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Antiretroviral therapy treatment interruption among Indigenous Peoples living with HIV in Canada – a Building Bridges study guided by community

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ABSTRACT

Introduction: Building Bridges was a collaboration between Indigenous and allied stakeholders and the Canadian Observational Cohort (CANOC) collaboration. Working with community and CANOC investigators, a review of HIV treatment interruptions was identified as a proxy for health care engagement. Accordingly, this endpoint of interest was compared between Indigenous and non-Indigenous CANOC participants.

Methods: CANOC participants are antiretroviral treatment-naïve individuals who began combination antiretroviral therapy (cART) on or after January 1, 2000. Cox proportional hazard models, a tool to mathematically review information, were used to estimate the effect of ethnicity on time to cART interruption. Treatment interruptions were defined as interruptions of all antiretroviral medications for at least 90 consecutive days. Multiple imputation is the statistical technique that was used to input values for missing ethnicity. Models were adjusted for age, gender, injection drug use, calendar year of cART initiation and province.

Results: This analysis included 7080 participants, including 443 Indigenous participants. At five years after beginning cART, 52% of Indigenous participants, 24% of Caucasian participants, 23% of African, Caribbean or Black (ACB) participants, 19% of participants of other ethnicity and 26% of participants of unknown ethnicity had at least one treatment interruption ($p<0.001$). Indigenous ethnicity, residing in British Columbia, injection drug use, female gender and initiating therapy with an unboosted protease inhibitor-based regimen remained independent

predictors of increased risk of treatment interruption. Treatment interruptions were less likely in later calendar years.[1]

Discussion: Stories of living experience from Indigenous women living with HIV in BC offer more context to frame the results. The context of Indigenous people's lives is important to consider when reviewing the results of statistical analyses both to interpret the findings and to identify meaningful responses. The strengths-based design of this study facilitated the identification of a new mechanism to address poorer health outcomes found in prior studies.

Conclusion: Among CANOC participants initiating cART, Indigenous participants were found to have a shorter time to treatment interruption. Efforts to provide culturally safe care and facilitate continuity of care may be helpful in reducing treatment interruptions among Indigenous peoples living with HIV.

INTRODUCTION

This research was conducted in the unceded territory of the Coast Salish peoples including the Musqueam, Squamish and T'seil-watuth nations. Let us share knowledge by beginning with a story from a study participant and research team member.

This is the story of Flo, a Métis woman and proud mother of seven. "I started antiretrovirals about a year after I was diagnosed so that I could prevent perinatal transmission of HIV. After my daughter was born, I stopped taking my medications. I then spent six years avoiding my HIV specialist, but in that time, I got my seven children back from foster care. After a life-threatening episode of pneumonia and countless experiences of stigma and discrimination from healthcare providers I relapsed back into my addiction. Eventually after recurrent infections and a CD4 count of 60 cells/mm^3, I found myself back on antiretrovirals. For several years, I struggled with my addiction and was on and off of my medications. When I was sober, I was taking my pills, and when I was using, I would have treatment interruptions. I would hide my pills because I was embarrassed and I didn't want my family or the child minders to see them. When they were hidden, I would forget about them. When I was depressed, my addiction would relapse and a treatment interruption would follow. When I had side effects, I would stop my treatment. Four years ago, I ended up in a shelter. When I was there, I had my medications delivered and the staff would give them to me and wouldn't leave until I swallowed them. I got past the initial side effects, got into recovery, got some pill boxes to help me manage my medications, got undetectable and haven't looked back."

