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MAJOR ARTICLE

Associations of Early Prolonged Secondary Amenorrhea in Women With and Without HIV

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Background. The menstrual cycle is a critical indicator of women's health. Early prolonged secondary amenorrhea increases risks for morbidity and mortality. Menstrual cycle research in women with HIV is inconsistent and often lacks an adequate comparison sample. We aimed to determine whether women with HIV have a higher lifetime prevalence of amenorrhea and whether this is independently associated with HIV and/or other biopsychosocial variables.

Methods. With data from 2 established HIV cohorts, participants assigned female at birth were eligible if aged ≥16 years, not pregnant/lactating, and without anorexia/bulimia nervosa history. Amenorrhea was defined by self-reported history of (1) no menstrual flow for ≥12 months postmenarche not due to pregnancy/lactation, medications, or surgery or (2) early menopause or premature ovarian insufficiency. Multivariable logistic regression models explored biopsychosocial covariates of amenorrhea.

Results. Overall, 317 women with HIV (median age, 47.5 years [IQR, 39.2–56.4]) and 420 women without HIV (46.2 [32.6–57.2]) were included. Lifetime amenorrhea was significantly more prevalent among women with HIV than women without HIV (24.0% vs 13.3%). In the multivariable analysis, independent covariates of amenorrhea included HIV (adjusted odds ratio, 1.70 [95% CI, 1.10–2.64]), older age (1.01 [1.00–1.04]), White ethnicity (1.92 [1.24–3.03]), substance use history (6.41 [3.75–11.1]), and current food insecurity (2.03 [1.13–3.61]).

Conclusions. Nearly one-quarter of women with HIV have experienced amenorrhea, and this is associated with modifiable risk factors, including substance use and food insecurity. Care providers should regularly assess women's menstrual health and advocate for actionable sociostructural change to mitigate risks.

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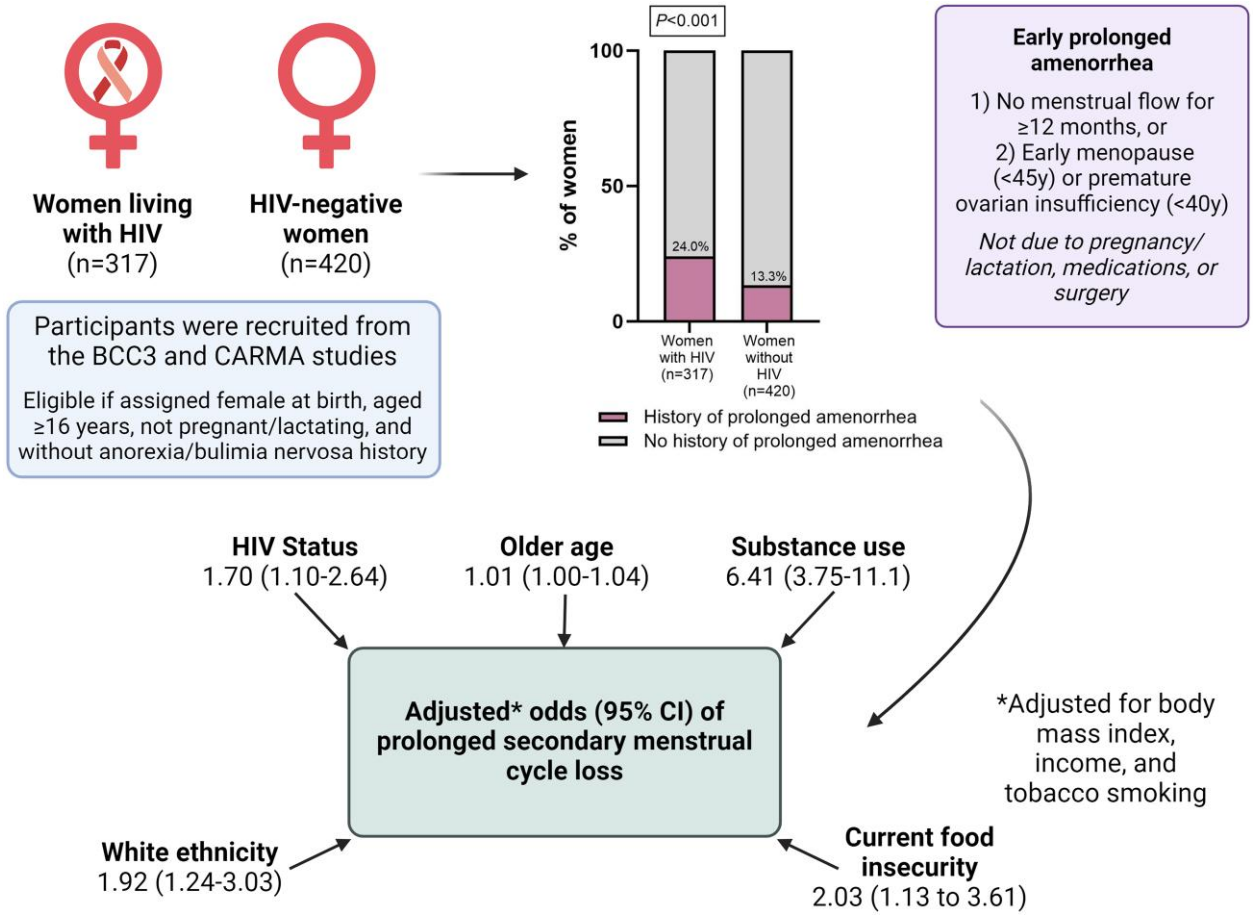
Graphical Abstract



Keywords. amenorrhea; human immunodeficiency virus; hypothalamic adaptive; menstrual cycle disturbances; women.

