


BMJ Open British Columbia CARMA-CHIWO Collaboration (BCC3): protocol for a community-collaborative cohort study examining healthy ageing with and for women living with HIV

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ABSTRACT

Introduction Women living with HIV (WLWH) experience accelerated ageing and an increased risk of age-associated diseases earlier in life, compared with women without HIV. This is likely due to a combination of viral factors, gender differences, hormonal imbalance and psychosocial and structural conditions. This interdisciplinary cohort study aims to understand how biological, clinical and sociostructural determinants of health interact to modulate healthy ageing in WLWH.

Methods and analysis The British Columbia Children and Women: AntiRetroviral therapy and Markers of Aging-Canadian HIV Women's Sexual and Reproductive Health Cohort Study (CARMA-CHIWO) Collaboration (BCC3) study will enrol WLWH (n=350) and sociodemographically matched HIV-negative women (n=350) living in British Columbia. A subset of BCC3 participants will be past participants of CARMA, n≥1000 women and children living with and without HIV, 2008–2018 and/or CHIWO, n=1422 WLWH, 2013–2018. Over two study visits, we will collect biological specimens for virus serologies, hormones and biological markers as well as administer a survey capturing demographic and sociostructural-behavioural factors. Sociodemographics, comorbidities, number and type of chronic/latent viral infections and hormonal irregularities will be compared between the two groups. Their association with biological markers and psychostructural and sociostructural factors will be investigated through multivariable regression and structural equation modelling. Retrospective longitudinal analyses will be conducted on data from past CARMA/CHIWO participants. As BCC3 aims to follow participants as they age, this protocol will focus on the first study visits.

Ethics and dissemination This study has been approved by the University of British Columbia Children's and Women's Research Ethics Board (H19-00896). Results will be shared in peer-reviewed journals, conferences and at community events as well as at www.hivhear.me and @HIV_HEAR_me. WLWH are involved in study design, survey

Strengths and limitations of this study

- This study takes an interdisciplinary 'cell-to-society' approach to understanding healthy ageing in women living with HIV by considering cellular markers of ageing, hormonal influences and psychosocial/structural factors and interactions between these factors.
- Women living with HIV and community partners representing key populations in British Columbia are meaningfully involved in the planning, knowledge generation and implementation of this research.
- As this study enrolls participants from two other well-established cohorts across Canada, we will have up to 10 years of longitudinal data for a subset of participants.
- This study is inclusive to cis-women and trans-women, but not cis-men. Sex-based analyses may be pursued, numbers permitting.
- As this study only considers women living in British Columbia, a setting with access to free HIV treatment, the degree to which findings can be generalised to other settings is to be determined.

creation, participant recruitment, data collection and knowledge translation. A Community Advisory Board will advise the research team throughout the study.

INTRODUCTION

Since the introduction of combination antiretroviral therapies (cART) in 1996, people living with HIV (PLWH) are less likely to die from AIDS-related illnesses and more likely to be affected by chronic diseases.^{1–3} PLWH are also living longer, highlighting the need to support healthy ageing, including

maintaining functional ability, access to health resources, autonomy, empowerment, social relationships, mental and spiritual well-being, freedom from stigma and sense of purpose.^{4 5} The prevalence and incidence of HIV in older Canadians have increased, with 45% of new diagnoses in 2018 occurring in people ≥ 50 years.⁶ In the western Canadian province of British Columbia (BC), there were 6556 PWLH ≥ 50 years in 2019, comprising the greatest proportion (61.8%) of total cases.⁷

Globally, there are ~18.8 million women living with HIV (WLWH), comprising $\geq 50\%$ of PLWH.⁸ In Canada, women represent 23% of the 63 110 PLWH and their proportion has steadily increased over the past 35 years, comprising ~30% of new infections in 2018.⁶ In BC, there were >11 000 PLWH in 2017, 18% of whom were women.⁹ Indigenous people comprised 4.9% of BC's population in 2017,¹⁰ yet Indigenous women constituted 33% of new infections among women.⁹

Sex and gender impact women's risk for acquiring HIV as well as morbidity and mortality risk following HIV acquisition.^{11–13} In Canada, WLWH have poorer health outcomes across the HIV care cascade compared with men, including lower rates of access to care and adherence to cART,^{14 15} more comorbidities^{16–18} and higher mortality rates.^{19 20} WLWH also experience significant psychological stressors, including gender-based violence, substance use, discrimination, the impacts of colonisation and isolation.^{21–23} These may further accelerate biological ageing and its health impacts. Even though WLWH live 5–10 years less than women without HIV and 7 years less than men living with HIV,¹⁹ there is a paucity of research on why this occurs.²⁴ Studies that primarily focus on men are not generalisable to women. Importantly, healthy ageing has been identified as a key research priority among WLWH. Understanding whether and how living with HIV uniquely affects ageing among women requires disentangling the effects of HIV alongside biomedical and sociostructural factors.

