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## ORIGINAL STUDY

# Menopause symptoms delineated by HIV clinical characteristics in African American women with HIV

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**Abstract**

***Objective:*** To obtain data on prevalence and severity of climacteric symptoms in women with HIV (WWH) during the menopausal transition and early menopause and to evaluate for any differences in symptoms by CD4 count and viral load.

***Methods:*** We conducted an in-person survey of female patients attending the Johns Hopkins HIV clinic, ages 40 to 50 years with at least one menstrual period within 6 months before the survey. Interviews utilized the Greene Climacteric scale, a validated menopause questionnaire. We also queried patients, (1) if they were informing their primary care physician of menopause symptoms and (2) if their menopause symptoms were being treated. The study used nonparametric Mann-Whitney rank sum tests with significance defined as $P < 0.05$ to perform symptom severity comparisons of distributions and Fischer exact tests for comparisons of categorical variables such as comparing prevalence of anxiety and depression in the population.

***Results:*** Twenty-three women aged 40 to 50 years were interviewed with a median age of 47 years [25 percentile = 46, 75 percentile = 49]. All were African American with median length of HIV diagnosis of 12 years [25 percentile = 7, 75 percentile = 20.5]. Most of the patients, 87% ($n = 20$), reported experiencing at least one menopause symptom with intense frequency and extreme detrimental effects on quality of life. All women interviewed, 100% ($n = 23$), reported hot flashes, ranging from infrequent to persistent. Sleeping difficulty was reported by 78% ($n = 18$) of women. Most women, 78% ($n = 18$), reported feeling tired or lacking energy with moderate frequency. The majority of the women, 87% ($n = 20$), said they reported menopause symptoms to their primary care provider. Of these, only 20% received treatment for menopause symptoms.

***Conclusions:*** These findings suggest that WWH undergoing the menopausal transition experience intense symptoms severely impacting quality of life. Although the majority of women reported experiencing menopause symptoms to medical providers, most remained untreated. An opportunity exists to educate providers caring for WWH on menopause medicine.

***Key Words:*** HIV-positive – Hot flashes – Menopause transition – Women's health.

As a group, women accounted for 19% of new human immunodeficiency virus (HIV) infections in 2018 and 23.5% of those living with HIV in the United States in 2016.[1] In 2016, 48% of people diagnosed with HIV in the United States and dependent areas were greater than 50 years of age.[2] With the advent of highly active antiretroviral therapy (HAART), the life expectancy of those infected with HIV has improved substantially.[3,4] In 1996, the life expectancy at age 20 years of an HIV positive person was 19 additional years. By 2011, the life expectancy for this group improved to 53 years, with an average age of death at 73.[5] For women with HIV (WWH), this increasing life expectancy is pertinent when it comes to menopause, as a growing population of women infected with HIV will experience perimenopause and menopause.

Menopause is defined as 12 consecutive months without menstruation in accordance with the World Health Organization,[6] and it is well known that the menopause trajectory differs in WWH compared to those without HIV. Schoenbaum et al (2005)[7] reported that HIV infection was independently associated with earlier onset of menopause with a median age of 46 years of age[7] and more recently Andany

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et al (2019)[8] redemonstrated an earlier onset of menopause in their Canadian study population with a median age of menopause of 48 years; 3 years younger than the general population.[8] This is in contrast to the Study of Women's Health Across the Nation, which found a median age at menopause of 51.4 years in a large, multiethnic sample of women in the general population.[9] Decreased quality of life (QOL) during the menopausal transition is related to the presence of climacteric symptoms including the following: hot flashes, difficulty sleeping, and depressed mood.[10]QOL reflects an individual's sense of well-being and satisfaction with daily life, relationships, and feeling of wellness.[11] Several studies demonstrate an increase in vasomotor symptoms and vaginal dryness among WWH.[6,10,12-14] One study specifically found that WWH experienced significantly higher scores on the Hot Flash Related Daily Interference Scale compared to women without HIV, suggesting that the impact of menopausal symptoms has a greater impact on QOL in WWH.[15] Another study found that WWH experienced a disproportionately high level of anxiety and depression compared to HIV negative women, even after controlling for smoking, substance use, and antidepressant use.[16] A third study evaluating WWH and HIV negative controls found that in both groups persistent vasomotor symptoms predicted elevated depressive symptoms, meaning that the vasomotor symptoms of menopause could be further exacerbating the already elevated rates of psychological symptoms in WWH.[17] Finally, a study by Schnall et al[18] noted that independent of aging, symptom burden in WWH may be exacerbated after menopause, specifically fatigue and muscle aches/joint pains.

