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Prolonged Amenorrhea and Resumption of Menses in Women with HIV

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Abstract

Objective: To compare etiologies of prolonged amenorrhea in a cohort of HIV-infected women with a cohort of similar uninfected at-risk women.

Materials and Methods: Women from the Women's Interagency HIV Study were seen every 6 months, and completed surveys including questions about their menstruation. Those who reported no vaginal bleeding for at least 1 year (''prolonged amenorrhea'') with subsequent resumption of bleeding were compared with women in whom bleeding had stopped permanently (''menopause''). Characteristics associated with reversible prolonged amenorrhea were ascertained.

Results: Of 828 women with prolonged amenorrhea, 37.6% had reversible amenorrhea and 62.4% never resumed menses. HIV-seropositive women with prolonged amenorrhea were significantly younger at cessation of menses than HIV-negative women ($p < 0.0001$). Of those with reversible prolonged amenorrhea, approximately half were taking medications associated with amenorrhea, including 95 (30.6%) hormonal contraception, 80 (25.7%) opiates/stimulants, 16 (5.1%) psychotropic medications, and 6 (1.9%) chemotherapy. HIV-seropositive women were less likely to have medications as a cause of amenorrhea than seronegative women ($p = 0.02$). In multivariable analysis, women with reversible prolonged amenorrhea of unknown etiology were younger ($p < 0.0001$), more often obese ($p = 0.03$), and less educated ($p = 0.01$) than those with permanent amenorrhea. Among HIV-seropositive women, markers of severe immunosuppression were not associated with prolonged amenorrhea.

Conclusion: Women with HIV infection have unexplained prolonged amenorrhea more often than at-risk seronegative women. This is especially common among obese, less-educated women. Prolonged amenorrhea in the HIV-seropositive women should be evaluated and not be presumed to be to the result of menopause.

Keywords: HIV, amenorrhea, menopause, anovulation

Introduction

Potent antiretroviral therapies have resulted in significantly increased survival of persons living with HIV infection.[1] Thus, increasingly, U.S. women with HIV infection are aging[2,3] and making the menopausal transition. Although the number of women living with HIV infection approaching menopause keeps increasing, there is a dearth of research in this population.[4]

Research initially suggested that HIV infection was associated with an earlier age of menopause than that seen in the general population.[5–8] However, subsequent research indicates

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that HIV infection itself may not be a major influence on age at final menstrual period, with comorbid conditions such as illicit substance and medication use contributing to the occurrence of amenorrhea in HIV-infected women.[9–11] Data on this topic, however, are conflicting, with some studies showing an earlier age of menopause in women who are HIV seropositive, and others showing a similar age of last menstrual period in seropositive women and in age, race, and socioeconomic status-matched controls.[12–14]

Amenorrhea can result from chronic anovulation, uterine factors such as Asherman's syndrome, thyroid disease, elevated prolactin from pituitary adenoma, pregnancy or lactation, or hormonal contraception.[15] If it lasts 1 year or longer, a woman may be mistakenly diagnosed as menopausal as per the World Health Organization guidelines.[16]

There are many conditions that might disproportionately affect HIV-infected women. Severe wasting from AIDS may contribute to a hypothalamic cessation of menses.[5] Anovulation may result from opiate or antipsychotic use,[17] cancer chemotherapy,[18] use of hormones as an appetite stimulant,[19] or even emotional stress[20] such as that associated with the initial diagnosis of HIV infection, stigma, and clinical disease progression. Furthermore, protease inhibitor use has been associated with insulin resistance[21] and polycystic ovarian syndrome (PCOS) in a single case report.[22] Amenorrhea has even been reported in an HIV-infected woman secondary to a cerebral toxoplasmosis infection affecting production of gonadotropins.[23]

Although all these conditions may be more common among women with HIV, their frequency in women with amenorrhea is unclear. It is also unclear whether HIV itself might contribute to a cessation of menses in the absence of severe immunosuppression or wasting, and by what mechanism.

The purpose of this study was to explore the potential etiologies of prolonged amenorrhea in a population of HIV-infected and demographically similar uninfected comparison women who are not menopausal. By looking at women who have a resumption of menses after prolonged cessation, we will be excluding menopause as a cause of amenorrhea. Our hypothesis is that amenorrhea associated with HIV infection is often secondary to comorbid conditions, and that HIV may be independently associated with an increase in prolonged amenorrhea that is reversible and not secondary to menopause.

Materials and Methods

The Women's Interagency HIV Study (WIHS) is an ongoing multicenter prospective cohort study of the natural history of treated HIV infection in women in the United States. WIHS enrollment began in 1994 at six study sites (Bronx/Manhattan, Brooklyn, Chicago, Los Angeles, San Francisco, and Washington DC), with expansions from 2001 to 2002 and from 2011 to 2012.

For the purpose of this study, to maximize follow-up, only women from the original enrollment and first expansion (including additional women from the original sites) were included, comprising a total of 4,137 women (3,067 HIV infected, 1,045 uninfected, and 25 seroconverted). Women who converted from HIV negative to HIV seropositive while in the study were excluded from this analysis. Study methods and cohort characteristics have been described in detail elsewhere.[24,25] At each site, human subjects committees reviewed and approved the study, and all participants gave written informed consent.

