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Ecological Momentary Assessment of HIV vs. Reproductive Health Symptoms in Women of Differing Reproductive Stages Living with HIV

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Abstract

Objective: To what extent menopause is related to symptom burden in women living with HIV (WLWH) is unclear, as a specific reproductive health analysis has seldom been undertaken, in part due to an inadequate assessment of reproductive status. The purpose of this study was to document and compare symptom frequency and attribution over 46 days and examine differences by reproductive status with a sample of 73 women living with HIV.

Methods: We conducted an ecological momentary assessment (EMA) using text messaging to follow 75 women confirmed for menopause stage with hormone profiles for 46 days. Participants were asked to respond to the following open-ended questions via a text message 3× weekly: 1) Did you have your period today? (Yes/No) 2) What were your top 3 menstrual/menopausal symptoms today? 3) What were your top 3 HIV related symptoms today?

Results: 74 women (mean± SD age = 51± 8 yrs, range= 24–67 yrs) completed the study (10 pre-, 20 peri, 44 post-menopause). The majority of volunteers were Black non-Hispanic (74%), non-smokers (61%), with some high school (68%) and reporting <$20,000 annual income. After controlling for co-factors, HIV symptom profiles differed by menopause stage: post-menopause predicted more fatigue, muscle aches and pains, nausea/vomiting and diarrhea (vs peri or pre-menopause). HIV-related depression was predicted by the peri stage. For reproductive symptoms, women endorsed fatigue (58%), hot flashes (52%) depression (49%), and muscle aches and pains (44%) as most common, but of these, only muscle aches and pains demonstrated group differences in period prevalence (post = 35%; peri = 45%; pre = 80%, p= 0.03) Surprisingly, hot flash frequency was similar, but fever/chills/sweats varied across menopause stage (period prevalence: post=42%; peri=15%; pre=0%, p=0.01). Reporting “a period today” predicted the profile of reproductive symptoms, but was not related to HIV symptoms.

Conclusions: Although fatigue, muscle aches/pains and depression are perceived as common attributes of both HIV infection and reproductive status in WLWH, they distinguish condition-specific symptom profiles that are dependent on menopause stage.

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Keywords

ecological momentary assessment; HIV; symptoms; text message; menopause; menstruation

Introduction

Sex steroids play a key role in female physiology owing to their ability to organize, differentiate, and maintain tissues and organs, including the central nervous system.[1] In addition, a reproductively mature woman will experience on average 13 menstrual periods/year and the effect that ovarian function may have on various non-reproductive conditions is clearly important.[2] For example, a number of sex-based differences and menstrual cycle related changes have been demonstrated in chronic diseases such as asthma[3], arthritis[4], migraine[5], diabetes[6], depression[7, 8], irritable bowel syndrome[9] and epilepsy[10] with a significant portion of women reporting a worsening of their symptoms pre-menstrually.[2, 11] In the same way, the menopause transition has been shown to accelerate or exacerbate cardiovascular disease and other chronic conditions such as depression, obesity, and hypertension[12] - common co-morbid conditions in persons living with HIV (PLWH).

Multi-site cross-sectional surveys have demonstrated that PLWH report fatigue, depression, poor sleep and difficulty concentrating among the ten most frequent and debilitating symptoms linked to HIV.[13] To what extent the menopause transition is related to symptom burden in PLWH is unclear, as a specific reproductive stage analysis has seldom been undertaken, in part due to an inadequate assessment of reproductive status in the female participants.[14] Cycle-related symptom experience or exacerbation has also not been well studied in women living with HIV. A few studies have examined the symptom experience of HIV-infected women[15], menopausal symptoms in women living with HIV,[16] early onset of menopause[17], and effect of HIV on ovarian dysfunction[18] with equivocal results. One recent review[19] concluded that the presumably earlier age of menopause in HIV women may be confounded by high rates of HIV-related amenorrhea. The Women's Interagency HIV Study (WIHS), a multicenter, observational study of HIV-infected women and non–HIV infected women of similar socioeconomic status, found that more than half of HIV-infected women with prolonged amenorrhea had hormone levels consistent with pre-menopause.[18]

To what extent other HIV symptoms (e.g. sleep problems, fatigue) overlap with those of reproductive stages also has not been well-studied. Not surprisingly, a number of clinical challenges exist for providers caring for women with HIV in differentiating and managing those symptoms due to HIV complications or therapies vs the common symptoms of menopause[20]. For example, in healthy women, menstrual irregularities and hot flashes are common in the early peri-menopausal transition, but also present as features of HIV secondary to illicit substance abuse, medications including psychotropics, narcotics, methadone, or corticosteroids; and comorbid conditions such as diabetes and liver disease[18, 21, 22]. One study of symptom attribution demonstrated a three-fold higher number of women with HIV who did not know why they had hot flashes or vaginal dryness vs the uninfected group[23] and in a study of WLWH in methadone treatment, fewer than 10% positively identified muscle aches and poor sleep as menopausal symptoms[24]. Taken

together, these findings suggest that an assessment of HIV symptom data taking into account female reproductive status is therefore timely and needed[25] as persons are living longer with the disease, more women are transitioning through the menopause, and women continue to be understudied.