Although there is some data regarding the prevalence of climacteric symptoms in WWH during the menopausal transition, the mechanisms of disparities in symptoms of menopause between WWH and HIV negative women are still unknown. Understanding what aspects of HIV impact disparities in symptoms of menopause could lead to opportunities to address those symptoms. The objectives of this study were to obtain data on prevalence and severity of climacteric symptoms in WWH during the menopausal transition and early menopause, when women are the most symptomatic;[19] to evaluate for any differences in symptoms by CD4 count and viral load; and to explore possible factors that could influence QOL during the menopausal transition.

## MATERIALS AND METHODS

### Study population

This study was approved by the Institutional Review Board at Johns Hopkins University School of Medicine. Female patients at Johns Hopkins Hospital in Baltimore, Maryland were recruited at the Moore Clinic, a specialty HIV clinic. Inclusion criteria included HIV seropositive women 40 to 50 years old who had at least one menstrual period within the last 6 months. Exclusion criteria included women with a history of bilateral salpingo-oophorectomy more than 12 months previously or those who were in postmenopause before bilateral salpingo-oophorectomy. Twenty-three women were found eligible.

### Demographic and clinical characteristics

Data obtained after patient consent included demographic characteristics (age, race, marital status, body mass index [BMI]) and HIV-related data (length of HIV diagnosis, most recent CD4 count and HIV viral levels). Participants were classified as underweight (BMI $< 18.5\,kg/m^2$), normal (BMI 18.5-24.9 $kg/m^2$), overweight (BMI 25-29.9 $kg/m^2$), and obese (BMI $>30\,kg/m^2$). CD4 counts and HIV RNA viral loads were the most recent values determined by Realtime PCR as found in review of the patient's medical chart. Participants were classified by CD4 count greater than or equal to 500 cells/$m^3$ or less than 500 cells/$mm^{320}$ and by HIV viral load detectable or undetectable.

### Assessment of menopausal symptoms

Personal interviews were conducted over an 18-month time period using The Greene Climacteric Scale, a validated menopause questionnaire that surveyed 21 items on a 4-point Likert scale. Additionally, we queried the patients on: (1) if they were informing their primary care physician of menopause symptoms and (2) if these symptoms were being addressed and treated by their providers.

The Greene Climacteric Scale (Figure 1) was used to assess the nature and severity of climacteric symptoms among participants. The Greene Climacteric Scale is a validated[21-23] and standard scale used to measure the prevalence and severity of climacteric symptoms which can serve as a proxy for the impact of menopausal symptoms on QOL.[24] The questionnaire includes 21 items that are subdivided into four domains: psychological, somatic, vasomotor, and sexual. Each symptom is self-rated by the participant using a four point Likert scale: not at all (0), a little (1), quite a bit (2), and extremely (3). Total score for each participant is the sum of all the scores overall and within each domain. The maximum score for each cluster of symptoms varies based on the number of survey items included in that cluster. The maximum scores were 44 for psychological, 28 for somatic, 8 for vasomotor, and 4 for sexual. The reliability coefficients for psychological, somatic, and vasomotor domains are 0.87, 0.84, and 0.83, respectively.[24]

Prevalence and severity of climacteric symptoms in the study population were described, with the prevalence of symptoms defined as the number of patients reporting the symptom with a score of 1 or greater on the 4-point Likert scale and with severity of symptoms defined as the average and median scores for that symptom on the 4-point Likert scale. Symptom severity was then described for the study population by the median scores for symptom clusters (maximum scores were 44 for psychological, 28 for somatic, 8 for vasomotor, and 4 for sexual) as well as anxiety and depression (maximum scores 18 and 15).

 

# THE GREENE CLIMACTERIC SCALE

NAME: ..... DATE: .....

NUMBER: .....

