RESEARCH CONSENT FORM

Title of Protocol: Pharmacologic Strategies for Etonogestrel Implants in HIV-Infected Women
Protocol Version this Consent Form Accompanies: Version 1.0
Protocol Date: 11 July 2017

Site Principal Investigator: Dr. Mohammed Lamorde
Site Location*: Infectious Disease Institute (IDI), Kampala, Uganda*
Principal Investigator Cell Phone and 24-Hour Contact: 0772-185-590

INFORMED CONSENT

We are asking you to volunteer for a research study at the Infectious Diseases Institute Clinic, Kampala, Uganda. We will first explain why we are doing this study, the good and bad about it, and what will be asked of you if you agree to be in the study. The Merck Investigator Studies Program, USA is paying for this study.

If you decide to be in the research study, we will ask you to sign two copies of this consent form or make your mark in front of a witness. We will give you a copy of this form. This consent form might contain some words that you do not know. Please ask us to explain anything you do not understand.

PURPOSE OF THE STUDY

A total of 72 women will participate in this study. This study is being done to compare the rate of ovulation when women receive two hormonal subdermal implant contraception devices (instead of only one device) while taking the HIV drug efavirenz. A *subdermal implant* is a device that is inserted under the skin on your upper arm by a nurse or doctor and releases a small amount of drug into your body every day over a long period of time to prevent pregnancy. It can be removed at any time and your ability to become pregnant will return to normal once it is removed. When the implant is used according to manufacturer recommendations', it can prevent pregnancy for 3 years. The name of the subdermal implant that we will be using is the etonogestrel implant.

Implant manufacturers don't recommend using the implant for contraception along with some HIV drugs. Specifically, recent research showed that when the etonogestrel implant was used in women taking the HIV drug efavirenz, the amount of etonogestrel available in the body is decreased over half, and some women receiving these drugs together became pregnant. However, implants are still used for contraception by women around the world who are also taking efavirenz for their HIV treatment. So, we would like to find if the implant is working at all in the lower dose by checking to see if women are releasing an egg or the cervix (opening of the uterus) is thin. In order to find this out, we are checking the blood for a hormone call progesterone which increases after the egg is released and taking a sample of the fluid from the opening of the uterus. We also want to know if the lower amount of etonogestrel in the body of a woman taking efavirenz can be prevented by using a higher dose (increased dose) of the implant along with efavirenz. In order to find out this information, we would like to know the difference in the amount of etonogestrel in the body over 12 months between women using the normal dose of the etonogestrel implant alone and women using two etonogestrel implant devices (one in each arm) with the HIV drug called efavirenz.

To sum it up, we know that the etonogestrel implant can prevent women from becoming pregnant over a 3-year time period when they are not on efavirenz. Also, we know that when women use the etonogestrel implant along with efavirenz, the amount of etonogestrel in the blood decreases by about over one-half and this may increase the woman's chance of becoming pregnant. However, we do not know how well a single implant works with efavirenz and if using an increased dose of the implant along with efavirenz will prevent this decrease from happening and if so, for how long it will work. This is why we are doing this research study.

You are being invited to take part in this study because you are an HIV-infected woman taking efavirenz as one of your HIV drugs who is interested in family planning services and the etonogestrel implant.

We think that the amount of etonogestrel in the blood will be the same in women using an increased dose of the etonogestrel implant along with efavirenz as it is in women using a normal dose of the etonogestrel implant but not taking efavirenz, but we are not sure. Therefore, the study requires that women taking efavirenz use an additional method of contraception to prevent pregnancy. Unless you have had surgery to prevent pregnancy permanently, you will be required to have a copper intrauterine device (IUD) placed for prevention of pregnancy in addition to the etonogestrel implants.

YOUR PARTICIPATION IS VOLUNTARY

Before you learn about the study procedures, it is important that you know these things:

- You do not have to be in this study if you do not want to.
- You may decide to not take part in the study.
- You may stop being in the study at any time.
- If you decide to not take part in the study, you can still join another research study later, if one is available and you qualify for that study.
- If you choose not to be part of this study, or if you decide to stop this study after starting, you will not lose any of the benefits of your regular medical care.