[1] Indigenous ethnicity (adjusted hazard ratio [aHR]=1.46, 95% CI:1.25-1.71), ACB ethnicity, (aHR=1.34, 95% CI:1.11-1.62) residing in British Columbia (aHR=1.85, 95%CI:1.62-2.12), injection drug use (aHR=2.46, 95% CI:2.18-2.78), female gender (aHR=1.37, 95% CI:1.21-1.54) and initiating therapy with an unboosted protease inhibitor-based regimen (aHR=1.41, 95%CI:1.19-1.67) remained independent predictors of increased risk of treatment interruption. Treatment interruptions were less likely in later calendar years (aHR=0.68, 95% CI:0.60-0.78 for 2003-05, aHR=0.50, 95% CI:0.43-0.57 for 2006-08 and aHR=0.31, 95% CI:0.26-0.36 for 2009-12 relative to 2000-02).

In Canada, Indigenous peoples are disproportionately affected by HIV and 21.2% of new HIV cases between 1998 and 2016 were among Indigenous peoples (Bourgeois, 2017). Furthermore, Indigenous peoples living with HIV in Canada have been found to have higher death rates compared to non-Indigenous peoples living with HIV (Antiretroviral Therapy Cohort C, 2013; Martin, 2011; Lima 2006). Canadian studies have also found Indigenous heritage to be associated with HIV incidence, prevalence and risk factors related to HIV transmission (Duncan, 2011).

As depicted in Flo's story there are many complex social, political and economic factors affecting access to and ability to continue with HIV-related care for Indigenous peoples in Canada. Experiences of colonization, trauma, violence, sexual abuse and substance use can impact HIV vulnerability and access to HIV-related care for Indigenous peoples (McCall, 2014). Experiences of trauma have been associated with both distrust of healthcare professionals and poorer combination antiretroviral therapy (cART) adherence (Mugavero, 2006; Meade, 2009).

Prior studies have identified Indigenous heritage as a risk factor for unplanned treatment interruptions (Samji, 2014), failure to achieve virologic suppression (when the virus is undetectable in standard tests) upon initiation of cART and virologic failure after virologic suppression (Martin, 2010). A parallel analysis in this study cohort identified lower rates of virologic suppression, but similar rates of virologic rebound (when the virus is detectable again after a period of time when it was undetectable) among Indigenous peoples living with HIV after adjusting for other complicating factors (Benoit, 2017). Unstructured treatment interruptions are significant as they have been associated with subsequent treatment failure (Jiamsakul, 2016). The purpose of this study was to compare time to treatment interruption between Indigenous and non-Indigenous individuals living with HIV initiating cART in Canada. This research was conducted collaboratively by a team of Indigenous peoples living with HIV, Indigenous Elders, Indigenous researchers and allied researchers.

METHODS

Study Methodology

Building Bridges was a community-based research collaboration between Indigenous and allied stakeholders and the Canadian Observational Cohort (CANOC) Collaboration. It used Indigenous methodologies and community-based research principles to conduct epidemiological health research on research questions of community relevance. Through the Building Bridges study an Indigenous Health Epidemiology Model emerged and was used to guide this research. The Indigenous Health Epidemiology Model is described elsewhere (Benoit, 2015).

In the Indigenous Health Epidemiology Model, Indigenous and epidemiological perspectives were complementary and the study was guided by a community advisory committee including Indigenous peoples living with HIV (Benoit, 2015). The advisory committee and research team included Indigenous peoples living with HIV, Elders, clinicians, epidemiologists and service providers who collectively provided expertise in Indigenous knowledge, lived experience, HIV research and clinical and social epidemiology. Indigenous methodology centred Indigenous

knowledge and worldviews and examined the research question in a holistic manner, considering the intersection of physical, mental, emotional, and spiritual domains in the health and wellbeing of a person. Research questions were developed by a collaboration of Indigenous peoples affected by HIV and allied researchers to reflect priorities of Indigenous stakeholders. Epidemiological perspectives were reflected through the use of statistical data analysis.