Participants were seen approximately every 6 months, at which time a physical examination was performed and self-reported data were obtained using standardized survey instruments administered by trained interviewers. Surveys included questions about medical, surgical, and obstetrical history, use of medications including antiretroviral therapy (ART), hormonal contraception, and prescription drugs, and use of illicit drugs, alcohol, and tobacco as well as menstrual data.

HIV serology was performed at baseline and at each visit on women with prior negative results. Among HIV-infected women, quantification of HIV RNA and lymphocyte subsets were measured semiannually using laboratories participating in the NIAID Division of AIDS Virology and Immunology Laboratory Quality Assurance Programs. Beginning in 2003, many WIHS participants underwent anti-Müllerian hormone (AMH) testing using a commercially available enzyme-linked immunosorbent assay (Gen II; Beckman Coulter, Inc., Chaska, MN) with a lower limit of detection 0.08 ng/mL as part of a different investigation.[26]

Questions about menses included the date of last menstrual period ad the presence of any vaginal bleeding in the previous 6 months. Prolonged amenorrhea was defined as at least three consecutive visits without reported vaginal bleeding, or at least 12 months of amenorrhea. Data were reported from the index visit, defined as the first visit at which prolonged amenorrhea was reported. Women who entered the WIHS reporting amenorrhea were not counted as having *prolonged* amenorrhea until this was reported at two consecutive visits. They were considered to have resumption of menses if they reported menses at any visit after having prolonged amenorrhea.

In an attempt to distinguish resumed menstruation from pathologic sources of vaginal bleeding, women diagnosed with cervical cancer or endometrial hyperplasia/cancer were excluded from analysis. Likewise, to exclude menopause as a cause of prolonged amenorrhea, those with an AMH level

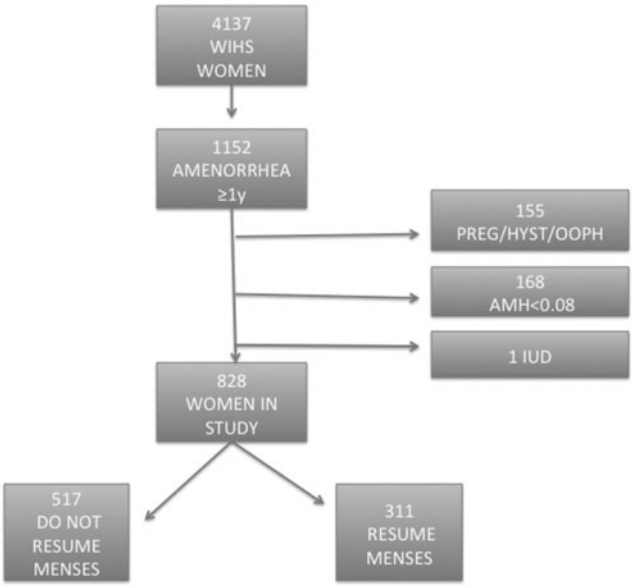

FIG. 1. Women in the WIHS with amenorrhea. WIHS, Women's Interagency HIV Study.

Table 1. Factors Associated with Reversible Amenorrhea and Permanent Amenorrhea ($n=828$)