SCREENING

If you decide to be in the study, we will ask you to read, discuss, and sign or make your mark on this form. If you enter the study, testing for this study will occur on a minimum of 17 separate days when you visit the IDI for HIV care. Today will be your first visit out of these 17 visits. If all safety measures are met, you will have 16 additional visits which will occur every 6 months for 4 weeks in a row. In addition to the study visits, you will receive a phone call from the study team on Day 3 of your study participation. The purpose of this phone call is to be sure that you are taking your HIV medication and you are not experiencing any problems. You will also receive visit reminder phone calls on the day before every scheduled visit.

If you agree, you will do the following during the screening process:

- Answer several questions about your health, medication, contraceptive use, and activities
- Complete questionnaires about your contraception and condom use
- You will receive HIV risk and family planning counselling
- Be examined by a study doctor. Your height, weight, and other vital signs such as your blood pressure will be recorded.

- Give a sample of blood (10 mL = 2 teaspoons). The tests that will be performed on this sample include a blood count and tests to see how your liver and kidneys are working.
- We will also collect blood to check the amount of efavirenz and the level of HIV virus in your blood (10 mL = 2 teaspoons).
- Pregnancy test

After the screening process the study doctor will let you know if you qualify for this research study. If you do not qualify for the study, you will not participate in any other procedures for this study but you will continue receiving your usual care at the IDI.

STUDY MEDICATION

It is important to understand that this study will not require any change to your HIV drug treatment or to the care that you receive through the IDI. You will continue taking the same HIV drugs and doses as already directed by your HIV doctor/nurse at IDI. The only medication change because of this study is that you will have an etonogestrel implant device inserted as contraception for family planning. You will be assigned by random chance (like rolling dice) to either receive one or two etonogestrel implant device(s). In addition, you will also have a copper IUD inserted at the same time as the etonogestrel implants; unless you have had surgery to be sterilized

The etonogestrel implant is currently approved for use in Uganda to prevent pregnancy. One implant system contains one small plastic rod that will be placed under the skin in your upper arm. For this study, you will either receive one or two etonogestrel implants depending on your study assignment. The implant systems will be inserted and either one or two rods will be placed under the skin in one arm.

The copper IUD is a small, flexible plastic with a very thin copper wire around it, which is currently approved for use in Uganda to prevent pregnancy. A trained health care worker in the IDI Family Planning Clinic will insert the IUD into your uterus by a passing a thin tube into your private part. Once inserted, the IUD can last for up to 10 years.

If you remove the IUD or etonogestrel implant, your ability to become pregnant returns without delay.

The manufacturer of the etonogestrel implant does not recommend etonogestrel implants for HIV-infected women on HIV drugs. Local and international HIV guidelines say that the implant can be used with efavirenz, as long as another type of contraception is used, like an IUD. We do not know if an increased dose of the etonogestrel implant contraception works well to prevent pregnancy when an HIV-infected woman is also taking the HIV drug efavirenz. That is why we are doing this study.

STUDY GROUPS

This research study includes women who are already taking efavirenz as part of their HIV care as directed by their HIV doctor/nurse at IDI. You will have either one or two etonogestrel implant for contraception placed into your arm by a nurse.

Some of the results of this study will be compared with another group of HIV-infected women from Uganda who were in a similar study without efavirenz as one of their HIV medicines.

STUDY PROCEDURES

As much as possible, we will try to have all visits for study related tests occur during your usual visit to IDI for family planning or HIV care. However, because we cannot predict when an egg will drop, we ask you to come to the clinic weekly certain visits, and thus some of these visits will be outside your regular HIV care. You will not need to schedule all of the study visits as additional visits, but we may ask you to come at certain times of the day or within a certain period of time.

Study procedures that will happen at <u>every visit</u>:
At each study visit, we will ask you about all of the medications or natural products that you are currently taking and discuss any new medical problems. It is important that you tell us all medications you are taking and any side-effects you are experiencing throughout the study. We will advise you if there are any medications you cannot take while on this study. We will ask you about how you have been taking your HIV medicines, or since your last visit, and we will ask what time you took the last dose of your HIV medication before your visit.

We will also measure your weight and other vital signs at each visit. A physical exam may be performed during any study visit, if the study staff feels an exam is needed.

This is what will happen at your Entry Visit:
A urine sample will be collected to perform a pregnancy test. If you are pregnant, you will not be able to continue in the study and you will be referred to the appropriate medical provider.

Blood samples (up to 25 mL or 5 teaspoons) will be taken to measure how much of certain proteins there are in your blood to attach to etonogestrel (called albumin and sex hormone binding globulin), to check for etonogestrel and efavirenz in your blood, and to check your CD4 cell count, and to check for elevated blood sugar or diabetes.