Study design and population

This study was a retrospective analysis (looking back at data that has already been collected) of data from the CANOC collaboration. A profile of the CANOC cohort has been published elsewhere (Palmer, 2011). In brief, CANOC is a collaboration of eight groups of people living with HIV on cART in three Canadian provinces. The majority (62%) of the cohort is comprised of individuals from British Columbia (BC) which includes a population-based cohort of all individuals who have been initiated on cART through the provincially administered Drug Treatment Program. Three clinic-based sites and a multicentre cohort study from the province of Ontario (29% of the cohort) and three clinic-based sites from the province of Québec (9% of the cohort) are included in CANOC. Indigenous people living with HIV comprise approximately 6% of the cohort.

Participating sites submitted information without personal details or names and clinical data to the CANOC data coordinating site which is housed in BC. Participants are eligible for inclusion in CANOC if they were aged 18 and over, had not previously been treated for HIV, initiated cART on or after January 1, 2000, started a cART regimen composed of at least three antiretroviral medications and had at least one measure of HIV plasma viral load (VL) and CD4 count within 1 year prior to or 15 days following the date of cART initiation. Data from one clinic in Ontario and one clinic in Québec were excluded from the analysis because information on ethnicity was not collected.

Demographic information included age, gender, ethnic origin as reported in CANOC, province of residence, and HIV risk factors including history of injection drug use (IDU), being a man who has sex with men (MSM) and indicating heterosexual status. Clinical variables included cART initiation date and year, baseline CD4 count and VL, baseline AIDS-defining illness (ADI), hepatitis B and C status (HBV and HCV), and antiretroviral medication class.

Participants were classified as Indigenous if they self-reported their identity as one of First Nations, Métis or Inuit. Participants with unknown ethnicity based on CANOC data were classified as non-Indigenous. The main question was treatment interruption, defined as the interruption of all antiretroviral medications for at least 90 consecutive days.

The Building Bridges study protocol was reviewed and approved by the University of British Columbia-Providence Health Care Research Ethics Board. CANOC ethics approval was obtained from all contributing sites. The data analysis protocol was reviewed and approved by the CANOC Steering Committee.

Statistical analysis

Statistical analysis is guided by mathematical approaches or "tests" that help to compare two or more variables – pieces of information – and look for relationships. The following description of the analysis uses the statistical names for each approach. The discussion section below explains what the research team learned from these tests and what all of the team members felt were important details about the relationships the mathematical tests identified.

Demographic and clinical characteristics were summarized for Indigenous and non-Indigenous participants using frequency (number of times something is counted) and proportions (fractions) for categorical variables and median (mid point) and interquartile range (IQR) for continuous variables. Characteristics were compared between Indigenous and non-Indigenous participants using the Pearson's χ^2 test or Kruskal Wallis test for categorical and continuous variables, respectively.

In order to work with records that were missing information about ethnicity, MSM and/or IDU, a complex statistical technique was used (the substantive model compatible version of the fully conditional specification model) (Bartlett, 2016). Imputation of ethnicity was performed using a discriminant function. Imputation for MSM and IDU was performed using logistic regression models. The imputation model contained specification of the survival distributions of time to treatment interruption in addition to all variables included in the substantive model.

Kaplan-Meier curves were used to compare time to treatment interruption. The association of Indigenous ethnicity with treatment interruption was estimated with Cox proportional hazards (PH) models after adjusting for confounding variables including age, gender, IDU, province of origin, and year of cART initiation. Data were analyzed using SAS® Statistical Software Version 9.4 by SAS Institute Inc., Cary, NC, USA and R 3.3.1 (R Development Core Team, Vienna, Austria).

RESULTS

A total of 7080 participants, including 443 Indigenous participants, were included in the analysis. 1611 (22.8%) had at least one treatment interruption during their enrollment in the cohort. 5566 (78.6%) identified as male, 1476 (20.8%) as female and 38 (0.5%) as transgender. The majority of participants resided in BC (4395, 62.1%). 1896 (26.8%) had a history of IDU. Indigenous participants were more likely to be female, reside in BC, have a history of IDU and have had at least one treatment interruption (Table 1). The cumulative probability (overall likelihood) of a treatment interruption was significantly higher for Indigenous peoples at 1, 3 and 5 years after starting antiretroviral therapy (Table 2).

