STUDY INFORMED CONSENT

Quantification of Estradiol's Impact on Nucleotides in Cellular Populations of the Lower GI Tract

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University of North Carolina at Chapel Hill
Consent to Participate in a Research Study
Adult Participants

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IRB Study # 19-0333
Title of Study: Quantification of Estradiol's Impact on Nucleotides in Different Cellular Populations of the Lower GI Tract

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CONCISE SUMMARY

Transgender women (TGW) have a 49-fold increased risk of becoming infected with HIV, yet they have been underrepresented in HIV prevention and treatment research. Estradiol (the main component of feminizing hormone therapy used by TGW) can alter the way the medications used for used for HIV pre-exposure prophylaxis (PrEP) are processed in the body through several means, but we do not know yet how, or if, that would affect clinical care. We want to study the impact of estradiol on this relationship, and if less invasive sampling procedures, such as taking only cells, can be used in the place of biopsies to study drug concentrations in TGW, as well as premenopausal women during times of peak estradiol.

We will be enrolling healthy cisgender female volunteers in this study. These participants will be given five doses of a Food and Drug Administration (FDA) approved antiretroviral (ARV) medication, Truvada®, before each of two sampling visits. These sampling visits will be scheduled to within the following windows of the participant's menstrual cycle: approximately days 2-5 and days 12-15. These timepoints correspond with when estradiol is at its lowest and highest concentrations in the body. By taking samples of blood, rectal tissue, and rectal cells at these timepoints, researchers will be able to evaluate how hormone levels affect the concentrations of Truvada®.

Those who participate in this study will receive $565.00 in Visa® gift cards, as well as food and parking tokens, as needed.

What are some general things you should know about research studies?

You are being asked to take part in a research study. To join the study is voluntary. You may choose not to participate, or you may withdraw your consent to be in the study, for any reason, without penalty.

Research studies are designed to obtain new knowledge. This new information may help people in the future. You may not receive any direct benefit from being in the research study. There also may be risks to being in research studies. Deciding not to be in the study or leaving the study before it is done will not affect your relationship with the researcher, your health care provider, or the University of North Carolina-Chapel Hill. If you are a patient with an illness, you do not have to be in the research study in order to receive health care.

Details about this study are discussed below. It is important that you understand this information so that you can make an informed choice about being in this research study.

You will be given a copy of this consent form. You should ask the researchers named above, or staff members who may assist them, any questions you have about this study at any time.

What is the purpose of this study?

The purpose of this study is to evaluate potential effects of female hormones on the concentration of a type of medication, called nucleotides. Nucleotides are one of several classes of antiretroviral (ARV) medications. Truvada® is an FDA approved ARV in this class, and is commonly prescribed to treat HIV infection, or to help prevent transmission of HIV to non-infected individuals. One of the populations with a higher risk of persons living with HIV, or becoming HIV infected, is transgender women (TGW). This is a population of individuals that are transitioning, or have already transitioned, from male to female. During this transition process, individuals may choose to start taking feminizing hormone therapy (FHT) to help achieve their desired goal. Estradiol, which is a naturally occurring hormone in persons born female, is given in high doses to transgender women during this transition. This hormone alters the concentration of the enzyme that breaks down the drug Truvada® in the body among different cell types, and therefore, transgender women on high doses of the hormone may have inappropriate medication concentrations.

In this study, we will be measuring concentrations of female hormones and antiretroviral (ARV) medications in different parts of the body, including blood, cells and tissues. When a patient takes a dose, or multiple doses of ARVs, we know how much of the medication will be seen in their blood and tissues, and in what time frame. What we do not know, is how that concentration will be affected in low estradiol versus high estradiol environments, or among different cell types, such as CD4 cells or epithelial cells which naturally occur in all human bodies. Premenopausal healthy female volunteers have naturally occurring estradiol in both low and high concentrations across the different phases of their regular menstrual cycle and allow the best opportunity to study this relationship.