You be asked to complete a condom use questionnaire and a baseline symptoms questionnaire. Study staff will review the use of your efavirenz as well as provide you with HIV risk and family planning counseling.

After these procedures have been completed, you will be assigned by random chance (like rolling dice) to either receive one or two etonogestrel implant device(s), a family planning nurse or doctor will place the etonogestrel implant(s) in your arm. Also, a copper IUD will be placed, if applicable.

After the entry visit to place the implant, visits will be scheduled 1 week, 4 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 21 weeks, 22, weeks, 23 weeks, 24 weeks, 36 weeks, 45 weeks, 46 weeks, 47 weeks, and 48 weeks after the implant(s) were placed in your arm(s). Just as with the first visit, as much as possible, the remaining visits will occur at the time that you are scheduled to visit IDI for your usual HIV care or family planning visit, however for some visit you will have to schedule outside of your regular HIV care or family planning visits. For some visits, we will ask that you come to the clinic in the morning. We will ask you to take your efavirenz at a special time the night before your visit.

On days when you are not visiting the clinic for the study, you can take your HIV medication at the time you usually do and as directed by your HIV nurse/doctor at IDI.

You will now learn about what will happen at each of your remaining visits as a result of this study:

Day 3 phone call:
The study staff will contact you by phone on Day 3 to discuss your efavirenz use as well as any symptoms you may be experiencing. Before each study visit, a study staff member will contact you by phone to confirm the visit time. The study staff will also review with you the time you should take efavirenz and remind you to write down the exact time that you take the drug the night before your visit.

Follow-up visits will occur after you receive your implant(s) at weeks 1, 4, 9, 10, 11, 12, 21, 22, 23, 24, 36, 45, 46, 47, and 48. The following study procedures will be completed as follows:

- At Weeks 1, 4, 12, 24, 36, 48, or at an Early Discontinuation Visit, you will have the following study procedures performed:
    - Pregnancy testing, if you are pregnant, you will not be able to continue in the study and you will be referred to the appropriate medical provider
    - Contraceptive Satisfaction Questionnaire
    - Condom Use Questionnaire
    - HIV risk and family planning counseling
    - Blood sample (6mL or approximately 1 teaspoon) taken to measure the amount of etonogestrel in your blood. With the exception of week 1, you will also have a blood sample (4mL or approximately 1 teaspoon) taken to measure the amount of efavirenz in your blood

- At Weeks 1, 4, 9, 12, 21, 22, 24, 36, 48, or at an Early Discontinuation Visit, you will have the following study procedure performed:
    - Study staff will review the use of your efavirenz with you to be sure you are taking your medication correctly

- At weeks 9, 10, 11, 12, 21, 22, 23, 24, 45, 46, 47, 48, or at an Early Discontinuation Visit, you will have the following study procedures performed:
    - Blood will be collected (5mL or approximately 1 teaspoon) to measure the amount of progesterone in your blood, which indicates that an egg has been released from your ovary in the past 1 week
    - You will have a vaginal exam. During the vaginal exam, a clinician will use a small instrument called a speculum to enable them to see the inside of your vagina and your cervix (the opening of the womb). The study clinician will then use a small plastic tube to collect mucus from your cervix. Doctors can tell whether the implant is still working to prevent pregnancy by examining the mucus obtained from a vaginal exam. The clinician will test your mucus to see if there are any signs that show that the implant you are using is still able to prevent pregnancy

- At weeks 4, 24, 48, or at an Early Discontinuation Visit, you will have the following study procedures performed:
    - At weeks 4, 24, and 48 (not at an Early Discontinuation visit), a blood sample (5 mL or 1 teaspoon) will be taken to measure how much of certain proteins

there are in your blood to attach to etonogestrel (called albumin and sex hormone binding globulin)
- At week 24, a blood sample will be checked for diabetes
- At week 48 and at an Early Discontinuation Visit, you will have blood collected (5 ml or 1 teaspoon) to check your CD4 cell count
- At weeks 24 and 48, or at an Early Discontinuation Visit, you will have blood collected (5 ml or 1 teaspoon) to check the level of HIV virus in your blood.