Table 1: Demographic and clinical characteristics of participants by ethnicity

	Caucasian (N=2471)		Black (N=787)		Indigenous (N=443)		Other (N=683)		Unknown (N=2696)		P-value
	N	%	N	%	N	%	N	%	N	%	
Gender											
Male	2154	87.2	-	-	255	57.6	591	86.5	2199	81.6	<0.001

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Female	310	12.5	-	-	179	40.4	86	12.6	482	17.9	
Transgender*	7	0.3	-		9	2.0	6	0.9	15	0.6	
Province											
BC	1160	46.9	85	10.8	359	81.0	306	44.8	2485	92.2	<0.001
ON	1113	45.0	460	58.4	66	14.9	303	44.4	93	3.4	
QC	198	8.0	242	30.7	18	4.1	74	10.8	118	4.4	
HIV risk IDU											
No	1653	66.9	714	90.7	99	22.3	557	81.6	1093	40.5	<0.001
Yes	724	29.3	26	3.3	3314	70.9	107	15.7	572	26.9	
Unknown	94	3.8	47	6.0	30	6.8	19	2.8	878	32.6	
First cART regimen											
NNRTI based	1110	44.9	373	47.4	203	45.8	331	48.5	1243	46.1	<0.001
Unboosted PI based	177	7.2	90	11.4	30	6.8	44	6.4	98	3.6	
Boosted PI based	1050	42.5	281	35.7	193	43.6	275	40.3	1244	46.1	
Other	134	5.4	43	5.5	17	3.8	33	4.8	111	4.1	
Era of cART initiation											
2000-2002	570	23.1	152	19.3	120	27.1	144	21.1	346	12.8	<0.001
2003-2005	582	23.6	201	25.5	90	20.3	156	22.8	1448	16.6	
2006-2008	677	27.4	223	28.3	121	27.3	177	25.9	684	25.4	
2009-2012	642	26.0	211	26.8	112	25.3	206	30.2	1218	45.2	
Median age in years at first ARV initiation (IQR)	41	(34-48)	37	(32-43)	39	(32-44)	38	(32-44)	41	(34-48)	<0.001
Median CD4 at baseline in cells/mm^3 (IQR)	210	(105-313)	189	(102-277)	160	(74-270)	201	(90-290)	230	(120-350)	<0.001
Median log10 viral load at baseline (IQR)	5.0	(4.5-5.2)	4.5	(4.0-5.0)	4.9	(4.4-5.0)	4.9	(4.3-5.2)	4.9	(4.4-5.0)	<0.001

BC, British Columbia; ON, Ontario; QC, Québec; HIV, human immunodeficiency virus; IDU, injection drug use; cART, combination antiretroviral therapy; NNRTI, non-nucleotide reverse transcriptase inhibitor; PI, protease inhibitor; IQR, interquartile range; ARV, antiretroviral

*Some data not reported to protect confidentiality (small cell size)

Table 2: Cumulative probability of a treatment interruption at 1, 2 and 5 years after initiating antiretroviral therapy by ethnicity.

	Caucasian (N=2471)	Black (N=787)	Indigenous (N=443)	Other (N=683)	Unknown (N=2696)	P-value
Probability of TI at 1 year	0.11	0.11	0.32	0.07	0.13	<0.001

Probability of TI at 2 years	0.16	0.14	0.40	0.11	0.18	<0.001
Probability of TI at 5 years	0.24	0.23	0.52	0.19	0.26	<0.001

TI, treatment interruption

In a Cox Proportional Hazards model for time to treatment interruptions, Indigenous heritage remained a significant predictor of treatment interruption (hazard ratio [HR]=1.43, 95% confidence interval [CI] 1.21, 1.70) after adjusting for significant covariates (see Table 3 for all the variables included). After imputation of missing values for ethnicity, the association remained significant (HR=1.46, 95% CI 1.25, 1.71). African, Caribbean or Black ethnicity, female gender, BC as a province of residence, history of IDU, initial antiretroviral regimen containing an unboosted protease inhibitor and year of cART initiation also had an elevated hazard ratio in multivariable analysis after imputation of missing values for ethnicity (Table 3). When compared to the reference period of 2000-2002, treatment interruptions were less likely in later years. A Kaplan Meier curve showing time to treatment interruption by ethnicity is presented in Figure 1. This figure shows the changes of being free from treatment interruption (staying on cART) over time for different ethnicities. As the line moves towards the bottom of the graph, the chances of staying on cART are lower for that group of people.

