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ORIGINAL STUDY

Prevalence and correlates of early-onset menopause among women living with HIV in Canada

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Abstract

Objective: Menopause is a pivotal transition for women. Previous studies have suggested increased risk of early menopause (40-45 years) and premature menopause (<40 years) for women with HIV. We aimed to determine age of menopause, prevalence of early menopause and premature menopause, and risk factors for menopause <45 years in Canadian women with HIV.

Methods: This was a cross-sectional analysis from the Canadian HIV Women's Sexual and Reproductive Health Cohort Study. Analyses were restricted to biologically female participants reporting being postmenopausal (regardless of etiology). Primary outcome was median age at menopause. Predetermined variables, and those with $P < 0.10$ in univariable analyses were considered for inclusion into multivariable logistic regression model, to determine independent correlates of menopause <45 years.

Results: 229 women were included. Median age of menopause was 48 years (interquartile range 43, 51); 29.7% of women experienced menopause <45 years: 16.6% with early menopause and 13.1% with premature menopause. In univariable analyses, menopause <45 years was more likely ($P < 0.05$) with birth in Canada, white ethnicity, less than high-school education, smoking, recreational drug use, and hepatitis C co-infection. In multivariable modeling, less than high-school education (adjusted odds ratio [aOR] 2.45, 95% confidence interval [CI] 1.22-4.93) and hepatitis C co-infection (aOR 1.90, 95% CI 1.04-3.50) were independently associated with menopause <45 years.

Conclusions: In Canadian women with HIV, median age of menopause was 48 years; 3 years younger than the general population. Only lower education and hepatitis C co-infection were independently associated with menopause <45 years, highlighting importance of socioeconomic factors and comorbidities. These findings have implications for counseling and management of women with HIV.

Key Words: HIV – Menopause – Premature ovarian failure – Women.

The epidemiology and prognosis of human immunodeficiency virus (HIV) infection has shifted dramatically.[1] Due to the rollout and uptake of combination antiretroviral therapy (cART), the prognosis of HIV infection has changed, such that infected individuals, who are adherent to therapy and are able to maintain a suppressed viral load, can expect to have a life expectancy approaching that of the general population.[2] Newly diagnosed individuals who initiate cART in their 20s can expect to live into their mid-70s or longer.[2] As a result of improved prognosis, aging in the context of HIV infection becomes an important consideration. In 2014, individuals aged ≥50 years accounted for 45% of those living with HIV

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in the United States,[3] and it is expected that by 2020, 70% of adults living with HIV will be ≥50 years.[4] Furthermore, aspects of sexual and reproductive health, including menopause, become paramount to consider, as women now make up >50% of adults living with HIV worldwide, and 22% to 25% of those living with HIV in Canada and in the USA.[5-7]

Menopause, a key age-related transition for women, is defined as the absence of menses for at least 12 months due to loss of follicular activity within the ovaries, and not due to other physiologic or pathologic processes.[8,9] The average age of menopause in Canada and in the United States is between 50 and 52 years.[10,11] However, several previous studies report that women living with HIV are at increased risk of early and premature menopause (also known as premature ovarian failure [POF]).[12-14] Possible explanations for this include the effects of HIV infection itself and higher prevalence of sociodemographic factors associated with early menopause, such as smoking, illicit drug use, hepatitis C co-infection,[15] and also possible effects of cART. Early menopause has several important implications, including changes in mood and sexual function, risk of other comorbidities such as osteoporosis and cardiovascular disease, changes in quality of life related to menopausal symptoms, and has been associated with earlier mortality.[16-18]

The objective of this study is to analyze data from a large, national prospective cohort study to determine average age of menopause; prevalence of early menopause (menopause between 40 and 45 years) and premature menopause (menopause <40 years); and correlates of menopause occurring at <45 years, in a cohort of Canadian women living with HIV.

METHODS

Study population

The Canadian HIV Women's Sexual and Reproductive Health Cohort Study (CHIWOS) is a community-based, prospective cohort study of women living with HIV ≥16 years of age in three Canadian provinces (British Columbia, Ontario, and Quebec).[19] Enrollment occurred between August, 2013 and May, 2015. This analysis included data from the baseline visit when participants completed an extensive questionnaire. The questionnaire was developed in conjunction with a national, multidisciplinary research team, operating within the framework of community-based research and meaningful involvement of women living with HIV.[20] In addition to sociodemographic and medical information, the survey included questions related to menstruation and menopause. All data collected was based on participant self-report. Questionnaires were administered by trained peer-research associates (PRAs).