Please indicate the extent to which you are bothered at the moment by any of these symptoms by placing a tick in the appropriate box.

| SYMPTOMS | Not at all | A little | Quite a bit | Extremely | Score 0–3 |
|---|---|---|---|---|---|
| 1. Heart beating quickly or strongly | | | | | |
| 2. Feeling tense or nervous | | | | | |
| 3. Difficulty in sleeping | | | | | |
| 4. Excitable | | | | | |
| 5. Attacks of panic | | | | | |
| 6. Difficulty in concentrating | | | | | |
| 7. Feeling tired or lacking in energy | | | | | |
| 8. Loss of interest in most things | | | | | |
| 9. Feeling unhappy or depressed | | | | | |
| 10. Crying spells | | | | | |
| 11. Irritability | | | | | |
| 12. Feeling dizzy or faint | | | | | |
| 13. Pressure or tightness in head or body | | | | | |
| 14. Parts of body feel numb or tingling | | | | | |
| 15. Headaches | | | | | |
| 16. Muscle and joint pains | | | | | |
| 17. Loss of feeling in hands or feet | | | | | |
| 18. Breathing difficulties | | | | | |
| 19. Hot flushes | | | | | |
| 20. Sweating at night | | | | | |
| 21. Loss of interest in sex | | | | | |

P ( 1–11) = ☐ A (1–6) = ☐

S (12–18) = ☐ D (7–11) = ☐

V (19–20) = ☐ S (21) = ☐

**FIG. 1.** Greene Climacteric Scale. The Greene Scale provides a brief measure of menopause symptoms. Three main areas are measured: 1. Psychological (items 1-11). 2. Physical (items 12-18). 3. Vasomotor (items 19, 20). Areas can also be classified as Anxiety (items 1-6), Depression (items 7-11), and Sexual (item 21).

### Assessment of anxiety and depression

Anxiety and depression could also be diagnosed based on the results of the Greene Climacteric Scale, with an anxiety score of 10 or more or a depression score of 10 or more diagnostic for clinical anxiety and depression, respectively. This is based on a comparison of the Greene Climacteric Scale with the Hospital Anxiety and Depression Scale, a scale validated to diagnoses psychiatric disorders among general hospital patients.[25-28]

### Statistical analysis

Demographic characteristics were described for the study population and were compared by CD4 count and HIV viral load using non-parametric Mann-Whitney ranks sum tests for comparison of distributions of continuous variables and Fischer exact tests for categorical variables. Medians were chosen due to the small sample size, as the data were not normally distributed. Analysis was further broken down by comparing the median scores on the Greene Climacteric Scale by viral load and CD4 count; comparisons of medians were performed using nonparametric Mann-Whitney rank sum tests with significance defined as $P < 0.05$. The prevalence of anxiety and depression diagnoses were also compared by Viral Load and CD4 count. Comparisons of the categorical variables (anxiety or depression present or absent) were performed using Fischer exact tests. Statistical analyses were performed using Microsoft Excel and the VassarStats website for statistical computation.

## RESULTS

Table 1 shows the demographics of the study population. The median age [25 percentile, 75 percentile] of the population was 47 [46, 49] years. All women surveyed were African American, 82.6% were single and 43.5% had a normal BMI.

Table 2 shows disease characteristics of the sample population. The majority of patients (65.2%) had been HIV seropositive for greater than or equal to 10 years. In terms of disease status, 52.2% had CD4 counts greater than or equal to 500 cells/mm$^3$, and 65.2% had undetectable HIV RNA viral loads (< 20 copies/mL) by realtime PCR. The most commonly used medication regimen was a combination of emtricitabine and tenofovir (56.2%).

**TABLE 2.** *HIV characteristics of study participants*

| Category | *n* = 23 | % |
|---|---|---|
| Duration of HIV diagnosis (y) | | |
| < 5 | 2 | 8.70 |
| 5-9 | 6 | 26.09 |
| 10+ | 15 | 65.22 |
| CD4 count | | |
| >/= 500 | 12 | 52.17 |
| < 500 | 11 | 47.83 |
| HIV viral load | | |
| Undetectable | 15 | 65.22 |
| Detectable | 8 | 34.78 |
| HAART medication | | |
| Emtricitabine | 13 | 56.52 |
| Tenofovir | 13 | 56.52 |
| Dolutegravir | 11 | 47.83 |
| Abacavir | 9 | 39.1 |
| Lamivudine | 9 | 39.1 |
| Ritonavir | 6 | 26.1 |
| Darunavir | 5 | 21.7 |
| Efavirenz | 3 | 13.0 |
| Other | 1 | 4.4 |

n = number of participants.
HIV, human immunodeficiency viruses; HAART, highly active antiretroviral therapy.