You are being asked to be in the study because you are at least 18 years of age and meet our eligibility criteria. If you choose to be in this study, you will receive the study medication, Truvada®, for the 5 days prior to each sampling visits. Truvada® tablets are fixed-dose combination tablets containing emtricitabine (FTC) 200mg and tenofovir disoproxil fumarate (TDF) 300mg in each tablet. Dosing for 5 days will allow the medication to be at a steady concentration in your system before each sampling. We will schedule two sampling visits during your menstrual cycle: when the estradiol is lowest (approximately days 2-5) and when estradiol is highest (approximately days 12-15). At these two visits, we will collect blood from your arm to measure your hormone levels and medication concentration. Then we will obtain samples of rectal cells and tissues to measure medication concentrations, allowing us to look for trends. The information gained from these sampling visits can then be used to simulate what this trend would look like in TGW that are on FHT.

Are there any reasons you should not be in this study?

You should not be in this study if you:

- Are younger than 18 years of age or older than 49 years of age
- Are HIV infected, Hepatitis B or C, or have other sexually transmitted infections
- Donated blood recently
- Have had a rectal biopsy in the last 6 months
- Are pregnant, possibly pregnant, or lactating
- Irregular or absent menses
- Are not able to swallow pills
- Unwilling to use at least one form of effective contraception during the entire study period. Examples of acceptable forms of birth control, but not limited to, are:
    - Non-continuous systemic hormonal contraceptive (oral, depot, transdermal or implant)
    - Non-hormonal IUD placed at least 1 month prior to study enrollment
    - Bilateral tubal ligation (Sterilization)
    - Vasectomized male partners
    - Condom + Spermicide
    - Same sex partners
    - Abstinence of at least 3 months, with no plan to become sexually active during the study period
- Any condition, which, in the opinion of the investigator, is likely to interfere with follow-up or ability to take the study medication appropriately.

How many people will take part in this study?

There will be approximately 10 people in this research study. For any participant unable to complete study sampling, they will be withdrawn, and a new participant will be enrolled as a

replacement.

How long will your part in this study last?
If you choose to participate in this study, you will be involved for two to three months, depending on scheduling around your menstrual cycle.

What will happen if you take part in the study?
Screening Visit

The screening visit is designed to ensure that you should be in this study.

Procedures that will take place at the screening visit include:

- A review of the Informed Consent document will occur. We will give you a chance to have all of your questions answered, review the forms in private, and sign if you choose.
- Vital Signs (blood pressure and heart rate, respiratory rate, temperature, height, weight). We will update your medical and surgical history and obtain a list of all of your prescription and over-the-counter medications.
- Obtain a menstrual history, so that your visits can be scheduled around the specific days of your monthly cycle.
- A full physical examination will be performed.
- A urine sample will be collected to perform a urine drug test.
- Blood will be taken for safety labs (requires 12 mL of blood, or about 1 tablespoon). These labs will include a comprehensive metabolic panel (CMP), a complete blood count with differential (CBC), and coagulation tests (aPTT/PTT). These labs will make sure your electrolytes, liver and kidneys are healthy and normal, that your blood clots properly, and that you have normal cell counts in your blood.
- A rapid plasma reagin test (RPR) will be performed in order to screen for syphilis (requires about 6mL of blood, or about one teaspoon). If you test positive for this infection, you will not be able to join the study at this time and will be referred for treatment. You may be eligible to rescreen after treatment if we are still enrolling subjects. If you are diagnosed with syphilis, we are required to report this in accordance with North Carolina state law.
- You will be asked to take an HIV test, along with a test for Hepatitis B and Hepatitis C. We estimate about one tablespoon of blood will be collected (12mL).
- Blood will be drawn for a pregnancy test (4 mL or about 1 teaspoon).

The total amount of blood drawn at this visit will be up to 34 mL, or about 2 tablespoons of blood. As soon as we have all of your screening tests resulted, you will either be contacted over the phone or through email. If your test results are positive for HIV, hepatitis, or syphilis, you will be counseled and referred to your primary care physician or other local providers for follow-up.

If you pass the screening process, your study visits will be scheduled in advance, keeping your availability and schedule in mind as much as possible. You will be assigned a random participant identification number which is a combination of letters and numbers, to be used to be used to label all

your samples, so that no one other than the study team will ever be able to link your name to your samples.

Enrollment Visit:
A urine pregnancy test will be obtained at this visit. If this is negative and you otherwise still meet the eligibility criteria, you will be given the first dose of study drug. The size of the tablet is about the same size as a normal multivitamin. This will be administered and witnessed by study staff. You will be provided with 4 more daily doses to take home. We will schedule dosing times with you so that each dose is witnessed by study staff.