The British Columbia Children and Women: AntiRetroviral therapy and Markers of Aging-Canadian HIV Women's Sexual and Reproductive Health Cohort Study (CARMA-CHIWOS) Collaboration (BCC3) is an interdisciplinary partnership between two cohorts of WLWH. CARMA is a pan-Canadian cohort of >1000 WLWH and their children, with sociodemographically matched HIV-negative women. CARMA studied the effects of HIV and cART on biochemical markers of ageing. CHIWOS is a pan-Canadian community-based research study examining women-centred HIV care and the sexual, reproductive and mental health outcomes of 1422 WLWH in BC, Ontario and Quebec.²⁵ BCC3 brings the expertise of these cohorts to comprehensively evaluate biochemical, clinical and sociobehavioural-structural factors that interact to modulate ageing in WLWH. Here, we describe the aims, *cell-to-society* methodology,²⁶ and community-based framework of the cross-section portion of the BCC3 study. We hypothesise that chronic viral infections and/or hormone dysregulation will (a) impact markers of cellular ageing in

WLWH, and that (b) these effects will intersect with sociostructural factors to affect comorbid illness. Results will both guide clinical practice and inform policy, to improve health outcomes for WLWH throughout the life course.

Factors that modulate women's healthy ageing

Ageing is modulated by numerous biological and sociostructural processes. Understanding the role of these factors and their interactions is critical to our aims.

Chronic/latent viral infections

WLWH are at risk for coinfection with other chronic/latent viral infections, such as hepatitis C virus (HCV),^{27 28} hepatitis B virus (HBV),²⁹ herpes simplex virus,^{30 31} cytomegalovirus^{27 31} and human papillomavirus.^{32 33} Chronic/latent viral infections are those that persist for life or until treatment with curative therapies.³⁴ These infections often coexist due to similar routes of transmission and sociostructural conditions, such as injection drug use or sexual contact^{35 36} and can impact the immune system, leading to immune senescence and chronic inflammation.^{37–39} It is currently unknown how coinfections with chronic/latent viruses impact ageing in WLWH.

Cellular ageing

Chronic inflammation and oxidative stress contribute to cellular ageing and development of age-related comorbidities (ie, cardiovascular disease, type 2 diabetes etc).^{40–42} Key markers of ageing include immune cell subset distribution, mitochondrial DNA (mtDNA) mutations/heteroplasmy and leucocyte telomere length (LTL).^{43 44} Immune cell activation in response to chronic/latent viral infections shifts the balance between cell subsets, affecting the body's ability to fight pathogens or malignancies.^{45 46} Mitochondria are central to metabolism, energy production and hormone synthesis. mtDNA is particularly susceptible to damage and mutagenesis⁴⁴; as mutations accumulate, pathological mtDNA heteroplasmy (the presence of different mtDNA species) and accelerated ageing occur.⁴⁷ Among WLWH, high HIV plasma viral loads and tobacco smoking have been associated with changes in mtDNA levels, higher mtDNA mutations and heteroplasmy,⁴⁸ but very little is known about the effects of psychosocial stressors on mtDNA. HIV itself decreases mtDNA levels, while some antiretrovirals are implicated in mitochondrial toxicity and mtDNA damage.⁴⁹ cART can modulate mtDNA levels, especially at initiation and interruption, promoting clonal amplification of mutations. It remains unclear how cART interruptions, planned or not, may affect cellular ageing.

Telomeres are protective caps at the ends of DNA chromosomes.⁴⁴ Shorter LTL is a predictor of cellular ageing and age-related morbidities, such as cardiovascular disease.⁵⁰ CARMA demonstrated that PLWH have shorter telomeres than people without HIV,⁵¹ which may partially explain the accelerated/accelerated ageing phenotype seen in this population.⁵² Indeed, cells infected with chronic/latent viruses may lose telomeres at

higher rates.⁵³ Immune senescence occurs when immune cell telomeres shorten past a critical length. Senescent cells can no longer divide but are proinflammatory and contribute to disease. The proportion of senescent CD8 T lymphocytes (ie, CD8 +CD28 T cells) increases with chronic/latent viral infections⁵³; however, it is unknown if these changes relate to the development of comorbidities in WLWH and how they are influenced by psychosocial factors.

Hormonal and reproductive health

WLWH experience disproportionate rates of amenorrhea (ie, lack of menstruation), early menopause and other endocrine abnormalities.^{54–56} In the CHIWOS cohort, 56% of WLWH reported abnormal menstruation.⁵⁵ In the CARMA cohort, 58% of WLWH had at least one endocrine abnormality, which was associated with having a peak viral load $\geq 1\ 000\ 000$ copies/mL.⁵⁷ Ovarian steroids, including estradiol and progesterone, assist in maintaining bone,^{58–60} renal,^{61–63} hepatic,^{20 64 65} metabolic,⁶⁶ cognitive⁶⁷ and cardiovascular health.⁶⁸ Estradiol also counteracts cellular ageing by preserving mitochondrial function⁶⁹ and telomere length.⁷⁰ Opioid use,⁷¹ post-traumatic stress disorder (PTSD),⁷² smoking⁷³ and chronic stress can all contribute to endocrinopathies.^{74 75} Furthermore, the CHIWOS study demonstrated that WLWH are rarely asked about their reproductive health by care providers,⁷⁶ further exacerbating stigma and poor reproductive health outcomes. Although it has been established that WLWH have a high burden of age-related comorbidities, the role of hormones and social factors in ageing remains unclear.

Sexual health

Healthy ageing includes positive, stigma-free experiences of sex and relationships.^{77 78} Due to stigma, stress and gender inequity, negative outcomes in sexuality and reproduction are common, including unintended pregnancies and sexual dissatisfaction. Despite decisive evidence that there is no risk of sexual HIV transmission in those who maintain an undetectable viral load,⁷⁹ 49% of WLWH in the CHIWOS cohort were sexually inactive.⁸⁰ Understanding these barriers will enable providers to support women's sexual health as they age.