Table 3 shows the percentage occurrence of all individualized menopausal symptoms queried upon in the Greene Climacteric Scale, as well as median scores for each item. The most prevalent symptoms were hot flashes ($n = 23$, 100%), feeling unhappy or depressed ($n = 20$, 87.0%), loss of interest in sex ($n = 20$, 87.0%), excitable ($n = 19$, 82.6%), muscle and joint pains ($n = 19$, 82.6%), and sweating at night ($n = 19$, 82.6%). The two vasomotor symptoms with the highest scores were hot flashes and sweating at night, with median scores of 2 and mean scores 2.09 and 1.96, respectively. The least prevalent symptoms were heart beating quickly or strongly and breathing difficulties.

Table 4 further divides the population based on disease status, viral load undetectable and detectable, and CD4 count. The analysis shows that patients with CD4 counts >/= 500 cells/mm$^3$ had noted more climacteric symptoms than

**TABLE 1.** *Demographic characteristics of study participants*

| Category | Total Cohort (*n* = 23) | Normal CD4 count >/= 500 cells/mm$^3$ (*n* = 12) | Low CD4 count <500 cells/mm$^3$ (*n* = 11) | *P value* | Undetectable RNA viral load < 20 copies/mL (*n* = 15) | Detectable RNA Viral Load >/= 20 copies/mL (*n* = 8) | *P* value |
|---|---|---|---|---|---|---|---|
| Age, years | 47 [46, 49] | 48.5 [47, 49.25] | 46 [44, 47] | 0.03 | 47 [46.5, 49] | 46.5 [44.75, 47.75] | 0.60 |
| Marital status | | | | | | | |
| Single | 19 (82.6%) | 8 (66.7%) | 11 (100%) | 0.09 | 11 (73.3%) | 8 (100%) | 0.25 |
| Married | 4 (17.4%) | 4 (33.3%) | 0 | .. | 4 (26.7%) | 0 | .. |
| Race | | | | | | | |
| African American | 23 (100%) | 12 (100%) | 11 (100%) | - | 15 (100%) | 8 (100%) | - |
| BMI | | | | | | | |
| Underweight <18 | 2 (8.7%) | 1 (8.3%) | 1 (9.1%) | 0.75 | 1 (6.7%) | 1 (12.5%) | 1 |
| Normal 18-25 | 10 (43.5%) | 4 (33.3%) | 6 (54.5%) | .. | 6 (40.0%) | 4 (50%) | .. |
| Overweight 26-30 | 1 (4.4%) | 1 (8.3%) | 0 | .. | 1 (6.7%) | 0 | .. |
| Obese >30 | 10 (43.5%) | 6 (50%) | 4 (36.4%) | .. | 7 (46.7%) | 3 (37.5%) | .. |

Data are median [25 percentile, 75 percentile] or *n* (%), unless otherwise stated.
*P* values are calculated by nonparametric Mann-Whitney rank sum tests for continuous variables and Fischer exact tests for categorical variables.
BMI, Body Mass Index; RNA, Ribonucleic Acid.

**TABLE 3.** *Prevalence[a] and severity[b] of climacteric symptoms in study participants based on Greene Climacteric Scale*