Dosing days
The four days following the enrollment visit, you will be asked to take a single oral dose of study medication at the times scheduled with the study staff. This will allow staff to witness each dose of medication and ensure your pills are taken in the appropriate time frame. These doses can either be witnessed in person or over video chat, depending on what is agreed upon at enrollment.

Sampling Visit 1 and 2:
You will be seen as an outpatient at the Clinical Translational Research Center (CTRC) at the University of North Carolina Chapel Hill. Your visits will be timed so that your samples are collected within a 24-hour window after your last dose of the study medication. Your visits will also be scheduled so that the first biopsy visit occurs on approximately Days 2-5 of your menstrual cycle, and the second biopsy visit occurs on approximately Days 12-15 of your menstrual cycle.

You will be asked to follow a low-fiber diet for the 3 days prior to each sampling visit. We will give you an information sheet at your screening visit with helpful tips about selecting foods with low-fiber.

Starting 12 hours before your scheduled visit times, you will be asked to not eat any solid food and follow a clear liquid diet in preparation for your rectal biopsy. Biopsies are also known as small pieces of tissue. A clear liquid diet allows water, fruit juices without pulp, clear sodas like Sprite, tea or coffee without milk/cream, clear broths like chicken broth, and plain gelatin. Any liquid that you can see through is generally acceptable but avoid drinks with red or purple dye. The following procedures will then be performed at the visit:

- Vital signs (weight, temperature, respiratory rate, blood pressure and pulse)
- Urine pregnancy test
- Physical exam
- Blood draw for research samples (a total of 17 mL or about 1 tablespoon)
    - A 3 mL EDTA tube of blood will be collected to measure the concentration of tenofovir/emtricitabine in your blood plasma.
    - An 8 mL CPT tube of blood will be used to measure the levels of active drug metabolites in your white blood cells.
    - A 6 mL SST tube of blood will be collected to measure the levels of sex hormones in your blood serum.
- You will then be taken into a private exam room and allowed to change into a patient gown. We will ask you to turn onto your left side and bring your knees up toward your chest. A Gastroenterologist will insert a tube into your rectum called an anoscope. This scope is about

as round as a quarter, and approximately 3-4 inches long. Through the anoscope, the team will take a sample of rectal cells by using a tool called a cytobrush, which is a small brush that looks like a mascara wand. The cytobrush will be inserted into your rectum and swirled around to obtain cells on the bristles. The team will then put a small forcep that will allow us to collect a total of 10 small biopsies. This procedure takes about ten minutes to complete, and you will feel some pressure in your rectum, similar to the feeling you have when you need to have a bowel movement. The total amount of tissue collected will be about the size of two grains of rice. Sedation is not necessary for this procedure. This is a common medical procedure that is usually painless and heals within 2-3 days. Some people experience slight discomfort and a feeling of being bloated. To improve the healing process, please do not insert anything into your rectum for several days.

- You will be asked about any discomfort or adverse events that you may be experiencing.
- After your rectal biopsy, you will be offered a meal and then will be discharged shortly afterward.
- A member of the study team will contact you the day after your sampling visits to make sure you are not experiencing any issues.

Follow-up Visit:

You will return to the CTRC for one last study visit within 14 days of your last sampling visit to check to make sure you are not having any problems as a result of the study procedures. You will have the following study procedures done during this visit:

- Vital signs will be measured (blood pressure, pulse, respiratory rate, temperature, and weight).
- A brief physical examination targeted at symptoms will be performed, if needed.
- A blood sample (about 9 mL or about 2 teaspoons) will be collected to check for safety labs. These labs will include a complete blood count (CBC), a comprehensive metabolic panel (CMP), and another HIV test. We will compare the results to the lab tests you had done at your screening visit, to make sure there have not been any changes.
- You will speak with the study coordinator to see if you are having any adverse events or if you had any difficulties with the study.

Unscheduled Visits

If you experience any adverse effects during the study, you may be asked, or need to return for additional, unscheduled visits. If an unscheduled visit occurs, we will do tests or exams needed to care for you appropriately.

What are the possible benefits from being in this study?