Intersecting determinants of health

Ageing is further modulated by sociostructural stressors, including adverse childhood events, discrimination, gender-based violence, housing and food insecurity, income inequality, substance use, smoking, lack of education, poor access to health services, impacts of COVID-19 and intergenerational impacts of colonisation.^{81–83} A gender-based approach is critical to understanding how these factors interact with cellular and hormonal factors to shape women's ageing experience. For instance, many WLWH have survived forced sex or childhood trauma, which has been associated with shorter LTL,⁸⁴ depression, post-traumatic stress and other mental health concerns

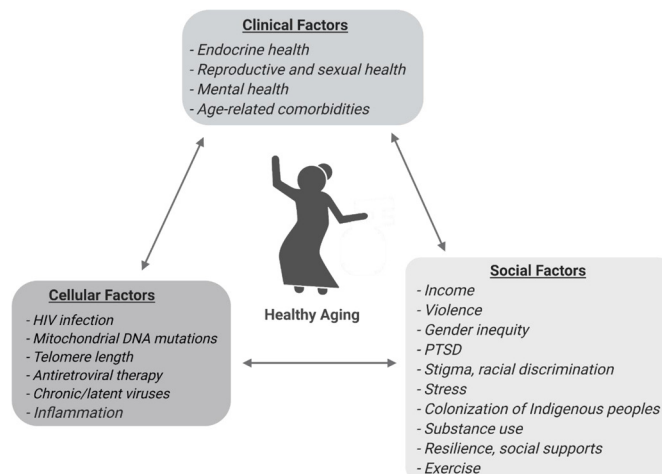


Figure 1 Interacting factors in women's healthy ageing. PTSD, post-traumatic stress disorder.

in adulthood.^{85 86} Mental health concerns may intersect with substance use, very low body fat, nutritional deficiencies and extreme stress—all risk factors for hypothalamic amenorrhea. Subsequent low oestrogen predisposes to numerous illnesses (ie, osteoporosis, cardiovascular disease) and mitochondrial and telomere decline. Substance use may result in coinfection with other chronic/latent viruses, exacerbating oxidative stress and cellular ageing. None of these factors exists in isolation (figure 1).

Study aims

We seek to address the following aims:

- ▶ To characterise and compare (1) comorbidities, (2) the burden of chronic/latent viral infections, (3) endocrine health/irregularities, (4) age of menopause, (5) psychosociostructural factors, (6) sexual and reproductive health and (7) markers of cellular ageing and inflammation in WLWH and HIV-negative women.
- ▶ To determine the modulating effects of treatment interruption, changes in cART regimens and HCV clearance on our outcome measures of interest.
- ▶ To investigate how the measures of interest (aim 1) interact to modulate women's experiences of healthy ageing.

Overarching aim

To nurture meaningful involvement of community in basic and clinical science research, integrate community-collaborative methods and build capacity in community-based research.

Study design

Patient and public involvement statement

Meaningful involvement of members of the HIV community is central to BCC3. Women of Indigenous, African, Caribbean and Black ancestry, transwomen, im/migrant and refugee women and women with histories of injection drug use and/or engagement in sex work are

Table 1 Description of historical CHIWOS (2013–2015) and CARMA (2008–2018) participant characteristics at baseline

	CHIWOS—British Columbia	CARMA	
	WLWH (N=356)	WLWH (N=275)	HIV-negative (N=291)
Sociodemographics			
Age (years), median (IQR)	44 (37–51)	40 (34–47)	43 (32–55)
Education, n (%)*			
Less than high school graduation	93 (26%)	93 (34%)	61 (21%)
High school graduation or greater	260 (73%)	162 (59%)	226 (78%)
Don't know/prefer not to answer†	3 (1%)	20 (7%)	3 (1%)
Income, n (%)‡			
<\$15,000/y (CARMA); <\$20,000/y (CHIWOS)	282 (79%)	135 (49%)	121 (42%)
≥\$15,000/y (CARMA); ≥40 000/y (CHIWOS)	53 (18%)	125 (45%)	168 (58%)
Don't know/prefer not to answer†	5 (3%)	15 (5%)	2 (<1%)
Sexual orientation, n (%)			
Heterosexual	294 (83%)		
LGBTQ2S§	61 (17%)		
Ethnicity, n (%)			
Indigenous—First Nations, Métis or Inuit	161 (45%)	77 (28%)	79 (27%)
African/Caribbean/Black	28 (8%)	44 (16%)	15 (5%)
White	139 (39%)	140 (51%)	162 (56%)
Other and mixed ethnicities¶	28 (8%)	31 (11%)	51 (18%)
Injection drug use history, n (%)			
Yes	225 (63%)	81 (29%)	33 (11%)
No/unknown	131 (37%)	194 (71%)	258 (89%)
Clinical characteristics			
Body mass index (kg/m ²), mean (SD)	27 (6.8)	27 (6.3)	26 (6.6)
Hepatitis C virus infection, n (%)	201 (56%)	114 (41%)	49 (17%)
Hepatitis B virus infection, n (%)	48 (13%)	17 (6%)	1 (<1%)
Ever/currently on cART, n (%)**	318 (89%)	275 (100%)	
Most recent HIV plasma viral load, n (%)††			
Undetectable‡‡	286 (82%)	169 (61%)	
Detectable§§	51 (14%)	104 (38%)	
Unknown	13 (4%)	2 (<1%)	
Most recent CD4 count, n (%)††			
<200 cells/mm ³	30 (9%)	31 (12%)	
200–500 cells/mm ³	114 (32%)	112 (41%)	
>500 cells/mm ³	166 (47%)	129 (47%)	
Unknown	42 (12%)	3 (<1%)	

Some (~130) participants may have been enrolled in both CARMA and CHIWOS.

