**Mechanism of Aging Following Exposure to HIV Antiretroviral Drugs**

CIHR Team Grant in HIV Therapy and Aging

**carma-1: mitochondrial and telomerE studies in pregnancy**

**AND**

**Placental Mitochondrial Toxicity of HIV Therapy during Pregnancy:**

Clinical Tool Development and Determination of Outcome Variables for Clinical Trials

**AND**

**MEASURING MITOCHONDRIAL AGING, APPLICATION TO HIV INFECTION AND THERAPY, AND**

**CELLULAR AGING AND HIV COMORBIDITIES IN WOMEN AND CHILDREN**

carma-1-preg

*~ Informed Consent ~ Study Participants ~*

## Site Principal Investigator: Dr Deborah Money

Obstetrician & Gynecologist ~ Oak Tree Clinic

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Local CIHR Team Co-Investigators

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**Emergency contact 24 hrs/7 days/week ~ Evelyn Maan RN at 604 767 5044**

**INTRODUCTION**

Throughout this consent form, when we say “you” or “your”, we mean you or your child.

You are being invited to participate in the research study, named above, because you are taking, or will be taking, anti-HIV drugs in order to reduce transmission of HIV-infection to your baby. The study team, listed above, is trying to better understand the effects of the drugs that you are taking on the cells of your body. This team also hopes to better understand contributing factors for preterm birth in women living with HIV.

This consent form will provide you with information on the purpose of the study, how it may help you, any risks to you during pregnancy, and what is expected of you during the study. Once you understand the study, if you agree to take part in the study, you will be asked to sign this consent form. You will be given a copy of this form to keep for your records. This project is funded by a grant from the Canadian Institute of Health Research (CIHR).

**PURPOSE**

As you know, anti-HIV drugs reduce the chance of HIV transmission from mother to child from 25% to less than 1%. Although you are taking some of the best and safest available anti-HIV drugs to prevent virus transmission to your baby, it has been shown that some anti-HIV drugs, may have a toxic effect on the cells of the body. We suspect these effects may be responsible for changes in your blood tests resulting in abnormal liver function tests and changes in blood count (e.g. decreased hemoglobin levels). In the longer term, mitochondrial (energy producing part of body cells) toxicity (mitochondria are not working properly) has been associated with changes in blood lipids (fats in your blood) and thinning of the bones (osteoporosis) that is seen at a younger age in HIV positive persons. Some of the medications can have an effect on different body systems that leads to mitochondrial dysfunction. When the mitochondria become toxic the body can start to build up high levels of lactate (a byproduct of cellular function). Some doctors have expressed concerns that mitochondrial toxicity may be even more common in pregnant women than in other adults on these medications. We have not had good tests to assess this in usual practice. Also, when mitochondria are affected, they make molecules (small particles called free radicals) that can cause damage to DNA.

Research has shown that pregnant women living with HIV are twice as likely to have a preterm (early) birth compared to a pregnant woman without HIV. Because preterm birth is a complicated condition with several possible contributing factors, it is unclear what, if any, role is played by HIV and HIV medications as well as disruptions in the normal ‘healthy’ bacterial environment of the vagina.

The purpose of this study is to investigate the effect of taking anti-HIV drugs on women during pregnancy and on their infants, using two experimental laboratory tests. One is for mitochondrial DNA (mtDNA) and will test the level of function of the mitochondria and the other test will look at damage drugs may do to the length of DNA at the end of chromosomes. Additionally, we would like to better understand the relationship between preterm birth, HIV, HIV medications, the bacterial environment of the vagina and other risk factors for preterm birth.

**STUDY ELIGIBILITY/SCREENING**

In order to be eligible to participate, you must:

1. Be a pregnant woman of any age.
2. Have a confirmed diagnosis of HIV infection.
3. Be taking, or be going to take anti-HIV drugs during your pregnancy consisting of at least three medications from two specific classes of drugs – nucleoside reverse transcriptase inhibitor (NRTI) and either a protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI).
4. Have a detailed medical and medication history done.
5. Have blood drawn from a vein for routine laboratory monitoring.

You are **not eligible** to participate if you:

1. Are not HIV infected.
2. Are not pregnant.

**STUDY ENTRY**

If you decide to take part in this study, and you sign this consent form, the following outline describes the study schedule.

