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

 CIHR Team Grant in HIV Therapy and Aging

**carma-2: mitochondrial & telomere studies in a PROSPECTIVE COHORT**

and

**measuring mitochondrial aging,**

**application to hiv infection and therapy**

and

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

carma-2

*~ Informed Consent ~ Study Participants ~*

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Local CIHR Team Co-Investigators

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**INTRODUCTION**

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

You are being asked to participate in the research study, named above, because you are living with HIV, or your mother has HIV and she took anti-HIV drugs when she was pregnant with you. The study team, listed above, is trying to better understand the effects of the HIV virus and the drugs that you are taking, or have taken, or were exposed to, on the cells of your body. Also we are trying to better understand the bone and endocrine health (a system of glands in the body that secrete hormones which help control the chemical reactions in the body needed to maintain life) of people living with HIV.

This consent form will provide you with information on the options available and purpose of the study, how it may help you, any risks to you, 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 Institutes of Health Research (CIHR).

**PURPOSE**

Anti-HIV drugs are used to treat people living with HIV and are also used to reduce the chance of HIV transmission from mother to child from 25% to less than 1%. It has been shown that some anti-HIV drugs, as an unwanted side effect, may have a toxic effect on the cells of the body. Some of the drugs can have an effect on different body systems that leads to mitochondrial (energy-producing part of body cells) dysfunction. When the mitochondria are not working properly (mitochondrial toxicity) the body can start to build up high levels of lactate (a byproduct of cell function). Also, when mitochondria are affected, they make molecules (small particles called free radicals) that can cause damage to DNA.

As people living with HIV are living much longer, there is increasing evidence that HIV may cause ‘early aging’ with several possible complications including endocrine system dysfunction and disturbance of normal bone metabolism which can cause low bone mass and increased fractures.

The purpose of this study is to investigate the effect of taking anti-HIV drugs on adults and children with HIV and on anti-HIV medication-exposed children who themselves do not have HIV (born to women with HIV), using two experimental laboratory tests. One is for mitochondrial DNA (mtDNA) and will test the level of function of the mitochondria and the other will look at the possible damage drugs may do to the length of DNA at the end of chromosomes. Additionally, we would like to better understand the bone health of adult women living with HIV using specialized x-ray scans in combination with several other measures. One of the x-rays is called a DXA scan (dual energy x-ray absorptiometry or bone scan) and is used to look at the mass (size and structure) of your bones, one is called a pQCT scan (peripheral quantitative computed tomography) and is used to assess the strength of your bones and the other is called a high-resolution (shows finer detail) pQCT scan, which can only be used on your lower arm or leg but can show the inside of your bones with much better detail than the other scans. The pQCT and HRpQCT will be offered to women who participated in the Bone Health Study conducted at the Oak Tree Clinic from 2001-2003. Each of these tests together offer very low levels of radiation; less than a dental x-ray and approximately equal to the amount of radiation you would get from taking a plane from Vancouver to Calgary and back. Lastly, we would also like to understand the endocrine system health of both women and girls (age 12 and up) living with HIV by doing some extra blood tests and asking some detailed endocrine health questions.

**You should not have X-RAYS done if you are pregnant**

This study has up to FOUR possible options for you to consider:

1. OPTION A – Core/Basic Aging Study
2. OPTION B – Bone Health Study
3. OPTION C – Endocrine Health Study
4. OPTION D – Hepatitis C Treatment Study

**STUDY ELIGIBILITY/SCREENING FOR OPTION A – Core Aging Study**

In order to be eligible to participate, you must:

1. Be either:
* living with HIV (any age) and taking or have taken anti-HIV drugs
* not living with HIV (any age) and exposed to anti-HIV drugs during your mother’s/your pregnancy
1. Agree to have a medical examination and detailed medication history done
2. Agree to have blood drawn from a vein at the same time as routine laboratory monitoring, if living with HIV – OR - blood drawn from a vein/finger poke for the study if not living with HIV and exposed to anti-HIV drugs during your mother’s pregnancy
3. Agree to have a mouthswab taken

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

1. Not living with HIV or have not been exposed to anti-HIV drugs during your mother’s/your pregnancy

**STUDY ELIGIBILITY/SCREENING FOR OPTION B – Bone Health Study**

In order to be eligible to participate, you must:

