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Undertreated midlife symptoms for women living with HIV linked to lack of menopause discussions with providers

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Abstract

Background: Increasingly, women living with HIV are entering menopause (i.e., cessation of menses for ≥1 year) and experiencing midlife symptoms. Menopausal hormone therapy (MHT) is first-line therapy for bothersome hot flashes and early menopause (i.e, before age 45), however, its use in women living with HIV is poorly described. We conducted a cross-sectional assessment of MHT uptake and barriers to use in this group.

Setting: This study was conducted across three Canadian provinces from 2015-2017.

Methods: Perimenopausal and postmenopausal women living with HIV (≥35 years) in the Canadian HIV Women's Sexual and Reproductive Health Cohort Study (CHIWOS) who answered questions related to MHT use were included. Univariable/multivariable logistic regression evaluated factors associated with MHT use, adjusted for age and contraindications.

Results: Among 464 women, 47.8% (222/464) had a first-line indication for MHT, however, only 11.8% (55/464) reported ever using MHT and 5.6% (26/464) were current users. Only 44.8% had ever discussed menopause with their provider despite almost all women having regular HIV care (97.8%). African/Caribbean/Black women had lower unadjusted odds of MHT treatment compared to white women (odds ratio [OR] 0.42 [0.18-0.89]; *P*=0.034). Those who had discussed menopause with their provider had higher odds of treatment (OR 3.13 [1.74-5.86]; *P*<0.001). In adjusted analyses, only having had a menopause discussion remained significantly associated with MHT use (OR 2.97 [1.62-5.61]; *P*<0.001).

Conclusion: Women living with HIV are seldom prescribed MHT despite frequent indication. MHT uptake was associated with provider-led menopause discussions underscoring need for provider education on menopause management within HIV care.

Keywords: *HIV, Women's Health, Menopause, Menopausal hormone therapy, Hormone replacement therapy*

Introduction

Preserving health-related quality of life for aging persons living with HIV is a global priority.[1] With effective antiretroviral therapy (ART), women living with HIV worldwide are increasingly aging. With this, a growing number of women are entering perimenopause (menstrual cycles more than a month apart but menstruated within the last year) and menopause (cessation of menses for ≥1 year).[2,3] These women often experience bothersome vasomotor symptoms (i.e., hot flashes, night sweats)[4-6] during the menopause transition and commonly

experience menopause at early ages (i.e., <45 years).[7-9] Both vasomotor symptoms and early menopause impact health-related quality of life[10-12] and are first-line indications for menopausal hormone therapy (MHT) which is comprised of ovarian hormones, estrogen and progesterone, given systemically.[13] However, the use of MHT in women living with HIV has been poorly described and its evaluation is limited to a handful of small studies.[4,7,14-16] These studies suggest that MHT uptake is low in this group but fail to investigate reasons for its infrequent use.

Several reasons have been proposed for the low rates of MHT treatment for women living with HIV, however none have been systematically evaluated. One reason postulated for low uptake is a lack of expertise of HIV care providers in treating symptomatic midlife women.[17] In addition, women's knowledge of MHT may be a limiting factor, as evidence by a recent study of women living with HIV where almost half of those experiencing menopausal symptoms had not heard of MHT.[16] Other patient-related factors, such as low socioeconomic status, may decrease affordability of MHT for some women. For those with other active medical issues such as poorly controlled HIV or substance use, menopausal care may be considered less of a healthcare priority.[15] Finally, drug interactions between MHT and ART and risk of adverse events secondary to MHT may further discourage providers from offering MHT.[2,17] Many of these factors, including drug interactions and many adverse events, need not contraindicate MHT and can be safely navigated with adjustments to formulations and risk/benefit discussions. Unfortunately, without systematic evaluation of barriers to use, it remains unclear which factors most impact MHT prescription practices and how to best mitigate these barriers. Therefore, we assessed patterns of MHT use and barriers to uptake in a cohort of women living with HIV in Canada. We hypothesized that treatment rates would be low and that lack of MHT use would relate to a combination of patient-related factors (i.e., low socioeconomic status and substance

use) and factors related to HIV care (i.e., provider training, HIV control, drug interactions, and contraindications).