Methods

The purpose of this study was to document and compare symptom frequency and attribution over 46 days and examine differences by reproductive status with a sample of 75 women living with HIV. We examined differences in symptom reporting of HIV and female sex-based symptoms (those linked to the menstrual cycle and menopause) in 75 women living with HIV stratified into the following 3 menopause stages: a) pre-menopausal women (regular periods not due to hormonal birth control); b) peri-menopausal women (at least one period within the last 3–12 months not due to hormonal birth control); c) postmenopausal women (no period in the last 12 months; no hysterectomy).[26]

Participants were recruited through study flyers at community-based organizations and a university-affiliated outpatient clinic in New York City (NYC) serving PLWH. This study was conducted as a follow-up study to our cross-sectional study described here.[27]

Inclusion Criteria:

Participants needed to be age 18 years or older, HIV+, self-identify as Black and/or Latina taking antiretroviral therapy (ART), and able to read, and provide written informed consent in English or Spanish. Women needed to have a history of regular menstrual cycles at some point after menarche. To reduce complexity, only volunteers who self-identified as cis-gender were included.

Exclusion Criteria included the following:

any form of hormonal birth control or hormone therapy (HT) within the last 3 months, pregnant or breastfeeding within the last 3 months, and history of hysterectomy.

Procedures.

Study participants arrived at our site and provided a timed blood draw through venipuncture to determine concentrations of FSH and estradiol. For women who reported a period in the past 3 months, the study visit was synchronized to fall between days 1–6 of the menstrual cycle (day 1 = first day of menses). Following a blood draw, participants completed a questionnaire on demographics and reproductive health status.

Study Instruments.

Reproductive health status was determined based on most recent menstrual bleeding and amenorrhea history using the Staging of Reproductive Aging in Women (STRAW) criteria, a standardized series of questions for assessing stages of the menopausal transition,[26] STRAW criteria have been used in studies of healthy peri-menopausal women,[28] and the cross-sectional survey of HIV-infected and uninfected participants in the WIHS.[29] The NIDA-Modified ASSIST V2.0 was used to collect information on substance use.

Blood Collection:

Blood was collected in red top 5mL vacutainer serum tubes (BD, Franklin Lakes, NJ, USA). Serum was separated within 6 h of collection, stored at −80 °C, and thawed on ice immediately prior to analysis.

Self-reported menstrual bleeding patterns in association with a measure of plasma FSH and estradiol drawn between cycle day 1–6 were used to assign participants to one of the following 3 menopause stages: a) pre-menopause (regular and predictable periods, FSH = <10mIU/ml; estradiol= >20pg/ml; b) peri-menopause (ranging from early menopause = irregular unpredictable periods within the last 3 months, to late peri-menopause = no period in the last 3–11months); FSH >10 mIU/ml; estradiol=>20pg/ml; c) post menopause (ranging from early = no period in the last 12–48mos to late = no period in the last 4 years); FSH>25mIU/ml; estradiol < 20pg/ml.[30]

Ecological Momentary Assessment (EMA)—Following the in-person study visit in which we collected blood samples and baseline demographic characteristics, we conducted an EMA, a sampling method developed to assess phenomena at the moment they occur in (participants') naturalistic environments, supporting the ecological validity of this approach.[31] EMA allows for repeated sampling of participants' behaviors and experiences in real time, while the participants are in their natural environments[32]. We followed our participants for 46 days using text messages. We chose a 46 day time period because we wanted to capture 2 menstrual cycles and the text messages were every 3 days and so we conservatively estimated that this time period would allow us to capture 2 time points at which women were menstruating in the pre-menopausal group. Through Qualtrics Software, we sent study participants text messages questions on Sunday, Tuesday, and Thursday evening for a total of 20 assessment points. Participants were asked to respond to the following open-ended questions via a text message at 6pm Eastern Time Zone: 1) Did you have your period today? (Yes/No) 2) What were your top 3 menstrual/menopausal symptoms today? 3) What were your top 3 HIV related symptoms today? To avoid response bias, participants were not provided with a pre-populated list of symptoms to choose from. At the end of the 46 days, participants received an Amazon code with $2 for each day they responded to the text message assessment for a total possible compensation of $40.

Data Analysis.

Category Development and Validity

Survey data was imported into Excel for analysis and for category/code development. We developed a coding scheme based on frequently reported symptoms in the literature using inductive category analysis of the open-ended narrative responses.[33, 34] Open coding was used to categorize each open text response into symptom categories A study team member created the coding scheme based on the symptom categories that we had identified in our previous work.[35, 36] Another study team member reviewed all of the individual symptom categories and grouped codes into main categories on the basis of similarities. For example, the main code *Fatigue* included open-ended text messages such as: exhaustion; low energy; tired, and tiredness. After the study team member completed coding the text messages, the

first author (RS) and study team member reviewed the codes and discussed any discrepancies until resolution was reached.