Variable	*Total* (n=*828*)	*Reversible amenorrhea* (n=*311*)	*Permanent amenorrhea* (n=*517*)	p	*OR (95% CI)*	*AOR (95% CI)*
	Frequency (%)					
HIV seropositive	660 (79.7)	244 (78.5)	416 (80.5)	0.49	0.88 (0.63–1.25)	0.82 (0.56–1.20)
Age, years						
<40	199 (24.0)	138 (44.4)	61 (11.8)	<0.0001	Reference	Reference
40–49	416 (50.2)	132 (42.4)	284 (54.9)		0.21 (0.14–0.30)	0.21 (0.14–0.30)
50+	213 (25.7)	41 (13.2)	172 (33.3)		0.11 (0.07–0.17)	0.10 (0.07–0.16)
Age. mean (median)	44.7 (46.9)	40.5 (41.4)	47.2 (48.4)	<0.0001[a], <0.0001[b]		
Race/ethnicity						
White non-Hispanic	126 (15.2)	49 (15.8)	77 (14.9)	0.63	Reference	
African American	224 (27.1)	89 (28.6)	135 (26.1)		1.04 (0.66–1.62)	
White Hispanic	478 (57.7)	173 (55.6)	305 (59.0)		0.89 (0.60–1.33)	
Parity, mean (range)	2.4 (2.0)	2.2 (2.0)	2.5 (2.0)	0.02[a], 0.01[b]	0.91 (0.85–0.99)	
Smoking status						
Never	184 (22.2)	84 (27.0)	100 (19.3)	0.03	Reference	
Current	442 (53.4)	158 (50.8)	284 (54.9)		0.66 (0.47–0.94)	
Former	202 (24.4)	69 (22.2)	133 (25.7)		0.62 (0.41–0.93)	
BMI						
<18.5	36 (4.4)	9 (2.9)	27 (5.2)	0.39	0.59 (0.27–1.32)	
18.5–24.9	270 (32.6)	97 (31.2)	173 (33.5)		Reference	
25–29.9	222 (26.8)	83 (26.7)	139 (26.9)		1.06 (0.74–1.54)	
30+	273 (33.0)	112 (36.0)	161 (31.1)		1.24 (0.88–1.75)	
Missing	27 (3.3)	10 (3.2)	17 (3.3)		1.05 (0.46–2.38)	
Education						
Less than high school	311 (37.6)	134 (43.1)	177 (34.2)	0.04	Reference	
High-school graduate	251 (30.3)	85 (27.3)	166 (32.1)		0.68 (0.48–0.95)	
Some college or more	266 (32.1)	92 (29.6)	174 (33.7)		0.70 (0.50–0.98)	
Income						
≤$6,000	168 (20.3)	72 (23.2)	96 (18.6)	0.38	Reference	
$6,001–$12,000	308 (37.2)	107 (34.4)	201 (38.9)		0.71 (0.48–1.04)	
$12,001–$18,000	112 (13.5)	42 (13.5)	70 (13.5)		0.80 (0.49–1.31)	
$18,001+	240 (29.0)	90 (28.9)	150 (29.0)		0.80 (0.54–1.20)	
Hepatitis C positive (RNA and AB positive)	255 (30.8)	86 (27.7)	169 (32.7)	0.13	0.79 (0.58–1.07)	
HIV-positive women only						
	$n=660$	$n=244$	$n=416$			AOR (95% CI)[c] $n=459$
HIV RNA detectable ($n=628$)	369 (58.8)	137 (60.6)	232 (57.7)	0.48	1.13 (0.81–1.57)	
Detectable HIV RNA ($n=367$)						
<4,000	167 (45.5)	54 (39.7)	113 (48.9)	0.02	Reference	
4,001–20,000	74 (20.2)	36 (26.5)	38 (16.5)		1.98 (1.13–3.47)	
20,001–100,000	70 (19.1)	31 (22.8)	39 (16.9)		1.66 (0.94–2.95)	
>100,000	56 (15.3)	15 (11.0)	41 (17.8)		0.77 (0.39–1.50)	
CD4 count ($n=633$)						
<200	125 (19.8)	41 (18.1)	84 (20.7)	0.72	Reference	
200–499	265 (41.9)	96 (42.3)	169 (41.6)		1.16 (0.74–1.82)	
500+	243 (38.4)	90 (39.7)	153 (37.7)		1.21 (0.76–1.90)	
Antiretroviral use since last visit	441 (66.8)	144 (59.0)	297 (71.4)	0.001	0.58 (0.41–0.80)	0.64 (0.45–0.92)
AIDS outcome	263 (39.9)	101 (41.4)	162 (38.9)	0.53	1.11 (0.80–1.53)	

Women who never resume menses.
[a]*t*-Test *p*-value.
[b]Median two-sample test *p*-value.
[c]HIV-positive women only, AOR and 95% CIs are adjusted for BMI, age, education, and ART use.
AOR, adjusted odds ratio; ART, antiretroviral therapy; BMI, body mass index; CI, confidence interval.

that was below assay detection (<0.08 ng/mL) were excluded. Women were censored from analysis at the time of a reported pregnancy or lactation and if they had either their uterus or one or both ovaries surgically removed. Women with several episodes of prolonged amenorrhea were only included for the first episode.

Statistics

Demographic and medical characteristics outlined previously were described by HIV status and reversible amenorrhea using bivariate statistics including chi-square test, unadjusted odds ratios (ORs), and 95% confidence intervals (CIs) for categorical variables and *t*-test and median two-sample tests for continuous variables. A multivariable logistic model was fit to determine independent risk factors associated with reversible amenorrhea in the WIHS cohort. A separate model was fit for just HIV-infected women to test the main hypothesis and determine whether specific HIV-related factors and reversible causes were associated with reversible amenorrhea.

Similar bivariate statistics and multivariable models were used to assess factors associated with unexplained reversible amenorrhea compared with women with permanent cessation of menses. Bivariate statistics were also used to describe etiology of amenorrhea by HIV status using chi-square tests. All analyses were conducted using SAS software version 9.4 (SAS Institute, Inc., Cary, NC) and STATA 13.1 software (StataCorp., College Station, TX).

Results

Of the 4,137 participants in the WIHS, only women with available self-reported menstrual data across at least three study visits and not meeting exclusion criteria were included in this analysis. Of 1,152 women in the WIHS with available data and reported amenorrhea for at least 1 year, 155 were excluded for pregnancy or a history of hysterectomy or removal of one or more adnexae, 168 were excluded for having an undetectable AMH level (<0.08 ng/mL), and 1 was excluded because we could not determine whether her intrauterine device was hormone secreting or not (Fig. 1).

