-20% increases in total cholesterol from baseline.

- Fat redistribution: Body fat may redistribute or accumulate in certain regions of the body, including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance." This phenomenon has been noted among patients taking antiretroviral therapy in general, and while it has not been specifically linked to EFV, it is a potential adverse reaction to this drug.

c. Justification and safety information if non-FDA approved drugs without an IND will be administered.

Not applicable

7. Study Statistics

a. Primary outcome variable.

Primary Outcome: Serum concentrations of ENG before and after two weeks of reduced-dose EFV

b. Secondary outcome variables.

Secondary Outcomes:
- Serum concentrations of EFV at the start and end of the study period
- Serum hormonal markers of ovulation (P, E_2, LH, FSH)
- Presence of dominant follicle(s) on transvaginal ultrasound during and after EFV dosing
- Change in cervical mucus quality suggesting ovulation during and after EFV dosing

c. Statistical plan including sample size justification and interim data analysis.

Sample size: We hypothesize that during co-administration of the ENG implant and reduced-dose EFV, we will detect a decrease in serum ENG concentrations, but that overall contraceptive effect will be maintained. We do not anticipate that any subjects will have a drop in ENG concentration below the threshold needed for ovulation suppression (90 pg/mL)[8]. Using a two-sided Wilcoxon test, a sample size of 15 will have 80% power (with an alpha of 0.05) to detect a 20% difference in ENG concentration between women taking EFV and historical controls. We plan to enroll 18 women to account for a potential 20% drop-out rate.

Data Analysis: We will calculate area under the curve (AUC) and maximum and minimum concentrations of each drug (C_{max} and C_{min}), as noted above. For hormone markers (LH, FSH, E_2, P) we will evaluate change over time as well as whether pertinent threshold levels are reached that could indicate that ovulation has occurred. All serum tests will be evaluated through the Johns Hopkins Division of Clinical Pharmacology, with the exception of etonogestrel concentrations as this assay is not widely available. Serum samples will be frozen and shipped to the Irving Institute for Clinical and Translational Research at Columbia University Medical Center in New York City, which will perform the etonogestrel assay.

Interpretation: If the pharmacokinetic parameters for etonogestrel that are seen in this interaction study are consistent with those published in the literature (less than 30% difference), we will conclude that there is no significant interaction between ENG and reduced-dose EFV. This would support the assertion that Nexplanon®/Implanon® is a safe and effective option for HIV-infected women taking reduced-dose EFV who desire long-acting reversible contraception. However, if two or more women out of a sample of 15 breach the threshold concentration needed for ovulation suppression, it will indicate a statistically and clinically significant decrease in ENG concentration and potential for decreased contraceptive efficacy.

d. Early stopping rules.

Participants may be removed from the study under the following circumstances:
- Participant requests to withdraw from the study
- Participant requests that she have the ENG implant removed prior to conclusion of the study. (Of note, removal would be performed by the subject's clinician and not performed as part of the study.)
- Participant judged by the investigator to be at significant risk of failing to comply with the provisions of the protocol as to cause harm to self or seriously interfere with the validity of the study results.
- Participant takes emergency contraception during the study

8. Risks

a. Medical risks, listing all procedures, their major and minor risks and expected frequency.

The medical risks related to participation in this study fall into two categories: medication side effects or adverse reactions, and possible contraceptive failure.

Medication Adverse Reactions:

The most common adverse reactions for EFV are:
- Psychiatric symptoms – severe depression (2.4%), suicidal ideation (0.7%), nonfatal suicide attempts (0.5%), aggressive behavior (0.4%), paranoid reactions (0.4%), and manic reactions (0.2%)
- Central nervous system symptoms (overall incidence 53%) – dizziness (28.1%), insomnia (16.3%), impaired concentration (8.3%), somnolence (7%), abnormal dreams (6.2%), and hallucinations (1.2%) (usually begin during the first 2 days of therapy and resolve after 2-4 weeks).
- Rash (26%) – usually mild to moderate maculopapular skin eruptions that occur within the first 2 weeks of initiating therapy and typically resolve within 1 month

Additional adverse reactions to EFV include elevated liver enzymes, convulsions, elevated total cholesterol and triglycerides, and fat redistribution. Adverse reactions attributed to EFV occurred less frequently with the 400 mg daily dose compared to 600 mg[27].

It is possible that any changes in ENG concentrations that occur during and after the course of EFV could lead to increased incidence of adverse reactions to ENG. The most common adverse reactions leading to discontinuation of Nexplanon®/Implanon® are[7]**Error! Bookmark not defined.**:
- Bleeding irregularities (11.1%)
- Emotional lability (2.3%)
- Weight increase (2.3%)
- Headache (1.6%)
- Acne (1.3%)
- Depression (1.0%)

Given that co-administration of EFV with the ENG implant may lead to decreased serum concentrations of ENG, participants may experience greater or lesser breakthrough bleeding than is typical with the ENG implant. They could also experience an improvement in progestin-related side effects with lower ENG concentrations.