Statistical Analysis

Data analysis was conducted in Version 9.4 of the SAS System for Windows software. Descriptive statistics were used to characterize the demographic characteristics of study participants. Fisher's exact test was used to calculate if there was a significant difference in substance use across menopausal groups. Period prevalence of each symptom, defined as the number of participants who reported that symptom divided by the total number of participants in the study, was calculated for the total sample, and post-, peri-, and pre-menopausal groups separately. Fisher's exact tests were used to examine whether period prevalence of each symptom was the same across different menopause groups. To fully use the data, we also calculated the point prevalence of each symptom at the report level, which was defined as the number of reports for each symptom divided by the total number of reports. Point prevalence of each symptom was also calculated for the total sample, post-, peri- and pre-menopausal groups separately. To explore the relationship between the two main independent variables and each individual symptom controlling for potential covariates, we built multilevel multivariable regression models. The two main independent variables were menopause status (three levels: post-menopausal women, peri-menopausal women, and pre-menopausal women) and having a period (if a women reported her period for that report and it was a time-variant variable). Given that the point prevalence of several symptoms was higher than 10%, we used risk ratios (RR) instead of odds ratios (OR) to measure association between factors (menopause status and having period)and outcomes (individual symptoms).[37] Past studies have suggested the use of Cox regression with time as a constant variable as a good model for estimating RR.[38, 39] RRs estimated by Cox regression is similar to those estimated by other methods such as log-binomial regression, but binomial models sometimes fail to find possible values and converge in the model. RRs were directly calculated by taking the exponential of the coefficient derived from the Cox regression with a constant time variable. We used the multi-level version of the Cox regression models to account for the clustering effect of 1277 reports nested within 73 participants. RRs and associated 95% confidence intervals (CI) were calculated to assess the strength and direction of relationship. Guided by minimal sample sizes required by similar generalized linear models for binary outcomes,[40, 41] for symptoms with at least 100 outcome events, we built multilevel Cox regression models. Past research has shown that season of the year has a significant effect on a number of symptoms such as depression,[42] fatigue,[43] gastrointestinal symptoms,[44] and neuropathy.[45]

Before building the final multivariable models, we assessed the bivariate relationship between each individual symptom and potential covariates such as number of co-morbid conditions (asthma, cardiovascular disease, chronic obstructive pulmonary disease, diabetes, liver disease, osteoporosis, renal failure, and arthritis), race, education, income, and season. Covariates with p-values less than 0.20 in bivariate association analysis was entered into final regression models. Multi-collinearity between independent variables were assessed using the variance inflation factor (VIF) or generalized VIF: values higher than 5, a

commonly used threshold, indicates high multicollinearity,[46] and these variables were not included in the final model.

Results:

Demographic and clinical characteristics.

The final sample was comprised of 73 women categorized by menopause stage (10 pre-menopausal, 20 peri-menopausal and 43 post-menopausal). As a group, the majority of volunteers were Black non-Hispanic (n = 54; 74%), with at least some high school education (n=50; 68%), and reporting less than $20,000 in annual income (n=48; 66%); participants self-reported their viral load. which was detectable in only one participant (1.4%)). The average age of the total sample was 51.4 years (SD= 8.3; range=24–67 yrs) and differed across the 3 study groups (mean ± SD = 36± 8 yrs vs 49±4 yrs vs 56±4 yrs for the pre, peri, post groups respectively; $F_{2,71}$=3306, p=<0.001).). Given the high multi-collinearity between age and menopause status (generalized VIF>5.0), it was not included as a potential covariate in multivariable regression models. Twenty-eight women reported occasional or regular smoking (38%) and 45 women were non-smokers (62%). In the past 3 months, 28 (38.4%) women reported using marijuana, 14 (19.4%) reported cocaine use, 13 (18.1%) reported sedative and prescription opioid use, 3 (4.2%) reported prescription stimulant and hallucinogen use, 2 (2.8%) reported inhalant and street opioid use and 1 (1.4%) reported methamphetamine use. There was a significant difference (p =0.015) in marijuana use across menopause groups with post-menopausal women being less likely to use marijuana. For all other substances, there was no significant difference (p>0.05) in use by menopause group.

EMA Response Rate.

Each study participant had an opportunity to report a total of 20 times during the 46-day period (one weekend day and two week days) and was asked to identify 3 HIV-related and 3 reproductive health symptoms at each report. We excluded one participant with only one report. Participants reported between 8 and 20 times with a mean of 17.4 (S.D.=2.9) times.

Reproductive Health Symptoms.