For the present analysis, women were included if they were postmenopausal (defined below); reported when they experienced menopause (such that age at menopause could be determined); were female sex at birth; had had at least one period in their lifetime; were not currently pregnant; and were not taking hormonal contraception.

Menopausal status was determined based on responses to 2 questions: ''*How would you describe your menstrual status as it related to menopause''*; and ''*When did you start your most recent menstrual period.''* Women were classified as being postmenopausal if they had not had a menstrual period within 12 months before completing the questionnaire. Women who reported being postmenopausal, but had experienced a period within the preceding 12 months, were excluded from this analysis. Subsequently, three categories of postmenopausal women were created based on the response to the question *''Which of the reasons below describes the main reason you haven't had your period in more than 12 months?''*. These subcategories were: ''postmenopausal—spontaneous,'' which referred to women who had undergone spontaneous menopause; ''postmenopausal—induced,'' which referred to women who had undergone surgery, or received chemotherapy and/or radiation therapy that led to menopause; and ''postmenopausal—unknown reason,'' which referred to women who had not had a period for more than 12 months, but did not specify the reason. For the primary analyses in this study, all postmenopausal women, regardless of the etiology, were included. A sensitivity analysis was also performed by excluding women with induced menopause.

Outcome measures

The primary outcome was the median age of menopause. This was assessed based on response to the question: ''*When did you complete menopause?''* Secondary outcomes included: prevalence of early menopause (EM) (menopause between 40 and 45 years); prevalence of premature menopause (PM) (menopause <40 years); and factors associated with early menopause and premature menopause (ie, all women with menopause <45 years). Premature menopause was defined as menopause occurring <40 years of age as per World Health Organization definition.[8] While there is no standardized or universally accepted definition of early menopause, previous studies have classified early menopause as menopause occurring before the age of 45 years.[12,13] As the present analysis intended to examine early menopause separately from premature menopause, a range of 40 to <45 years was chosen.

Statistical analyses

Baseline characteristics were summarized with medians, with interquartile ranges (IQR) for continuous variables and frequencies with proportions for categorical variables. The primary outcome, age of menopause, was reported as a median with IQR and compared between the three Canadian provinces using the Kruskal-Wallis test (as age of menopause was not normally distributed, Shapiro-Wilk $P < 0.001$). The prevalence of early menopause was determined by calculating the proportion of all menopausal women who reported an age of menopause between 40 and <45 years (with 95% confidence interval [CI]). The prevalence of premature menopause was determined by calculating the proportion of all menopausal women who reported an age of menopause of <40

years (with 95% CI). Etiology of menopause was compared between women experiencing menopause within different age categories with Fisher's exact test.

To determine correlates of early and premature menopause, sociodemographic and clinical variables were compared for women with and without menopause <45 years using Wilcoxon rank-sum tests (for continuous variables) and chi-square or Fisher's exact test for categorical variables, as appropriate. Specific variables included province of residence, region of birth, ethnicity, marital status, education, source of income, annual household income, housing, smoking status, recreational drug use, injection drug use, duration of HIV infection, method of HIV acquisition, nadir CD4 count, current CD4 count, virologic suppression, current use of antiretroviral therapy, antiretroviral regimen, hepatitis C co-infection, body mass index, age at menarche, and number of pregnancies (Table 1). Those variables with $P < 0.10$ in the univariable analysis, and also certain preselected variables based on pre-existing data supporting an association with early menopause in HIV (ethnicity, smoking, recreational drug use, injection drug use [IDU], hepatitis C infection) were considered for inclusion into regression analyses. Injection drug use, recreational drug use, and method of HIV acquisition were considered collinear; therefore, only recreational drug use was included if more than one met the cut-off criteria. Odds ratios (ORs) with 95% CIs were determined with univariable logistic regression, with the outcome of interest being menopause <45 years (vs menopause ≥45 years). To build the final multivariable model assessing for risk factors for menopause <45 years, a backward stepwise technique based on type III *P* values and the Akaike Information Criteria (AIC) was used. The variable with the highest type III *P* value was dropped at each step of the selection process, until the model reached the lowest AIC. Sensitivity analyses were performed, whereby all aforementioned analyses were repeated after excluding women who reported that the etiology for menopause was induced. A *P* value of <0.05 was considered statistically significant. All analyses were performed using SAS Statistical Software (version 9.4; Cary, NC).