*Income and education increments differ between CARMA and CHIWOS.

†'Don't know/prefer not to answer' for CHIWOS participants, 'Unknown' for CARMA participants.

‡Canadian dollars/year.

§LGBTQ2S, lesbian, gay, bisexual, transgender, queer or two-spirited.

¶Other ethnicities include Chinese/Filipino/Japanese/Korean/Latin American/Hispanic/Southeast Asian/Arab/West Asian/Multiple ethnicities.

**Ever on cART in CARMA, currently on cART in CHIWOS.

††HIV viral load and CD4 counts based on self-report in CHIWOS and clinical blood work data in CARMA.

‡‡HIV viral load <50 copies/mL among CHIWOS participants or <40 copies/mL among CARMA participants.

§§HIV viral load >50 copies/mL among CHIWOS participants or >40 copies/mL among CARMA participants.

CARMA, Children and Women: AntiRetroviral therapy and Markers of Aging; cART, combination antiretroviral therapy; CHIWOS, Canadian HIV Women's Sexual and Reproductive Health Cohort study; WLWH, women living with HIV.

Table 2 Overview of clinical and community visits

	Part 1—clinical visit	Part 2—community visit	Part 3—optional timed hormone visit
Location	Oak Tree Clinic, in person	Community site, in person or virtually	Remote testing or in person
Data collected	<ul style="list-style-type: none"> ▶ Height (cm) ▶ Weight (kg) ▶ Blood pressure (mm Hg) ▶ Waist circumference—Iliac crest (cm, NIH method)¹⁰⁹ and Iliac/rib midpoint (cm, WHO method)¹¹⁰ ▶ Clinical survey 	<ul style="list-style-type: none"> ▶ Community survey 	
Biospecimens collected	<ul style="list-style-type: none"> ▶ Venous blood ▶ Urine ▶ Hair ▶ Buccal swab ▶ Rectal swab (self-collected, optional) 		<ul style="list-style-type: none"> ▶ Venous blood for estradiol and progesterone measurements in women who are menstruating
Data collection leader	Research coordinator	Peer research associate	
Visit duration	1.0–2.0 hour	1.0–1.5 hour	

disproportionately affected by HIV in BC. Historically, biomedical research has excluded persons with living and lived experience, using extractive rather than collaborative approaches to data collection and utilisation. These practices are damaging; they preclude valuable insights into community voices and inadequately study the sociocultural lenses that shape health. Women, in particular, have been vastly under-represented in biomedical research, yielding consequences, whereby the health priorities of WLWH are undervalued and underaddressed.²⁴ Experiences from the CHIWOS study consistently demonstrate that coproduced knowledge by researchers and community is more accessible, relevant and inclusive of the diverse experiences of WLWH.^{87 88} To help address the structural inequities these populations face, we must change the structure of our research teams. Therefore, BCC3 uses a ‘research with and for’ rather than ‘research on’ approach, informed by the principles of Greater Involvement of PLWH/AIDS (GIPA),⁸⁹ Meaningful involvement of WLWH/AIDS (MIWA)^{90 91} and Ownership, Control, Access and Possession (OCAP). GIPA and MIWA refer to the rights of PLWH and WLWH to self-determination in knowledge generation, translation and implementation. OCAP refers to the rights of Indigenous communities ‘to own, control, access and possess information about their people’.⁹² Given the inherently colonial nature of research practices, histories of unethical research on Indigenous communities in BC and the over-representation of Indigenous WLWH, it is critical that we strive to do research in ‘a good way’.^{93 94} Based on these principles and the framework established in CHIWOS,^{95 96} our community-collaborative study is conducted by, with and for WLWH from study conceptualisation to knowledge translation (see online supplemental table S1).

To honour MIWA and GIPA principles, peer research associates (PRAs), who are essential members of our research team, have been hired, trained and supported, as pioneered by the CHIWOS study.⁹⁶ PRAs are:

self-identified women living with HIV (cis- and trans-inclusive) who share social identities (eg, Indigenous, racialized, sexual minority, and trans women) and lived experiences (eg, injection drug use, sex work, incarceration, childhood and adulthood violence experiences) with the community of women living with HIV...⁹⁶

Through an iterative process of consultation, review and implementation, PRAs lend their living and lived experiences, and community expertise, to this project at every step, from study design to data collection and knowledge translation. They completed multiphase experiential training in research ethics, research methods, survey administration, self-care and knowledge translation and studied the biomedical elements of this project. They are engaged in designing data collection instruments to ensure that questions are acceptable, safer, inclusive and relevant to community priorities. For example, community members identified the importance of studying chronic pain in WLWH. As this was not previously in our questionnaire, we worked with PRAs to identify relevant questions now included in the study. PRAs currently assist with recruitment, survey administration and provide leadership in knowledge translation to participants and the wider community. They continue to be invited to lead and coauthor conference presentations and peer-reviewed manuscripts. PRAs coauthored the present article and have presented at local research conferences as well as our inaugural Community Advisory Board (CAB) meeting. Engaging a team of both experienced and novice PRAs

