Dr Hélène Côté, along with her colleagues, is unveiling the mechanisms behind age-related comorbidities in HIV+ women and children. Her work hopes to guide improved antiretroviral drug combinations for these vulnerable groups.

What is your research background?

I am a biochemist and molecular biologist by training. I initially did basic research on blood coagulation proteins and became involved in HIV research 15 years ago. I became interested in HIV drug toxicities and related comorbidities early on, particularly in vulnerable groups such as women and children.

Could you introduce the Children and Women: Anti-Retrovirals and Markers of Ageing (CARMA) research study?

The CARMA cohort study started in 2008 and will continue until 2018. It involves more than 1,000 participants, including HIV+ women (both pregnant and not), their children (both HIV+ and HIV-exposed uninfected), as well as a control group of HIV- women who share sociodemographic characteristics.

How do you plan to investigate the clinical and epidemiological manifestations of comorbidities in HIV+ women and children?

The CARMA cohort allows us to ask many questions related to HIV comorbidities. At each study visit, we can measure a number of parameters in our participants, including metabolic, hormonal, immunological or inflammatory, and relate these to HIV and combination antiretroviral treatment (cART) factors as well as to cellular ageing biomarkers that we measure in the laboratory. We can also determine how these various factors are related to a woman’s health, a child’s development or a pregnancy outcome.

Can you explain the relationship between HIV and the reproductive health of women?

It is still unclear how HIV affects the reproductive health of women but there is mounting evidence of early ovarian failure. Once again, it can be difficult to determine whether it is the virus itself or the anti-HIV treatment that is playing a role. But it has been suggested that HIV+ women may experience hormonal changes that affect their ageing and reproductive health. In addition, there is clear evidence that HIV+ women have an increased risk of premature delivery.

It remains unclear whether accelerated ageing is due to the HIV infection itself, to cART, or to both. How do you intend to address this issue?

The development of antiretroviral (ARV) prophylaxis now prevents perinatal mother-to-child HIV transmission, but how does exposure to ARV affect uninfected children?

The benefits of ARV prophylaxis clearly outweigh the risks to the infant but there are potential dangers, as with any prescription drug. Some of the effects, such as anaemia, appear transient but other subtle effects that may affect cellular ageing or the immune system could be longer term. Although we now have an arsenal of more than 20 ARVs, current recommendations suggest treating pregnant women with a few older drugs for which more clinical data are available. While these are effective and safe, they are not necessarily the least toxic. It is therefore important that we study which ARV combinations are best for pregnant HIV+ women and their children.

Could you comment on the importance of understanding how HIV and cART are associated with comorbidities for the long-term health of HIV+ individuals?

If we find that cART has a negative impact on the health of HIV+ people, then we need to figure out which drugs are less toxic, either through observational studies or clinical trials. Evidence-based treatment choices can be made if we have data guiding those choices. On the other hand, if we find that uncontrolled HIV is the culprit, we could consider adapting treatment guidelines to start therapy earlier or intensify it if needed.

Is there anyone to whom you would like to extend a special mention?

Women and children have often been understudied, and this is also true in HIV research. Of course, research on pregnancy and children presents special challenges. I would therefore like to mention our exceptional research staff and thank the hundreds of Canadian women and their children who are participating in our research. They are phenomenal partners and more than 90 per cent of all those approached to date have agreed to participate in our studies.
Customising cARTs

Through the Cellular Ageing and HIV Comorbidities in Women and Children project, researchers at the University of British Columbia are revealing the roles of HIV infection and combination antiretroviral treatment in cellular ageing and related comorbidities. The study promises to pave the way for better tailored HIV treatments.

Since the 1980s, HIV has claimed the lives of more than 25 million people worldwide. When HIV first emerged, contracting the lentivirus meant almost certain death as it rapidly led to AIDS. Fortunately, significant progress has been made in effective HIV treatments in recent years and infected individuals can now expect to live relatively long and healthy lives with the help of anti-HIV drugs.