There were 828 women included in the study met the definition of prolonged amenorrhea. Of these, 517 (62.4%) did not subsequently report vaginal bleeding during follow-up, and were considered probably menopausal (63.0% of HIV-positive, 60.1% HIV-negative women, NS). The mean age of this group of women was 47.2 years overall, and was significantly younger in the HIV-seropositive women (46.6 years) than in the HIV-negative women (49.6 years), $p < 0.0001$.

The remaining 311 (37.6%) women subsequently reported a resumption of menses at some time after 1 year, and they were considered to have reversible prolonged amenorrhea and not to be in menopause (Table 1). As expected, when comparing women with prolonged amenorrhea that is reversible with those who never resumed bleeding again, those with reversible amenorrhea were younger (mean age 40.5 years vs. 47.2 years, $p < 0.0001$). They also reported fewer pregnancies in the past, were less likely to be current or former tobacco users, and reported fewer years of education than women who did not resume menstruation. In a multivariable model, only younger age remained a significant factor, where women with reversible amenorrhea were younger than women without subsequent menses.

Among HIV-infected women who had prolonged amenorrhea ($n = 660$), indicators of HIV morbidity such as a history of CD4 lymphocyte count <200 or a history of clinical AIDS were similar whether women resumed menses or not. In a multivariable model controlled for age, body mass index (BMI), years of education, and ART use, HIV-seropositive women with reversible amenorrhea were younger (40–49 years, adjusted OR [AOR] = 0.26, 95% CI = 0.17–0.40, $p < 0.0001$; 50+ years, AOR = 0.15, 95% CI = 0.09–0.26, $p < 0.0001$ vs. <40 years) and less likely to be underweight (AOR = 3.0, 95% CI = 0.11–0.82, $p = 0.02$), be a high school graduate (AOR = 0.57, 95% CI = 0.38–0.87, $p = 0.009$), and use ART (AOR = 0.64, 95% CI = 0.49–0.92, $p = 0.001$) than women without subsequent menses.

Of the 311 women who resumed menses, the majority (54.7%) had at least one known potential cause for cessation of menses, and many ($n = 33$, 10.6%) reported multiple potential causes for amenorrhea (Table 2). Hormonal

Table 2. Etiology of Reversible Amenorrhea ($n = 311$)

Etiology	*Total* (n = *311*)	*HIV seropositive* (n = *244*)	*HIV seronegative* (n = *67*)	p
		Frequency (%)		
Any cause				
Known	170 (54.7)	125 (51.2)	45 (67.2)	0.02
Unknown	141 (45.3)	119 (48.8)	22 (32.8)	
No. of possible causes[a]				
0	141 (45.3)	119 (48.8)	22 (32.8)	Reference
1	137 (44.1)	104 (42.6)	33 (49.3)	0.08[b]
>1	33 (10.6)	21 (8.6)	12 (17.9)	0.007[c]
Hormonal contraception	95 (30.6)	72 (29.5)	23 (34.3)	0.45
Opiate/stimulant	80 (25.7)	53 (21.7)	27 (40.3)	0.002
Psychological medications	16 (5.1)	14 (5.7)	2 (3.0)	0.37
Cancer diagnosis	6 (1.9)	3 (1.2)	3 (4.5)	0.09

[a]Global chi-square *p*-value indicates there is a significant difference between HIV status and number of causes ($p = 0.02$).
[b]Compares 0 versus 1 cause. No significant difference in 0 versus 1 cause by HIV status ($p = 0.08$).
[c]Compares 0 versus 2 causes. Compared with having no causes, HIV-seronegative women were more likely to have more than 1 cause ($p = 0.007$).

TABLE 3. COMPARISON OF WOMEN WITH UNEXPLAINED REVERSIBLE AND PERMANENT AMENORRHEA ($n=658$)