Table 3 Clinical survey

Clinical survey section	Subsections
Sociodemographics	Sex, gender, sexual orientation, age, legal status in Canada, relationship status, ethnicity, education, employment, income, housing, Indigeneity, residential school history, early life experiences
Immune status (vaccine or natural infection)	History of vaccination for or natural infection of: Human Papilloma virus, Varicella Zoster virus, Hepatitis B virus
Non-HIV medications	Opiates, vitamins/supplements, prescribed and over-the-counter medications
HIV medical history	Diagnosis, nadir CD4, latest CD4 count, viral load, current/historical ARVs, current/historical ARV side effects, adherence (%)
Medical history	Diagnoses of and treatment for specific comorbid medical conditions (ie, respiratory, renal, cardiovascular, endocrinological, reproductive, hepatic, cancer). Family medical history Hearing loss, loss of vision, motor disabilities Mental health (ie, mood, anxiety, PTSD, addiction/substance use, neurocognitive, personality, psychotic, eating disorders and trauma-related disorders) Transgender health (ie, hormone therapy, transition surgery)
Reproductive health	Menstrual history, current menstrual status (ie, duration, frequency, associated symptoms), symptoms of perimenopause/menopause, treatments for symptoms of menopause, reproductive organ surgeries, pregnancy/parity/spontaneous or medical abortion, use of fertility services, contraceptive use and history
Substance use	Current/historical use of alcohol, tobacco, cannabis and illegal or legal drugs not used in the manner for which they were prescribed; discrimination due to drug use

Each item listed under 'subsections' is associated with one or more detailed questions.
ARVs, antiretrovirals; PTSD, post-traumatic stress disorder.

supports mentorship within the team, while expanding PRA capacity building, collaboration and career advancement. PRAs receive financial remuneration (\$25 CAD/hour) for their work and expertise and for attending team meetings.

Consistent with the recommendations of the Canadian Truth and Reconciliation Council for conducting research with Indigenous communities,^{97 98} the BCC3 team is honoured to include two Indigenous Elders with

Table 4 Community survey

Community survey sections	Subsections
Sociodemographics	Food security, childcare, incarceration history
Sleep and oral health	Sleep quality and quantity, sleep aids, oral health
Women's sexual health	Sexual history, experiences and history of consensual and non-consensual sex, relationship history, impacts of HIV on sexual health, experiences of exchanging sex for money/goods/services, experiences of sexual violence, sexual desire/pleasure/satisfaction
Stigma and discrimination	HIV-related stigma/discrimination, racism, sexism
Physical activity	Duration, frequency and intensity
Violence and abuse	Adulthood and childhood experiences of verbal, physical and sexual violence
Social support	Relationships with others (ie, visits, advice, love, affection, assistance)
Emotional and social well-being and health	Mental health diagnoses, thought patterns, peer support, quality of life, energy, perceived health, spiritual health, sense of purpose in life
Resilience	Life direction and goals, sense of accomplishment and determination
Impacts of COVID-19	Diagnoses; impacts on social life, healthcare, mental health

Some questions in this section are repeated from the clinical survey as an internal validation measure. For sensitive questions, participants will have the option of completing the section on their own or with a PRA.
PRA, peer research associate.

whom we have long-standing relationships. Elder Valerie Nicholson is Mi'kmaq and Haida, an award-winning researcher, and experienced PRA from the CHIWOS study who will lead our team in Indigenising research. Elder Sheila Nyman is Syilx Metis from the Lower Similkameen in the Okanagan Valley. She has extensive experience working with WLWH as both an elder and a clinical social worker and is available to support our research team and participants.

As a respected leader within African, Caribbean and Black communities, Patience Magagula, Executive Director of Afro-Canadian Positive Network of BC, is a knowledge user on this study to promote the meaningful inclusion and cultural safety of the diverse Black communities of BC. Magagula has worked with our study team to investigate barriers to recruiting members of African, Caribbean and Black communities in HIV research in BC.

In accordance with best-practices in community-based research, the BCC3 study has established a CAB—consisting of WLWH, Indigenous Elders, policymakers, HIV/AIDS Service Organisations representatives,

Table 5 Validated measures in the British Columbia CARMA-CHIWORDS Collaboration (BCC3) questionnaire

Survey item	Validated scale
Comorbidities	
Liver fibrosis	Fibrosis-4 score (cut-off >1.45) ¹¹¹ , aspartate aminotransferase/platelet ratio (cut-off ≥1.2) ¹¹²
Kidney fibrosis, failure	Kidney Failure Risk Equation (cut-off stage ≥3 renal disease) ¹¹³
Dyslipidaemia	Canadian Cardiovascular Society Guidelines ^{114 115} One or more of: (a) triglycerides ≥1.7 mmol/L; (b) high-density lipoprotein cholesterol (HDL-C) ≤1.3 mmol/L; (c) low density lipoprotein cholesterol (LDL-C) ≥5 mmol/L; (d) Framingham Risk Score 10%–19% and LDL-C ≥3.5 mmol/L or non-HDL-C ≥4.3 mmol/L And/or answers yes to the question 'do you have high cholesterol or lipids' and/or prescribed lipid medications
Depression	Center for Epidemiological Studies Depression Scale ¹¹⁶ (validated in people living with HIV). ¹¹⁷ Positive score is ≥10 on a scale of 0–30
Anxiety	Generalised Anxiety Disorder 7-item scale ¹¹⁸
Post-traumatic stress disorder (PTSD)	6-item PTSD checklist, cut-off ≥14 ¹¹⁹
Excess/dependent alcohol use	The 3-item Alcohol Use Disorder Identification Test ¹²⁰
Diagnoses such as liver disease, kidney disease, osteoporosis/osteopenia, diabetes, hypertension, dyslipidaemia, cardiovascular disease, peripheral vascular disease, cognitive impairment and depression	Canadian Longitudinal Study on Aging (<i>survey and data publicly available online</i>) ¹²¹ will be used to compare to the general Canadian population.
Sexual and reproductive health	
Menopausal and perimenopausal symptoms	Adapted from Women's Health Interagency HIV Study Menopause Symptoms Questionnaire; ¹²² Study of Women's Health Across the Nation Questionnaire ¹²³ and the North American Menopause Society Menopause Health Questionnaire ¹²⁴
Sexual functioning	Adapted from the Brief Index of Sexual Functioning for Women scale, ¹²⁵
Sexual satisfaction	Adapted from the Sexual Satisfaction Scale for Women ¹²⁶
Sexual power	Sexual Relationship Power Scale ¹²⁷