1. Be an adult female living with HIV and age 19 or older
2. Agree to answer detailed questions about diet, exercise and any broken bones you may have had
3. Agree to have blood drawn from a vein for bone-specific lab tests at the same time as routine laboratory monitoring
4. Agree to have a bone density scan
5. Agree to have a pQCT scan and an HRpQCT scan if you were in the 2001-2003 Bone Health Study

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

1. Pregnant
2. Unable to communicate/read in English where the presence of an interpreter is not available

**STUDY ELIGIBILITY/SCREENING FOR OPTION C – Endocrine Health Study**

In order to be eligible to participate, you must:

1. Be a youth or adult female living with HIV, age 12 or older and having had your first menstrual period
2. Agree to answer detailed questions about your endocrine system health
3. Agree to have blood drawn from a vein for endocrine-specific lab tests at the same time as routine laboratory monitoring

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

1. Pregnant
2. Unable to communicate/read in English where the presence of an interpreter is not available

**STUDY ELIGIBILITY/SCREENING FOR OPTION D – Hepatitis C Treatment Study**

In order to be eligible to participate, you must:

1. Be an adult female living with HIV and Hepatitis C (HCV), age 19 or older
2. Be planning to start HCV treatment with interferon-free medications
3. Agree to have blood drawn from a vein at the same time as routine laboratory monitoring, once within 3 months of starting treatment and a second time at 3 months after treatment completion
4. Agree to have a mouthswab taken

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

1. Planning to start HCV treatment with medications that include interferon
2. Unable to communicate/read in English where the presence of an interpreter is not available

**STUDY ENTRY**

If you decide to take part in this study, and you sign this consent form, the following outline describes the study schedule. You can choose to do any or all of the following:

**Schedule of Visits for OPTION A – Core Aging Study**

If you are living with HIV:

You will have one study visit every 1 ½ to 2 years for up to 5 years.

Each study visit will be linked to a routine clinic visit for your regular health care. At the same time as your regular blood work, a study blood sample and a mouthswab will be collected.

At each of these visits the following will be done:

* General health questions will be asked
* A brief examination (as routine for your visit) will be conducted
* A mouthswab will be collected

Blood will be 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, blood will be drawn to test for mtDNA quantity, quality, mtRNA, DNA length, mitochondrial proteins, nutritionally relevant biomarkers (elements in the blood such as vitamin B12, vitamin D, folate and omega-3 fatty acids), inflammation biomarkers (elements in the blood that show inflammation is present) and if you are age 14 years and above, a few endocrine-health tests will also be done. 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 testing (a protein in the blood made in response to a foreign substance or a toxin - like an infection) 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. Twenty ml of blood will be collected for adults and children 6 years or older, 5-10 ml for young children 2 to 5 years old and 0.5-2 ml for infants less than 2 years.

The study visits **do** require a small amount of additional time over a usual clinic appointment. About 15-20 minutes at each visit 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, nutritionally relevant biomarker, inflammation biomarker and viral infection tests; these tests require 20 ml (4 teaspoons of blood) for adults and children (6 years or older), 5-10ml (1 -2 teaspoons) for young children (2 to 5 years) and 0.5-2 ml for infants (less than 2 years), which will be drawn at the same time as the routine blood tests. The results of all the blood tests and mouthswabs will be charted in the study paperwork.

Baseline information will be extracted from the clinical record and, if available, will include information such as: health history, anti-HIV drug history, other drugs, any toxic exposures, etc. If you participated in the Bone Health Study done at the Oak Tree Clinic between 2001-2003 and consent to participate in OPTION B (below), we will also access the data from that study to provide a 10-year reflection of your bone health.

If you have been exposed to anti-HIV drugs in your mother’s/your pregnancy but are not living with HIV:

You will have one study visit every 1 ½ to 2 years for up to 5 years.

Each study visit will not necessarily be linked to a routine clinic visit. A study blood sample and a mouthswab will be collected.

At each of these visits the following will be done:

* General health questions will be asked
* A mouthswab will be collected
* Blood will be drawn from a finger poke or an arm vein (20 ml of blood for adults and children 6 years or older, 5-10 ml for young children 2 to 5 years and 0.5-2 ml for infants less than 2 years).