Variable	*Total* (n=*658*)	*Unexplained reversible amenorrhea* (n=*141*)	*Permanent amenorrhea* (n=*517*)	p	*OR (95% CI)*	*AOR (95% CI)*
		Frequency (%)				
HIV seropositive	535 (81.3)	119 (84.4)	416 (80.5)	0.29	1.31 (0.79–2.17)	1.44 (0.85–2.45)
Age, years						
<40	95 (14.4)	34 (24.1)	61 (11.8)	0.0005	Reference	Reference
40–49	358 (54.4)	74 (52.5)	284 (54.9)		0.47 (0.29–0.76)	0.47 (0.28–0.78)
50+	205 (31.2)	33 (23.4)	172 (33.3)		0.34 (0.20–0.60)	0.32 (0.18–0.57)
Age, mean (median)	46.6 (48.1)	44.5 (45.8)	47.2 (48.4)	<0.0001[a], 0.003[b]		
Race/ethnicity						
White non-Hispanic	93 (14.1)	16 (11.4)	77 (14.9)	0.51	Reference	
African American	176 (26.8)	41 (29.1)	135 (26.1)		1.46 (0.77–2.78)	
White Hispanic	389 (59.1)	84 (59.6)	305 (59.0)		1.33 (0.73–2.39)	
Parity, mean (range)	2.3 (2.0)	2.2 (2.0)	2.5 (2.0)	0.27[a], 0.30[b]	0.95 (0.86–1.04)	
Smoking status						
Never	134 (20.4)	34 (24.1)	100 (19.3)	0.10	Reference	
Current	347 (52.7)	63 (44.7)	284 (54.9)		0.65 (0.41–1.05)	
Former	177 (26.9)	44 (31.2)	133 (25.7)		0.97 (0.58–1.63)	
BMI						
<18.5	30 (4.6)	3 (2.1)	27 (5.2)	0.03	0.55 (0.16–1.91)	0.44 (0.12–1.56)
18.5–24.9	208 (31.6)	35 (24.8)	173 (33.5)		Reference	Reference
25–29.9	175 (26.6)	36 (25.5)	139 (26.9)		1.28 (0.76–2.14)	1.28 (0.75–2.18)
30+	224 (34.0)	63 (44.7)	161 (31.1)		1.93 (1.21–3.08)	2.20 (1.35–3.58)
Missing	21 (3.2)	4 (2.8)	17 (3.3)		1.06 (0.37–3.67)	1.18 (0.37–3.82)
Education						
Less than high school	241 (36.6)	64 (45.4)	177 (34.2)	0.01	Reference	Reference
High-school graduate	195 (29.6)	29 (20.6)	166 (32.1)		0.48 (0.30–0.79)	0.51 (0.31–0.84)
Some college or more	222 (33.7)	48 (34.0)	174 (33.7)		0.76 (0.50–1.17)	0.94 (0.60–1.47)
Income						
≤$6,000	124 (18.8)	28 (19.9)	96 (18.6)	0.69	Reference	
$6,001–$12,000	250 (38.0)	49 (34.8)	201 (38.9)		0.84 (0.49–1.41)	
$12,001–$18,000	87 (13.2)	17 (12.1)	70 (13.5)		0.83 (0.42–1.64)	
$18,001+	197 (29.9)	47 (33.3)	150 (29.0)		1.07 (0.63–1.83)	
Hepatitis C positive (RNA and AB positive)	211 (32.1)	42 (29.8)	169 (32.7)	0.51	0.87 (0.58–1.31)	

HIV-positive women only

	$n=535$	$n=119$	$n=416$			AOR (95% CI)[c]
HIV RNA detectable ($n=513$)	293 (57.1)	61 (55.0)	232 (57.7)	0.60	0.89 (0.59–1.36)	
HIV RNA ($n=292$)						
<4,000	142 (48.6)	29 (47.5)	113 (48.9)	0.22	Reference	
4,001–20,000	51 (17.5)	13 (21.3)	38 (16.5)		1.33 (0.63–2.82)	
20,001–100,000	53 (18.2)	14 (23.0)	39 (16.9)		1.40 (0.67–2.92)	
>100,000	46 (15.8)	5 (8.2)	41 (17.8)		0.48 (0.17–1.31)	
CD4 count ($n=516$)						
<200	106 (20.5)	22 (20.0)	84 (20.7)	0.91	Reference	
200–499	213 (41.3)	44 (40.0)	169 (41.6)		0.99 (0.56–1.77)	
500+	197 (38.2)	44 (40.0)	153 (37.7)		1.10 (0.62–1.95)	
Antiretroviral use since last visit	375 (70.1)	78 (65.6)	297 (71.4)	0.22	0.76 (0.49–1.18)	
AIDS outcome	208 (38.9)	46 (38.7)	162 (38.9)	0.95	0.99 (0.65–1.50)	

[a] *t*-Test *p*-value.
[b] Median two-sample test *p*-value.
[c] AOR and 95% CIs: None of the HIV variables were significant so were not included in the final model. The final model included age, BMI category, and education status. Similar findings were seen in those who were HIV positive in terms of age, BMI, and education being associated with amenorrhea status as seen in all women. (AOR for age, BMI, and education not shown).

contraception was the most common, with 95 (30.6%) women reporting the use of oral or injectable hormones at the index visit. The most common type of hormonal contraception used in those with prolonged amenorrhea was intramuscular depo-medroxyprogesterone acetate that was used in 72 (75.8%) of those women. The remaining 23 women in this group (24.2%) used oral contraceptives. Of interest, four of the women in the hormonal contraception group reported previous surgical sterilization, and were likely using hormones only to control bleeding or menopausal symptoms.

Other identifiable causes of reversible prolonged amenorrhea were opiate or stimulant use in 80 (25.7%), use of psychiatric medications in 16 (5.1%), and a diagnosis of cancer in 6 (1.9%). Of the cancers diagnosed, the majority were lymphomas, with the remaining being cancers of the lung, brain, breast, and thyroid. Amenorrhea in most of these women was most likely a result of chemotherapy. There were two women with thyroid cancer who most likely did not receive chemotherapy, and so cancer was not included as a possible etiology of their amenorrhea.

There were 141 women (45.3%) who had no identified etiology of reversible prolonged amenorrhea. Almost half of the HIV-infected women (48.8%) with prolonged amenorrhea had no identifiable cause, compared with 32.8% of seronegative women ($p = 0.02$). Likewise, HIV-negative women were significantly more likely (17.9%) than seropositive women (8.6%) to have multiple causes of amenorrhea ($p = 0.007$).

