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In People Living with HIV (PLWH), Menopause (natural or surgical) Contributes to the Greater Symptom Burden in Women: results from an online US survey

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Abstract

Objective—The majority of people living with HIV in the US are now over the age of 50, but symptom burden research has seldom included older women or the potential role of menopause. To examine the influence of menopause as part of sex differences in HIV symptom burden.

Methods—A cross-sectional study was conducted that included both a sex-based analysis of previously reported HIV symptom characteristics of 1342 respondents to an online survey (males, $n = 957$; female, $n = 385$) and a follow-up online survey of menstrual bleeding patterns (inferred menopause) in eligible females ($n = 242$) from the respondent pool. Using linear mixed models, we identified predictors of symptom burden scores in female respondents.

Results—For the most troublesome symptoms assessed in the sex-based analysis, depression scores were similar ($p > .05$), but higher (worse) burden scores for fatigue ($p = 0.013$) and muscle aches/pains ($p = .004$) were exclusively observed in females after adjusting for covariates. Respondents to the female survey ($n = 222$) were predominantly Black, heterosexual, non-smokers and obese, with an HIV diagnosis of approximately 16 years and at least one co-morbid condition. Burden scores were higher in women reporting amenorrhea due to natural menopause or hysterectomy ($n = 104$) vs. the menstruating group ($n = 118$) for muscle aches/pains ($p = 0.05$),

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fatigue ($p=0.03$), and difficulty falling asleep ($p=0.04$), independent of age, HIV duration, and # of HIV associated non-AIDS conditions.

Conclusions—Two of the most common symptoms in people living with HIV (PLWH) – fatigue and muscle aches/joint pains - invoke additional burden in women. Independent of aging, symptom burden may be exacerbated after menopause, supporting a shifting paradigm for HIV care management.

Keywords

HIV; sex differences; symptoms; menopause

Introduction

Multi-site cross-sectional surveys have demonstrated that persons living with HIV (PLWH) report fatigue, depression, poor sleep, and difficulty concentrating among the most frequent and debilitating symptoms linked to HIV,¹ but much of the research on the symptom experience among PLWH is dated,^{2–10} restricted to single site studies,^{11–13} and based on old symptom indices.^{7,8,12–18} Moreover, the demographic profile of PLWH has changed considerably in the last decade with substantial numbers of females affected by the disease.¹⁹ Adding further to the complexity of the contemporary symptom experience is the greater proportion of women over the age of 50 now living with the illness.²⁰

As a result of these demographic changes, sex and gender differences in disease processes/ progression, complications and treatment outcomes are emerging. Given the vast proportion of women living with HIV (WLWH) who are, and will be, transitioning through the menopause, the ability to distinguish HIV-related symptoms (including those due to co-morbid conditions) from those common to reproductive aging is important for improving health care management and reducing sex/gender-based disparities. Despite this, the symptom experience of WLWH in the context of the female reproductive cycle has been largely understudied or compared to men. In one of the first online national surveys of 1373 PLWH (mean age of 48.5 years) where co-morbid conditions were common and the majority (92%) were receiving cART,²¹ we reported that fatigue, depression, muscle aches/pains, and difficulty falling asleep were the most frequently reported symptoms, with significant race/ ethnicity and income differences evident in symptom burden. In this sample, composed of 70% males, sex differences in symptom burden were few: only muscle aches and pains, reported as the third most common symptom next to depression and fatigue, was associated with higher burden scores in women vs. men, although strong trends were observed for fatigue and staying asleep. Because in healthy populations these symptoms are known to be exacerbated after menopause,^{22,23} independent of age, we carried out a more precise sex-based analysis of the original data set along with a follow-up survey in eligible female respondents to explore the role of menstrual cycle status (to infer menopause) in symptom burden in this same PLWH population.

Materials and Methods

Design and sample

The study was approved by the Columbia University Medical Center IRB prior to the start of any research activities. As reported in the parent study, we conducted an anonymous, cross-sectional online survey of the symptom profile of 1373 PLWH in the US from February to August 2016.²¹ Study participants from the US were recruited through banner ads placed on five large social networking websites. Participants were eligible for the study if they were HIV+, 18 years or older, able to read and respond in English, resided within the US, reported having experienced at least one bothersome symptom in the past 30 days, and were willing to participate in an online survey about their health.