The menstrual cycle is so important to women's health that some have advocated that it be classified as a fifth vital sign [1]. Secondary amenorrhea, the absence of menstruation in reproductive-aged previously menstruating women, can be due to hypothalamic adaptive reproductive suppression [2]. This hypothalamic amenorrhea is a state of ovarian hormone deficiency that can be caused by poor nutrition, excess exercise, psychological distress, and/or opioid use [3]. Early menstrual cycle loss can also include premature ovarian insufficiency (menopause before age 40 years) or early menopause (before age 45 years). Early and prolonged secondary amenorrhea (henceforth, amenorrhea) predisposes women to higher rates of cardiovascular disease, lower bone density, cognitive dysfunction, mental health disorders, and greater all-cause mortality [4]. As women with HIV are more likely to have these health conditions and experience shorter life expectancies than women without HIV [5, 6], assessing the prevalence and covariates of menstrual cycle loss in this population may give insights into potentially reversible etiologies.

Several studies have evaluated the prevalence of amenorrhea in women with HIV as compared with women without HIV, ranging from as early as 1996 to 2020 [7–13]. Three of these studies used data from the Women's Interagency HIV Study [9–11]. In 2 additional studies, Valiaveettil et al and Cejtin et al reported on the prevalence of amenorrhea in women with HIV without a comparison group, citing frequencies of 6% and 27%, respectively [14, 15]. Studies comparing women with HIV and women without HIV report mixed results, with 4 showing higher frequencies of amenorrhea in women with HIV [8, 11–13] and 3 reporting no difference [7, 9, 10]. In a meta-analysis by King et al [16], women with HIV had 70% greater odds of amenorrhea than women without HIV. Definitions of amenorrhea were inconsistent among studies, ranging from no menses for 3 to 12 months. One study excluded menopausal women according to follicle-stimulating hormone (FSH) levels [11] and others by age or self-report. Most studies examined current amenorrhea rather than lifetime prevalence. Longitudinal data demonstrate that past menstrual

cycle and ovulation changes predict future risks for morbidity and mortality [17, 18]. Additionally, most studies enrolled participants prior to modern HIV treatment guidelines, which promote universal antiretroviral therapy regardless of CD4 count [19].

The knowledge gap that remains is whether women with HIV have higher lifetime frequencies of amenorrhea, based on the stringent criterion of no menses for at least 1 year, and whether this is independently associated with HIV or may be driven by other biological or psychosocial confounders. Thus, we tested the hypothesis that, when compared with women without HIV, women with HIV will be more likely to self-report a history of amenorrhea.

METHODS

Study Setting and Participant Selection

These analyses utilize cross-sectional data from 2 prospective cohort studies of women with and without HIV in British Columbia, Canada. The Children and Women: Antiretroviral Therapy and Markers of Aging (CARMA) study is a cohort of persons with HIV (primarily women and their children) with sociodemographically similar women without HIV that collected data from 2008 to 2018. Visits were completed once every year from 2008 to 2012 and then twice every 5 years. The British Columbia CARMA-CHIWOS Collaboration (BCC3) investigates healthy aging in women with HIV from cell to society [20]. Data collection for BCC3 began in December 2020 and is ongoing, with purposive enrollment of women with and without HIV who share similar demographics and social identities. At the time of writing, 1 baseline BCC3 visit has been completed.

Questionnaires used in the CARMA and BCC3 studies were similar (Supplementary Table 1). Participants were included in this analysis if they were assigned female at birth, ≥16 years of age, and not pregnant or lactating in the last 3 months. For participants enrolled in both studies, only data from the most recent visit were included. Participants were excluded if they had primary amenorrhea or a history of anorexia or bulimia nervosa, as this is commonly associated with amenorrhea [21]. Participants were excluded if they did not complete the study survey.

Patient Consent Statement

Written consent was obtained from all participants involved with this work. CARMA and BCC3 received ethical approval from the University of British Columbia Children's and Women's Research Ethics Board (H09-02867 and H19-00896).

Variables

Amenorrhea was defined as self-report of ever experiencing absent menses for at least 12 consecutive months, not due to pregnancy or lactation, hormonal contraceptive use, bilateral oophorectomy or hysterectomy, chemotherapy, or other endocrinopathies (including polycystic ovarian syndrome or untreated hypo-/hyperthyroidism, adrenal insufficiency, or Cushing disease). This definition of "prolonged amenorrhea" was chosen as amenorrhea lasting for at least 1 year is most likely to cause adverse health outcomes [22]. Women who self-reported early menopause or premature ovarian insufficiency were also considered to have amenorrhea. For women who were currently amenorrheic and aged >45 years, plasma FSH levels were assessed to ensure that the women were not menopausal (cutoff for menopause, FSH ≥25 IU/mL). FSH was measured in real time by the BC Women's Hospital Laboratory with the VITROS Immunodiagnostic Products FSH Reagent Pack, with intra- and interassay coefficients of variation of 2.6% and 6.2% at 20.6 IU/mL, respectively (Ortho-Clinical Diagnostics).