When we compared women with unexplained reversible amenorrhea with women without subsequent menses (Table 3), the results were similar to Table 1. Women with unexplained reversible amenorrhea were significantly younger ($p < 0.0001$), more likely to be obese (AOR = 2.20, 95% CI = 1.35–3.58), and less likely to have graduated from high school (AOR = 0.51, 95% CI = 0.31–0.84). In a multivariable model, all three associations persisted. Looking at HIV-infected women, once again severity of HIV infection was not associated with amenorrhea, and ART use was no longer associated with sustained amenorrhea.

Discussion

HIV is an independent risk factor for prolonged amenorrhea that is not associated with medication or drug use, and that may be misinterpreted as menopause. Amenorrhea has been reported with the use of hormonal contraception,[7,27,28] opiates and stimulants,[29–34] antipsychotics,[17] chemotherapy,[35] and even with emotional stress.[36] In this study, prolonged amenorrhea over 1 year in duration associated with the use of hormones, medications, and opiate or stimulant use is commonly seen in both HIV-infected women and sociodemographically similar uninfected women. As recreational drug use, mental illness, and stress are more common in women living with HIV infection,[17,37,38] this is a group more likely to experience prolonged amenorrhea as a result of these factors.

Among women without these causes, prolonged amenorrhea is associated with younger age, higher BMI, and less education than seen in counterparts who do not resume menses. The association between amenorrhea and less education is difficult to explain biologically. There are reports in the literature including a large meta-analysis demonstrating an association between menopause and decreased socioeconomic status in general and level of education more specifically.[39] Whether this is because of the association between adverse childhood events and both low level of education and early timing of menopause has been proposed.[40,41] The association of amenorrhea with high BMI suggests that many women in our study with reversible amenorrhea have anovulation that is related to obesity such as that seen with PCOS.

The results of this study show that seropositive women often have prolonged reversible amenorrhea for a variety of reasons, and previous reports of an earlier age of menopause in women with HIV infection may have reflected inclusion of women with prolonged but reversible amenorrhea.[29,42,43] We previously demonstrated that the median age at cessation of menses was 47 years in the WIHS cohort, but when follicle-stimulating hormone (FSH) was analyzed, approximately half of the HIV-infected nonmenstruating women did not have a level consistent with menopause.[9]

The majority of seropositive women in this study (65.6%) are on ART, and the severity of HIV disease is not associated with amenorrhea, suggesting that HIV does not often induce hypothalamic amenorrhea through wasting. HIV-seropositive women have an increase in insulin resistance/diabetes and a 50% increase in the metabolic syndrome, with older age, higher BMI, and tobacco use all being risk factors.[21,44] PCOS with amenorrhea and obesity are frequently associated with the metabolic syndrome. Thus, it is possible that the prolonged reversible amenorrhea in HIV-infected women who are obese is from chronic anovulation.

It is unclear from our study whether stress plays a role in amenorrhea, but a very high prevalence of significant stress and abuse was noted in the WIHS cohort.[38] AMH levels are directly associated with antral follicle count, and thus are decreased with menopause and increased with PCOS.[45] Studies have demonstrated that AMH levels are not related to BMI, but are reflective of insulin resistance.[46] AMH level was found to be useful in predicting the age at menopause in HIV-infected women,[47] and when analyzed in a group of women from the WIHS cohort, amenorrhea was associated with a 20%–25% increase in AMH.[26] Thus, the increased AMH seen in HIV-infected women with amenorrhea may be related to chronic anovulation mediated by high levels of obesity and the stress and insulin resistance associated with HIV infection.

Limitations of this study include lack of information on other potential causes of amenorrhea, such as thyroid disease, disorders of prolactin secretion, and hypothalamic etiologies, and information about comorbidities such as diabetes and renal disease. It is unclear whether the women who never resume menses are all postmenopausal, and some may have chronic diseases associated with anovulation such as hypothalamic hypogonadotropism. Menstrual data and substance use information are only based on self-report. The strengths are the large sample size and the longitudinal database spanning over 20 years. Areas for future research include evaluating women in the WIHS with prolonged amenorrhea for level of stress and markers of chronic anovulation, such as the presence of multiple follicles on ultrasound, and ruling out thyroid disease and disorders of prolactin secretion in this group.

Conclusions

It is very important to understand whether the etiology of prolonged amenorrhea is menopause in the HIV-infected

women, in whom reversible amenorrhea is common. With an increase in diseases of bone mineral density and coronary artery disease associated with HIV infection,[48] menopause represents a time when diagnosis and active management of these associated conditions is crucial, especially in cases of early ovarian insufficiency. If amenorrhea is indeed associated with chronic anovulation, contraceptive needs should be addressed and endometrial evaluation and active management to prevent endometrial hyperplasia/cancer is essential.[49] Liberal use of serum FSH and AMH levels and ultrasound can help determine if such a woman is menopausal or in a chronic anovulatory state. Prolonged amenorrhea in the HIV-infected women should never be ignored or assumed to be menopause.