Schedule of Visits

All of the study visits will be linked to routine clinic visits for your pregnancy and the routine follow-up of your baby. You will have 3 study visits during pregnancy, generally between 16-20 weeks gestation (or prior to starting anti-HIV drugs if you were not taking them before becoming pregnant), and at 24-28 weeks and 32-36 weeks. Another study visit will be scheduled during the time of delivery as well as at 4-8 weeks after delivery. Blood samples will be drawn at these same visit times, cord blood will be collected at the time of delivery (if possible), a small piece of cord tissue and placenta will be collected and sampled as well (if available), You will be asked to self-collect a vaginal swab which will be used to assess the types of bacteria in your vagina at each visit. At delivery and if there are any signs of preterm birth, additional swabs will be gathered during a routine exam by your doctor. Shortly after your baby is born, two swabs will be collected from your baby’s earlobe (this does not hurt at all). One blood sample will be also collected from your child between 1 and 3 days of age, and a second blood sample will be collected along with routine bloodwork between 4 and 8 weeks of age.

At each of your study visits the following will be done:

* General health questions will be asked
* Some specific questions regarding factors known to be associated with preterm birth, such as hygiene, sex and domestic violence will be asked
* A mouth swab will be collected
* Two vaginal swabs will be self-collected
* You will have blood drawn from an arm vein for routine laboratory tests including HIV viral load, CD4 cell count, routine chemistry, routine hematology, and lactate. At the same time as your routine tests 20 ml (4 teaspoons) of blood will be drawn to test for mtDNA quantity, quality, mtRNA, DNA length, mitochondrial proteins, vitamins, hormone levels and inflammation biomarkers (elements in the blood that show inflammation is present). We will also test for a series of viral infections that are very common in humans and can be in the body for a long time with no symptoms if the immune system is healthy. We will test for viruses such as those that cause chickenpox (varicella zoster virus or VZV), herpes (herpes simplex virus or HSV), mononucleosis (Epstein Barr virus or EBV) as well as cytomegalovirus (CMV), and the virus formerly known as Hepatitis G (GB virus C or GBVC). This testing may include antibody (a protein in the blood made in response to a foreign substance or a toxin - like an infection) testing and viral DNA (molecules in the blood that carry the virus’ genetic information) and viral RNA (molecules that carry the virus’ instructions from the DNA into proteins) testing. Because we are using non-diagnostic methods of testing (for research use only), we will not be giving these results to you or your doctor.

Regarding your baby:

* Two earlobe swabs will be collected shortly after birth
* The amount of blood drawn will be approximately 5 drops, or ¼ teaspoon for the one scheduled with newborn bloodwork at about 2 days of life, and approximately 10 drops or about ½ teaspoon for the one at 4 to 8 weeks of age.

The study visits **do** require a small amount of additional time over a usual clinic appointment. About 20-25 minutes at the first study visit and then 15-20 minutes at each of the other visits will be needed for study related activities. All of the scheduled blood work is routine except for the mtDNA quantity, quality, mtRNA, DNA length, mitochondrial proteins, vitamins, hormone levels, inflammation biomarker and viral infection; tests; these tests require 20 ml or 4 teaspoons of blood which will be drawn at the same time as the routine blood tests. The results of all the blood tests, mouth swabs, vaginal swabs and earlobe swabs will be charted in the study paperwork. The blood, cord tissue and placenta samples will be stored for up to 25 years except in cases where the Optional Tissue Banking Consent has been signed and then tissues may be stored for an indefinite period.

Baseline information will be extracted from the clinical record and, if available, will include information such as: the ethnicity of both parents, maternal health history, current and prior pregnancy histories, maternal drug/toxic exposures, delivery and neonatal events.

RISKS AND/OR DISCOMFORTS

**Risks from Blood Drawing**

Blood drawing may cause some discomfort, bleeding or bruising where the needle enters the body. A small blood clot may form where the needle enters the body or there may be swelling in the area. Rarely, fainting or a local infection at the puncture site may occur.

You may find the domestic violence questions upsetting. If this happens for you, or if you screen as positive for domestic violence with our questions, we will connect you right away with the nursing staff at the clinic. The nurses will help you and further connect you with other Oak Tree Clinic team members such as a social worker, a counsellor, an outreach worker or a physician.

The vaginal self-swabbing might cause a small amount of discomfort; however, by self-swabbing you can control the speed and location of the sample collection.

The earlobe swab is collected from the outer ear and is not painful at all for the baby.

We will make every effort to protect your privacy and confidentiality during the study; however, it is possible that people may learn that you are participating in the study, and this may make you uncomfortable.