Methods

Study Participants

We conducted a cross-sectional analysis of the Canadian HIV Women's Sexual and Reproductive Health Cohort Study (CHIWOS), a large, community-based project conducted in three Canadian provinces. Participants were recruited to reflect the diversity of women living with HIV in Canada using a purposive sampling strategy, described in detail elsewhere.[18,19] This analysis uses data from the second timepoint from June 2015 to January 2017 (survey available at: http://www.chiwos.ca/wp-content/uploads/2012/04/CHIWOS-Wave-2-Survey-2016.02.12-EN_clean.pdf). Survey data was collected by peers with living experience and research training. Participants were included if they were: i) assigned female sex at birth, ii) ≥35 years, and iii) perimenopausal or postmenopausal by self-report, or if their menstrual history was suggestive of having experienced menopause (i.e., cessation of menses for ≥ one year not due to secondary causes).[3] Those who answered any question on MHT use as "don't know" or "prefer not to answer" were excluded from the analysis.

Measures

Use of menopausal hormone therapy

Self-reported ever and current use of MHT were primary outcomes. Women were considered to have "current use" if they reported use within the 18 months prior to the CHIWOS interview. Use of non-hormonal therapies was also assessed by asking whether any of the

following had been used in the past for management of hot flashes: anti-depressants, clonidine, gabapentin, natural health products, or nothing.

Covariates

Correlates for MHT use included sociodemographic factors (age, ethnicity, education, employment, income), substance use, menopausal characteristics (early menopause/primary ovarian insufficiency [POI], symptoms), sexual and reproductive health care (last pap smear, type of care provider, menopause discussion with provider), contraindications to MHT, and parameters of HIV care (self-reported viral load, CD4 count, ART adherence, potential MHT/ART drug interaction, and barriers to care access).

Early menopause/POI (menopause at age <45 and 40 years, respectively) was assessed only in postmenopausal women. The menopause rating scale (MRS), previously validated in women living with HIV, was used to evaluate menopausal symptoms (range 0-44).[4,6,20] Menopause discussion was assessed by the following: "Have you ever discussed menopause with your healthcare provider?" with choices of "Yes", "No", "Don't know" and "Prefer not to answer." Barriers of access to care (BAC) was based on a 12 item-scale (range 12-48) with higher scores indicative of increased barriers.[21] First-line indications for MHT included early menopause (age <45) and moderate/severe vasomotor symptoms as per guideline indications.[13,22] Contraindications included self-reported history of any one of the following: breast cancer, endometrial cancer, cardiovascular disease, stroke, venous thromboembolism, and dementia.[13] Drug interactions between MHT and ART included those anticipated to decrease (efavirenz, etravirine, nevirapine) or increase (unboosted atazanavir, cobicistat/ritonavir-boosted regimens) hormone levels.[23]

Statistical analysis

Baseline characteristics were summarized with descriptive statistics. Univariable/multivariable logistic regression examined factors associated with: i) MHT use ever and ii) current use. Models were constructed first by assessing preselected variables in unadjusted univariable analysis (see **Appendix, Table 1**), then entering variables with $P<0.1$ into a multivariable model, adjusting for contraindications to MHT and age ($P<0.05$). Covariates assessed were limited to ≤ one for every 10 events to ensure adequate power.[24] Only univariable analysis was conducted for current MHT use given limited number of events. Women were excluded from analyses if they had missing values for any of the model variables. Analyses were performed using R (version 4.0.4; Vienna, Austria).[25]

Results

Baseline characteristics

Among 1244 participants assessed, 464 peri- and postmenopausal women living with HIV met inclusion/exclusion (*exclusions:* n=54 not female, n=678 not in peri/menopause, n=48 missing MHT data). Baseline characteristics are summarized in **Table 1**. Median age was 54 years [IQR 49.5 to 58.0]. Approximately half of the women identified as white (50.6%), 25.2% African/Caribbean/Black (ACB) and 18.5% Indigenous. Many women had low annual household income (62.9%). A total of 44.6% were current smokers and 21.1% recently used recreational drugs. HIV was well-controlled in the majority with 88.6% reporting undetectable viral load and 81.2% CD4≥200 cells/mm^3.