Unintended Pregnancy

Since the goal of the study is to determine whether reduced-dose EFV lowers the serum concentration of ENG to a level where ovulation might occur, there is the possibility that a participant could ovulate during

or after taking reduced-dose efavirenz. If she is sexually active during the study, this would put her at risk of an unintended pregnancy. There is also some concern that EFV may cause neural tube defects when taken during the first trimester. This risk was suggested by isolated case reports; however, larger reviews have found no increased risk in congenital anomalies with EFV.

b. Steps taken to minimize the risks.

Participants will be advised to take EFV at bedtime and on an empty stomach in an effort to minimize the central nervous system effects. They will also be counseled about the potential for psychiatric effects and rash as part of the informed consent process, and will be provided with contact information for study personnel should they experience any concerning symptoms. If needed, depending on the nature of the psychiatric symptoms or effects, participants will be referred for appropriate clinical care. This may include the emergency department, a psychologist, or the participant's primary care physician.

Participants will also be encouraged to either abstain from intercourse during the study period, or to use an additional backup method such as male or female condoms. They will be counseled about the potential for unintended pregnancy and teratogenic effects as part of the informed consent process. Participants will also be counseled about the availability of emergency contraception (either over-the-counter or by prescription) if they ever feel at risk for unintended pregnancy during the study (i.e. in the event of condom breakage).

c. Plan for reporting unanticipated problems or study deviations.

If there is an emergency protocol deviation, it will be reported to the IRB by the study team as soon as possible, but no later than 5 business days after the occurrence. The PI will submit a report through eIRB as a Further Study Action using the Problem/Event Report. Any major, non-emergent protocol deviations will be submitted to the IRB as a Change in Research prior to the change being implemented. Minor or administrative protocol deviations will be reported to the IRB as part of a continuing review application.

d. Legal risks such as the risks that would be associated with breach of confidentiality.

If there is a breach of confidentiality during the study, it could lead to disclosure of sensitive health information such as a participant's sexual history or contraceptive use. All specimens and study documentation will be labeled with a participant ID number to prevent identification of each participant. Identifiable participant information will be maintained in secure documents, either in a locked file cabinet or password protected computer files that are accessible only to study personnel.

e. Financial risks to the participants.

The risk of a drug-related adverse event occurring during the study is low, but if such an event occurs the study participant will be financially responsible for the evaluation and treatment of the adverse event. For example, if a participant experiences a rash related to efavirenz, she will be responsible for the costs of medication used to treat the rash. Such treatments may be covered by health insurance or paid for out of pocket.

9. Benefits

a. Description of the probable benefits for the participant and for society.

The results of this pilot study will provide greater understanding of whether reduced-dose efavirenz, a commonly used NNRTI, affects etonogestrel concentrations in women using Nexplanon®/Implanon® such

that contraceptive effect is compromised. By investigating the effects of one component of HAART on Nexplanon®/Implanon® in a population of healthy volunteers, this preliminary data will help guide future studies of the efficacy of Nexplanon®/Implanon® in HIV-infected women on multi-agent therapy. Determining whether this highly-effective reversible contraceptive method is a safe and viable option for HIV-infected women on HAART will broaden these patients' contraceptive options, particularly when they wish to avoid pregnancy for an extended period of time. The knowledge gained from this study will also help determine whether the lifespan of Nexplanon®/Implanon® is reduced in women taking reduced-dose efavirenz. After Nexplanon®/Implanon® is inserted, there is an initial burst release of etonogestrel, and peak serum concentration is reach at a mean of 4 days after placement[7]. Serum ENG concentrations decline slowly over the three-year lifespan of the implant, and this study will provide information as to whether ENG concentrations remain sufficient to reliably suppress ovulation when EFV is taken simultaneously. If reduced-dose EFV causes ENG concentrations to decrease below the ovulation suppression threshold, the ENG implant may need to be replaced prior to the licensed three years.

10. Payment and Remuneration

a. Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol.

Participants will be compensated as follows:

- Screening visit = $75
- Enrollment visit = $45
- Follow-up visits (total of 12) = $60 each = $720 total
- Bonus payment for completion of study = $180
- Parking/Bus tokens (total of 14) = $5 each = $70 total

This comes to a total of $1090 for each participant at the end of the study. The bonus payment at the completion of the study will be made if there have been no significant deviations from the study protocol. Participants will not be compensated for visits that are not completed, and they will not receive the bonus if they are missing data for three or more visits.

11. Costs

a. Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.

There will be no costs incurred by the participants. In order to be eligible for the study, participants must already be using Nexplanon®/Implanon® for contraception, so they will not be provided with the implant by the study. The two-week course of reduced-dose efavirenz costs $285 per participant and will be provided by the study through the Johns Hopkins Bayview Medical Center Pharmacy Service for Clinical Investigations. Phlebotomy for all blood samples will be performed at the Johns Hopkins Bayview Medical Center Clinical Research Unit and will not be charged to participants. These costs will be paid for by the study. Members of the study team will be performing all transvaginal ultrasounds and cervical mucous assessments, so there is again no cost to participants.

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