TABLE 1. *Baseline characteristics of postmenopausal women living with HIV in Canada (N = 229)*

Variable	Median or frequency[a]	IQR or proportion[a]
Age (y)[a]	55	(52-59)
Province		
British Columbia	74	32.3
Ontario	70	30.6
Quebec	85	37.1
Region of birth		
Canada	159	69.4
Africa	32	14.0
Asia	1	0.4
Europe	13	5.7
North America (not Canada)	3	1.3
Central America	18	7.9
South America	1	0.4
Oceania	1	0.4
Ethnicity		
African/Caribbean/Black	52	22.7
White	121	52.8
Indigenous	43	18.8
Other	13	5.7
Marital status		
Single	101	44.1
Married/relationship	40	17.5
Separated/widowed/other	88	38.4
Education		
Less than high school	47	20.5
High school or higher	180	78.6
Source of income		
Employment	38	16.6
Other methods[b]	11	4.8
Social assistance	143	62.4
Pension/saving/loans/disability	36	15.7
Annual household income		
<$20,000	150	65.5
$20,000-$39,999	54	23.6
≥$40,000	21	9.2
Housing		
Own	32	14.0
Rent	155	67.7
Single-room	23	10.0
Transitional	10	4.4
Facility	8	3.5
Other	1	0.4
Smoking status		
Ever	149	65.1
Never	80	34.9
Recreational drug use (ever)	128	55.9
Injection drug use (ever)	90	39.3
Methadone use (current)	8	3.5
Duration of HIV infection (y)[a]	15.3	(9.7-19.8)
HIV method of acquisition		
Sexual transmission	141	61.6
Sharing/contaminated needles	54	23.6
Transfusion/medical procedure	19	8.3
Perinatal	2	0.9
Unknown/no answer	13	5.7
Nadir CD4 count		
<200 cell/mm^3	111	48.5
200-500 cells/mm^3	79	34.5
>500 cells/mm^3	10	4.4
Unknown	27	11.8
Current CD4 count		
<200 cells/mm^3	16	7.0
200-500 cells/mm^3	69	30.1
>500 cells/mm^3	121	52.8
Unknown	23	10.0
Undetectable viral load	199	86.9
Current antiretroviral therapy	217	94.8
Antiretroviral class (third agent)		
NNRTI	63	27.5
Protease inhibitor	84	36.7
Integrase inhibitor	36	15.7
Another regimen	21	9.2
Unknown	13	5.7
Hepatitis C co-infection (ever)	90	39.3
Body mass index (kg/m^2)[a]	24.5	(21.2-29.2)
Age menarche (y)	13	12-14
Pregnancies resulting in live birth[a]	2	(1.0-3.0)

NNRTI, non-nucleoside reverse transcriptase inhibitor.
[a]Median with interquartile range for continuous variables [age, duration of HIV infection, body mass index, pregnancies resulting in live births]; frequency with proportion for categorical variables [all other variables].
[b]Other sources: sex work, selling drugs, pan-handling, honoraria (workshops, training, etc).

RESULTS

Baseline characteristics

There were 1,422 women who participated in CHIWOS during the enrollment period and completed the baseline questionnaire. There were 387 postmenopausal women, of whom 229 had reported an age of menopause and were included in this analysis. Baseline characteristics are summarized in Table 1. Median age was 55 years (IQR 52-59) and median duration of HIV infection was 15.3 years (IQR 9.7-19.8). There was similar representation from each of the three Canadian provinces included in the study (37% from Quebec, 31% from Ontario, and 32% from British Columbia). The majority (69.4%) of women were born in Canada; 52.8% were white, 22.7% African/Caribbean/Black, and 18.8% Indigenous. With regards to HIV outcomes, 94.8% of women were on cART, 86.9% had an undetectable viral load, and 52.8% had a current CD4 count >500 cells/mm^3.

Of the 229 postmenopausal women, 190 (83.0%) underwent spontaneous menopause; 35 (15.3%) experienced induced menopause, and 4 (1.7%) had an unknown reason for cessation of menses for more than 12 months. Of the 35 women with induced menopause, 33 (94.3%) underwent surgery leading to menopause and 2 (5.7%) had menopause caused by chemotherapy and/or radiation therapy.