For the 63 participants who reported symptoms, 31 reproductive health symptoms were identified. Table 1 presents the numbers of reproductive health symptoms according to participant level. Among all participants, fatigue (58%), hot flashes (52%), and depression (49%) were the three symptoms with the highest period prevalence. Eleven (15%) women reported no reproductive health symptoms throughout the study period. Using Fisher's exact tests, the period prevalence for muscle aches and pains, cramps, fevers/chills/sweats, and stomach pain differed across the post-, peri-, and pre-menopause groups (all less than p = 0.05).. To fully use the longitudinal data information, we also calculated the frequency and point prevalence of each reproductive health symptom by menopause status (Table 2). Among all participants, there were a total of 1277 reports, with hot flashes (19%) depression (16%) and fatigue (16%) reported most frequently. By menopause stage, the most frequently reported symptoms in the pre-menopause group were cramps (24%), headache (15%), fatigue (12%) and muscle aches and pains (12%) respectively. In the peri-menopause group, the most common symptoms were fatigue (25%), hot flashes (24%) and depression (20%).

Finally, hot flashes (21%), depression (17%), and fevers/chills/sweats (14%) were the most frequently reported in the post-menopause group.

Table 3 reports the findings from the multi-level Cox regression models with time as a constant variable assessing the relationship between factors (menopause stage and having a period that day ie yes or no) and reproductive health symptoms controlling for potential covariates such as number of co-morbid conditions, race, education, income, reporting trend and season. Bivariate relationships between each potential covariate and individual symptoms were assessed and covariates with p-values less than .20 were included in following multi-level Cox regression models. As compared to post-menopausal women, peri-menopausal women were more likely to have fatigue (RR: 1.87; 95% CI: 1.30–2.69), and cramps RR: (2.41; 95% CI: 1.38–4.22), and less likely to have headaches (RR: 0.28; 95% CI: 0.15–0.54), and muscle joint aches (RR: 0.34; 95% CI: 0.19–0.62), As compared to post-menopausal women, pre-menopausal women were more likely to have cramps (RR: 2.41; 95% CI: 1.34–4.35), and less likely to have depression (RR: 0.19; 95% CI: 0.09–0.43) and hot flashes (RR: 0.08; 95% CI:0.03–0.22). Finally, women who reported having a period that day were more likely to report headache (RR:3.12; 95% CI 1.59–6.12), muscle aches and joint pain (RR: 3.67; 95% CI: 1.81–7.44), fatigue ((RR: 1.68; 95% CI: 1.03–2.73), and cramps (RR: 8.00; 95% CI:5.17–12.38) vs those who did not.

HIV-related Symptoms.

For the 63 women who reported any symptom, there were 25 HIV-related symptoms identified. Table 4 presents the numbers of HIV-related symptoms at participant level. Among all participants, fatigue (59%), muscle aches and joint pains (44%), and depression (40%) were the three symptoms with the highest period prevalence, along with nausea/vomiting, appetite change, fevers/chills or sweats, diarrhea, and headache (35–30%), but only headache differed by menopause stage (period prevalence: post = 23%; peri = 25%; pre = 70%; Fisher's exact test, p = <.05). Twenty (27%) women reported no HIV-related symptoms throughout the study period.

Table 5 presents the frequency and point prevalence of each HIV-related symptom by menopause stage. Across the full sample, reports of fatigue (26%) were highest, followed by muscle aches and joint pain (15%) and nausea/vomiting (10%). In the pre-menopausal group, the most commonly reported symptoms were fatigue (24%), muscle aches/joint pain (23%) and stomach pain (16%). In the peri-menopausal group, the highest symptom reports were for fatigue (32%), followed by depression (15%) and muscle aches and joint pain (10%) and nausea/vomiting (10%). Finally, reports of fatigue (23%), followed by muscle aches/joint pain (15%) and nausea/vomiting (11%) were the highest in the post-menopause group.

Table 6 reports the findings from multi-level Cox regression models with time as a constant variable assessing the relationship between factors (menopause stage and having a period) and HIV-related symptoms controlling for potential covariates such as number of co-morbid conditions, race, education, income, reporting trend and season. Following the same procedure, covariates with p-values less than 0.20 were included in multi-level Cox regression models. As compared to the post-menopausal group, peri-menopausal women

were more likely to have depression (RR:2.03; 95% CI: 1.26–3.29) and changes in appetite (RR: 2.66; 95% CI: 1.59–4.46), and less likely to have muscle aches and joint pain (RR: 0.33; 95% CI:0.22–0.51), and diarrhea (RR: 0.54; 95% CI: 0.30–0.96). As compared to post-menopausal women, pre-menopausal women were more likely to have changes in appetite (RR: 2.23; 95% CI: 1.22–4.10), and less likely to have fatigue/loss of energy (RR: 0.67; 95% CI: 0.47–0.97), and nausea (RR: 0.22; 95% CI:0.08–0.58)). “Having my period today” was not a predictor of HIV-related symptoms.