Research is designed to benefit society by gaining new knowledge. You will not benefit personally from being in this research study.

What are the possible risks or discomforts involved from being in this study?

Blood Draws

Risks with blood draws include pain, bleeding, bruising, infection, or swelling at the site of the needle sticks**,** as well as the possibility of dizziness or fainting during needle sticks. A finger stick is a bit uncomfortable and may cause some soreness and bruising. Very rarely, the

site can become infected. These risks will be minimized by using an aseptic (clean) technique as well as having experienced nursing and lab staff perform blood draws.

STI Screening/Reporting:

Disclosure of STI status may cause sadness or depression in volunteers. Partner notification of STI status may cause problems in their relationships with their sexual partners. Additionally, participants could misunderstand the current experimental status of the study medication and as a result increase their HIV risk behaviors while in the study. The following STIs are required by law to be reported to the NC State Department of Health if positive: HIV, Syphilis, gonorrhea, Chlamydia, Hepatitis B and C.

Anoscopy with rectal biopsy and cells:

This is a commonly practiced medical procedure and the procedures done in this trial will not involve any unusual risks of discomforts. The risks associated with these procedures include mild discomfort and the feeling of having a "bloated stomach." Anoscopic biopsies are painless and heal quickly (usually within three days). On extremely rare occasions, the procedure or biopsies may lead to pain, infection (sepsis), bleeding or perforation of the gastrointestinal tract. Perforation occurs approximately once out of every 100,000 procedures. If this extremely rare complication occurs, antibiotics and surgery to repair the perforation may be necessary.

Confidentiality:

Participation in clinical research includes the risks of loss of confidentiality and discomfort with personal nature of questions. Although the study site makes every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the study could become known to others, and that social harms may result.

Study Drug:

Truvada® tablets are fixed-dose combination tablets containing emtricitabine (FTC) 200mg and tenofovir disoproxil fumarate (TDF) 300mg in each table. There is experience in healthy volunteers taking Truvada®. No new or unexpected side effects are observed with the fixed-dose tablet than those observed when each drug is given separately. In our previous studies using the fixed-dose tablet in healthy volunteer research projects, there were no serious adverse advents attributed to study drug. About 5 out of 100 people with HIV taking Truvada® have these occasional side effects, which usually go away after stopping the drug: Upset stomach, dizziness, abdominal pain, rash or allergic reaction. In multiple dose studies involving uninfected HIV individuals, adverse reactions that were reported by more than 2% of Truvada® subjects and more frequently than by placebo subjects were headache, abdominal pain and weight decrease.

There may be uncommon or previously unknown risks. You should report any problems to the researcher.

If you choose not to be in the study, what other treatment options do you have?
You do not have to be in this research study in order to receive treatment.

What if we learn about new findings or information during the study?
You will be given any new information gained during the course of the study that might affect your willingness to continue your participation.

How will information about you be protected?
The investigators will protect your privacy in the following ways:

- All study records are kept in a locked drawer in a locked office under badge access.
- Only the study team will have access to any personally identifiable information about you.
- No samples or study report forms will contain your name. You will be assigned a study identification number that only contains your initials and a set of numbers. One study investigator will keep the file that connects this number to you on a secure internal computer network.
- All interviews will take place in a private examination room.
- Identifiable phone messages will not be left on your answering machine, and you will only be contacted by study staff in a manner that you agree upon.
- All samples will be destroyed within 6 months of the study being published.

No participants will be identified in any report or publication resulting from this study. Although every effort will be made to keep research records private, there may be times when federal or state law requires the disclosure of such records, including personal information. This is very unlikely, but if a disclosure is ever required, UNC-Chapel Hill will take any steps allowable by law to protect the privacy of personal information. In some cases, your information in this research study could be reviewed by representatives of the University, research sponsors, or government agencies (for example, the FDA) for purposes such as quality control or safety.

Under North Carolina law, confidentiality does not extend to certain communicable diseases, such as syphilis, gonorrhea, and chlamydia or other illnesses that put others at risk. If the researchers become aware that subjects have such an illness, they are required to report it to state authorities.

The study coordinator will keep the signed original consent form and a copy will be given to you. A Placeholder Form that does not have any mention of HIV medications or testing will be placed in your medical chart. This identifies you as a healthy volunteer participating in a research study and provides contact information for the study investigators.