Prevalence and risk factors of early menopause

The median age of menopause for all women was 48 years (IQR 43-51 years). There was no difference in the median age of menopause between women in British Columbia, Ontario, and Quebec ($P = 0.118$). The proportions of women experiencing menopause within different age categories are summarized in Table 2. Of the 229 women in this analysis, 29.7% experienced menopause before the age of 45 years (95% CI 23.7%-35.7%): 16.6% reported early menopause and 13.1% reported experiencing premature menopause. Women who experienced premature menopause were more likely to report induced menopause as the etiology than those with early menopause or those who underwent menopause at ≥45 years of age ($P < 0.001$) (Table 3).

Sociodemographic and clinical characteristics associated with undergoing any early-onset menopause (menopause <45 years) are reported in Tables 4 and 5. In univariable analyses, women were more likely to experience menopause <45 years if they had less than high school education (OR 2.61, 95% CI 1.32-5.13: compared with secondary school or higher), history of smoking (OR 1.99, 95% CI 1.04-3.81: compared with never smoked), had ever used recreational drugs (OR 2.02, 95% CI 1.10-3.70: compared with never used recreational drugs), or had a history of hepatitis C co-infection (OR 2.17, 95% CI 1.20-3.91: compared with no history of hepatitis C). Birth outside of Canada (OR 0.46, 95% CI 0.23-0.91: compared with birth within Canada) and Black ethnicity (OR 0.42, 95% CI 0.19-0.96: compared with white ethnicity) were protective. There was also borderline significance for those with a longer duration of HIV infection (OR 1.03, 95% CI 0.99-1.08) being at higher risk of early menopause, and those who were separated/widowed/divorced having a lower risk of earlier menopause than those who were married (OR 0.44, 95% CI 0.19-1.02). Women with menopause <45 years did not differ from women with menopause ≥45 years with respect to province of residence, body mass index, parity, age of menarche, or HIV-related factors such as nadir or current CD4 count, use of antiretroviral therapy, or having undetectable viral load (Table 4).

Results of the final multivariable logistic regression model are reported in Table 5. After conditioning on other variables in the model, having less than a high-school education (adjusted odds ratio [aOR] 2.45, 95% CI 1.22-4.93) and hepatitis C co-infection (aOR 1.90, 95% CI 1.04-3.50) were associated with increased odds of menopause occurring at <45 years.

TABLE 2. *Age at menopause for Canadian women living with HIV (N = 229)*

Menopausal category	Age, y	Frequency of women (n)	Proportion (×100) [95% CI]
Premature menopause	<40	30	13.1% [8.7%-17.5%]
Early menopause	40 to <45	38	16.6% [11.7%-21.4%]
Normal	45 to 50	91	39.7% [33.4%-46.1%]
	≥50	70	30.6% [24.6%-36.6%]

CI, confidence interval.

TABLE 3. *Etiology of menopause among women with premature ovarian failure and early menopause*

Etiology of menopause	Premature menopause (<40 y) (n = 30)	Early menopause (40 to <45 y) (n = 38)	Menopause ≥45 y (n = 161)	P^a
Spontaneous	13 (43.3%)	29 (76.3%)	148 (91.9%)	<0.001
Surgical	15 (50.0%)	9 (23.7%)	9 (5.6%)	
Chemotherapy/ radiation	0	0	2 (1.2%)	
Other	2 (6.7%)		2 (1.2%)	

[a]Etiology of menopause compared between women experiencing menopause at different age groups using Fischer's exact test.

Sensitivity analyses (excluding women with induced menopause)

After excluding 35 women with induced menopause, the median age of menopause was 49 years (IQR 45-52 years). Of the 194 women in this analysis, 22.7% (95% CI 16.7%-28.6%) underwent menopause <45 years: 14.9% (95% CI 9.9%-20.0%) reported menopause 40 to <45 years, and 7.7% (95% CI 3.9%-11.5%) reported premature menopause at <40 years.