When an individual is infected with a virus, the body attempts to defend itself by activating the immune system and inducing inflammation. This natural defence mechanism is usually a short-term phenomenon and subsides once the virus has been cleared. In the case of HIV, however, the virus lingers in the host and the defence mechanisms are kept on permanently, which can ultimately lead to cellular ageing. Some medications used to treat HIV may also contribute to accelerating the ageing process. As a result, people who are HIV+ are more likely than healthy individuals to experience age-associated comorbidities such as cardiovascular disease. According to the World Health Organization (WHO), more than 34 million people were living with HIV in 2011, hence improving our understanding of the links between HIV comorbidities and cellular ageing is emerging as a priority research area.

Premature diseases

Based at the University of British Columbia (UBC), Dr Hélène Côté is principal investigator of 'Cellular Ageing and HIV Comorbidities in Women and Children', a five-year project that has received funding of CAD $2.5 million from the Canadian Institutes of Health Research (CIHR). The project forms part of the long-term research cohort study, Children and women, Anti-Retrovirals and Markers of Aging (CARMA). Started in 2008, CARMA set out to uncover steps to measure markers of ageing, to understand how to slow down premature ageing and related diseases – or comorbidities – in people who are HIV+. "Our CARMA research team hypothesised that we could measure differences in biological markers of ageing between HIV+, HIV-exposed uninfected (HEU), and HIV unexposed uninfected (HUU) people of all ages," explains Côté.

In all people, whether infected with HIV or not, ageing leads to increased instances of certain illnesses and slower recovery times. However, there appears to be a tendency for HIV+ people to develop diseases that are more often seen in older individuals. These comorbidities include liver disease, heart disease, bone disease and diabetes, as well as neurocognitive decline. In women with HIV, changes in reproductive health usually associated with age have also been noted and researchers have started to suspect this might relate to the virus or the anti-HIV drugs being administered. By understanding the role the HIV virus itself plays in accelerated senescence and segregating this from the role played by therapies such as combination antiretroviral treatment (cART), Côté and her colleagues hope to be able to define safer, more effective treatments for those infected with HIV.

Vulnerable children

More than 3 million HIV+ women give birth globally each year. Fortunately, the discovery of antiretroviral (ARV) prophylaxis during pregnancy and infancy has greatly reduced perinatal mother-to-child HIV transmission. The UBC researchers are asking whether biological ageing related to exposure to HIV products or ARV treatment may also affect the HEU children born to HIV+ mothers.

In addition to increased risks of premature birth, HEU children also show increased morbidity and mortality compared to HUU children born to HIV-uninfected (HIV-) mothers. HEU children have more neonatal infections, which might indicate a long-lasting influence of exposure to HIV and/or ART on the immune systems of these children, despite the absence of HIV infection. With the number of ARV-exposed HEU children increasing every year, the importance of Côté and her colleagues' work becomes ever more apparent.

Cellular power plant

In her latest project, Côté wants to discover if it is the HIV virus itself, or the cART, or a combination of the two, that is behind cellular ageing in HIV+ women and children. However, the cART for participants in the CARMA cohort involves at least...
Fine-tuning the various ARVs used in treatments for HIV+ women and children will lower ARV drug toxicity and help to prevent damage to mitochondrial DNA, which in turn will reduce the likelihood of age-related comorbidities.

Three ARVs, which makes it difficult to discern the effect of each individual drug. Côté describes the method her team uses to overcome this hurdle: “By exposing cultured cells to various doses of each drug and to combinations of drugs, we can better isolate and identify their effects on cellular ageing processes such as mitochondrial ageing and telomere shortening”.

Mitochondria can be envisaged as the power plants for the production of cellular energy, while mitochondrial DNA can be viewed as the instruction manual defining the type of cellular energy produced. However, this process also produces oxidants, which can be considered a ‘pollutant’ by-product. While this is a natural process, research has shown that smoking tobacco, using illicit drugs, stress, poor diet and lack of exercise can all lead to similar cell pollution or ‘oxidative stress’ in the human body. The oxidants can have an adverse affect on mitochondrial DNA, leading to the malfunctioning of the mitochondria. This in turn affects the body’s ability to reproduce cells and fight off infection. “Damage to mitochondrial DNA is linked to ageing in general and we know from our past work that HIV and/or ARV drugs can harm mitochondrial DNA,” emphasises Côté.