To enrich the data for female sex characteristics, a follow-up survey of menstrual cycle history was conducted approximately 4 weeks after study completion in those self-reported females who provided email addresses for re-contact (n = 385). Each respondent to the follow-up survey received a \$10 gift card. Details of the methods for recruitment, eligibility, consent, and confidentiality as well as a description of the symptom features and co-morbid conditions of the parent study's sample are reported elsewhere.²⁴ In this report, we describe a secondary analysis of symptom burden features by sex assigned at birth and in a follow-up survey in eligible female respondents compare HIV symptoms based on menstrual bleeding history to infer menopause status.

Measures

Demographic and clinical characteristics

The original survey collected the following demographic information: current age, gender identity (male, female, transgender male, transgender female, gender queer), sex assigned at birth (male or female), sexual orientation (homosexual, heterosexual, bisexual), Hispanic or Latino ethnicity, race, level of education and income level. All questions had a "prefer not to answer" response option. Age was grouped according to the National Center for Health Statistics categories.²⁵ In analyses, race and ethnicity were combined into 5 categories: White, non-Hispanic; Black, non-Hispanic; Hispanic; Other, and Missing. Income by category (<\$20,000, \$20,000-\$59,000, and \$60,000). Participants were asked questions about body weight in pounds and height in feet and inches, the year in which they first tested positive for HIV, use of cART, and use of cigarettes or e-cigarettes (regular smoker, occasional smoker, former smoker, and I don't smoke). BMI was calculated by converting data to the metric system, dividing body mass (kg) by the square of the body height (mm) to yield values expressed as units of kg/m².

HIV symptom questionnaire

The symptom questions used in the checklist for the parent survey were based in part on the 45-item Revised Sign and Symptom Check-List for HIV (SSC-HIVrev).²⁶ We selected the 20 most frequently reported items by PLWH in a 775 person multi-site study¹ and in another multi-site study of 359 PLWH.²⁷ In addition, 8 other symptoms (balance difficulties, dry eyes, heartburn, painful sex, sensitivity to noise, speech difficulties, urination difficulties and

erection problems) identified by the clinician members of our study team who treat PLWH with HIV Associated Non-AIDS (HANA) conditions were added to yield a final set of 28 symptoms common to both HIV and HANA conditions: anxiety, change in appetite, change in weight, clumsiness, constipation, cough, decreased sex drive, depression, diarrhea, difficulty concentrating, difficulty falling asleep, difficulty staying asleep, difficulty urinating, difficulty with speech, dizziness, dry eyes, erection problems, fatigue, fever, forgetfulness, heartburn, muscle aches/joint pain, nausea, neuropathy, noise intolerance, pain during sex, shortness of breath, and thirst or dry mouth. The Memorial Symptom Assessment Scale was used to assess symptom burden,²⁸ a well-validated self-report index that combines frequency and bothersomeness, and has been used in various clinical populations including AIDS patients.^{29,30}

For all 28 symptoms, participants were asked to distinguish those experienced in the past 30 days that made it difficult to carry out daily activities (Yes or No). For each symptom selected, respondents were asked how much it interfered with day-to-day activities (a little bit, somewhat, quite a bit, and very much) to yield a burden score ranging from 0 (no impact on daily activities) to 4 (interfered very much with daily activities). For the sex-based comparison reported here, we omitted erection problems from the analyses for a total of 27 symptoms assessed.

Menstrual bleeding patterns

A follow-up survey was developed to assess patterns of menstrual bleeding and amenorrhea based on the STRAW (Staging of Reproductive Aging in Women) criteria, a standardized series of questions for assessing stages of the menopause transition,³¹ which has been used in studies of healthy peri-menopausal women,³² and the cross-sectional survey of HIV-infected and uninfected participants in the Women's Interagency HIV Study.³³ Specifically, we used a subset of STRAW questions about the nature of the vaginal bleeding pattern at the time of study (periods are regular and predictable not due to birth control pills/hormones; regular and predictable due to birth control pills/hormones; less predictable and more irregular not due to pregnancy or breastfeeding; very irregular, no period in the last 3–11 months), and amenorrhea: (periods are absent due to natural menopause in the last 12–48 months; absent due to natural menopause in the last 5 years or more; absent due to hysterectomy). We also collected information about the use of hormones for menopause.