Discussion:

This paper offers an expanded perspective on the symptom profiles of WLWH. Notably, our study makes three important methodological contributions to the literature. First, we assessed women’s symptoms in their everyday settings and in those still menstruating, considered whether they reported a period that day. Second, we allowed women to provide spontaneous, unprompted reports of their symptoms which broadened the scope of the standardized checklists which are often limited in the type of symptoms that are investigated.[47–49] Finally this study allowed women living with HIV to distinguish between their HIV and reproductive health symptoms. Past studies of WLWH have described symptoms in broad terms[50–52], or have focused solely on menopause-related symptoms[53] without characterizing the associated HIV symptoms for context. The goal of this was work was to allow women to provide their own attributions of the day-to-day symptom experience to better understand how menopause symptoms are perceived and distinguished from HIV.

Using this approach, we were able to demonstrate that WLWH, perceived a common set of symptoms (including fatigue, muscle aches and pain, and depression) as attributable to both their HIV and reproductive status which was unique to their menopause stage, defined endocrinologically and by the STRAW classification. These data not only confirm the typology of HIV symptoms described by us and others in earlier cross-sectional surveys and interviews using standard HIV symptom questionnaires, but also extend the findings by simultaneously depicting spontaneously-elicited, reproductive symptoms in a naturalistic setting (ie cell phone text messaging). For example, HIV-related fatigue and muscle aches and pains have been shown by us and others to be magnified after menopause,[54, 55] but the relative contribution of menopause to their attribution has seldom been assessed.

Notably, WLWH were able to self-identify and distinguish between HIV and reproductive health symptoms. For example,, post-menopausal women reported hot flashes as the most frequent reproductive health symptom and fatigue as the most frequent HIV-related symptom, even though fatigue was also reported as a common reproductive symptom. Hot flashes have been well-described as part of the normal menopause transition[56] as well as a more burdensome symptom for peri-menopausal women living with HIV as compared to those from the general population.[57] Interestingly in the present study, fever, chills or night sweats were also perceived as a common reproductive symptom (sixth most common), demonstrating significant differences in point prevalence by menopause stage (post = 42%, peri = 15%, pre = 0%, p = 0.01) In healthy women, night sweats and chills are a prominent feature of the perimenopause transition, seldom delineated as discrete from hot flashes, and typically attributed to vasomotor instability. At the same time, fevers, chills or night sweats

were also the 6th most common symptom identified as an HIV symptom and did not vary by menopause stage (post = 28%, peri = 40%, pre = 30%, p = 0.59). In people living with HIV, fevers, chills and night sweats are typically attributed to opportunistic infections, such P*neumocystis* pneumonia[58]. Taken together, these data suggest that vasomotor instability symptoms in WLWH due to HIV pathophysiology may be compounded by the menopause-related decline in estrogen. How the fever, sweats and chills associated with menopause may overlap and differ from those attributed to HIV requires further study, perhaps using biomarkers and electronic monitoring to characterize physiologic features.

As for other reproductive health symptoms, pre-menopausal women were significantly more likely to report cramps than women in the other groups, and having your period was a significant predictor of this symptom. Moreover, pre- and peri-menopausal women who were menstruating were more likely to report a headache and muscle aches and joint pain which is also consistent with the symptom profile of menstruating women in the general population.[59]..

The most frequently reported HIV-related symptoms were fatigue followed by muscle aches and joint pain (same for reproductive health-related symptoms) and nausea/vomiting. Muscle aches and joint pain has consistently been shown to be a frequent and burdensome symptom in PLWH and particularly among post-menopausal women.[60] Interestingly, although nausea/vomiting had previously been noted as a frequently occurring HIV-related symptom, this has been less frequently been reported since the introduction of non-nucleoside reverse-transcriptase inhibitors.

Our findings also support the view that post-menopausal women more frequently report neuropathy. It is difficult to determine if age alone, living longer with the disease, increased exposure to the virus or ARTs[61] or diminished serum estrogen[62] may have contributed to the higher frequency of neuropathy in this subset of our study sample. Further investigation to better understand the physiologic pathways that contribute to neuropathy in post-menopausal women living with HIV is needed.

An important limitation in our study was the inclusion of women who reported substance use, including methadone which can alter menstruating patterns[63]. This may have reduced our ability to distinguish HIV, reproductive health and substance use symptoms.

Other limitations include the small sample size particularly in the pre-menopausal group. It was difficult to enroll and recruit participants in this group for several reasons: 1) many were excluded due to the use of oral contraceptives; 2) others were unable to attend a daytime clinic appointment due to employment and conflicts with work schedules; and 3) the HIV epidemic in the US particularly among women has a shifting age demographic such that fewer young women are being infected with HIV and women are living longer with the disease.[64] Our study was also limited by the cross-sectional design and so we were only able to evaluate associations between demographic characteristics and symptoms. Additionally, we did not collect data on duration of HIV, which may have influenced the nature and severity of HIV symptom. Finally, we included women who were using substances, which can influence menstrual patterns[65]. Given the small sample and other and limitations noted

above, these findings are preliminary and meant to provoke larger, better controlled studies using this approach.