Data were extracted on age, current body mass index (BMI), current income (dichotomized at CAD $20 000 per year in the BCC3 questionnaire and CAD $15 000 per year in CARMA), ethnicity (African/Caribbean/Black, Indigenous, White, other/mixed), past or current substance use (prescription or nonprescription opioids, crack/cocaine, and/or methamphetamines; henceforth, substance use), past or current tobacco smoking, and menstrual history. Ethnicity was dichotomized as White vs non-White, where non-White ethnicity is a surrogate marker of the inequitable experience that may be experienced by those who have a racialized identity. Since amenorrhea is highly correlated with nutrition and stress [2], we included data on food insecurity, posttraumatic stress disorder (PTSD), and violence for BCC3 participants. Current food insecurity was measured by 3 items from the Household Food Security Survey Module [23]; current PTSD by the 6-item PTSD Checklist–Civilian Version (cutoff ≥14) [24]; and past/current violence by 4 items from the BCC3 questionnaire, inclusive of physical, sexual, verbal, and controlling violence [25]. These variables were not assessed in CARMA. Among women with HIV, chart data were also collected for nadir CD4 count as well as most recent CD4 count and HIV viral load (within 6 months prior to the study visit when possible). Current antiretroviral use and years since HIV diagnosis were self-reported.

Statistical Analysis

Continuous variables were compared by *t* test or Mann-Whitney *U* test and categorical variables by chi-square test. Covariates of amenorrhea were assessed by univariable and multivariable logistic regression, including living with HIV, age, BMI, income, ethnicity, tobacco smoking, and substance use. Variables were chosen a priori by literature review and clinical expertise. Missing data were removed from the multivariable model by listwise deletion. Among BCC3 participants only, associations with food insecurity, violence, and PTSD were also assessed. Given the smaller sample size due to missing

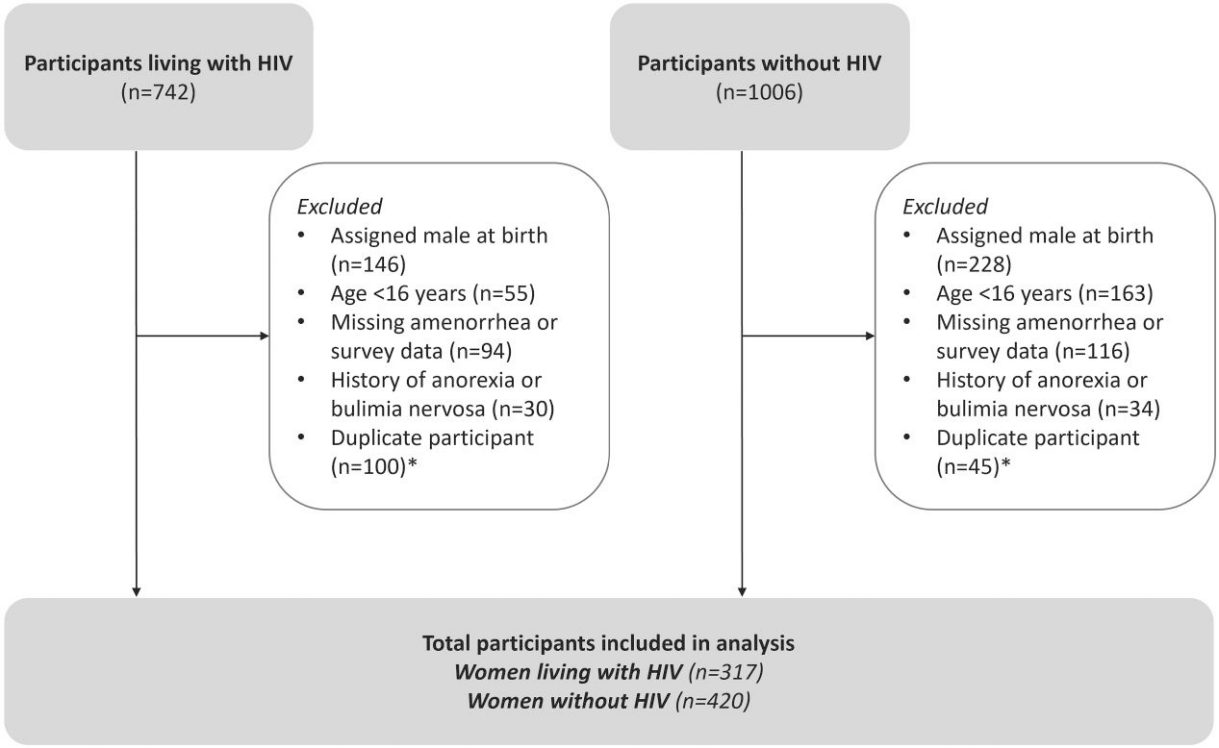


Figure 1. Inclusion and exclusion flowchart of BCC3 and CARMA participants included in the prevalence of early prolonged amenorrhea analyses. **Duplicate participant* refers to someone who was enrolled in both BCC3 and CARMA, in which case their BCC3 data were used. BCC3, British Columbia CARMA-CHIWOS Collaboration; CARMA, Children and Women: Antiretroviral Therapy and Markers of Aging.