Data Management and Analysis

As part of a larger study to examine the symptom profile and self-care strategies of PLWH with HANA conditions²⁴, we collected the following information as co-variables: education, age, sex, sexual orientation, smoking status, BMI, years living with HIV diagnosis, and HANA conditions. HANA conditions included: asthma, bronchitis, cardiovascular disease, COPD, diabetes, liver disease, osteoporosis, renal failure, or arthritis.^{34,35} For the sex-based analysis, the data collected in the follow-up reproductive status survey was linked through study identifiers to the data collected in the original symptom survey. All data were entered into a data management program (*Excel*), and data integrity and assumptions were checked. Descriptive statistics, such as mean score and standard deviation, proportions, two sample t-

tests, Chi-square tests and Fisher's exact test were performed to examine sample characteristics and bivariate correlations between variables of interest. SAS V9.3 (SAS Institute Inc., Cary, NC, USA) was used for analyses. To examine the association between self-reported sex and each symptom, we conducted a linear mixed model analysis, controlling for the effect of covariates known to influence the HIV symptom experience (age, smoking status, BMI, years living with HIV diagnosis, number of HANA conditions). To explore the influence of menopause on symptom burden, we dichotomized respondents in the follow-up survey according to two non-overlapping menstrual bleeding categories: those reporting at least one menses episode within the last 12 months were categorized as "menstruating"; those with no period for at least the last 12 months due to natural menopause or hysterectomy, were defined as "amenorrheic." The impact of menstruation status (i.e. inferred menopause) on symptom burden score was estimated using the same linear mixed model described above, adjusting for the following covariates: age, duration of HIV infection and HANA conditions. For all analyses, $P < 0.05$ was considered statistically significant.

Results

Sex-based analysis of the original survey

Demographics—There were 1342 survey respondents who self-identified as male or female in response to questions for both sex at birth and gender identity (males = 957; females = 385). We excluded transgender participants from the final sample since their number was very small (genderqueer = 4 (0.29%); transgender female = 8 (0.59%); transgender male = 2 (0.15%), and unlikely to yield a significant finding in our final analysis. Except for similar smoking rates, there were significant differences between males and females for all other characteristics. Self-identified females were more likely to be Black (46.5% females vs. 19.2% males, $p < .001$), heterosexual (91.2 % females vs. 4.5% males, $p < .001$), and report less education (less than high school: 9.9% females vs. 1.7% males, $p < .001$) and lower income (<\$20,000: 50.7% females vs. 31.6% males, $p < .001$) compared to males. Although younger on average (female vs. male: 46.9 ± 11.2 years vs. 49.5 ± 11.8 years, $p < .001$), females were more likely than males to be obese (females vs. males: 32.8 ± 8.9 mm/kg² vs. 27.9 ± 5.3 mm/kg², $p < .001$), report a longer duration of HIV infection (females vs. males: 15.5 ± 8.8 years vs. 14.4 ± 10.1 years, $p < .001$) and greater number of non-HIV associated conditions (females vs. males: 1.1 ± 1.0 vs. 0.86 ± 0.9). Approximately 93% ($n=1247$) of the participants reported taking cART with no significant difference in use rates between males and females.

Symptom burden scores—Table 1 presents a comparison of mean scores for symptom burden (combined frequency and bother) between males and females for the 27 symptoms assessed. For both sexes, the most common symptoms contributing to burden were fatigue, muscle aches and pains, and depression. In women, burden scores for both fatigue and muscle aches/pains were significantly worse compared to men; the burden score for depression in females though higher, was not different. Compared to males, symptom burden was also higher (worse) in females for shortness of breath (11th most common), thirst

(14th) and nausea (19th), after adjusting for covariates; no symptom was associated with higher burden in males.