Conclusions:

This paper reports on findings from an EMA to better characterize day-to-day perceptions of reproductive vs. HIV-related symptoms in women living with HIV according to menopause stage.. Through this approach used for the first time in studies of WLWH, we were able to demonstrate menopause stage-specific symptom profiles for both HIV an reproductive symptoms. Although fatigue, muscle aches and pains and depression are common complaints in WLHIV and attributable to both HIV and reproductive status, women distinguish condition-specific symptom profiles unique to their reproductive stage. As the symptom profiles in the aging HIV cohort of women is better understood, future work can be focused on symptom amelioration targeted to symptom attribution as well as menopause status.

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Table 1.

Frequency and Period Prevalence of Reproductive Health-Related Symptoms(n=73 participants)

Symptom	Post-menopausal (N=43 participants)		Peri-menopausal (N=20 participants)		Pre-menopausal (N=10 participants)		Total Women (N=73 participants)		P-value[b]
	Frequency	Period Prevalence (%)[a]	Frequency	Period Prevalance (%)[a]	Frequency	Period Prevalance (%)[a]	Frequency	Period Prevalance (%)[a]	
No symptom	14	33	4	20	2	20	20	27	0.50
Fatigue/Loss of Energy	20	47	14	70	8	80	42	58	0.07
Hot Flashes	26	60	9	45	3	30	38	52	0.20
Depression	22	51	9	45	5	50	36	49	0.94
Muscle aches/Joint Pain	15	35	9	45	8	80	32	44	0.03
Cramps	7	16	11	55	9	90	27	37	<.0001
Fevers/chills/sweats	18	42	3	15	0	0	21	29	0.01
Headache	12	28	6	30	3	30	21	29	1.00
Constipation/bloating/gas	10	23	5	25	5	50	20	27	0.24
Changes in appetite	8	19	4	20	5	50	17	23	0.11
Sleeping issues	8	19	4	20	0	0	12	16	0.40
Heavy bleeding	2	5	5	25	2	20	9	12	0.05
No period	8	19	1	5	0	0	9	12	0.25
Diarrhea/loose bowel movement	6	14	1	5	1	10	8	11	0.76
Dizziness/lightheadedness	4	9	3	15	0	0	7	10	0.63
Nausea/vomiting	5	12	2	10	0	0	7	10	0.74
Stomach pain	1	2	2	10	3	30	6	8	0.02
Sore breast	2	5	1	5	3	30	6	8	0.05
Vaginal dryness	6	14	0	0	0	0	6	8	0.16
Itchy/dry skin	4	9	1	5	0	0	5	7	1.00
Muscle weakness	3	7	1	5	1	10	5	7	1.00
Low/no sex drive	4	9	1	5	0	0	5	7	1.00
thirst/dry mouth	3	7	1	5	0	0	4	5	1.00
Unplanned weight changes	2	5	2	10	0	0	4	5	0.61
Shortness of breath	1	2	2	10	0	0	3	4	0.23
Swollen feet	2	5	1	5	0	0	3	4	1.00
Pain/numbness/tingling in hands or feet	3	7	0	0	0	0	3	4	0.71
Trouble concentrating/diff remembering	3	7	0	0	0	0	3	4	0.71

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Symptom	Post-menopausal (N=43 participants)		Peri-menopausal (N=20 participants)		Pre-menopausal (N=10 participants)		Total Women (N=73 participants)		P-value[b]
	Frequency	Period Prevalence (%)[a]	Frequency	Period Prevalance (%)[a]	Frequency	Period Prevalance (%)[a]	Frequency	Period Prevalance (%)[a]	
Heartburn/acid reflux	1	2	0	0	0	0	1	1	1.00
Cough	1	2	0	0	0	0	1	1	1.00
Difficulty with urination	1	2	0	0	0	0	1	1	1.00
Boils/rash	1	2	0	0	0	0	1	1	1.00

[a] Period prevalence was calculated as number of participants who reported the symptom divided by total number of participants.

[b] p-value from Fisher's exact test

Table 2.