data, these analyses were adjusted only for substance use. As an a priori secondary analysis, substance use was trichotomized into never vs past vs current. Among those who ever used substances (n = 289), this variable was categorized into use of opioids vs stimulant use only. As a post hoc exploratory analysis, ethnicity was categorized into White, Indigenous, African/Caribbean/Black, and other/mixed, and associations with amenorrhea were reassessed. All analyses were completed with R version 4.2.2 and RStudio [26]. Figures were made with Prism version 10.0.0 for Windows (GraphPad Software).

RESULTS

Participant Demographics

Of the 742 people with HIV and 1006 participants without HIV in BCC3 and CARMA, 317 and 420 were eligible for inclusion (Figure 1). Groups were similar in age, at a median 47.5 years (IQR, 39.2–56.4) in women with HIV and 46.2 years (32.6–57.2) in women without HIV ($P = .14$). BMI and income were also similar between groups ($P > .05$; Table 1). More women with HIV than women without HIV reported identifying as a non-White ethnicity (62.3 vs 53.7%, $P = .04$), had ever used substances ($P < .001$), and had ever smoked tobacco ($P < .001$).

Lifetime Prevalence of Early Prolonged Secondary Amenorrhea

Overall, 76 (24.0%) women with HIV and 56 (13.3%) women without HIV had ever experienced amenorrhea (Figure 2). With this sample size, we had 96% power to detect a difference of 10.7% between groups at $\alpha = .05$. A breakdown of amenorrhea subtype is provided in Supplementary Table 2. Women with amenorrhea were more likely to be White and have a current household income CAD <$20 000 per year, current/past smoking, and current/past substance use (Table 2). Of those with amenorrhea histories, 70.5% were BCC3 participants and 29.5% were CARMA participants. BCC3 participants were significantly older than CARMA participants (median [IQR] age, 47.6 years [37.6–57.3] vs 44.8 [34.4–55.4]) and more likely to have ever used opioids (155 [31.8%] vs 49 [20.1%]). For BCC3 participants, those with amenorrhea histories also had higher frequencies of food insecurity. Among women with HIV, those with a history of amenorrhea were more likely to have a lower nadir CD4 count as compared with those without amenorrhea. Among the 76 women with HIV who experienced amenorrhea, 36 cases occurred after HIV diagnosis, 31 before diagnosis, and 9 had unknown timing. Of those occurring before HIV diagnosis, 16 were within 5 years of diagnosis.

Table 1. Clinical and Demographic Characteristics of Women With HIV and Women Without HIV Included in Analyses of Early Prolonged Amenorrhea Prevalence

	Women With HIV (n = 317)	Women Without HIV (n = 420)	*P* Value
Cohort			.99
CARMA	107 (33.8)	142 (33.8)	
BCC3	210 (66.2)	278 (66.2)	
Clinical characteristics			
Age, y	47.5 (39.2–56.4)	46.2 (32.6–57.2)	.14
BMI, kg/m^2	26.7 (22.3–32.1)	25.8 (22.0–30.5)	.26
History of prolonged amenorrhea[a]	76 (24.0)	56 (13.3)	**<.001**
Sociobehavioral characteristics			
Ethnicity			**<.0001**
African/Caribbean/Black	58 (18.5)	24 (5.8)	
Indigenous	102 (32.5)	106 (25.4)	
White	118 (37.6)	193 (46.3)	
Other/mixed	36 (11.4)	94 (22.5)	
Ethnicity			**.02**
Non-White[b]	196 (62.3)	224 (53.7)	
White	118 (37.6)	193 (46.3)	
Household income,[c] CAD $/y			.10
≥20 000	175 (57.0)	257 (63.3)	
<20 000	132 (43.0)	149 (36.7)	
Tobacco smoking			**<.001**
Never	119 (37.7)	228 (54.5)	
Ever	197 (62.3)	190 (45.5)	
Substance use[d]			**<.001**
Never	162 (51.4)	280 (67.3)	
Past	36 (11.4)	44 (10.6)	
Current	117 (37.1)	92 (22.1)	
Type of substance ever used			**<.0001**
Opioids only	17 (5.4)	12 (2.9)	
Stimulants only	34 (10.8)	51 (12.3)	
Both opioids and stimulants	102 (32.4)	73 (17.5)	
Neither	162 (51.4)	280 (67.3)	
HIV-related variables			
Current antiretroviral therapy	288 (90.9)	…	…
Undetectable viral load, <40 copies/mL	260 (85.2)	…	…
Current CD4 count, cells/μL		…	…
<200	25 (10.0)		
200–500	60 (24.0)		
>500	165 (66.0)		
Nadir CD4 count, cells/μL		…	…
>200	109 (44.9)		
100–200	68 (28.0)		
50–99	30 (12.3)		
<50	36 (14.8)		
Years since HIV diagnosis	16 (10–23)	…	…
Variables measured in BCC3 participants only			
Food insecurity[e]	76 (42.9)	89 (34.2)	.08
Current PTSD[f]	70 (33.8)	81 (30.0)	.43
Ever experienced violence	159 (90.3)	226 (87.6)	.46
Type of violence experienced			
None	17 (9.7)	32 (12.4)	.38
Physical	111 (63.1)	142 (55.0)	.10
Verbal	150 (85.2)	216 (83.7)	.67
Control	83 (47.2)	100 (38.8)	.08
Sexual	81 (46.0)	111 (43.0)	.54