Continued

Table 5 Continued

Survey item	Validated scale
Physical, verbal, control and/or sexual violence	Canadian HIV Women's Sexual and Reproductive Health Cohort study (CHIWORDS) Questionnaire ¹²⁸
Socio-behavioural–structural determinants of health	
HIV-related stigma	12-item HIV Stigma Scale-Short Form, ^{129 130} CHIWORDS Enacted HIV Stigma Scale ¹³¹
Gender inequity, racism, sexism	9-item Everyday Discrimination Scale ¹³²
Drug use discrimination	Drug Use Discrimination Scale ¹³³
Social supports	19-item Medical Outcome Study Social Support Score ¹³⁴
Resilience	10-item Resiliency Scale ^{135 136}
Health-related quality of life	12-item Short Form Survey/Short Form Measure of General Health ¹³⁷
Food security	Household Food Security Survey Module ¹³⁸
Spiritual health	Spiritual Health Scale ¹³⁹
Sense of purpose in life	Oregon Brief Purpose Measure ¹⁴⁰
Impacts of COVID-19	Canadian Longitudinal Study on Aging, WHO Survey Tool ¹⁴¹

This is not an exhaustive list of all questions in the BCC3 study, but rather those that have come from previously used or validated questionnaires. In some instances, modified/shortened versions of the survey tools are used. The BCC3 survey can be found in it's entirely on our website at <https://hivhearmeca/resources/>.

clinicians, researchers and other stakeholders. The CAB, cochaired by one academic and one community representative, meets annually to exchange knowledge, provides insight and ensures the relevance of our study to the realities of the community. Members of the CAB with specific expertise in subsections of this study (ie, chronic pain, sexual health etc) are invited to join Community Advisory Working groups that will meet more frequently.

Study team

We are a diverse team of basic scientists, infectious disease physicians, epidemiologists, social scientists, trainees and community members, including four PRAs, two Indigenous Elders and several organisational partners. Our team also includes a research nurse and research coordinators from the basic, clinical and social sciences. Trainees include undergraduate, graduate, medical students and fellows.

Participant recruitment

We aim to enrol n=350 WLWH and n=350 sociodemographically matched HIV-negative women. Among participants, 400/700 will be premenopausal women, while 300/700 will be menopausal. We will preferentially recruit from the BC samples of CHIWORDS (n=356 WLWH)

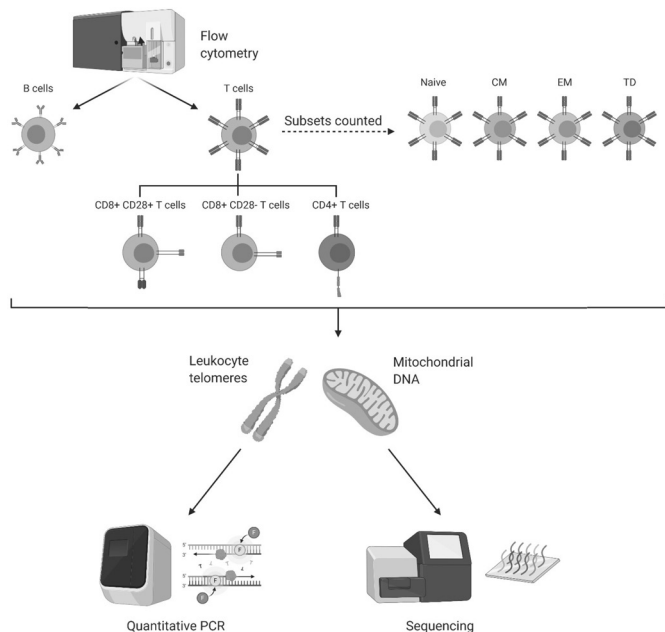


Figure 2 Cell sorting and analysis. Cells will be sorted by flow cytometry into B and T cells. Number of T cells in each subset will be counted (naïve, CM, EM, TD). T cells will be further sorted into CD8+CD28+ (proliferating), CD8+CD28- (senescent) and CD4+ populations. DNA will be extracted from sorted cells and used for LTL and mtDNA content determination by monochrome multiplex qPCR and next-generation sequencing, respectively. CM, central memory; EM, effector memory; LTL, leucocyte telomere length; TD, terminally differentiated.

and CARMA (n=275 WLWH and n=291 HIV-negative controls) (table 1). CHIWOS and CARMA have an overlap of n~130 BC women and >95% of participants have given permission to be contacted for future studies. We will recruit new participants using posters at community centres and clinics, social media outreach and via