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The steadily increasing life expectancy of HIV+ older age, HIV infection, smoking and infection with the hepatitis C virus could all significantly affect telomere maintenance and therefore cellular ageing.

Heathier Living

The introduction of new combination treatments such as cART has started to have a significant impact on the global HIV epidemic. The steadily increasing life expectancy of HIV+ individuals highlights the growing importance of the team’s work: fine-tuning the various ARVs used in treatments for HIV+ women and children will help lower ARV drug toxicity and help to prevent damage to mitochondrial DNA and telomeres, which in turn should reduce the likelihood of age-related comorbidities.

With the help of participants in the CARMA cohort, Côté and her team have demonstrated that people living with HIV do seem to have shorter telomeres, but also that people can have some control over the rate at which they age. In particular, research by many laboratories has shown that individuals can slow premature ageing by adhering to healthier lifestyle choices such as not smoking, maintaining a healthy weight, avoiding illicit drugs and sticking to a healthier diet, especially one rich in natural antioxidants.

Looking ahead, Côté would like to see more young researchers entering this field of study and continued funding for this critical area. She also emphasises the importance of a multidisciplinary approach: “In addition to basic scientists and HIV clinicians, our team also includes investigators who are new to HIV research but have extensive experience in endocrinology, neurodevelopment, bone research, maternal health etc. By working together, I believe we can achieve much more”.

**Key Collaborators**

Dr Deborah Money; Dr Neora Pick; Dr Melanie Murray; Dr Ariane Alimenti; Dr John Forbes; Dr Patricia Janssen; Dr Jerilynn Prior; Dr Heather Macdonald; Dr Joel Singer; Dr Isabelle Bouchoiran, University of British Columbia, Vancouver, Canada • Dr Hugo Soudeyns; Dr Fatima Kakkar; Dr Normand Lapointe; Dr Valerie Lamarre, Centre Hospitalier Universitaire Sainte-Justine, Montreal, Canada • Dr Ari Bitun; Dr Mary-Lou Smith; Dr Michael Silverman, University of Toronto, Canada • Dr Jason Brophy; Dr Cindy Samson, University of Ottawa, Canada • Dr Sandi Seigel, McMaster University, Hamilton, Canada • Ms Marcie Summer, Positive Women Network, Vancouver, Canada

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**Dr Hélène Côté** was born in Paris, France, and raised in Quebec City. She undertook her undergraduate studies at Laval University, her PhD in Biochemistry at UBC, followed by postdoctoral fellowships at UBC and the University of Washington in Seattle. During her training, Côté worked in a field unrelated to HIV, namely fundamental research in blood coagulation proteins. In 1998, she joined the BC Centre for Excellence in HIV/AIDS where she worked as a research associate for Dr Richard Harrigan, in collaboration with Dr Julio Montaner. In 2005, she accepted a faculty position at UBC and established her own research programme, focused on antiretroviral drug toxicity, especially in women and children. Côté’s current research aims at understanding how treatment of HIV-positive pregnant women with anti-HIV therapy during pregnancy may influence pregnancy outcomes such as premature delivery, or the long-term health of their children.

**Objectives**

• To understand how treatment of HIV-positive pregnant women with anti-HIV therapy during pregnancy may influence pregnancy outcomes such as premature delivery, or the long-term health of their children.

• To determine how HIV infection and anti-HIV therapy affect cellular ageing and comorbidities in women and children.

**Markers of Ageing**

The length of telomeres in blood cells called a leukocyte is a marker of ageing. “Telomeres are DNA repeats that cap and protect our chromosomes,” Côté states. “Their length influences how many times a cell can still divide before it stops or dies, and appears to be shortened faster by HIV and/or cART.”

Using established techniques to study the length of telomeres in blood samples from CARMA cohort participants, Côté investigated whether or not HIV infection might accelerate the shortening of telomeres. The results showed that while shorter leukocyte telomere length (TLT) was naturally associated with older age, HIV infection, smoking and infection with the hepatitis C virus could all significantly affect telomere maintenance and therefore cellular ageing.