Data are presented as No. (%) or median (IQR). Bold indicates $P < .05$. Data were missing for BMI (n = 9), viral load (n = 12), current CD4 count (n = 67), nadir CD4 count (n = 58), ethnicity (n = 6), income (n = 24), smoking (n = 3), substance use (n = 6), food insecurity (n = 51), violence (n = 54), and PTSD (n = 11). In total, 145 participants from CARMA were excluded as they were enrolled in both cohorts, in which case their BCC3 data were used.

Abbreviations: BCC3, British Columbia CARMA-CHIWOS Collaboration Study; BMI, body mass index; CARMA, Children and Women: Antiretroviral Therapy and Markers of Aging; PTSD, posttraumatic stress disorder.

[a]Prolonged amenorrhea: menses stopped for at least 12 consecutive months, not due to pregnancy or lactation, hormonal contraceptive use, bilateral oophorectomy or hysterectomy, chemotherapy, or other endocrinopathies, and includes early menopause or premature ovarian insufficiency.

[b]Non-White: Indigenous, African/Caribbean/Black, and other/mixed.

[c]Household income: dichotomized at CAD $15 000/y in CARMA and CAD $20 000/y in BCC3.

[d]Substance use: prescription or nonprescription opioids, cocaine, crack, and/or methamphetamine.

[e]Food insecurity: measured by 3 items from the Household Food Security Survey Module (Canadian Community Health Survey).

[f]Current PTSD: measured by the 6-item PTSD Checklist–Civilian Version.

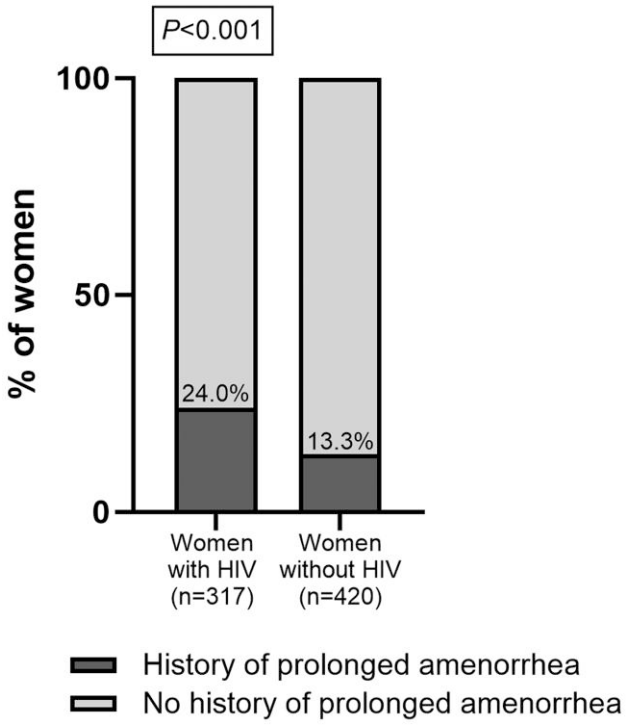


Figure 2. Prevalence of prolonged amenorrhea in women with HIV (n = 317) and women without HIV (n = 420). Proportions were compared by chi-square test. Prolonged amenorrhea was defined as lifetime self-reported history of no menstrual periods for at least 12 consecutive months not due to pregnancy, lactation, hormonal contraceptive use, bilateral oophorectomy or hysterectomy, chemotherapy, or other endocrinopathies.

Table 2. Demographic and Clinical Differences Between Women With and Without Histories of Prolonged Amenorrhea