Females-only follow-up survey

As shown in Table 2, a total of 222 of the original 385 respondents (58%) who self-identified as female (sex at birth concordant with current gender identity) completed the follow-up online questionnaire. Of these, 118 reported at least one period in the last 12 months (menstruating group): 63 (53%) had regular and predictable periods, not due to birth control pills/hormones; 37 (31%) had less predictable and more irregular periods, and 18 (15%) had regular and predictable periods due to birth control pills/hormones, while 104 had not had a period in 12 months or more due to natural menopause (n = 53) or hysterectomy (n= 51). Thirteen women reported taking hormone replacement therapy; of these 4 women were in the menstruating group and 9 were in the post-menopausal group.

As shown in Table 2, the menstruating group was younger on average by approximately 15 years (39 ± 8.6 years vs. 54.3 ± 7.3 years, $p < 0.001$). Not surprisingly, they reported a shorter duration of HIV infection by approximately 5 years (13.1 ± 8.5 years vs. 18.2 ± 7.8 years, $p < 0.001$) and fewer HANA conditions (0.65 ± 0.87 vs. 1.34 ± 1.03 , $p < 0.001$) vs. those reporting amenorrhea due to menopause or hysterectomy. There were no between-group differences for BMI, race, smoking, sexual orientation, income, or educational attainment. In the menstruating group, the five HIV symptoms with the highest mean burden scores were muscle aches/pains, depression, neuropathy, fatigue and difficulty falling asleep, respectively. After adjusting for age, duration of HIV infection and number of co-morbid conditions, mean symptom burden scores remained higher (worse) in the non-menstruating group for three of these symptoms: muscle aches and pains (1st), fatigue (3rd), and difficulty falling asleep (5th) (Table 3).

Discussion

Improvements in survival have led to increasing numbers of WLWH reaching menopause age and beyond,³⁶ but how this accounts for the higher HIV morbidity and worse quality of life observed in women is not clear.^{36,37} In this study, we sought to better characterize the role of female sex in the contemporary HIV symptom experience using a sample of male and female respondents to a national online survey, supplemented with a follow-up menstrual bleeding questionnaire to infer menopause status. With this approach, we confirmed a more adverse picture of contemporary HIV infection in females vs. males including a greater burden (frequency and bother) imposed by the most commonly reported HIV symptoms: fatigue, muscle aches/joint pains, depression and poor sleep^{38–40}. Our results support earlier sex-based analyses of data obtained from face-to-face interviews where mean burden scores were higher (worse) in women vs. men for both fatigue and muscle aches/joint pain.^{30,41,42} The consequences of this health disparity is not trivial: individually and in tandem, this adverse symptom profile in women has been associated with a worse quality of life,^{30,40,43,44} higher global burden,³⁰ more adverse frailty,⁴⁵ and higher rates of neurocognitive impairment.⁴⁶

The magnified profile of the symptom experience in women living with HIV (WLHIV) has previously been attributed to sex-based nuances in symptom appraisal and assessment, potential biases in self-reporting,^{47,48} higher rates of poverty and low education¹⁹ as well as biological differences in the disease process itself.³⁰ However, as the proportion of women expands within the aging cohort of affected individuals, the extent to which sex-based differences in HIV symptomatology can be explained by menopause has become of increasing interest. Specifically, the hypoestrogenism induced by menopause has been indicted as the cause of magnified morbidity in women due to effects on the cardiovascular, skeletal, and immune systems.^{49,50} Despite this, most attention has focused on the impact of HIV on the menopause experience rather than the converse.^{36,51} For example, in contrast to a rich body of work on menopause features (age of the final menstrual period; menopause symptoms) in WLHIV, the authors of several reviews note the scarcity of attention to menopause effects on HIV outcomes, including quality of life with negligible findings to date.^{51,52}

To overcome one limitation in prior sex-based HIV symptom research, we enriched our female survey with follow-up questions about menstrual bleeding patterns. By dichotomizing the female sample on this variable and accounting for other relevant characteristics, we were able to demonstrate that inferred menopause (natural or surgical) was an independent predictor of distress for the same HIV symptoms as those with markedly worse female burden in our sex-based analysis. The higher burden incurred for fatigue, muscle aches/joint pain and impaired sleep in the post-menopause women after adjusting for age, comorbid conditions and HIV duration is especially troubling given the already increased risk for accelerated bone loss, sarcopenia and frailty in this population.⁵³