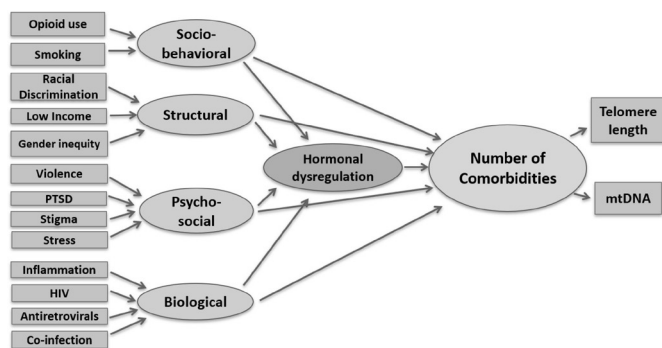


Figure 3 Latent variable structural model. Structural equation modelling will test direct effects, via socio-behavioural (eg, smoking, opioid use), structural (eg, gender inequity, discrimination), psychosocial (eg, violence, PTSD, stigma), and viral (HIV, cART, co-infections) factors and indirect effects via hormonal disturbances, on the latent variables of number of comorbidities, LTL and mtDNA. cART, combination antiretroviral therapy; LTL, leucocyte telomere length; mtDNA, mitochondrial DNA; PTSD, post-traumatic stress disorder.

community networks, including through the CAB. This will ensure that HIV-negative participants reflect the sociodemographic profile of HIV-positive participants.

Inclusion criteria

Cis-gender and trans-gender women living in BC ≥ 16 years of age, who can provide written, informed consent in English and attend in-person study visits will be included in this study. Given the collection of biospecimens for hormonal analysis, women who are currently pregnant/breast feeding will be invited to enrol at least 3 months after pregnancy/cessation of breast feeding.

Data collection

Eligible participants are asked to provide written, informed consent prior to enrolment. Survey data are collected and stored using the secure Research Electronic Data Capture web service.^{99 100} Biological specimens are processed at the BC Women's Hospital Research Laboratory and then stored in the Côté laboratory. Data are collected during a two-part study visit, one in clinic and one in community (table 2). For in-person visits, we strictly adhere to current COVID-19 safety measures. Whenever possible, community visits are conducted remotely.

The in-clinic portion of the visit takes place first, where research assistants and/or coordinators collect anthropometric data, obtain biological specimens and administer the first series of survey questions (table 3). For menstruating women who are not at the optimum time of their cycle for hormone analyses, additional visit(s) are scheduled. The community visit occurs within 1 month of the clinic visit and includes a detailed questionnaire, based on validated/published tools (tables 4 and 5).

Sample processing

Cellular outcomes

Clinical laboratory testing of blood and urine samples is completed by BC Women's Hospital Research Laboratory, including complete blood count, haemoglobin, albumin, creatinine, haemoglobin A1c, aspartate aminotransferase, alanine aminotransferase and non-fasting lipids. Serum samples are assayed by the BC Centre for Disease Control for the presence of HCV (Ab+), HBV (Ag+), herpes simplex virus-1 and 2 (Ab+) infections. We perform qualitative HCV RNA analysis and serology for cytomegalovirus and Epstein-Barr virus IgG. Varicella zoster virus status is determined by history. We also perform hair, saliva and real-time hormonal analyses for estradiol, progesterone, prolactin, luteinising hormone (LH), androstenedione and dehydroepiandrosterone sulfate.

Fluorescence-activated cell sorting on a flow cytometer is used to separate and collect CD8 T cells, CD4 T cells and B cells (figure 2). Total DNA is extracted and mtDNA content is measured by monochrome multiplex qPCR.¹⁰¹ mtDNA mutations and degree of heteroplasmy are measured by next-generation sequencing using a previously described method.⁴⁸ LTL is measured in CD8 + CD28+ and CD28- cells using a monochrome multiplex

qPCR assay, as we described previously.¹⁰² We will investigate the impact of cART interruptions on these markers of cellular ageing based on participant self-reported cART adherence and HIV plasma viral load. Data from CHIWOS indicate that self-reported cART data have high reliability in WLWH.¹⁰³

We use a custom Mesoscale V-Plex panel to assess chronic inflammation, including cytokines (ie, interleukin-6) and C reactive protein.¹⁰⁴ We also calculate the C reactive protein/albumin ratio.

We have up to 10 years of data/biospecimens for CARMA participants enrolled in BCC3 to investigate the association between rate of decline in LTL and/or mtDNA content, the development of comorbidities and age at menopause. For those who have undergone curative therapy for HCV, we assess the impact of clearance on markers of cellular ageing. Finally, we explore the longitudinal effects of switching to an integrase strand transfer inhibitor-based cART regime, as we have preliminary data suggesting that these medications may affect mitochondrial health (*unpublished*). These analyses are based on the first and last blood samples for BCC3/CARMA participants.