If all safety measures for the study have been met, your study participation will continue and you will have follow-up visits during years 2 and 3 of your implant insertion. These visits will occur at weeks 69, 70, 71, 72, 93, 94, 95, 96, 117, 118, 119, 120, 141, 142, and 144. At these visits you will have the following study procedures:

- Contraceptive Satisfaction Questionnaire
- Condom Use Questionnaire
- HIV risk and family planning counseling
- Study staff will review the use of your efavirenz with you to be sure you are taking your medication correctly

- In addition to the procedures listed above, at weeks 72, 96, 120 and 144, you will also have the following procedures:
    - Pregnancy testing, if you are pregnant, you will not be able to continue in the study and you will be referred to the appropriate medical provider
    - Blood samples (15mL or approximately 3 teaspoon) will be taken to measure the amount of etonogestrel in your blood, to measure the amount of efavirenz in your blood, and to check the level of HIV virus in your blood
    - At week 96 ONLY, you will have blood collected (10 ml or 2 teaspoon) to check your CD4 cell count a test for diabetes

In total, you will have a maximum of 33 blood draws over the 3 years of the study.

WHAT HAPPENS AT THE END OF THE STUDY

After the study ends, you should continue taking your HIV medicines normally, without missing any doses. The etonogestrel implant can remain in place if you still desire it. If you had an IUD inserted, then it can remain in place if you still desire it. You will continue your usual HIV care and Family Planning care at the IDI clinic.

RISKS AND DISCOMFORTS

The risks of taking part in the study are some pain or bruising at the site where we take blood. Rarely, an infection or prolonged bleeding can occur at the site where we take blood.

After the implant is inserted, there may be slight pain, discomfort, redness or swelling associated with the implant. This should decrease after a few days. If it does not, please contact the study staff or family planning nurse at IDI. Medications may have side effects related to them. Side effects that occur in >10% of users include increased or decreased menstrual blood flow, spotting, irregular or no menstrual flow, weight gain, headache, depression or mood changes, nausea, nervousness, or dizziness. Less common side effects are listed in the table:

Category	**1-10% of users**	**0.1-1% of users**	**<0.1% of users**

Mental health	Mood changes, depression, changes in libido, painful intercourse		
Brain	Severe headache		
Heart	Irregular heartbeat, chest pain		
Blood	High blood pressure, swollen veins		
Lungs	Difficulty breathing		
Stomach	Upset stomach		
Liver	Changes in a blood test called bilirubin		
Skin	Acne, rash, itching hair loss or overgrowth, changes in skin color		
Kidney	Problems with urine system		
Reproductive system and breasts	Itching, growth in ovaries or breasts, breast discharge		
Other	Itching where implant is inserted, pain, fatigue, back pain, weight loss	Bruising or infection where implant is inserted	Implant falls out, arm pain, numbness, tingling and scaring, difficulty removing implant, nerve injury, changes in skin color where implant is inserted

We do not know if the increased dose etonogestrel implant will work as well or for how long it will work when it is taken by women who are also taking the HIV drug efavirenz. This means that you may become pregnant if the etonogestrel implant is the only form of contraception that you use. This is why we are also asking you to use an IUD during the study if you have not had surgery to be sterilized. Hormonal contraception, like the implant, and the copper IUD do not prevent HIV transmission; therefore, it is important to also continue to use a barrier method (such as condoms) to prevent transmission of HIV to your partner.

If you have not had surgery to be sterilized, we require you to have a copper IUD inserted. The IUD works for 10 years, however it can be removed after Week 48 of the study or anytime afterwards if you would like. The IUD is one of the recommended forms of family planning for HIV-infected women in Uganda. The most common side effects of the IUD are heavy or irregular bleeding and increased cramping, which occurs more commonly in the first three to six months of use. Rare risks include: 1) infection 2) injury to the uterus, which usually heals without treatment, 3) the IUD can fall out, 4) pregnancy, and 5) difficult IUD removal. If you experience any of these side effects, please let the study team know.

BENEFITS
You may not receive any direct benefit by participating in this study. However, you or others may benefit in the future from what is learned in this study. You also may get some personal satisfaction from being part of research on HIV.

If you are not receiving HIV drugs, the etonogestrel implant is expected to prevent pregnancy for up to 3 years. Many women use this type of contraception when they are on HIV medicines, so we expect that you will get some benefit from this contraception method. However, we cannot be certain how well or for how long the etonogestrel implant will work when you are also taking efavirenz.

NEW FINDINGS
You will be told any new information about both HIV drugs and etonogestrel learned during this study. It may be important for your health. It might cause you to change your mind about participating in the study. You may be told when the results of the study are available and how to learn about them.