To what extent this finding is confounded by an overlap between symptoms of menopause and consequences of HIV is difficult to untangle as this interaction is likely multidimensional and bidirectional, i.e. menopause exacerbates HIV and HIV exacerbates menopause.⁵⁴ For example, the muscle aches/pains, fatigue and sleep problems attributed here to HIV, are not only common features of menopause in healthy ethnically-diverse populations,^{22,23,55,56} but when studied as menopause symptoms in WLWH, have demonstrated greater prevalence and severity vs. uninfected peers in most^{30,57,58} but not all investigations.⁵⁹ Whether this magnified symptomatology is due to the earlier debut of ovarian aging as measured by lower antimullerian hormone levels in WLWH compared to uninfected counterparts⁶⁰ awaits a more comprehensive assessment.

With the exception of a well-established link between HIV and hot flash severity,⁵⁷ consistent evidence for an influence of HIV on menopause-related changes in depressed mood and sleep symptoms is lacking when the most rigorous designs are used. The Women's Interagency HIV Study (WIHS), a large, US multicenter study of HIV-infected and non-HIV-infected women of similar socioeconomic status, found that despite higher rates of depressed mood in the early perimenopause in both groups (when studied as a menopause symptom), it was not related to HIV status.⁶¹ In a second evaluation of the same cohort, only verbal memory as part of a subset of cognitive symptoms was greater in seropositive women; sleep symptoms worsened with more advanced menopause stage but were not predicted by HIV status.³³ In our study, we did not see an additive effect of

menopause status on symptom burden for depression, although burden scores were second only to those for muscle aches/joint pains. Taken together, these data strengthen the view that depression is a complex and pervasive health problem in WLWH which may not be significantly worsened by menopause.

Such inconsistent findings have led the authors of recent reviews to conclude that factors such as unhealthy lifestyle, economic adversity, accelerated aging, disease mechanisms, and cART pharmacokinetics have been proposed as likely contributors to the magnified symptoms in midlife WLHIV,⁵² but in a symptom-dependent fashion and with variable interplay across study populations.^{36,51} Moreover, symptoms such as depressed mood,^{62,63} fatigue,⁶⁴ pain³⁹ and impaired sleep⁶⁵ are known to co-vary for both HIV manifestations as well as menopause,⁶⁶ demonstrating moderating and mediating effects on one another. To what extent this was a factor here requires further study with both HIV-infected and uninfected peers to examine symptom cluster patterns using biobehavioral measures of menopause status, HIV characteristics and changes over time.

To reduce confusion regarding symptom attribution, we intentionally avoided asking questions about menopause symptoms in either survey. Moreover in our sample, the burden score was low for the item “fever/night sweats/chills” compared to other symptoms and not different between women and men, or elevated in the amenorrheic subsample, suggesting that the female respondents did not confuse HIV manifestations with the night sweats or hot flashes of menopause.

At the same time, both women living with HIV as well as their clinicians may be confused as to the source of symptoms. One study of menopause symptom attribution demonstrated a 3-fold higher number of women with HIV who did not know why they had hot flashes or vaginal dryness vs. the uninfected group.⁵⁴ In an investigation in WLWH in methadone treatment fewer than 10% of the sample positively identified muscle achiness and poor sleep as menopause symptoms.⁶⁷ While several researchers have acknowledged the need for greater recognition by clinicians of muscle aches and pains and sleep-related problems as hallmark features of menopause,^{68,69} for HIV care providers this may be especially true. Taken together, our findings support the inclusion of measures of menopause status in both clinical practice as well as research to better account for the differential symptom burden between men and women living with HIV.