	History of Menstrual Cycle Loss (n = 132)	No History of Menstrual Cycle Loss (n = 605)	*P* Value
Cohort			**<.001**
CARMA	39 (29.5)	395 (65.3)	
BCC3	93 (70.5)	210 (34.7)	
Clinical characteristics			
Living with HIV	76 (24.0)	56 (13.3)	**<.001**
Age, y	49.2 (41.3–57.2)	46.9 (34.7–56.6)	**.008**
BMI, kg/m^2	27.0 (21.8–31.5)	25.9 (22.2–31.1)	.85
Sociobehavioral characteristics			
Ethnicity			**.04**
Non-White[a]	64 (48.9)	356 (59.3)	
White	67 (51.1)	244 (40.7)	
Household income,[b] CAD $/y			**<.001**
≥20 000	60 (46.5)	372 (63.7)	
<20 000	69 (53.5)	212 (36.3)	
Tobacco smoking			**<.001**
Never	30 (22.9)	317 (52.6)	
Ever	101 (77.1)	286 (47.4)	
Substance use[c]			**<.001**
Never	29 (22.1)	413 (68.8)	
Ever	102 (77.9)	187 (31.2)	
Type of substance			**<.0001**
Opioids only	7 (5.4)	23 (3.8)	
Stimulants only	17 (13.1)	68 (11.3)	
Both opioids and stimulants	77 (59.2)	98 (16.3)	
Neither	29 (22.3)	413 (68.6)	
HIV-related variables[d]			
Currently on antiretroviral therapy	75 (89.3)	263 (89.5)	>.99
Undetectable viral load, <40 copies/mL	63 (86.3)	197 (84.9)	.92
Current CD4 count, cells/μL			.19
<200	35 (56.6)	130 (69.1)	
200–500	19 (30.6)	41 (21.8)	
>500	8 (12.9)	17 (9.0)	
Nadir CD4 count, cells/μL			**.02**
>200	22 (37.3)	87 (47.3)	
100–200	14 (23.7)	54 (29.3)	
50–99	7 (11.9)	23 (12.5)	
<50	16 (27.1)	20 (10.9)	
Years since HIV diagnosis	16 (12–23)	16 (9–23)	.33
Variables measured in BCC3 participants only[e]			
Current food insecurity	49 (63.6)	116 (32.2)	**<.001**
Current posttraumatic stress disorder	31 (34.4)	120 (31.0)	.61
Ever experienced violence [f]	68 (90.7)	317 (88.3)	.70

Data are presented as No. (%) or median (IQR). Bold indicates $P < .05$. Prolonged amenorrhea was defined as absent menses for at least 12 consecutive months, not due to pregnancy or lactation, hormonal contraceptive use, bilateral oophorectomy or hysterectomy, chemotherapy, or other endocrinopathies, and includes early menopause or premature ovarian insufficiency. Data were missing for BMI (n = 9), viral load (n = 12), current CD4 count (n = 67), nadir CD4 count (n = 58), ethnicity (n = 6), income (n = 24), smoking (n = 3), substance use (n = 6), food insecurity (n = 51), violence (n = 54), and PTSD (n = 11). In total, 145 participants from CARMA were excluded as they were enrolled in both cohorts, in which case their BCC3 data were used.

Abbreviations: BCC3, British Columbia CARMA-CHIWOS Collaboration Study; BMI, body mass index; CARMA, Children and Women: Antiretroviral Therapy and Markers of Aging.

[a]Non-White: Indigenous, African/Caribbean/Black, and other/mixed.

[b]Household income: dichotomized at CAD $15 000/y in CARMA and CAD $20 000/y in BCC3.

[c]Substance use: prescription or nonprescription opioids, cocaine, crack, and/or methamphetamine.

[d]n = 317 women with HIV.

[e]n = 210 women with HIV and n = 278 women without HIV.

[f]Violence: ever experienced physical, verbal, sexual, or control violence as an adult.

Covariates of Early Prolonged Secondary Amenorrhea

In univariable analyses, living with HIV (odds ratio, 2.05; 95% CI, 1.40–3.01), older age (1.02; 1.01–1.04), White ethnicity (1.50; 1.02–2.19), income CAD <$20 000 per year (2.02; 1.37–2.97), smoking (3.73; 2.44–5.87), and substance use (7.77; 5.03–12.3) were associated with greater odds of

Table 3. Odds of Prolonged Amenorrhea Assessed by Univariable and Multivariable Logistic Regression in Women With HIV (n = 317) and Women Without HIV (n = 420)

	Unadjusted OR (95% CI)	*P* Value	Adjusted OR (95% CI)	*P* Value
Women with HIV (ref: women with out HIV)	2.05 (1.40–3.01)	**.0002**	1.70 (1.10–2.64)	**.01**
Age (per 1-y increase)	1.02 (1.01–1.04)	**.002**	1.02 (1.00–1.04)	**.02**
BMI (per kg/m^2 increase)	1.00 (0.97–1.03)	.94	0.99 (0.96–1.03)	.75
White ethnicity[a] (ref: non-White)	1.50 (1.02–2.19)	**.04**	1.92 (1.24–3.03)	**.004**
Income <20 000 CAD $/y (ref: ≥20 000 CAD $/y)	2.02 (1.37–2.97)	**.0004**	1.21 (0.75–1.96)	.43
Ever tobacco smoking (ref: never)	3.73 (2.44–5.87)	**<.0001**	1.28 (0.72–2.27)	.40
Ever substance use[b] (ref: never)	7.77 (5.03–12.3)	**<.0001**	6.41 (3.75–11.3)	**<.0001**
Current food insecurity (ref: not food insecure)	3.68 (2.22–6.22)	**<.0001**	2.03 (1.13–3.61)	**.01**
History of PTSD (ref: no PTSD)	1.17 (0.71–1.89)	.53	0.97 (0.57–1.62)	.91
Ever experienced violence (ref: never)	1.29 (0.59–3.24)	.56	0.75 (0.31–1.98)	.53

Bold indicates $P < .05$. Food insecurity, PTSD, and violence were adjusted only for substance use. Likelihood ratio test comparing the full model vs a null model (no predictors): $P < .0001$.