Table 3: Univariable and multivariable Cox proportional hazard models for time to treatment interruption

	Unadjusted model				Adjusted models			
	Univariable		Missing Data Imputed		Missing Data Excluded		Missing Data Imputed	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Age at first cART initiation (years)	0.97 (0.97, 0.98)	<0.001	0.97 (0.97, 0.98)	<0.001	0.97 (0.97, 0.98)	<0.001	0.97 (0.97, 0.98)	<0.001
Gender								
Male/Transgender	Ref.	<0.001	Ref.	<0.001	Ref.	<0.001	Ref.	<0.001
Female	1.98 (1.78, 2.20)		1.98 (1.78, 2.20)		1.41 (1.25, 1.58)		1.37 (1.21, 1.54)	
Province								
ON/QC	Ref.	<0.001	Ref.	<0.001	Ref.	<0.001	Ref.	<0.001
BC	2.12 (1.89, 2.37)		2.12 (1.89, 2.37)		1.90 (1.65, 2.18)		1.85 (1.62, 2.12)	
Ethnicity								
Caucasian	Ref.	<0.001	Ref.	<0.001	Ref.	<0.001	Ref.	<0.001
ACB	0.94 (0.79, 1.12)		0.99 (0.83, 1.17)		1.25 (1.03, 1.53)		1.34 (1.11, 1.62)	
Indigenous	2.82 (2.40, 3.31)		2.61 (2.26, 3.01)		1.43 (1.21, 1.70)		1.46 (1.25, 1.71)	
Other	0.72 (0.59, 0.89)		0.74 (0.63, 0.87)		0.78 (0.64, 0.96)		0.80 (0.68, 0.95)	
Unknown	1.16 (1.03, 1.31)				1.09 (0.96, 1.24)			
HIV risk IDU								
No/Unknown	Ref.	<0.001	Ref.	<0.001	Ref.	<0.001	Ref.	<0.001
Yes	3.23 (2.91, 3.60)		3.23 (2.91, 3.60)		2.50 (2.24, 2.80)		2.46 (2.18, 2.78)	
First cART regimen								

NNRTI based	Ref.	<0.001	Ref.	<0.001	Ref.	<0.001	Ref.	<0.001
Unboosted PI based	1.79 (1.52, 2.11)		1.79 (1.52, 2.11)		1.40 (1.18, 1.66)		1.41 (1.19, 1.67)	
Boosted PI based	0.93 (0.84, 1.04)		0.93 (0.84, 1.04)		1.01 (0.90, 1.12)		1.01 (0.90, 1.13)	
Other	1.13 (0.90, 1.42)		1.13 (0.90, 1.42)		1.12 (0.89, 1.41)		1.12 (0.88, 1.41)	
Era of cART initiation Ref.	Ref.	<0.001	Ref.	<0.001	Ref.	<0.001	Ref.	<0.001
2003-2005	0.65 (0.58, 0.74)		0.65 (0.58, 0.74)		0.68 (0.60, 0.78)		0.68 (0.60, 0.78)	
2006-2008	0.47 (0.41, 0.54)		0.47 (0.41, 0.54)		0.49 (0.43, 0.57)		0.50 (0.43, 0.57)	
2009-2012	0.32 (0.28, 0.38)		0.32 (0.28, 0.38)		0.32 (0.27, 0.37)		0.31 (0.26, 0.36)	
Baseline viral load (Log10 copies/mL)	0.92 (0.90, 0.95)	<0.001	0.92 (0.90, 0.95)	<0.001	0.94 (0.91, 0.97)	<0.001	0.95 (0.91, 0.98)	<0.001
Baseline CD4 (per 100 cells/mm^3)	1.02 (0.99, 1.05)	0.176	1.02 (0.99, 1.05)	0.176	1.07 (1.03, 1.10)	<0.001	1.07 (1.04, 1.11)	<0.001