Limitations

There are several limitations to our study. The generalizability of the results is limited to US populations of HIV-infected individuals who are Internet users. Our follow-up survey had a modest response rate and nonresponse bias is possible. At the same time, the use of an online recruitment strategy and survey method may have contributed substantially to the efficient and cost-effective approach for engaging a large research sample where the use of social media is widespread. Additionally, the lack of compensation for respondents may have helped to reduce the potential for fraudulent responses, a special concern in online data collection. We also recognize the selection bias in comparing a largely gay male subsample who was mostly white (70%) with a largely Black, heterosexual female subsamples of lower

income and education. Nonetheless, the demographics of our respondents correspond with those typical of the HIV population in the US where African American women with similar backgrounds are disproportionately affected by HIV (61% of diagnoses in 2015) compared to White and Hispanic/Latino women (19% and 15%, respectively).¹⁹ As this was a secondary analysis of an existing web-based data set, we were also constrained by the cross-sectional nature of the design limiting our ability to assess causality, the threat of recall bias in responses, and the lack of medical records and clinical biomarkers to confirm HIV characteristics and menopause status. Moreover, it is possible that in some women, especially those in the younger age ranges, the prolonged amenorrhea reported as spontaneous menopause was due to HIV morbidity. Additionally a comparison group of demographically-similar women without HIV would have reduced the risk of inadequate control for other confounding factors likely to explain the association between menopause and symptom burden. Because the SSC-HIVrev survey²⁶ asks questions pertaining to symptoms associated with HIV infection, and does not ask questions specific to menopausal symptoms, direct causality (menopause status) cannot be established. Finally, gender role was not assessed as a potential contributor to sex-based symptom profiles. Recently, Norris et al⁷⁰ demonstrated that the difference in angina scores between male and female cardiac patients was attenuated with the inclusion of a gender index tool to differentiate psychosocial factors from biologic sex. Such an approach may be especially valuable in studies of PLWH.

Conclusion

Although women in the US comprise less than one fifth of those with an HIV diagnoses and have a similar life expectancy as men living with HIV, they experience greater symptom burden. This paper reports on findings from a sex-based analysis of an online survey of PLWH enriched with follow-up data on menopause status in the female subsample. We demonstrated that two of the most common symptoms in PLWH – fatigue and muscle aches/pains - invoke additional burden in women compared to men, independent of aging-related co-morbidities or other clinical factors. The higher symptom burden observed in those reporting natural or surgical menopause suggests that symptom burden may be further exacerbated once menses ceases. As the number of women transitioning through menopause expands within the aging HIV cohort, the needs of this population are likely to require a multidisciplinary team of health care experts and new directions for HIV care management.

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Table 1Symptom Burden Scores (mean \pm SD) in Female and Male Respondents

	Female n = 385	Male n = 957	Adj p-value ^{&}
<i>General</i>			
Overall low energy/fatigue *	1.48 \pm 1.40	1.34 \pm 1.34	0.013
Cough	0.21 \pm 0.67	0.25 \pm 0.72	0.27
Fever/night sweats/chills	0.28 \pm 0.81	0.16 \pm 0.57	0.65
Shortness of breath with activity *	0.51 \pm 1.03	0.38 \pm 0.88	0.04
<i>Gastrointestinal</i>			
Nausea/vomiting *	0.35 \pm 0.88	0.15 \pm 0.55	0.002
Diarrhea	0.49 \pm 1.05	0.48 \pm 0.95	0.42
Constipation/gas/bloating	0.5 \pm 1.02	0.35 \pm 0.83	0.55
Heartburn/reflux	0.31 \pm 0.76	0.27 \pm 0.72	0.88
Thirst/dry mouth *	0.45 \pm 0.98	0.30 \pm 0.73	0.04
Changes in appetite	0.33 \pm 0.90	0.21 \pm 0.66	0.48
Unplanned weight loss/gain	0.39 \pm 0.98	0.28 \pm 0.77	0.71
<i>Pain</i>			
Muscle aches/joint pain *	1.31 \pm 1.50	0.90 \pm 1.27	0.004
<i>Neurological</i>			
Lightheadness/dizziness	0.39 \pm 0.87	0.29 \pm 0.74	0.79
Neuropathy (numbness or tingling in hands/feet)	0.69 \pm 1.22	0.58 \pm 1.11	0.07
ringing in ears/noise intolerance	0.21 \pm 0.67	0.26 \pm 0.67	0.18
Clumsy walking/balance difficulties/dropping things frequently	0.42 \pm 0.95	0.31 \pm 0.82	0.89
<i>Cognitive</i>			
Speech difficulties (e.g. slowed speech, reversing numbers, words)	0.14 \pm 0.59	0.13 \pm 0.57	0.35
Difficulty concentrating/easily distracted	0.56 \pm 1.15	0.62 \pm 1.17	0.63
Difficulty remembering things	0.70 \pm 1.22	0.61 \pm 1.13	0.58
<i>Sleep</i>			
Difficulty falling asleep	1.08 \pm 1.47	0.87 \pm 1.32	0.92
Difficulty staying asleep	0.98 \pm 1.39	0.78 \pm 1.22	0.11
<i>Mood/Emotions</i>			
Anxiety or fear (e.g. feeling nervous)	0.90 \pm 1.36	0.82 \pm 1.26	0.26
Depression (e.g. feeling worthless, hopeless)	1.12 \pm 1.46	0.99 \pm 1.36	0.09
<i>Eyes/Vision</i>			
Dry eyes	0.35 \pm 0.87	0.23 \pm 0.65	0.09
<i>Urogenital</i>			
Difficulty with urination	0.11 \pm 0.58	0.21 \pm 0.65	0.68
Pain or discomfort during sex	0.90 \pm 0.49	0.04 \pm 0.35	0.99
Decreased sex drive	0.42 \pm 0.96	0.60 \pm 1.07	0.24