Abbreviations: BMI, body mass index; OR, odds ratio; PTSD, posttraumatic stress disorder; ref, reference.

[a]Non-White: Indigenous, African/Caribbean/Black, and other/mixed.

[b]Substance use: prescription or nonprescription opioids, cocaine, crack, and/or methamphetamine.

amenorrhea (Table 3). In the multivariable analyses, independent covariates of amenorrhea included having HIV (1.70; 1.10–2.64), older age (1.01; 1.00–1.04), White ethnicity (1.92; 1.24–3.03), and substance use (6.41; 3.75–11.1). Among BCC3 participants (n = 210 women with HIV and 278 women without HIV), current food insecurity was significantly associated with greater odds of amenorrhea (3.86; 2.22–6.22) and remained an independent predictor after controlling for substance use (2.03; 1.13–3.61).

In the sensitivity analyses, greater proportions of women with amenorrhea histories had either past (14.4%) or current (62.9%) substance use as compared with those without amenorrhea (past, 10.1%; current, 20.8%; $P < .0001$; Supplementary Figure 1). Current and past substance use was associated with greater odds of amenorrhea in univariable analyses (odds ratio [95% CI], 4.44 [2.32–8.35] and 9.38 [5.49–15.2], respectively; both $P < .0001$). Most women with a history of amenorrhea also had histories of opioid use (64.6%; Table 2). Among those who used substances, opioid use was more common among women with amenorrhea (83.3% vs 63.6%, $P = .001$; Supplementary Figure 2), and this was associated with 2.86 (1.60–5.34, $P = .0006$) greater odds of amenorrhea as compared with using only stimulants. Given this, we conducted a post hoc analysis whereby "substance use" was replaced with "opioid use" in the multivariable logistic regression model. Opioid use was significantly and independently associated with greater odds of amenorrhea (6.62 [4.00–11.22], $P < .0001$), as were having HIV (1.65 [1.06–2.59], $P = .03$) and White ethnicity (2.08 [1.31–3.33], $P = .002$; Supplementary Table 3).

Given that people of non-White ethnicities were less likely to have amenorrhea, this variable was categorized into African/Caribbean/Black, Indigenous, and other/mixed ethnicities in a post hoc exploratory analysis. Among women with and without amenorrhea, 51.1% vs 40.6% were White, 38.9% vs 26.1% were Indigenous, 2.3% vs 13.1% were African/Caribbean/Black, and 7.7% vs 20.1% were other/mixed (Supplementary Figure 3). African/Caribbean/Black and other/mixed ethnicities were associated with lower unadjusted odds of amenorrhea (odds ratios [95% CI], respectively: 0.14 [0.03–0.39], $P = .001$; 0.30 (0.14–0.59), $P = .001$) as compared with the White reference category. However, after adjusting for substance use history, Indigenous (0.60 [0.38–0.96], $P = .03$) and African/Caribbean/Black (0.30 [0.07–0.87], $P = .046$) ethnicities were associated with lower odds of amenorrhea, whereas associations with other/mixed ethnicities (0.60 [0.27–1.23], $P = .16$) were no longer significant.

DISCUSSION

These results add to the growing literature demonstrating a higher lifetime prevalence of early amenorrhea in women with HIV. In this study, women with HIV had nearly 11% higher lifetime prevalence of amenorrhea when compared with women without HIV. After controlling for relevant biological and psychosocial confounders, women with HIV had 70% greater odds of amenorrhea. Importantly, history of opioid use and current food insecurity were associated with 6.62 and 2.02 times greater odds of amenorrhea, respectively.

These findings align with previous research, particularly a meta-analysis by King et al [16], who also found 70% greater odds of amenorrhea in this population. Of the 6 studies included in that meta-analysis, 5 controlled for substance use, indicating that the effect of HIV on amenorrhea is robust, consistent across studies, and independent of the effects of substance use. However, we saw much higher frequencies of amenorrhea in both groups vs that commonly seen in the general population, at 24.0% in women with HIV and 13.3% in women without HIV vs <5% in the general population [27]. This high

prevalence is consistent with Canadian data from the CHIWOS study, which found that 55.9% of 521 premenopausal women with HIV were currently experiencing "menstrual irregularities" [14], defined as deviations from normal in terms of regularity, frequency, volume, duration, and intermenstrual bleeding. In that study, 6% of participants were currently amenorrheic for at least 3 months. Our results are similar to those by Cejtin et al [15], who reported a 27% prevalence of amenorrhea vs the 24% shown here. Furthermore, we found that HIV acquisition preceded or occurred within 5 years of HIV diagnosis in 68% of cases. To our knowledge, this is the first analysis to consider timing of amenorrhea relative to HIV infection.