In univariable regression analyses, women were more likely to experience menopause <45 years if they had less than high school education (OR 3.35, 95% CI 1.53-7.34: compared with secondary school or higher), had a history of smoking (OR 2.20, 95% CI 1.01-4.81: compared with never having smoked), had ever used recreational drugs (OR 2.28, 95% CI 1.10-4.71: compared with no history of drug use) or had a history of hepatitis C co-infection (OR 2.12, 95% CI

TABLE 4. *Factors associated with menopause <45 years*

Variable	Menopause <45 y (n = 68) Median (IQR) or n (%)[a]	Menopause ≥45 y (n = 161) Median (IQR) or n (%)[a]	P^b
Province			0.139
British Columbia	28 (41.2)	46 (29.0)	
Ontario	20 (29.4)	50 (31.0)	
Quebec	20 (29.4)	65 (40.0)	
Born in Canada	54 (79.4)	105 (65)	0.033
Region of birth			0.224
Canada	54 (79.4)	105 (65)	
Africa	6 (8.8)	26 (16)	
Asia	0	1 (1.0)	
Europe	4 (5.9)	9 (6.0)	
North America (not Canada)	1 (1.5)	2 (1.2)	
Central America	2 (2.9)	16 (10.0)	
South America	0 (0)	1 (1.0)	
Oceania	1 (1.5)	0 (0)	
Ethnicity			0.129
African/Caribbean/Black	9 (13.2)	43 (27.0)	
White	41 (60.3)	80 (50.0)	
Aboriginal	15 (22.1)	28 (17.0)	
Other	3 (4.4)	10 (6.0)	
Marital status			0.054
Single	36 (52.9)	65 (40.0)	
Married/relationship	14 (20.6)	26 (16.0)	
Separated/widowed/other	18 (26.5)	70 (43.0)	
Education			0.010
Less than high school	21 (30.9)	26 (16.0)	
High school or higher	46 (67.6)	134 (83.0)	
Source of income			0.394
Employment	7 (10.3)	31 (19.0)	
Other method[c]	3 (4.4)	8 (5.0)	
Social assistance	46 (67.6)	97 (60.0)	
Pension/saving/loans/disability	12 (17.6)	24 (15.0)	
Annual household income			0.190
<$20,000	47 (69.1)	103 (64.0)	
$20,000-$39,999	12 (17.6)	42 (26.0)	
≥$40,000	9 (13.2)	12 (7.0)	
Housing			0.199
Own	11 (16.2)	21 (13.0)	
Rent	39 (57.4)	116 (72.0)	
Single-Room	11 (16.2)	12 (7.0)	
Transitional	4 (5.9)	6 (4.0)	
Facility	3 (4.4)	5 (3.0)	
Other	0	1 (1.0)	
Smoking status			0.040
Ever smoker	51 (75.0)	98 (60.9)	
Never	17 (25.0)	63 (39.1)	
Recreational drug use (ever)	46 (67.6)	82 (51.0)	0.018
Injection drug use (ever)	36 (52.9)	54 (34.0)	0.006
Methadone use (current)	3 (4.4)	5 (3.1)	0.627
Duration of HIV Infection, y[a]	17 (10.3-21.3)	14.2 (9.3-19.4)	0.057
HIV method of acquisition			0.060
Sexual transmission	37 (54.4)	104 (64.6)	
Sharing/contaminated needles	24 (35.3)	30 (18.6)	
Transfusion/medical procedure	5 (7.4)	14 (9.0)	
Perinatal	1 (1.5)	1 (1.0)	
Unknown/no answer	1 (1.5)	12 (7.0)	
Nadir CD4 count			0.548
<200 cell/mm^3	37 (54.4)	74 (46.0)	
200-500 cells/mm^3	22 (32.4)	57 (35.4)	
>500 cells/mm^3	2 (2.9)	8 (5.0)	
Unknown	7 (10.3)	20 (12.4)	
Current CD4 count			0.703
200 cells/mm^3	5 (7.4)	11 (7.0)	
200-500 cells/mm^3	24 (35.3)	45 (28.0)	
>500 cells/mm^3	35 (51.5)	86 (53.0)	
Unknown	4 (5.9)	19 (12.0)	
Undetectable viral load	59 (86.8)	140 (87.0)	0.726
Current antiretroviral therapy	67 (98.5)	150 (93.0)	0.115

(Continued on next page)