To help us protect your privacy, the study team has obtained a Certificate of Confidentiality from the National Institutes of Health (NIH). With this certificate, the researchers cannot be forced to disclose any information that can be used to identify you, even by court subpoena, in any federal, state, local or civil, criminal, administrative, legislative or other proceedings. The researchers would use the certificate to resist any demands for information that would identify you, as described.

The Certificate cannot be used to resist a demand for information from personnel of the United States government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug

Administration (FDA).

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an employer, insurer, or other person receives your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

The Certificate does not limit the researchers from disclosing information that may include details about child abuse, homicidal or suicidal intent, or other information deemed appropriate. The researchers will not voluntarily release any information about you under this Certificate.

What will happen if you are injured by this research?

All research involves a chance that something bad might happen to you. If you are hurt, become sick, or develop a reaction from something that was done as part of this study, the researcher will help you get medical care, but the University of North Carolina at Chapel Hill has not set aside funds to pay you for any such injuries, illnesses or reactions, or for the related medical care. Any costs for medical expenses will be billed to you or your insurance company. You may be responsible for any co-payments and your insurance may not cover the costs of study related injuries. However, by signing this form, you do not give up any of your legal rights. You will be told where you can receive additional treatment for injuries if needed.

What if you want to stop before your part in the study is complete?

You can withdraw from this study at any time, without penalty. The investigators also have the right to stop your participation at any time. This could be because you have had an unexpected reaction, or have failed to follow instructions, or because the entire study has been stopped.

Will you receive anything for being in this study?

You will be compensated for your time and participation in this research study. If you complete all aspects, you will receive $565.00 in the form of a Visa® gift card.

You will only be paid for the portions of the study that you complete. If you do not complete the study, your payment will be pro-rated:

- You will be given $40.00 for the screening visit.
- You will be given $50.00 for taking the study drug ($5 per day)
- You will be given $225.00 for each sampling day.
- You will be given $25.00 for the follow-up visit

You will also receive parking tokens and snacks/meals as needed for the duration of your participation in this study.

Payment will be provided at the screening and follow-up visits only. We will do everything we can to try to have your Visa® gift card available on the date of your visit, but in extenuating circumstances; there could be an occasion where we do not have it available. In these cases, once your gift card is available, we can provide it at your next visit, or we can schedule a time to meet or even mail it based on your preferences.

We do not reimburse for travel and child care.

Will it cost you anything to be in this study?
It will not cost you anything to be in this study. If by chance you ever receive a bill for study activities, please notify the study team right away so this can be fixed.

What if you are a UNC student?
You may choose not to be in the study or to stop being in the study before it is over at any time. This will not affect your class standing or grades at UNC-Chapel Hill. You will not be offered or receive any special consideration if you take part in this research.

What if you are a UNC employee?
Taking part in this research is not a part of your University duties and refusing will not affect your job. You will not be offered or receive any special job-related consideration if you take part in this research.

Who is sponsoring this study?
This research is funded by the NIH National Institute of Allergy and Infectious Disease (NIAID). This means that the research team is being paid by the sponsor for doing the study. The researchers do not, however, have a direct financial interest with the sponsor or in the final results of the study.

What if you have questions about this study?
You have the right to ask, and have answered, any questions you may have about this research. If you have questions about the study (including payments), complaints, concerns, or if a research-related injury occurs, you should contact the researchers listed on the first page of this form.

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

What if you have questions about your rights as a research participant?
All research on human volunteers is reviewed by a committee that works to protect your rights and welfare. If you have questions or concerns about your rights as a research subject, or if you would like to obtain information or offer input, you may contact the Institutional Review Board at 919-966-3113 or by email to IRB_subjects@unc.edu.

IRB Study # 19-0333
Title of Study: Quantification of Estradiol's Impact on Nucleotides in Different Cellular Populations of the Lower GI Tract

Participant's Agreement:

I have read the information provided above. I have asked all the questions I have at this time. I voluntarily agree to participate in this research study.

_____ _____

Signature of Research Participant Date

_____

Printed Name of Research Participant

_____ _____

Signature of Research Team Member Obtaining Consent Date

_____

Printed Name of Research Team Member Obtaining Consent