In addition to the factors measured here, other HIV-related variables could be elevating the risk for amenorrhea. For example, although 85.2% of participants reported an undetectable viral load, this may not have been the case throughout their lifetimes, and many may have once experienced HIV-related wasting or metabolic derangements. This is corroborated by our finding that women with amenorrhea were more likely to have a low nadir CD4 count. Also, persistent inflammation is observed in people with HIV despite effective antiretrovirals [28], potentially contributing to hypogonadism [29]. Women with HIV have been found to have lower antimüllerian hormone levels and shorter telomere lengths, suggesting accelerated reproductive and cellular aging [30, 31]. Emotional distress may also play a role, as well as intersecting experiences of HIV-related stigma, racism, and gender-based discrimination [32].

Substance use, especially opioid use, is a strong correlate of amenorrhea. Opioids suppress the hypothalamic-pituitary-gonadal axis [33], leading to downstream attenuation of ovarian hormones. It would be beneficial to screen for opioid use in the workup of amenorrhea, especially as women with HIV have a higher prevalence of opioid use than women in the general population [34], which was reflected in our data. Future studies should consider whether there are differential effects of opioid type, quantity, duration, and frequency of use on the development of amenorrhea. This is especially salient given the toxic drug and overdose crisis in British Columbia, particularly considering the high prevalence of current substance use among women with HIV in our study.

Food insecurity stands out as a covariate of amenorrhea, independent of substance use. This is unfortunately common among women with HIV [35], with low income, unaffordable housing, employment loss, systemic racism, and impacts of COVID-19 as potential drivers [36]. Insufficient energy intakes for the energy expenditures can lead to cessation of menses, as the body directs limited resources away from fertility toward necessary functions [3]. Macronutrient balance is important, as diets low in fat and carbohydrates are more likely to contribute to amenorrhea [37]. Regularity of calorie consumption also plays a role [38]: those relying on food banks and income assistance may be less likely to regularly consume adequate calories throughout the day. Nutritional inadequacy and subsequent psychological impacts may elevate cortisol levels, which suppress ovarian hormones [39]. Overall, this points to the need for structural change to address food insecurity among equity-deserving women in British Columbia.

Ethnicity was independently associated with amenorrhea, with lower odds in African/Caribbean/Black and other/mixed ethnicity women, likely related to lower frequencies of substance use in these groups. After controlling for substance use, odds of amenorrhea were lower in women of Indigenous and African/Caribbean/Black ethnicities.

Recognizing the high prevalence of amenorrhea in women with HIV is clinically meaningful given the impact of menstrual and ovulatory disturbances on health and all-cause mortality [4]. A Canadian analysis of women with HIV demonstrated that only 34.3% of reproductive-aged women discussed reproductive health goals with health care providers [40], indicating that conversations around sexual and reproductive health are lacking. Health care providers initiating conversations about menstrual health may improve women's understanding of the importance of the menstrual cycle and possible consequences of amenorrhea; it may also increase detection of abnormalities, especially if women are empowered to understand and monitor their cycles. In many cases, amenorrhea may be reversible, as indicated by data from Cejtin et al, who found that 37.6% of women with HIV with 1 year of amenorrhea eventually recovered menses [15]. Actionable risk factors for amenorrhea, such as those identified here, may offer an opportunity to screen and evaluate. However, given that these modifiable risk factors are not easily mutable, future work should consider whether hormone therapy is appropriate and effective for improving health outcomes in this population [41].

Strengths and Limitations

This analysis has important limitations. First, we combined data from 2 related but distinct cohorts; therefore, some variables were not measured consistently (ie, different cutoffs for income) or at all (eg, food insecurity, PTSD, and violence), which may affect the precision of the results. However, menstrual history questions were similar and comparable between the studies. Second, we measured lifetime history of amenorrhea and potential causes by self-report, which is subject to recall bias. To increase precision, we excluded anorexia or bulimia nervosa and screened each case of amenorrhea for confounding by pregnancy, lactation, hormone use, reproductive organ surgery, chemotherapy, and other endocrinopathies. However, we did not have data on use of androgenic drugs, antipsychotics, and other medications that could cause amenorrhea at the time that the participant reported experiencing amenorrhea. Furthermore, we did not have data on antimüllerian hormone levels, which could have aided us in

distinguishing current amenorrhea from menopause. Last, some variables were based on lifetime exposures (ie, substance use, smoking, and amenorrhea), whereas others were current experiences (ie, age, BMI, income, and food insecurity). This limits our ability to determine whether these factors preceded the development of amenorrhea. Thus, these measures may not reliably capture the participant's state at the time of amenorrhea. This is not the case for the important confounder of substance use, for which past and current use was captured. A strength of this study is the cohort size, which allowed for consideration of numerous biological, behavioral, and psychosocial variables. This analysis also utilized a stringent definition of prolonged amenorrhea (lasting ≥1 year), with careful consideration of alternative causes in each case.

CONCLUSIONS

These data, corroborated by previous literature, indicate that lifetime amenorrhea is common in women with HIV and should be evaluated regularly by health care providers. In particular, women should be empowered to understand the importance of their menstrual cycles and recognize signs, potential sources of disturbances, and their consequences. The implications of amenorrhea for women's health outcomes represent an important area of future study.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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