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References

1. Lohse N, Hansen AB, Gerstoft J, Obel N. Improved survival in HIV-infected persons: Consequences and perspectives. J Antimicrob Chemother 2007;60:461–463.
2. Centers for Disease Control and Prevention. HIV among people aged 50 and over, 2018. Available at: www.cdc.gov/hiv/group/age/olderamericans/index.html Updated February 12, 2018. [Accessed February 14, 2018].
3. High KP, Brennan-Ing M, Clifford DB, et al. HIV and aging: State of knowledge and areas of critical need for research. A report to the NIH Office of AIDS Research by the HIV and Aging Working Group. J Acquir Immune Defic Syndr 2012;60:s1–s18.
4. Adam GP, Di M, Cu-Uvin S, et al. Strategies for improving the lives of US women aged 40 and above living with HIV/AIDS: An evidence map. Syst Rev 2018;7:25.
5. Grinspoon S, Corcoran C, Miller K, et al. Body composition and endocrine function in women with acquired immunodeficiency syndrome wasting. J Clin Endocrinol Metab 1997;82:1332–1337.
6. Clark RA, Cohn SE, Jarek C, et al. Perimenopausal symptomatology among HIV-infected women at least 40 years of age. J Acquir Immune Defic Syndr 2000;23:99–100.
7. Schoenbaum EE, Hartel D, Lo Y, et al. HIV infection, drug use, and onset of natural menopause. Clin Infect Dis 2005;41:1517–1524.
8. Bromberger JT, Matthews KA, Kuller LH, Wing RR, Meilahn EN, Plantinga P. Prospective study of the determinants of age at menopause. Am J Epidem 1997;145:124–133.
9. Cejtin HE, Kalinowski A, Bacchetti P, et al. Effects of human immunodeficiency virus on protracted amenorrhea and ovarian dysfunction. Obstet Gynecol 2006;108:1423–1431.
10. Seifer DB, Golub ET, Lambert-Messerlian G, et al. Biologic markers of ovarian reserve and reproductive aging: Application in a cohort study of HIV infection in women. Fertil Steril 2007;88:1645–1652.
11. Massad LS, Evans CT, Minkoff H, et al. Effects of HIV infection and its treatment on self-reported menstrual abnormalities in women. J Womens Health 2006;15:591–594.
12. Tariq S, Delpech V, Anderson J. The impact of the menopause transition on the health and wellbeing of women living with HIV: A narrative review. Maturitas 2016;88:76–83.
13. Imai K, Sutton MY, Mdodo R, Del Rio C. HIV and menopause: A systematic review of the effects of HIV infection on age at menopause and the effects of menopause on response to antiretroviral therapy. Obstet Gynecol Int 2013;2013:340309.
14. Andany N, Kennedy VL, Aden M, Loutfy M. Perspectives on menopause and women with HIV. Int J Womens Health 2016;8:1–22.
15. Heiman DL. Amenorrhea. Prim Care 2009;36:1–17.
16. WHO Scientific Group on Research on the Menopause in the 1990s. WHO Technical Report Series Geneva, Switzerland: WHO, 1996.
17. De Vos M, Devroey P, Fauser BC. Primary ovarian insufficiency. Lancet 2010;376:911–921.
18. Hillard PA. Menstrual suppression: Current perspectives. Int J Womens Health 2014;6:631–637.
19. Berga S, Naftolin F. Neuroendocrine control of ovulation. Gynecol Endocrinol 2012;28 Suppl 1:9–13.
20. Sobieszczyk ME, Hoover DR, Anastos K, et al. The Women's Interagency HIV Study. Prevalence and predictors of metabolic syndrome among HIV-infected and HIV-uninfected women in the Women's Interagency HIV Study. J Acquir Immune Defic Syndr 2008;48:272–280.
21. Vigano A, Manzoni P, Riva S, Brambilla P, Ferrazzi E, Marzi MM. Hyperinsulinemia induced by highly active antiretroviral therapy in an adolescent with polycystic