| Item | Symptom | Number of symptomatic patients $n = 23$ | % of patients reporting symptom | Mean Likert Score | Median Likert Score |
|---|---|---|---|---|---|
| 1 | Heart beating quickly or strongly | 11 | 47.83 | 0.78 | 0 |
| 2 | Feeling tense or nervous | 15 | 65.22 | 1.22 | 1 |
| 3 | Difficulty in sleeping | 18 | 78.26 | 1.74 | 2 |
| 4 | Excitable | 19 | 82.61 | 1.35 | 1 |
| 5 | Attacks of pain | 14 | 60.87 | 1.39 | 2 |
| 6 | Difficulty in concentrating | 15 | 65.22 | 1.09 | 1 |
| 7 | Feeling tired or lacking in energy | 18 | 78.26 | 1.78 | 2 |
| 8 | Loss of interest in most things | 18 | 78.26 | 1.61 | 2 |
| 9 | Feeling unhappy or depressed | 20 | 86.96 | 1.91 | 2 |
| 10 | Crying spells | 15 | 65.22 | 1.09 | 1 |
| 11 | Irritability | 18 | 78.26 | 1.48 | 2 |
| 12 | Feeling dizzy or faint | 12 | 52.17 | 0.65 | 0 |
| 13 | Pressure or tightness in head or body | 13 | 56.52 | 0.83 | 1 |
| 14 | Parts of body feel numb or tingling | 14 | 60.87 | 1.26 | 1 |
| 15 | Headaches | 15 | 65.22 | 0.96 | 1 |
| 16 | Muscle and joint pains | 19 | 82.61 | 1.74 | 2 |
| 17 | Loss of feeling in hands or feet | 13 | 56.52 | 0.91 | 1 |
| 18 | Breathing difficulties | 9 | 39.13 | 0.70 | 0 |
| 19 | Hot flashes | 23 | 100 | 2.09 | 2 |
| 20 | Sweating at night | 19 | 82.61 | 1.96 | 2 |
| 21 | Loss of interest in sex | 20 | 86.96 | 1.70 | 2 |

$n$ = number of participants reporting score $\geq 1$ on 4-point Likert scale: not at all (0), a little (1), quite a bit (2), and extremely (3)
[a]Prevalence defined as percentage of participants reporting score $\geq 1$ on four point Likert scale: not at all (0), a little (1), quite a bit (2), and extremely (3)
[b]Severity defined as mean and median scores on four point Likert scale: not at all (0), a little (1), quite a bit (2), and extremely (3)

their counterparts with CD4 counts $< 500$ cells/mm$^3$ with symptoms grouped together into themed clusters. However, these differences did not meet statistical significance.

Table 5 shows the percentage of patients who screened positive for anxiety and depression and that there were no significant differences in prevalence of anxiety and depression by viral load or CD4 count. Regarding patient experiences with their primary care providers, the vast majority ($n = 20$, 87.0%) of patients shared their problems with their providers. Of the patients who shared their experiences, only 20% were treated with either hormones or selective serotonin reuptake inhibitors.

## DISCUSSION

This study obtained data on prevalence and severity of climacteric symptoms in WWH during the menopausal transition and early menopause, and evaluated for differences in symptoms by CD4 count and HIV viral load. The study also evaluated patients' experiences with their providers in reporting menopause symptoms and receiving treatment. The findings show that WWH experience significant climacteric symptoms, with vasomotor symptoms predominating. WWH may have worse symptoms than women who are HIV negative, however there is a need for normative data with HIV negative women for similar age and ethnicity. The study notes the high prevalence of depression in the HIV population. Our study also highlights the current lack of treatment by primary care providers regarding menopause symptoms in WWH. This is a lost opportunity to improve QOL.

The Greene Climacteric Scale was selected to gather data on menopause symptoms because it independently measures psychological, somatic, vasomotor, and sexual clusters. The Guide to the Greene Climacteric Scale provides normative data of 200 menopause urban Scottish women. The mean scores for the