The study visits **do** require some of your time. About 15-20 minutes will be needed for study related activities. Your blood will be tested for mtDNA quantity, quality, mtRNA, DNA length, mitochondrial proteins, nutritionally relevant biomarker, inflammation biomarker and viral infection tests; these tests require 20 ml or 4 teaspoons of blood for adults and children (6 years or older), 5-10 ml (1-2teaspoons) for young children (2 to 5 years) and 0.5-2 ml for infants (less than 2 years). The results of all the blood tests and mouthswabs will be charted in the study paperwork.

Baseline information will be extracted from the existing clinical record if available, and will include information such as: health history, anti-HIV drug exposure history, other drugs, any toxic exposures, etc.

**Schedule of Visits for OPTION B – Bone Health Study**

In addition to the visit details outlined for OPTION A above, you will have one study visit for the Bone Health Study. If we are successful with additional funding we may offer you a second visit approximately 1.5-3 years after the first. At each of these visits the following will be done:

* A few additional bone-health specific blood tests will be done such as calcium, phosphate, and vitamin D (about 15 ml or 3 teaspoons of blood will be needed for these tests)
* A detailed history of your diet, exercise and any broken bones will be asked
* One x-ray is called a DXA scan (dual energy x-ray absorptiometry or bone scan) and is used to look at the mass (size and structure) of your bones. You will have had this scan does as part of your routine clinical care and we will collect the results from your chart.
* If you were in the 2001-2003 Bone Health Study, two more x-rays will do done: one is called a pQCT scan (peripheral quantitative computed tomography) and is used to assess the strength of your bones and the other is called a high-resolution (shows finer detail) pQCT scan, which can only be used on your lower arm or leg but can show the inside of your bones with much better detail than the other scans. These 2 additional scans will be done at the Centre for Hip Health and Mobility (CHHM) at Laurel and 10th Avenue in Vancouver. Each of these x-rays offer very low levels of radiation; less than a dental x-ray and if you have **all three** of them the radiation you will be exposed to is approximately equal to the amount of radiation exposure you would get from taking a plane from Vancouver to Calgary and back.

**You should not have X-RAYS done if you are pregnant**

This study visit does require some of your time. Participating in OPTION B will require about 90-120 minutes (120 if having scans at the CHHM) for study related activities.

**Schedule of Visits for OPTION C – Endocrine Health Study**

In addition to the visit details outlined for OPTION A above, you will have one study visit for the Endocrine Health Study. If we are successful with additional funding we may offer you a second visit approximately 1.5-3 years after the first. At each of these visits the following will be done:

* A few additional endocrine-health specific blood tests will be done (about 15 ml or 3 teaspoons of blood will be needed for these tests). Whenever possible this blood sample will be collected in the morning in the fasting state (no food or drink after midnight the night before (water is ok))
* You will be sent home with a kit to collect saliva samples two times. Once is at 10pm and then at 8am. We will also provide you with a stamped and addressed envelope to return the samples to us.
* A detailed endocrine health history will be asked

The study visits do require some of your time. Participating in OPTION C will require about 20-30 minutes for study related activities.

Participating in all of the options listed above (A, B and C including the scans at the CHHM) would require approximately 4-5 hours of your time and approximately 35 ml or 7 teaspoons of your blood for research. All of the study procedures can be completed over the course of 2-3 routine clinical visits and 2 blood collections and within a total of 6 months.

**Schedule of Visits for OPTION D – Hepatitis C Treatment Study**

You will have two study visits – the first visit will be within 3 months of starting your HCV treatment and the second visit will be 3 months after you finish your HCV treatment.

Each study visit will be linked to a routine clinic visit for your regular health care. At the same time as your regular blood work, a study blood sample and a mouthswab will be collected.

At each of these visits the following will be done (the same as described for Option A):

* General health questions will be asked
* A brief examination (as routine for your visit) will be conducted
* A mouthswab will be collected

Blood will be drawn from an arm vein for the same laboratory tests and using the same blood volumes as described for Option A.

The study visits **do** require a small amount of additional time over a usual clinic appointment. About 15-20 minutes at each visit will be needed for study related activities. The results of all the blood tests and mouthswabs will be charted in the study paperwork.