HR, hazard ratio; CI, confidence interval; Ref, reference; cART, combination antiretroviral therapy; ON, Ontario; QC, Québec; BC, British Columbia; ACB, African Caribbean or Black; HIV, human immunodeficiency virus; IDU, injection drug use; NNRTI, non-nucleotide reverse transcriptase inhibitor; PI, protease inhibitor

Figure 1. Probability of remaining free from treatment interruption by ethnicity

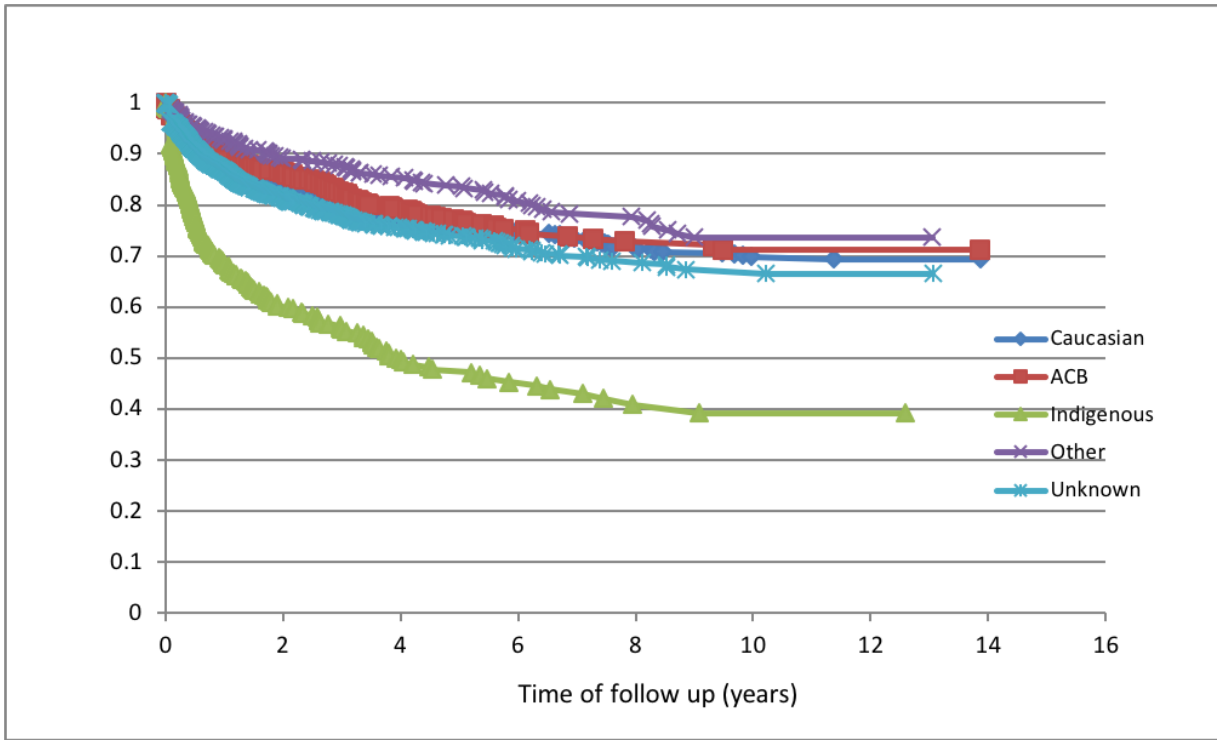

Figure 1 depicts the Kaplan Meier probability curves for remaining free from a treatment interruption by ethnicity.