TABLE 4 *(Continued)*

Variable	Menopause <45 y (n = 68) Median (IQR) or n (%)[a]	Menopause ≥45 y (n = 161) Median (IQR) or n (%)[a]	P[b]
Antiretroviral class (third agent)			0.818
NNRTI	19 (27.9)	44 (27.0)	
Protease inhibitor	25 (36.8)	59 (36.6)	
Integrase inhibitor	13 (19.1)	23 (14.0)	
Another regimen	8 (11.8)	13 (8.1)	
Unknown	2 (2.9)	11 (7.0)	
Hepatitis C infection (ever)	36 (52.9)	54 (34.0)	0.006
Body mass index (kg/m^2)[a]	24.8 (20.5-31.3)	24.2 (21.3-28.4)	0.643
Age menarche (y)	13 (12-14)	13 (12-14)	0.699
Pregnancies resulting in live birth[a]	2 (1-3)	2 (1-3)	0.119

NNRTI, non-nucleoside reverse transcriptase inhibitor.
[a]Median with interquartile range for continuous variables[duration of HIV infection, body mass index, pregnancies resulting in live births]; frequency with proportion for categorical variables [all other variables].
[b]Comparison between women with menopause <45 years versus menopause >45 years using chi-square test for categorical variables and Wilcoxon rank-sum test for continuous variables.
[c]Other sources: sex work, selling drugs, pan-handling, honoraria (workshops, training, etc).

1.06-4.25: compared with no hepatitis C infection). Being separated/divorced/widowed was protective (OR 0.24, 95% CI 0.09-0.66) compared with being married. Being born outside of Canada and ethnicity were no longer statistically significantly associated with menopause <45 years after excluding women with induced menopause. There continued to be no difference between women with menopause <45 years and women with menopause ≥45 years with respect to province, body mass index, parity, age of menarche, or HIV-related factors such as nadir or current CD4 count, use of antiretroviral therapy, or having an undetectable viral load (data not shown). Based on the stepwise selection algorithm for non-induced menopause <45 years, variables selected for the final model included education, marital status, and hepatitis C co-infection. After conditioning on other variables in the model, having less than a high-school education (OR 3.11, 95% CI 1.35-7.19) was the only factor significantly associated with increased odds of menopause occurring at <45 years, although there was a trend for increased risk with hepatitis C co-infection (OR 1.96, 95% CI 0.93-4.14). Being separated/divorced/widowed was protective against early (non-induced) menopause (OR 0.23, 95% CI 0.08-0.65; data not shown).

DISCUSSION

In this cohort of Canadian women living with HIV, median age of menopause was 48 years, which is 3 years lower than average age of menopause in the general Canadian population (51 years).[6,7] Additionally, almost 30% of women experienced menopause at <45 years, and 14% met the definition of premature menopause, substantially higher than the general population where 5% of women experience menopause <45

TABLE 5. *Multivariable analysis of factors associated with menopause <45 years (vs ≥45 years) (n = 220)*

Variable[a]	Univariable logistic regression			Multivariable logistic regression		
	Odds ratio	95% CI	P	Odds ratio	95% CI	P
Relationship status			0.061	Not selected		
Married[b] (ref)						
Single	0.91	0.42-1.99				
Separated[c]	0.43	0.19-1.01				
Education						
SS or higher (ref)						
Less than SS	2.61	1.32-5.13	0.006	2.45	1.22-4.93	0.012
Ethnicity			0.168	Not selected		
White (ref)						
Black	0.42	0.19-0.96				
Aboriginal	1.07	0.49-2.32				
Other	0.59	0.15-2.27				
Born outside of Canada	0.46	0.23-0.91	0.025	Not selected		
Recreational drug use (ever)	2.02	1.10-3.70	0.024	Not selected		
Hepatitis C	2.17	1.20-3.91	0.010	1.90	1.04-3.50	0.038
Smoking (ever)	1.99	1.04-3.81	0.038	Not selected		
Duration of HIV infection (y)	1.03	0.99-1.08	0.117	1.03	0.99-1.08	0.143

CI, confidence interval; SS = secondary school.
[a]Reference groups as follows: relationship status [married/in-a-relationship/common-law], education [completed secondary school or higher], ethnicity [white], region of birth [birth outside Canada vs birth within Canada], ever recreational drug use [vs no history of recreational drug use], ever hepatitis C infection [vs no history of hepatitis C infection], ever smoked [vs never smoked], duration of HIV infection [or per each 1 additional year of HIV infection].
[b]Married/in a relationship/common-law.
[c]Separated/divorced/widowed.