[&]linear mixed model, adjusted for race/ethnicity and income, education, age, sex, sexual orientation, smoking status, BMI, years living with HIV diagnosis and HIV Associated non-AIDS (HANA) conditions.

*
p < 0.05.

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Table 2

Sample Characteristics of Female Respondents According to Menstrual Bleeding Status (n = 222)

	Menstruating* (n = 118)	Amenorrhea** (n = 104)	Total Sample (n = 222)	P [^]
Age (years, mean ± SD) *	39.0 ± 8.6	54.3 ± 7.3	46.2 ± 11.1	<0.001
BMI (kg/mm2, mean ± SD)	33.9 ± 9.5	32.5 ± 7.8	33.3 ± 8.8	0.235
Duration of HIV (years, mean ± SD) *	13.1 ± 8.5	18.2 ± 7.8	15.5 ± 8.5	<0.001
Number of HIV Associated non-AIDS (HANA) conditions (mean ± SD) *	0.65 ± 0.87	1.34 ± 1.03	0.97 ± 1.0	<0.001
	n (%)	n (%)	n (%)	
<i>Age (years)</i>				<0.001
18–44	81 (68.6)	11 (10.6)	92 (41.4)	
45–54	32 (27.1)	41 (39.4)	73 (32.9)	
55–64	2 (1.7)	42 (40.4)	44 (19.8)	
65+	0 (0)	8 (7.7)	8 (3.6)	
Missing	3 (2.5)	2 (1.9)	5 (2.3)	
<i>Race</i>				0.109
White, non-Hispanic	43 (36.4)	38 (36.5)	81 (36.5)	
Black, non-Hispanic	63 (53.4)	46 (44.2)	109 (49.1)	
Hispanic	6 (5.1)	15 (14.4)	21 (9.5)	
Other	6 (5.1)	5 (4.8)	11 (5.0)	
<i>Smoking</i>				0.813
Regular	22 (18.6)	24 (23.1)	46 (20.7)	
Occasional	10 (8.5)	6 (5.8)	16 (7.2)	
Former	14 (11.9)	15 (14.4)	29 (13.1)	
Nonsmoker	70 (59.3)	57 (54.8)	127 (57.2)	
Missing	2 (1.7)	2 (1.9)	4 (1.8)	
<i>Sexual orientation</i>				0.795
Heterosexual	108 (91.5)	97 (93.3)	205 (92.3)	
Bisexual	7 (5.9)	4 (3.9)	11 (5.0)	
Homosexual	3 (2.5)	3 (2.9)	6 (2.7)	
<i>Income</i>				0.313
Missing	8 (6.8)	11 (10.6)	19 (8.6)	
<\$20,000	58 (49.2)	58 (55.8)	116 (52.3)	
\$20,000–\$59,999	45 (38.1)	28 (26.9)	73 (32.9)	
\$60,000	7 (5.9)	7 (6.7)	14 (6.3)	
<i>Education</i>				0.73
< High school	10 (8.5)	10 (9.6)	20 (9.0)	
High school/some college	83 (70.3)	68 (65.4)	151 (68.0)	
College graduate or higher	25 (21.2)	26 (25.0)	51 (23.0)	

BMI = body mass index;

* menstruating = at least one menstrual period in the last 12 months

** no period in the last 12 months due to natural menopause or hysterectomy,

^ Two sample t-test for continuous data and X^2 test for categorical data.