ovary syndrome who was infected with human immunodeficiency virus. Fertil Steril 2003;79:422–423.
22. Yoganathan KT, Sadiq S, Yoganathan KG. An unusual cause of isolated secondary ovarian failure due to cerebral toxoplasmosis in an African woman with AIDS. BMJ Case Rep 2017 Aug 7;2017. pii: bcr-2017-221337. DOI: 10.1136/bcr-2017-221337.
23. Barkan SE, Melnick SL, Preston-Martin S, et al. The Women's Interagency HIV Study. Epidemiology 1998;9:117–125.
24. Bacon MC, von Wyl V, Alden C, et al. The Women's Interagency HIV Study: An observational cohort brings clinical sciences to the bench. Clin Diagn Lab Immunol 2005;12:1013–1019.
25. Scherzer R, Bacchetti P, Messerlian G, et al. Impact of CD4+ lymphocytes and HIV infection on anti-mullerian hormone levels in a large cohort of HIV-infected and HIV-uninfected women. Am J Reprod Immunol 2015;73:273–284.
26. Hubacher D, Lopez L, Steiner M, Dorfinger L. Menstrual pattern changes from levonorgestrel subdermal implants and DMPA: A systematic review and evidence-based comparisons. Contraception 2009;80:113–118.
27. Kantartzis KL, Sucato GS. Menstrual suppression in the adolescent. J Pediatr Adolesc Gynecol 2013;26:132–137.
28. Miller L, Hughes JP. Continuous combination oral contraceptive pills to eliminate withdrawal bleeding: A randomized trial. Obstet Gynecol 2003;101:853–881.
29. Cooper OB, Brown TT, Dobs AS. Opiate drug use: A potential contributor to the endocrine and metabolic complications in human immunodeficiency virus disease. Clin Infect Dis 2003;37:132–136.
30. Fantry LE, Zhan M, Taylor GH, Sill AM, Flaws JA. Age of menopause and menopausal symptoms in HIV-infected women. AIDS Patient Care STDS 2005;19:703–711.
31. Schmittner J, Schroeder JR, Epstein DH, Preston KL. Menstrual cycle length during methadone maintenance. Addiction 2005;100:829–836.
32. Cofrancesco J Jr., Shah N, Ghanem K, et al. The effects of illicit drug use and HIV infection on sex hormone levels in women. Gynecol Endocrinol 2006;22:244–245.
33. Reddy RG, Aung T, Karavitski N, Wass JAH. Opioid induced hypogonadism. BMJ 2010;341:c4482.
34. Harlow SD, Cohen M, Ohmit SE, et al. Substance use and psychotherapeutic medications: A likely contributor to menstrual disorders in women who are seropositive for human immunodeficiency virus. Am J Obstet Gynecol 2003;188:881–886.
35. Sukumvanich P, Case LD, Van Zee K, et al. Incidence and time course of bleeding after long-term amenorrhea after breast cancer treatment: A prospective study. Cancer 2010;116:3102–3111.
36. Liu JH, Bill AH. Stress-associated or functional hypothalamic amenorrhea in the adolescent. Ann N Y Acad Sci 2008;1135:179–184.
37. Ickovics J, Hamburger ME, Vlahav D, et al. Mortality, CD4 cell count decline and depressive symptoms among HIV-seropositive women: Longitudinal analysis from the HERS. JAMA 2001;285:1466–1474.
38. Cohen M, Hoffman RG, Cromwell C, et al. The prevalence of distress in persons with human immunodeficiency virus infection. Psychosomatics 2002;43:10–15.
39. Schoenaker D, Jackson CA, Rowlands JV, Mishra GD. Socioeconomic position, lifestyle factors and age at natural menopause: A systematic review and meta-analyses of studies across six continents. Int J Epidemiol 2014;43:1542–1562.
40. Mishra GD, Cooper R, Tom SE, Kuh D. Early life circumstances and their impact on menarche and menopause. Womens Health 2009;5:175–190.
41. Ruth KS, Perry JRB, Henley WE, Melzer D, Weedon MN, Murray A. Events in early life are associated with female reproductive ageing: A UK biobank study. Sci Rep 2016;6:24710.
42. Calvet GA, Grinsztejn BG, Quintana Mde S, et al. Predictors of early menopause in HIV-infected women: A prospective cohort study. Am J Obstet Gynecol 2015:212:765e1–13.
43. Cicconi P, Ammassari A, Ladisa N, et al. DIDI Study Group. Prevalence of prolonged amenorrhea in HIV-infected women: Results from the Italian DIDI study. J Acquir Immune Defic Syndr 2012;61:e19–e21.
44. Nansseu JR, Biona JJ, Kaza AD, Noubian JJ. Incidence and risk factors for prediabetes and diabetes mellitus among HIV infected adults on antiretroviral therapy: Systematic review and meta-analysis. Epidemiology 2018;29:431–441.
45. Pigny P, Jonard S, Robert Y, Dewailly D. Serum anti-Mullerian hormone as a surrogate for antral follicle count for the definition of polycystic ovary syndrome. J Clin Endocrinol Metab 2006;91:941–945.
46. Skalba P, Cygal A, Madej P, et al. Is the plasma anti-Mullerian hormone (AMH) level associated with body weight and metabolic, and hormonal disturbances in women with and without polycystic ovary syndrome? Eur J Obstet Gynecol Reprod Biol 2001;158:254–259.
47. Scherzer R, Greenblatt RM, Merhi ZO, et al. Use of anti-mullerian hormone to predict the menopausal transition in HIV-infected women. Am J Obstet Gynecol 2017;216:46.e1-11.
48. Kojic EM, Wang C, Cu-Uvin S. HIV and menopause: A review. J Womens Health 2007;16:1402–1411.
49. Goodman NF, Cobin RH, Futtenweit W, Glueck JS, Legro RS, Carmina E. American Association of Clinical Endocrinologists (AACE): American College of Endocrinology ACE); Androgen Excess and PCOS Society: Guide to the best practices in the evaluation and treatment of polycystic ovary syndrome-Part 2. Endocr Pract 2015;21:1415–1426.

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