years and 1% experience menopause at <40 years of age.[12] These findings are consistent with previous observational studies that have similarly found that women living with HIV transition through menopause earlier than the general population. In a study of 667 women living with HIV in Brazil, the average age of menopause was 48 years; this was lower than the average age of menopause in the general Brazilian population.[9] Similarly, in a study of women living with HIV in Thailand, average age of menopause was 2 years earlier than the general population.[21] Several studies have also found higher rates of earlier menopause and premature menopause among women living with HIV. In a recent study of 253 women attending an outpatient clinic in Nigeria, 27.9% of women with HIV experienced menopause at ≤45 years of age, which was significantly higher than the 2.7% of women without HIV to experience menopause at this age.[22] In a French study, prevalence of early menopause (<45 years) and premature menopause (<40 years) was 22% and 12%, respectively.[23]

There have been several explanations proposed for these findings. First of all, women living with HIV may have a higher prevalence of sociodemographic factors that are also associated with early menopause, such as African/Caribbean (Black) ethnicity,[15] substance use,[10,15,24] hepatitis C infection,[9,14] and smoking.[10] This was also demonstrated in our study of Canadian women living with HIV, as 65.1% had a history of smoking, 55.9% had ever used recreational drugs, 39.3% had a history of injection drug use, and 39.3% had a history of hepatitis C co-infection. Secondly, there may be some contribution of HIV infection itself, and/or antiretroviral therapy, though this relationship has not been consistently identified. In one observational study from the United States, HIV infection itself was independently associated with higher odds of early menopause (OR 1.73).[14] Furthermore, while some studies have suggested that those with lower CD4 counts are at higher risk of early menopause,[9,14] this has not been consistently demonstrated.[13,25] Importantly, the majority of these observational studies have defined age of menopause based on self-report. While this is consistent with the World Health Organization definition, it may be problematic in this setting, as women with HIV may be at higher risk of amenorrhea (without menopause) than the general population.[25] Therefore, classifying women as postmenopausal based on self-report, without laboratory testing and hormonal confirmation, may not be appropriate in this patient population and may lead to overestimating the prevalence of EM and PM. There was also a high rate of surgical menopause in our population: 15.3% of the entire cohort and 50% of those with menopause <40 years reported surgery as the etiology. This would be expected to overestimate prevalence of EM and PM and reduce average age of menopause in our study. However, the reasons for this high rate of surgical menopause also require further investigation. Previous studies have found a higher incidence of hysterectomy among women with HIV, likely for cervical neoplasia.[26]

Our results also identified, in univariable analyses, several risk factors for menopause <45 years, including a two-fold increased risk with smoking, hepatitis C co-infection, and recreational drug use, and approximately 2.5-fold increased risk with having less than a high-school education. There also appeared to be a protective effect of being born outside of Canada (54% reduced risk), Black ethnicity (58% reduced risk compared with white ethnicity), and a trend for being separated/divorced/widowed (56% reduced risk) being protective compared with being married. In the final multivariable model, only less than high-school education and history of hepatitis C co-infection were selected and remained independently associated with early menopause. Results were fairly consistent after excluding women with induced menopause, with the protective effect of separated marital status becoming significant when looking only at noniatrogenic menopause. Previous studies have established that smoking, hepatitis C, and recreational drug use are risk factors for early menopause, including in women living with HIV infection.[13,23,27] While lower education has not previously been associated with early menopause in women living with HIV, it is a marker of lower socioeconomic status, and has been shown to predispose women to early menopause in the general population.[28-30] This relationship between lower socioeconomic status and early menopause may be mediated by differences in health behavior, such as smoking and/or drug use, poorer overall health, nutritional status, and levels of stress.[31,32] Our results suggest that women who were separated/divorced/widowed are less likely to experience early menopause than women who were married. This is in contrast to previous studies in the general population, which have found that separated/divorced and single women are more likely to experience early menopause.[27,33] This may potentially be due to differences between married and nonmarried women in our cohort compared with other studies, and merits further investigation. The findings that Black ethnicity and birth outside of Canada may be protective against early menopause are also interesting. Ethnicity has not consistently been shown to be associated with menopause in previous studies, but one study of age of menopause in women living with HIV found that African-American ethnicity was associated with an eight-fold increased risk of early menopause, which is contrary to the potentially protective effect found in our study.[23] The possible protective effect of Black race in our study was not statistically significant, so there may, in fact, be no relationship between ethnicity and risk of early menopause. However, it is possible that Black women in this study (Canada) are different from Black women in the study with contrary findings (France), in terms of region of origin, socioeconomic status, and prevalence of other behavioral risk factors such as method of HIV acquisition, smoking, recreational drug use, and so on.