Frequency and Point Prevalence of Reproductive Health-Related Symptoms

Symptom	**Post-menopausal (N=43 participants with 762 total reports)**		**Peri-menopausal (N=20 participants with 338 total reports)**		**Pre-menopausal (N=10 participants with 177 total reports)**		**Total Women (N=73 participants with 1277 total reports)**	
	Frequency	**Point Prevalence (%)[a]**	**Frequency**	**Point Prevalence (%)[a]**	**Frequency**	**Point Prevalence (%)[a]**	**Frequency**	**Point Prevalence (%)[a]**
No symptom	384	50	150	44	97	55	631	49
Hot Flashes	160	21	82	24	5	3	247	19
Depression	127	17	67	20	7	4	201	16
Fatigue/Loss of Energy	94	12	84	25	21	12	199	16
Cramps	31	4	49	15	42	24	122	10
Fevers/chills/sweats	109	14	3	1	0	0	112	9
Headache	60	8	17	5	26	15	103	8
Muscle aches/Joint Pain	59	8	21	6	21	12	101	8
Constipation/bloating/gas	29	4	13	4	15	9	57	5
Changes in appetite	9	1	17	5	19	11	45	4
Itchy/Dry Skin	28	4	5	2	0	0	33	3
Dizziness/Light-headedness	18	2	13	4	0	0	31	2
Nausea/Vomiting	23	3	4	1	0	0	27	2
Unplanned Weight Changes	16	2	8	2	0	0	24	2
Sleeping Difficulty	19	3	4	1	0	0	23	2
Vaginal Dryness	22	3	0	0	0	0	22	2
Stomach Pain	2	0	6	2	12	7	20	2
Heavy Bleeding	3	0	10	3	4	2	17	1
No Period	14	2	1	0	0	0	15	1
Muscle Weakness	8	1	2	1	1	1	11	1
Pain numbness tingling in hands or feet	9	1	0	0	0	0	9	1
Sore Breasts	4	1	1	0	4	2	9	1
Diarrhea/loose bowel movement	6	1	1	0	1	1	8	1
Thirst/Dry Mouth	6	1	2	1	0	0	8	1

Symptom	Post-menopausal (N=43 participants with 762 total reports)		Peri-menopausal (N=20 participants with 338 total reports)		Pre-menopausal (N=10 participants with 177 total reports)		Total Women (N=73 participants with 1277 total reports)	
	Frequency	Point Prevalence (%)[a]	Frequency	Point Prevalence (%)[a]	Frequency	Point Prevalence (%)[a]	Frequency	Point Prevalence (%)[a]
Decreased Sex Drive	5	1	2	1	0	0	7	1
Trouble concentrating/ Difficulty Remembering	5	1	0	0	0	0	5	0

[a]Point Prevalence = the number of times each symptom was reported divided by total number of reports.

Table 3.

Multi-level Cox regression models with time as a constant variable assessing the relationship between menopause status and having period and each Sex-Related Symptom (n=1277 reports)[a,b]

Symptom	Fevers/chills/sweats				Headache			
	Risk Ratio	95% Confidence Interval		p-value	Risk Ratio	95% Confidence interval		p-value
Effect		lower	upper			lower	upper	
meno :peri vs post	NA**	NA	NA	NA	0.28	0.15	0.54	<0.001
meno: pre vs post	NA	NA	NA	NA	1.11	0.58	2.14	0.75
Period	0.20	<0.05	1.46	0.11	3.12	1.59	6.12	<0.001
Symptom	**Muscle/joint aches/pains**				**Fatigue/loss of energy**			
meno :peri vs post	0.34	0.19	0.62	<0.001	1.87	1.30	2.69	<0.001
meno: pre vs post	0.98	0.51	1.87	0.95	0.63	0.37	1.06	0.08
Period	3.67	1.81	7.44	<0.001	1.68	1.03	2.73	<0.05
Symptom	**Depression**				**Cramps**			
meno :peri vs post	1.40	0.99	1.96	0.05	2.41	1.38	4.22	<0.001
meno: pre vs post	0.19	0.09	0.43	<.0001	2.41	1.34	4.35	<0.01
Period	0.70	0.34	1.47	0.34	8.00	5.17	12.38	<.0001
Symptom	**Hot Flash**							
meno :peri vs post	1.02	0.74	1.40	0.89				
meno: pre vs post	0.08	0.03	0.22	<.0001				
Period	0.45	0.20	1.04	0.06				

[a] Models control for number of co-morbid conditions, race, education, income, reporting trend and season if p_value <.20 in bivariate association analysis.

[b] Not estimated when cell event outcome<5

Table 4.

Frequency and Period Prevalence of HIV-Related Symptoms(n=73 participants)

Symptom	Post-menopausal (N=43 participants)		Peri-menopausal (N=20 participants)		Pre-menopausal (N=10 participants)		Total Women (N=73 participants)		P-value[b]
	Frequency	Period Prevalence (%)[a]	Frequency	Period Prevalence (%)	Frequency	Period Prevalence (%)	Frequency	Period Prevalence (%)	
No symptoms	8	19	3	15	0	0	11	15	0.33
Fatigue or loss of energy	23	53	14	70	6	60	43	59	0.52
Muscle joint aches/pains	18	42	8	40	6	60	32	44	0.56
Depression	16	37	8	40	5	50	29	40	0.75
Nausea/vomiting	14	33	9	45	2	20	25	34	0.41
Appetite Changes	10	23	8	40	6	60	24	33	0.07
Fevers/chills, sweats	12	28	8	40	3	30	23	32	0.59
Diarrhea/loose bowel movement	14	33	5	25	3	30	22	30	0.93
Headache	10	23	5	25	7	70	22	30	<.05
Sleeping issues	10	23	7	35	1	10	18	25	0.34
Stomach pain	7	16	4	20	5	50	16	22	0.08
Constipation/bloating/gas	9	21	2	10	2	20	13	18	0.62
Itchy/dry skin	10	23	2	10	0	0	12	16	0.16
Pain/numbness/tingling in hands or feet (neuropathy)	9	21	2	10	1	10	12	16	0.60
Muscle weakness	6	14	4	20	1	10	11	15	0.81
Thirst/dry mouth	6	14	3	15	0	0	9	12	0.68
Unplanned weight changes	5	12	2	10	2	20	9	12	0.77
Dizziness/lightheadedness	5	12	3	15	1	10	9	12	0.88
Boils/rash	5	12	2	10	1	10	8	11	1.00
Swollen feet	3	7	2	10	2	20	7	10	0.31
Sore throat/throat discomfort	4	9	1	5	2	20	7	10	0.38
Trouble concentrating/diff remembering	6	14	1	5	0	0	7	10	0.45
Cough	2	5	1	5	0	0	3	4	1.00
Heartburn/acid reflux	2	5	0	0	0	0	2	3	1.00
Shortness of breath	1	2	0	0	0	0	1	1	1.00
Dry eyes	1	2	0	0	0	0	1	1	1.00