DISCUSSION

In this study, we found that Indigenous participants were at increased risk of treatment interruption. It is likely that there are many causes explaining this finding. Frequency of changing residences stemming from historical lands dispossession can impact health behaviour (Jongbloed, 2015) and access to care and homelessness has been well documented to impact primary care use (Health Quality Ontario, 2016). Transitions between Indigenous communities and urban centres can lead to fragmented care. In addition, Indigenous peoples in Canada are over-represented in the criminal justice system and transitions in and out of prison can also lead to fragmented care and treatment interruption (McNeil, 2016). Also, experiences of racism in health care settings have been well documented for Indigenous peoples in Canada (Czyzewski, 2011; Lawrence, 2016; Loppie, 2014) and this can impact HIV care and ART use. Furthermore, Indigenous peoples in Canada have been found to be less likely to receive optimal HIV therapy and more likely to be treated by a physician with less experience in managing HIV (Miller, 2006).

Despite many of the complex social challenges that many Indigenous peoples with HIV have encountered, client-centered care and support programs can successfully support continuous cART use for individuals, as illustrated in the story of Valerie. "My story began with denial. My partner was diagnosed with HIV, but it took me two years and a battle with substance use as a coping mechanism before I found the strength to get tested. Eventually, I was diagnosed with HIV with a CD4 count of 90 cells/mm^3. It took another two years to get on treatment, but when I started treatment, I had a suppressed viral load within one month and I've remained suppressed for the past seven years. After being diagnosed with HIV, I was linked with a family physician who helped me become educated about HIV and I realized it was not a death sentence. At times, I was homeless, but my team of community nurses and physicians that hunted me down, delivered my medications and ensured that I remained on antiretroviral therapy. I know that if these nurses were doing all this for me, I needed to take my medications every day."

Valerie's story demonstrates the role that health care professionals can play in supporting people living with HIV. A study in rural Kenya found that health care professionals can facilitate continuity of care by providing the appropriate documentation for patients transitioning between clinics (Hickey, 2016). This highlights the need for a more pro-active role for physicians and nurses in ensuring continuity of care for Indigenous peoples with HIV that transition from rural to suburban or urban areas. Inter-clinic communication and timely referrals can facilitate this process. This may be particularly important for individuals who may not have experience navigating the Canadian health care system outside of Indigenous communities. In this study, women and people who use injection drugs were both found to be related to treatment interruption and this is consistent with data showing poorer engagement throughout the HIV continuum of care for these populations (Lourenço, 2014). This highlights the need for supportive programming for these populations.

This study has several strengths. The first is that community-based research is embodied and a research question that was identified by Indigenous community members is addressed. The second is that it included a large number of Indigenous participants from diverse geographic regions in Canada. However, CANOC is a cohort that enrolls individuals through clinics or

through a provincial cART program, so enrollment is biased towards individuals linked to and retained in care. Indigenous peoples living with HIV most at risk for treatment interruption may be missed by this cohort and this could lead to an underestimation of the hazard ratio. This study also does not include data on individuals who have not yet started cART, a group that may be over-represented by Indigenous peoples. Finally, there is a risk of misclassification bias as experiences of racism within health care settings may lead some Indigenous participants to refrain from self-identifying as Indigenous. Community-based collaborations and recruitment may be helpful in addressing these limitations in the future.

In conclusion, this study found that Indigenous peoples living with HIV were at an increased risk of treatment interruption compared to peoples of other ethnicities living in Canada. Prior studies have identified discrepancies in HIV outcomes for Indigenous peoples in Canada, but this current study unveils one of many ways through which Indigenous people may be at risk for that contribute to poorer HIV outcomes. Treatment interruptions may be related to individual or systemic factors and improved support for Indigenous peoples living with HIV must also be coupled with structural changes that address the underlying determinants of health.

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