Endocrinology outcomes

Participants will be categorised as having either ‘normal’ or ‘ever abnormal’ ovarian function. ‘Abnormal’ will be defined as ever having experienced primary ovarian insufficiency, menopause at <45 years or amenorrhea for >1 consecutive year not related to pregnancy, lactation, birth control, oophorectomy or hysterectomy. Menopause will be defined as no menses for ≥ 1 year and follicle-stimulating hormone ≥ 25 IU/mL.¹⁰⁵ In women with amenorrhea ≥ 3 months, menopausal status and cause of amenorrhea were determined by doing a urine pregnancy test and measuring estradiol, progesterone, prolactin, LH, androstenedione and dehydroepiandrosterone sulfate. Untimed follicle-stimulating hormone, testosterone and thyroid-stimulating hormone are measured in plasma for all participants. Free progesterone is assessed if thyroid-stimulating hormone is abnormal. Average cortisol over the previous month is assayed from the 2.5 cm of hair closest to the scalp (~20 hairs).¹⁰⁶ For menstruating women not using hormonal contraceptives, we measure early follicular phase estradiol (cycle days 2–5) and mid-luteal phase progesterone (days 21–23 or 7 days before next flow). For postmenopausal women, we measure untimed estrone rather than estradiol.

Data analysis

Descriptive statistics will be used to summarise all measures. The Mann-Whitney U-test and χ^2 or Fisher’s exact test will be used to compare data by HIV status.

We will compare the total number of viruses between groups (WLWH vs HIV-negative women) by unpaired t-test or Mann-Whitney tests and the Kruskal-Wallis test when multiple viruses are present. MtDNA mutations will be compared between groups by the unpaired t-test or Mann-Whitney test. Fisher’s exact test will be used

to compare the presence of heteroplasmy (yes/no). Differences in the measures of cellular ageing (mtDNA and LTL) in immune cell subsets and comorbidities will be compared between groups according to number of viruses (\pm HIV) by Kruskal-Wallis or one-way analysis of variance tests, correcting for multiple comparisons. Associations between number of chronic/latent viruses and mtDNA mutations will be explored using Spearman’s or Pearson’s correlations. We will examine independent associations between these measures using multivariable linear regression and/or logistic regression, considering demographic, psychosocial and behavioural covariates/confounders. Among WLWH, associations between plasma viral load and cART regimen will be examined by Kruskal-Wallis test, with Dunn’s adjustment.

For longitudinal analyses, within-individual changes in markers of cellular ageing will be assessed using a paired t-test or a Wilcoxon test. Survival analyses will be used to examine the rate of LTL or mtDNA decline and age at menopause. This analysis will be restricted to women ≥ 35 years, using this age as time 0. Estimated age at menopause will be the outcome and data will be censored at last age if menopause has not been reached, regressing on rate of decline in LTL and mtDNA.

Associations between history of prolonged secondary amenorrhea (outcome variable) and HIV status will be examined using multivariable logistic regression, adjusting for potential founders (ie, age, smoking, opioid use). Multiple linear (estrone, estradiol, testosterone, cortisol) and logistic regression (progesterone; dichotomised at 3 ng/mL as the accepted threshold to confirm if a cycle is ovulatory)¹⁰⁷ will estimate the association between hormone levels (outcome variable) and HIV status (predictor), adjusting for confounders.

Poisson regression will be used to investigate the relationship between history of prolonged secondary amenorrhea (yes/no; dependent variable) and number of comorbidities (0–10). We will use linear regression to determine associations between history of prolonged secondary amenorrhea and LTL/mtDNA. Models will be adjusted for covariates/confounders. We will use Poisson regression to examine the association of estradiol levels and number of comorbidities. Multivariable linear regression will be used to assess the association between each hormone of interest (ie, levels of estrone, estradiol, progesterone, testosterone, cortisol) and cellular ageing.

Unadjusted and adjusted linear regression will estimate the regression coefficients of number of comorbidities (primary outcome) and LTL/mtDNA content (secondary outcome). Any history of prolonged amenorrhea will be the proposed mediator.

The impact of sociostructural behaviour determinants on number of comorbidities and cellular ageing will be explored using structural equation modelling ([figure 3](#)). The model will be assessed for goodness of fit using the χ^2 test (acceptable fit= $p < 0.05$), Root mean square error of approximation (acceptable fit=score < 0.05 , 90% CI of 0.02

to 0.08) and Comparative Fit Index (acceptable fit=score >0.9).¹⁰⁸

Analyses will be performed using GraphPad Prism, SPSS v25, R, SAS v9.4 and Mplus.

With a sample of 350 per group, we will have sufficient power for all proposed analyses (see online supplemental file 1).

Ethics and dissemination

This study has been approved by the UBC Children's and Women's Hospital Research Ethics Board (H19-00896).

In collaboration with community partners, PRAs and knowledge users, we will share research findings through peer-reviewed publications, conference presentations, Sharing Circles, community forums, scientific cafes and healthcare provider events. To facilitate knowledge exchange, we will create an atmosphere for consultation and partnership. Elders will guide us in Indigenising the process of knowledge translation. Results, protocols and procedural documents are found on our website <https://hivhearmeca/resources/>. We also share study updates with WLWH, academics and our many community partners (online supplemental table S2) on Twitter @HIV_HEAR_me. Biospecimens and questionnaire data can be accessed according to our data sharing plan (online supplemental file 1).

We present here the protocol for an innovative approach to *cell-to-society*, community-based research for healthy ageing among WLWH. Our diverse research team is built from a mutual desire to improve the lives and health outcomes of WLWH. Central to this partnership is a shared understanding of the value of each team member and their respective field of expertise, be it clinical, bench science, social sciences or living and lived experience as well as the diversity of our participants. This research is powerful in its ability to build capacity and empower all team members, including PRAs. The results of this study will be used to guide clinical practice, public health policy and activism, improving the ageing experience, health outcomes and longevity of WLWH and all women across BC and beyond.

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