**TABLE 4.** *Severity of climacteric symptoms in study participants by viral load and CD4 count*

| Clusters | HIV positive $n = 23$ | Viral load undetectable $n = 15$ | Viral load detectable $n = 8$ | $P$ | CD4 >/=500 $n = 12$ | CD4 < 500 n = 11 | $P$ |
|---|---|---|---|---|---|---|---|
| Psychological | 16 [10, 21.5] | 16 [11.5, 22.5] | 14 [9.75, 18.75] | 0.60 | 19 [12.25, 23.25] | 13 [9.5, 17.5] | 0.17 |
| Anxiety | 7 [5, 11] | 8 [4.5, 11.5] | 7 [5.75, 8] | 0.98 | 8.5 [5, 12.5] | 7 [4, 8.5] | 0.28 |
| Depression | 9 [4, 11.5] | 9 [5, 12] | 7 [4, 10.25] | 0.26 | 10 [5, 12.25] | 6 [4, 10] | 0.12 |
| Somatic | 7 [4.5, 8.5] | 7 [5, 8.5] | 6.5 [4, 8.5] | 0.79 | 7 [5, 8] | 7 [4, 10] | 0.95 |
| Vasomotor | 4 [3, 6] | 3 [2.5, 5] | 5.5 [4, 6] | 0.11 | 3 [2.75, 4.5] | 5 [4, 6] | 0.18 |
| Sexual | 2 [1, 3] | 2 [1, 2.5] | 2 [1, 3] | 0.60 | 2 [1, 3] | 1 [0.5, 3] | 0.60 |
| Total | 27 [25, 35.7] | 28.5 [22, 36] | 28.5 [25.5, 33.75] | 0.82 | 28.5 [24.75, 37.75] | 26 [25, 33.5] | 0.40 |

$n$ = number of participants.
Severity is described by median [25 percentile, 75 percentile].
$P$ values are calculated with nonparametric Mann-Whitney rank sum tests.
Maximum scores for symptoms clusters were 44 for psychological, 28 for somatic, 8 for vasomotor, and 4 for sexual.
Maximum scores psychological subclusters were 18 for anxiety and 15 for depression.
HIV, human immunodeficiency viruses.

**TABLE 5.** *Prevalence of depression and anxiety based on a score > 10 in the study population and by viral load and CD4 count*

| Group | All $n = 23$ | Viral loadundetectable $n = 15$ | Viral load detectable $n = 8$ | $P$ value | CD4 >/= 500 $n = 12$ | CD4 < 500 n = 11 | $P$ value |
|---|---|---|---|---|---|---|---|
| Anxiety | 8 (34.78%) | 6 (40.00%) | 2 (25.00%) | 0.66 | 5 (41.67%) | 3 (27.27%) | 0.67 |
| Depression | 11 (47.83%) | 7 (46.67%) | 4 (50%) | 1.0 | 5 (41.67%) | 6 (54.55%) | 0.68 |

Prevalence = number of participants reporting score $\geq 1$ on four point Likert scale: not at all (0), a little (1), quite a bit (2), and extremely (3).
Data are n (%)

psychological, somatic and vasomotor clusters were $7.42 \pm 6.41$, $3.25 \pm 3.64$, and $1.79 \pm 1.12$, respectively.[24] By comparison, in our study population the mean scores were $15.43 \pm 7.48$, $7.04 \pm 4.01$, and $4.04 \pm 1.74$. Means are reported here for direct comparison with normative data, however medians were used in our tables due to small sample size; with medians (25 percentile, 75 percentile) for the pyschologic, somatic, and vasomotor clusters of 16 (10, 21.5), 7 (4.5, 8.5), and 4 (3, 6). Several other studies have provided normative data for different populations, including Dutch,[29] Ecuadorian,[30] Australian,[31] Indian,[4] and Portuguese.[22] There currently is no normative data for African Americans, which comprised 100% of our study population. There is a notable increase in mean scores among the WWH in this study compared to the means from other available populations. However, it is difficult to make conclusions between the two groups without this normative data.

Studies to date have demonstrated mixed findings regarding HIV infection and its association with an earlier onset of menopause and increased symptoms of menopause but the etiology of these differences is not known.[7,12,32,33] In our study, patients with CD4 counts >/= 500 cells/mm$^3$ had noted more climacteric symptoms than their counterparts with CD4 counts < 500 cells/mm$^3$. Interestingly, in examining the subclusters, women with CD4 counts >/= 500 cells/mm$^3$ had increased psychological symptoms, whereas women with CD4 counts < 500 cells/mm$^3$ had increased somatic and vasomotor symptoms, although these differences did not achieve statistical significance. Given the small size of our study population, we were likely underpowered to detect significant differences within these variables, and larger studies are needed to further explore the relationship between HIV-related characteristics and menopause symptoms in this population. Alternatively, it is possible there are other qualities of WWH that lead to disparities in menopause symptoms by HIV status that are not evaluated in our study.