We did not find any relationship between clinical HIV factors, such as CD4 count, having an undetectable viral load, or use of antiretroviral therapy and risk of early menopause. This is consistent with previous literature. While some studies

have found that low CD4 counts among women with HIV predispose to early menopause,[13,14] others have found no association.[23,25] Of note, the population of women in this study had fairly well-controlled HIV infection, as 94.8% were on antiretroviral therapy, 86.9% had undetectable viral loads, and only 7% had a CD4 count of <200 cells/mm^3, which may have limited our ability to demonstrate an effect of these variables.

There are several limitations to this study. This is a cross-sectional analysis; the observational design allows an assessment of associations, but does not allow demonstration of causation. The lack of an HIV-negative control group results in an inability to attribute age of menopause and prevalence of early menopause/premature menopause to the presence of HIV infection. Rather, comparisons could only be made to the general population. Identification and classification of menopausal status was based on self-report of lack of menses for >12 months; however, women with HIV may be at higher risk of amenorrhea without menopause,[25] and the present study does not allow a distinction between these two entities, nor was it possible to objectively confirm postmenopausal status. It would be important to determine if women who have not had menses for >12 months are truly menopausal, as this has implications regarding symptoms, consideration for hormone therapy, contraception counseling, and risk of other comorbidities.[16] The small sample size reduces power, which would have limited ability to find significant associations. Women participating in this study likely represent a select group of women living with HIV in Canada; these women are aware of their HIV status, engaged in care, and voluntarily participated in the study. Additionally, this population of women has well-controlled HIV infection, with the vast majority ($\sim$95%) being on antiretroviral therapy, having an undetectable viral load ($\sim$85%), and having a normal CD4 count >500 cells/mm^3 ($\sim$53%). Therefore, results may not be generalizable to the broader female population living with HIV in Canada. There were 158 women who were classified as postmenopausal based amenorrhea for ≥ 12 months, but who were excluded from this analysis due to missing age of menopause. It is not clear how inclusion of these women into the analysis might alter results. A comparison of known baseline characteristics between women included and excluded from the study was performed, and the only differences appeared to be related to province of origin, number of pregnancies, and marital status (data not shown). Women who were excluded from this study based on missing age of menopause were more likely to be married; however, as being married appeared to increase the risk of early menopause in this study, inclusion of these women would likely have dropped the age of menopause further (if at all), and therefore, it does not appear that this difference would negate the results of this study. There were no other differences between included and excluded women based on measured sociodemographic and clinical variables. Finally, it is important to recognize that the primary analysis in this study did not exclude women who reported induced/iatrogenic menopause, which would potentially bias the results towards earlier age of menopause. These women were included to highlight the high rates of induced menopause (15%), a finding that likely merits further investigation given the implications of early menopause. Additionally, excluding these women from the primary analysis would further reduce sample size and power. To account for this methodology, and to determine if mechanism of menopause influenced our results, a sensitivity analysis was performed. This sensitivity analysis demonstrated similar results for variables influencing age of menopause in women living with HIV.

CONCLUSIONS

This study is the first study to examine age of menopause in Canadian women living with HIV. Similar to other studies from across the world, we found that women living with HIV experienced menopause at a younger age and had higher rates of early menopause and premature menopause than the general population. We also found that education and hepatitis C co-infection influenced risk of early menopause, with other possible modifying factors including marital status and region of birth. Menopause is associated with changes in mood and sexual function, reduced quality of life, and impacts the risk of developing other comorbidities, such as cardiovascular disease and osteoporosis.[12] Therefore, occurrence of early menopause among women living with HIV has implications for medical practitioners caring for these women, as it may impact counseling and management. Furthermore, earlier development of certain comorbidities may also have public health implications in terms of timing of screening and healthcare costs associated with early menopause. Finally, determination of whether biochemical confirmation of menopause should be required in the setting of HIV infection is a dilemma that warrants further investigation and consideration.

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