Baseline information will be extracted from the clinical record and, if available, will include information such as: health history, anti-HIV drug history, other drugs, any toxic exposures, etc.

RISKS AND/OR DISCOMFORTS

**Risks from Blood Drawing for OPTIONS A, B, C and D**

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.

**Risks from the DXA and pQCT scans for OPTION B**

The DXA scan (done as part of routine care) and the pQCT scans are types of x-rays. All three x-rays will expose you to less radiation than a dental x-ray and approximately equal the amount of radiation you would be exposed to from taking a plane from Vancouver to Calgary and back (this is a natural form of radiation called ‘cosmic-radiation’, mainly from the sun, that is always around us and when you are in a plane flying high above the earth where the atmosphere is thinner, the radiation exposure is somewhat higher than when you are on the ground).

Participants will be exposed to:

* 7.4 μSv (microsievert, a measure of radiation) from the DXA scan
* 0.72 μSV from the pQCT scan
* <3 μSV from the HRpQCT scan

This equals a maximum total of 11.12 μSv of radiation exposure from all three scans.

**Radiation is not safe during pregnancy and you should not have these tests done if you are or think you may be pregnant.**

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 known risks associated with participation in this study.

**BENEFITS for OPTION A:** 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 and you will not receive any benefit from these results. However, knowledge gained from this study may, in the future, help others who are living with HIV.

**BENEFITS for OPTION B:** We will not be able to use any of the results from the PQCT and HRpQCT scans to tell you whether or not you are at an increased risk of bone problems because these tests are for research only and you will therefore not receive any benefit from these results. Your DXA however, done as part of routine care, and the bone-specific extra blood tests may be used by your doctor as part of your care and treatment (the extra blood tests are done in batches for research and there may be a delay of a few months before results are available). Knowledge gained from this study may, in the future, provide information about proper dosing of vitamin D and calcium for women living with HIV and may recommend changes to current guidelines for the screening and prevention of problems with bone health.

##### **BENEFITS for OPTION C:** The endocrine-specific extra blood tests may be used by your doctor as part of your care and treatment (the extra blood tests are done in batches for research and there may be a delay of a few months before results are available), yet you may not receive any benefit from this study. However, knowledge gained from this study may, in the future, help others who are living with HIV.

**BENEFITS for OPTION D:** You will not receive any benefit from participating in this parto of the study. However, knowledge gained from this study may, in the future, help others who are living with HIV and/or HCV.

##### **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 yourself 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 for OPTION A: 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.

COSTS AND REIMBURSEMENT for OPTION B: You will be paid $20 in addition to the $20 indicated above for Option A (Option A is built into both Options B and C), for a total of $40, if you are not doing the 2 extra scans at the CHHM; and $30 in addition to the $20 indicated for Option A, for a total of $50 if you are doing the 2 extra scans 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.

COSTS AND REIMBURSEMENT for OPTION C: You will be paid $10 in addition to the $20 indicated above for Option A, for a total of $30, (Option A is built into both Options B and C) 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 and 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.

COSTS AND REIMBURSEMENT for OPTION D: 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.

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 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).

Mechanism of Aging Following Exposure to HIV Antiretroviral Drugs,

CIHR Team Grant in HIV Therapy and Aging, CARMA-2: Mitochondrial & Telomere Studies in a Prospective Cohort, and Measuring Mitochondrial Aging, Application to HIV Infection and Therapy, and Cellular Aging and HIV Comorbidities in Women and Children

**PARENT/GUARDIAN and 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 or my child’s participation in this study is voluntary and that myself or my child are 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 myself or my child receive.
* I understand that I am not waiving any of my or my child’s legal rights as a result of signing this consent form.
* I understand that this study may provide no specific benefit to myself or my child.
* 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.**

I would like to participate in OPTION A – Core Aging Study

 OPTION B – Bone Health Study

OPTION C – Endocrine Health Study

OPTION D – Hepatitis C Treatment Study

OPTION A, B, C and D (if applicable)

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Printed name and signature of **participant** Date

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Printed name of **parent or legal guardian**, relationship to child, and signature Date

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Printed name of **second parent/legal guardian** (if applicable), relationship to child, signature, 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