Others have noted similar findings. The Women's Interagency HIV Study reported that lower CD4 counts in both HIV infected and noninfected women were associated with lower antimullerian hormone levels, a marker typically used to evaluate ovarian reserve. This suggests that CD4 helper T cells may have an important role in ovarian granulosa cell function and follicle physiology and may have a role in earlier menopause in WWH.[34] Schoembaum et al[7] also examined the association of CD4 cell count among WWH with age at menopause. They reported that CD4 counts of >500 cells/mm$^3$ (OR: 0.19, 95% CI [confidence interval] 0.08-0.48, $P = 0.001$) and 200 to 500 cells/mm$^3$ (OR: 0.35, 95% CI 0.15-0.81, $P = 0.015$) were independently associated with a decreased risk or premature menopause compared with a CD4 count < 200 cells/mm$^3$. The median age of menopause was 42.5 years in women with CD4 counts < 200 cells/mm$^3$, in comparison to the median age of menopause of 46.0 years in those with CD4 cell counts of 200 to 500 cells/mm$^3$ and 46.5 years in those with CD4 cell counts >500 cell/mm$^3$.[7] Pommerol et al[35] found that in a prospective open cohort of HIV-infected individuals, women of African origin (hazard ratio [HR] = 8.16; 95% CI = 2.23-29.89) and history of injecting drug use (HR = 2.46; 95% CI = 1.03-5.85) were associated with an increased risk of earlier menopause and that women with a CD4 cell count < 200 cells/mm$^3$ tended to reach menopause earlier (HR = 2.25; 95% CI = 0.94-5.39).[35] These findings suggest that factors associated with HIV such as injecting drug use and African ethnicity, as well as HIV-related immunodeficiency, could all influence the earlier onset of menopause in this patient population.[36]

This study specifically looked at menopause symptoms. Without HIV, African American women were found to have more vasomotor symptoms of menopause than other ethnic groups. More specific to our findings, Fantry et al[13] compared HIV affected and unaffected African American women and found a higher prevalence of hot flashes and vaginal dryness among HIV-infected, African-American women between 40 and 57 years old.[13] HIV infection has also been found to be independently associated with menopause symptoms in a cross sectional study in Brazil[37] and specifically with increased severity of menopause symptoms in a population of Nigerian women.[38] Early or premature menopause has important implications for a woman's mood, sexual function, QOL, and other comorbidities such as cardiovascular disease or osteoporosis.[39]

Notably, 13 of the 23 women in our study (56.5%) had symptoms consistent with either clinical anxiety or depression. In a meta-analysis, Ciesla and Roberts demonstrated that HIV-positive individuals have a twofold increased risk of developing depression compared with seronegative controls.[40] In the United States, nearly half of HIV positive adults presented with a psychiatric illness. Thirty six percent were diagnosed with depression, whereas, 16% were diagnosed with generalized anxiety disorder.[41] The relationship between anxiety and depression and HIV pathophysiology, the psychological impact of carrying an HIV diagnosis, and the onset of perimenopause is complicated and not yet well understood. One longitudinal study found that HIV status was associated with higher depression and anxiety scores, and also that depressive symptoms and anxiety were associated with

 

hot flash severity.[16] Another study stated that the presence of moderate to extremely severe hot flashes was associated with increased anxiety, and worse attention span and processing speed.[16,42] Further research could look into the causal relationships between these factors. However, our study does lend evidence to support that perimenopause could be a critical time for screening for and treating anxiety and depression in WWH.

In an attempt to understand patient experiences with their primary care providers regarding their perimenopause symptoms, we noted that patients commonly described their symptoms to their providers, however only 20% were addressed with either medications or lifestyle modifications. With the advent of antiretroviral therapy, AIDS-related opportunistic infections and malignancies are no longer primary issues. Instead, traditional age and lifestyle-related conditions are growing concerns.[43] Menopause symptoms may be more difficult to identify by clinicians or by WWH themselves due to the earlier onset of menopause or to patients' other comorbidities.[44] Particularly, Johnson et al[32] found that younger WWH were less likely to associate their symptoms of hot flashes or vaginal dryness with menopause even if they were missing periods. There are also unique considerations for menopause management in WWH, such as potential medication interactions with antiretroviral therapy or possible predisposition for decreased bone mineral density and potentially increased cardiovascular risk in WWH,[45] which may make providers less confident in offering treatment.