[a]Period prevalence was calculated as number of participants who reported the symptom divided by total number of participants.

[b]p-value from fisher's exact test

Table 5.

Frequency and Point Prevalence of HIV-related Symptoms

Symptom	Post-menopausal (N=43 participants with 762 total reports)		Peri-menopausal (N=20 participants with 338 total reports)		Pre-menopausal (N=10 participants with 177 total reports)		Total Women (N=73 participants with 1277 total reports)	
	Frequency	Point Prevalence (%)[a]	Frequency	Point Prevalence (%)[a]	Frequency	Point Prevalence (%)[a]	Frequency	Point Prevalence (%)[a]
No symptom	322	42	122	36	72	41	516	40
Fatigue/Loss of Energy	179	23	109	32	43	24	331	26
Muscle aches/Joint Pain	116	15	33	10	41	23	190	15
Nausea/Vomiting	85	11	32	9	5	3	122	10
Diarrhea/loose bowel movement	78	10	23	7	17	10	118	9
Depression	51	7	50	15	10	6	111	9
Changes in appetite	36	5	49	14	22	12	107	8
Sleeping Difficulty	55	7	32	9	2	1	89	7
Headache	45	6	17	5	25	14	87	7
Fevers/chills/sweats	44	6	28	8	3	2	75	6
Pain numbness tingling in hands or feet (neuropathy)	64	8	4	1	3	2	71	6
Stomach Pain	14	2	9	3	29	16	52	4
Itchy Dry Skin	37	5	10	3	0	0	47	4
Boils/Rash	22	3	23	7	1	1	46	4
Constipation/bloating/gas	23	3	5	1	6	3	34	3
Dizziness/Light-headedness	19	2	11	3	1	1	31	2
Thirst/Dry Mouth	22	3	6	2	0	0	28	22
Unplanned Weight Changes	23	3	2	1	2	1	27	23
Muscle Weakness	15	2	10	3	1	1	26	15
Swollen Feet	7	1	17	5	2	1	26	7
Trouble concentrating/ Difficulty Remembering	14	2	1	0	0	0	15	1
Sore Throat	7	1	1	0	2	1	10	1
Cough	6	1	1	0	0	0	7	1

[a]Point Prevalence = the number of times each symptom was reported divided by total number of reports.

Table 6.

Multi-level Cox regression models with time as a constant variable assessing the relationship between menopause status and having period and each HIV-Related Symptom (n=1277 reports)[a]

	Risk ratio	95% Confidence Interval		p-value	Risk Ratio	95% confidence interval		p-value
Effect		**lower**	**upper**			**lower**	**upper**	
Symptom	**Muscle/joint aches/pains**				**Fatigue/loss of energy**			
meno :peri vs post	0.33	0.22	0.51	<.0001	0.99	0.74	1.32	0.94
meno: pre vs post	0.80	0.53	1.21	0.29	0.67	0.47	0.97	<0.05
Period	0.85	0.46	1.56	0.60	1.15	0.75	1.78	0.52
Symptom	**Depression**				**nausea/vomiting**			
meno :peri vs post	2.03	1.26	3.29	<.0001	0.82	0.49	1.38	0.45
meno: pre vs post	0.53	0.25	1.10	0.09	0.22	0.08	0.58	<.001
Period	1.59	0.82	3.11	0.17	0.99	0.43	2.29	0.98
Symptom	**change appetite**				**Diarrhea**			
meno :peri vs post	2.66	1.59	4.46	<.0001	0.54	0.30	0.96	<0.05
meno: pre vs post	2.23	1.22	4.10	<0.05	0.86	0.46	1.63	0.65
Period	1.31	0.68	2.50	0.42	1.30	0.63	2.68	0.48

[a]Models control for number of co-morbid conditions, race, education, income, reporting trend and season if p-value <.20 in bivariate association analysis.