COSTS TO YOU
There is no cost to you for being in the study. All study procedures, the etonogestrel implants, and the IUD provided to you during the study will be free of charge.

REASONS WHY YOU MAY BE WITHDRAWN FROM THE STUDY
You may be removed from the study without your consent for the following reasons:

- If the study is stopped or canceled
- If the study staff feel that staying in the study would be harmful to you
- If you become pregnant during the study
- If you are not able to attend study visits, complete the study procedures, or take your HIV drugs as instructed by your doctor
- If you have to switch from efavirenz to a different HIV drug during the study
- If you chose to remove your IUD before week 48

ALTERNATIVES TO PARTICIPATION
You do not have to participate in this study. You can choose to use any family planning method offered by the IDI family planning service. These options may include hormonal implants, hormonal birth control pills, intrauterine devices, or hormonal injections to prevent pregnancy. The family planning nurse will discuss all options with you.

REIMBURSEMENT
You will receive 43,000 Ugandan Shillings (approximately $12.00 US) per study visit to compensate for inconveniences incurred by this study.

PARTICIPANT RIGHTS
Participation in this study is entirely voluntary. You have the right to refuse to participate in this study and this decision will not affect your treatment at IDI in any way. If you choose to participate in the study you have the right to withdraw from the study at any time. Any identifiable research or medical information recorded for, or resulting from, your participation in this research study prior to the date that you formally withdrew your consent may continue to be used and disclosed by the investigators for the purposes described above. You may

contact the chairman of the Research Ethics Committee if you have any questions regarding your rights as a study participant at any time.

Dr Jesse Kagimba
JCRC IRB Chairman
JCRC IRB Office,
Plot 101, Lubowa, Off Entebbe Road
Kampala
Telephone (Office): **0414-201-148**; Mobile: **0712-531-656**

CONFIDENTIALITY
Efforts will be made to keep your personal information confidential. However, absolute confidentiality cannot be guaranteed. Your personal information may be disclosed if required by law. Any sample from you or information about you will be identified only by code. The link between your name and code will be kept in a secure location at the IDI where only the IDI study Principal Investigator can access it. Some of your samples will be shipped to the United States for the measurement of the etonogestrel levels. Any samples and data that are sent to the United States for analyses will not include any of your personal information and will only be identified by a code. Any publication of this study will not use your name or identify you personally.

Your study records may be reviewed by study staff and representatives of:
- Infectious Diseases Institute, Makerere University
- University of Pittsburgh, IRB
- The JCRC IRB
- Uganda National Council for Science and Technology

RESEARCH-RELATED INJURY
The study staff will track your health while you are in this study. If you have any health problems between study visits, please contact the study staff. If you have a medical emergency that requires immediate care, please go to the nearest clinic that can care for your problem.

The study sponsor has provided insurance for this study. If you suffer harm to your health that is caused by the study, the study insurance will pay for the cost of your treatment.

By signing this consent form and agreeing to be in this study, you are not giving up any of your rights.

PROBLEMS OR QUESTIONS
Dr. Lamorde or his designee will explain this study to you. If you have any questions you may ask Dr. Lamorde or his designee now or any time during the study. You may ask to speak to:

Dr Lamorde Mohammed
Infectious Diseases Institute,
Mulago Hospital Complex
Makerere University, Kampala
Email: mlamorde@idi.co.ug
Telephone (Office): 0414-307-291
Mobile: 0772-185-590

INFORMED CONSENT FORM

I have read this form or had it read to me. I have discussed the information with study staff. My questions have been answered. I volunteer to take part in the study. I have been told that my decision whether or not to take part in the study is voluntary. I have been told that if I decide to join the study I may withdraw at any time. By signing this form, I do not give up any legal rights that I have as a research participant.

_____ _____

Name of Participant (printed) Signature of participant

or if illiterate, make a thumbprint * in the box below

Date: _____ / _____ / _____

Day Month Year

_____ _____

Name of Person Administering Consent (printed) Position/Title

_____

Signature of Person Administering Consent **Date:** _____ / _____ / ____

Day Month Year

**If the patient is unable to read and/or write, an impartial witness should be present during the informed consent discussion. After the written informed consent form is read and explained to the participant, and after they have orally consented to their participation in the study, and have either signed the consent form or provided their fingerprint, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the patient and that informed consent was freely given by the patient.*

_____ _____

Name of Person Witnessing Consent (printed) Signature of Person Witnessing Consent

Date: _____ / _____ / ____

Day Month Year