Menopause management can improve QOL for patients. In a study of hormone therapy (HT) in postmenopausal WWH, which is only one of several options for menopause management, 52% of the patients in the study who were offered HT accepted the treatment. Of the women of black ethnicity in the study, 91% of the patients who accepted HT reported having good symptom control on the medication and 17% subsequently discontinued the medication.[46] Menopause management in WWH may also improve women's HIV treatment and potentially their overall health and safety. A study by Duff et al[47] reported that severe menopausal symptoms were associated with decreased adherence with antiretroviral therapy and were also associated with increased injection drug use and physical/sexual violence.

Chirwa et al[48] found that primary care physicians reported limited experience with and low levels of confidence in managing menopause-related symptoms in WWH. In fact, in their study almost all of the providers had concerns about managing menopause-related symptoms in WWH and many stated that this management should occur outside of primary care.[48] WWH have earlier onset of menopause, and younger WWH are less likely to have their menopause symptoms identified. For these reasons, in addition to provider's low confidence in management, the women in our patient population are at risk of having their symptoms missed or not addressed. This theory was confirmed by the low frequency of providers addressing menopause symptoms in our study.

**Strengths and limitations**

The strengths of this study include the use of the validated and standard Greene Climacteric Scale to evaluate symptoms and symptom severity, the access to this specific HIV positive patient population, and the assessment of this novel research question in an understudied African American patient population. This study is also unique in its evaluation of the patient's experiences with care providers.

Limitations include the lack of a direct comparison of African American women with the Greene Climacteric Scale to provide a more equivalent control for our population. It would also be helpful to compare our findings to normative data for nonmenopause seropositive HIV patients to decrease the confounding symptoms associated with a positive HIV diagnosis such as increased psychiatric illness or medication side effects. Timing of last menstrual period or number of periods in the last 6 months were not assessed. This information could be collected in future studies to give insight into the menopause stage of the study participant and the timing in the menopausal transition that symptoms are more or less severe. Data on use of HT, antidepressants, or other treatment modalities were not collected. Therefore, the influence of treatment on the study findings could not be determined. Our small study size is an additional limitation. Our study also did not survey the providers for the patients regarding their knowledge and comfort level with menopause management or the interventions offered to the patients and what interventions they did or did not accept.

**Study implications**

Further research is needed on this subject. Tariq et al[49] have also noted a gap in the knowledge regarding the impact of menopause on the health and well-being of WWH and published that they have conducted a longitudinal cohort study to follow a larger group of patients in the UK on this subject.[50] The results of their study have not yet been published. Further study could also be performed to investigate treatment of menopause symptoms in this patient population to optimize care and improve QOL for WWH in this phase of their lives. Finally, one could also evaluate the relationship between menopause and HIV-related comorbidities, progression of HIV, CD4 count over time, or response to HAART.

Our study notes the high prevalence of depression in the HIV population. Based on this finding we hypothesize that there may be an increased role for use of antidepressants in the HIV population, which may have a beneficial effect of improving vasomotor symptoms such as hot flashes and night sweats.

Our study also highlights the current lack of treatment by primary care providers regarding menopause symptoms in WWH. This is a lost opportunity to improve QOL. It is possible that this is due to lack of guidelines and also the high level of comorbidities often associated with patients who are HIV positive. We believe our study findings can be addressed on a clinical level with simple educational interventions. For example, one of the authors (WS) has developed

and implemented a smartphone application for use by all primary providers, including HIV providers, to care for their patients with menopause symptoms. This point of care application serves to increase provider knowledge of menopause symptoms and treatments, and improve patient satisfaction.

## CONCLUSIONS

WWH experience significant climacteric symptoms, with vasomotor symptoms predominating. In comparison to known normative data, WWH may have worse symptoms, however there is a need for normative data for similar age and ethnicity. Furthermore it may be beneficial to obtain normative data for nonmenopause seropositive HIV patients to decrease the confounders associated with a positive HIV diagnosis such as increased depression and side effects from HIV treatment.[40,51,52] Our study also highlights the high prevalence of depression in the HIV population, identifying antidepressants as a potential treatment that would address mood and vasomotor symptoms. Finally, our study emphasizes the current lack of treatment by primary care providers regarding menopause symptoms in WWH, which is an opportunity for providers to improve QOL for HIV positive patients.

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