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Table 3

Mean Scores and Estimates of Symptom Burden Difference Between Menstruating (n = 118) and Amenorrheic Groups (n = 104) adjusting for age, duration of HIV infection and number of HIV Associated non-AIDS (HANA) conditions

Symptom	Menstruating (n = 118)		Amenorrhea (n = 104)		Difference	
	Score	SE	Score	SE	Beta	Adjusted p
<i>General</i>						
Overall low energy/fatigue *	0.75	0.21	1.29	0.19	0.55	0.03
Cough	0.21	0.09	0.27	0.08	0.06	0.54
Fever/night sweats/chills	0.14	0.12	0.24	0.11	0.10	0.45
Shortness of breath with activity	0.37	0.15	0.30	0.14	-0.06	0.70
<i>Gastrointestinal</i>						
Nausea/vomiting	0.18	0.14	0.23	0.12	0.04	0.78
Diarrhea	0.40	0.16	0.38	0.15	-0.02	0.93
Constipation/gas/bloating	0.47	0.16	0.49	0.14	0.03	0.88
Heartburn/reflux	0.28	0.12	0.29	0.11	0.01	0.96
Thirst/dry mouth	0.34	0.15	0.30	0.13	-0.05	0.77
Changes in appetite	0.17	0.14	0.26	0.13	0.10	0.52
Unplanned weight loss/gain	0.12	0.14	0.38	0.13	0.25	0.10
<i>Pain</i>						
Muscle aches/joint pain *	0.99	0.23	1.47	0.21	0.48	0.05
<i>Neurological</i>						
Lightheadedness/dizziness	0.39	0.14	0.29	0.12	-0.10	0.53
Neuropathy (numbness or tingling in hands/feet)	0.77	0.19	0.81	0.17	0.04	0.84
ringing in ears/noise intolerance	0.17	0.11	0.30	0.10	0.14	0.26
Clumsy walking/balance difficulty/dropping things frequently	0.39	0.13	0.25	0.11	-0.14	0.31
<i>Cognitive</i>						
Speech difficulties (e.g. slowed speech, reversing numbers, words)	0.13	0.10	0.11	0.09	-0.01	0.94
Difficulty concentrating/easily distracted	0.17	0.17	0.47	0.15	0.31	0.10
Difficulty remembering things	0.32	0.18	0.55	0.16	0.24	0.23
<i>Sleep</i>						

Symptom	Menstruating (n = 118)			Amenorrhea (n = 104)			Difference		
	Score	SE	Score	SE	Beta	SE	Adjusted p		
Difficulty falling asleep*	0.66	0.24	1.22	0.21	0.56	0.27	0.04		
Difficulty staying asleep	0.65	0.22	0.99	0.19	0.35	0.25	0.17		
<i>Mood/Emotions</i>									
Anxiety or fear (e.g. feeling nervous)	0.65	0.22	0.84	0.19	0.19	0.25	0.44		
Depression (e.g. feeling worthless, hopeless)	0.78	0.24	1.15	0.21	0.35	0.27	0.19		
<i>Eyes/Vision</i>									
Dry eyes	0.15	0.14	0.35	0.13	0.20	0.16	0.21		
<i>Urogenital</i>									
Difficulty with urination	0.18	0.10	0.21	0.09	0.03	0.10	0.77		
Pain or discomfort during sex	0.02	0.08	0.06	0.08	0.04	0.10	0.67		
Decreased sex drive	0.12	0.15	0.30	0.13	0.18	0.17	0.28		

† symptom #26, erectile dysfunction, removed from the follow-up female survey;

* = significant p value = 0.05 for linear mixed model; Beta= regression coefficient, SE = standard error