There are no other risks associated with participation in this study.

##### **BENEFITS**

We will not be able to use any of the results from this study to tell you whether or not you are at an increased risk of these side effects or for preterm birth and you will not receive any direct benefit from these results. However, knowledge gained from this study may, in the future, help other pregnant women who suffer from HIV/AIDS and their children.

##### **NEW FINDINGS**

You will be told of any new information learned during the course of the study that might cause you to change your mind about staying in the study. At the end of the study, you will be told when study results may be available and how to learn about them.

**VOLUNTARY PARTICIPATION**

Your participation in this research study is strictly voluntary. You may choose not to participate in this study or to withdraw from participation in the study at any time without providing any reasons for your decision. It will not influence the availability or quality of your present or future health care at this facility.

Please take time to read this information carefully and to discuss it with your family, friends, and doctor before you decide.

COSTS AND REIMBURSEMENT

You will be paid $20.00 for each study visit to help with the cost of transportation, parking or childcare. No receipts are required for this and you will be paid at the time of each visit.

Dr Money or any of the other doctors involved in the study will not receive any money for your participation in this study.

You should know that one of the investigators, Dr. Cote, is an inventor on a patent that has been filed by the University of British Columbia, on the mtDNA test used in this study. Therefore, she and UBC could one day receive a financial benefit from this research. You have the right to request more information about this financial benefit. You will not be eligible to receive any additional financial benefit from participating in this study even if the test should become commercialized.

IN CASE OF RESEARCH RELATED INJURIES

Signing this consent form in no way limits your legal rights against the sponsor, investigators, or anyone else, and you do not release the study doctors or participating institutions from their legal and professional responsibilities.

CONFIDENTIALITY

Your confidentiality will be respected.

You will be assigned a unique study number as a participant in this study. Only this number will be used on any research-related information collected about you during the course of this study, so that your identity [i.e. your name or any other information that could identify you] as a participant in this study will be kept confidential. Information that contains your identity will remain only with the Principal Investigator and/or designate. The list that matches your name to the unique study number that is used on your research-related information will not be removed or released without your consent unless required by law.

Your tissue samples will be stored in a deep-freezer at the Cote laboratory at the UBC Hospital, Department of Pathology. The freezer is located in a locked room which is further located in the Cote laboratory which is locked after hours and on weekends. The custodian of these samples is Dr. Helene Cote. Samples are batched and tests are run in batches for quality assurance. All tissue samples are identified with your study ID only and will be stored for up to 25 years, except in cases where the Optional Tissue Banking Consent has been signed and then tissues may be stored for an indefinite period.

No information or records that disclose your identity will be published without your consent, nor will any information or records that disclose your identity be removed or released without your consent unless required by law.

Your rights to privacy are legally protected by federal and provincial laws that require safeguards to insure that your privacy is respected and also give you the right of access to the information about you that has been provided to the sponsor and, if need be, an opportunity to correct any errors in this information. Further details about these laws are available on request to your study doctor.

**ADDITIONAL INFORMATION**

If you have any questions or need more information about this study at any time, please contact Dr Deborah Money at 604 875 3459, or the study coordinator, Evelyn Maan RN at 604 767 5044.

If you have any concerns or complaints about your rights as a research participant and/or your

experiences while participating in this study, contact the Research Subject Information Line in the University of British Columbia Office of Research Services by e-mail at RSIL@ors.ubc.ca or by phone at 604-822-8598 (Toll Free: 1-877-822-8598).

## PARTICIPANT CONSENT

* I have read and understood the participant information and consent form.
* I have had sufficient time to consider the information provided and to ask for advice if necessary.
* I have had the opportunity to ask questions and have had satisfactory responses to my questions.
* I understand that all of the information collected will be kept confidential and that the result will only be used for scientific objectives.
* I understand that my participation in this study is voluntary and that I am completely free to refuse to participate or to withdraw from this study at any time without changing in any way the quality of care that I receive.
* I understand that I am not waiving any of my legal rights as a result of signing this consent form.
* I understand that this study will provide no specific benefit to me.
* I have been told that I will receive a dated and signed copy of this form.

**I have read this form and I consent to participate in this study.**

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Printed name of and signature of **participant** Date

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Printed name and signature of person obtaining consent Date

This consent was done in the following language: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

The person signing below acted as an interpreter/translator for the participant, during the consent process.

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Printed name and signature of **person assisting in consent discussion** Date