Menopausal experience and treatment

Almost half of women in our assessment (47.8%; 222/464) had a first-line indication for MHT (143 moderate/severe hot flashes, 54 early menopause, 25 both).[12] Despite this, only 11.8% (55/464) reported ever using MHT and 5.6% (26/464) were currently on therapy. A minority (16.5%) of women with early menopause had ever received MHT. Non-hormonal therapies were used by 13.6% (63/464) including antidepressants (n=26), alternative health products (n=24), gabapentin (n=16) and clonidine (n=9); twelve had tried ≥2 therapies. Contraindications to MHT were present in 16.4% (n=76; 10 with >1 contraindication) and did not significantly vary between women with or without MHT use. These included breast cancer (n=10), endometrial cancer (n=11), cardiovascular disease (n=16), stroke (n=32), venous thromboembolism (n=12) and dementia (n=5). Forty percent (40.5%) of participants were prescribed ART with potential for interaction with MHT.

Surprisingly, fewer than half (44.8%) of the women in our assessment reported ever having discussed menopause with their care provider despite the large majority (97.8%) reporting regular follow-up with an HIV provider. Care providers were predominantly Infectious Disease specialists (71.8%), followed by General Practitioners (17.2%) and other providers (10.3%). Menopause discussions were less common in women of ACB and Indigenous descent (35.9% and 37.2%, respectively) than white women (50.6%).

Correlates of MHT use

Income, education, substance use, viral load suppression, early menopause, drug interactions, and contraindications to MHT were not associated with ever using MHT (**Appendix, Table 1**). ACB women had lower unadjusted odds of MHT treatment compared to

white women (odds ratio [OR] 0.42 [95% confidence interval 0.18-0.89]; *P*=0.034); those who discussed menopause with their provider had higher odds of MHT treatment (OR 3.13 [1.74-5.86]; *P*<0.001). In adjusted analysis, only having discussed menopause with a provider remained significantly associated with ever using MHT (adjusted OR 2.97 [1.62-5.61]; *P*<0.001). Women with higher symptom scores had increased odds of current MHT use; a one unit increase in MRS increased the odds of current use by 7% (OR 1.07 [1.02 to 1.11]; *P*= 0.002; **Appendix, Table 1**).

Discussions

In this cohort of peri- and postmenopausal women living with HIV in Canada, rates of MHT treatment were low despite nearly half having an indication. These data build on previous findings of low MHT use amongst women living with HIV which have consistently shown rates around or below 10%.[4,7,14,16] In surveys of HIV-negative women conducted in North America over a similar timeframe, uptake was approximately double that observed in our cohort, with 21-28% of HIV-negative women reporting ever using MHT (9-10% reporting current use).[26,27] The disparity observed between low treatment rates and high indications hints at a gap in care for midlife women living with HIV and establishes the need to assess factors contributing to such a disparity.

Discussing menopause with one's care provider emerged as an important factor associated with MHT prescription. This finding was surprising, as we had hypothesized that several patient and provider-related factors would account for MHT use. Our findings to the contrary suggest that a lack of menopause discussions is a major barrier to care, and its influence surpassed other barriers. Several factors may be leading to this low frequency of menopause

discussions, ranging from lack of confidence of providers in managing menopause to low awareness or self-efficacy amongst women. We observed that many women living with HIV answered "don't know" to questions about menopause phase or timing, a finding that may reflect low health literacy of reproductive midlife changes and need for education in this area. Similarly, a low awareness of MHT, which been previously described amongst women living with HIV,[16] may make women less inclined to bring up symptoms of menopause. Lack of provider confidence in menopause management is likely also contributing to these low rates of discussion, as a past study reported that 96% (85/88) of primary care providers surveyed in the UK had concerns about managing menopause in the context of HIV.[17] In North America, where much of HIV care is provided by Infectious Disease specialists,[28] confidence in managing menopause is likely equally low, as typically very little menopausal training is afforded during specialty training.[29] The startlingly low number of midlife women who had discussed menopause with their provider demonstrates the pressing need for increased menopause education for HIV providers and patients, particularly as HIV care focuses on preserving quality of life during aging.[1,30]

The trend we observed of lower MHT uptake in women of ACB descent may relate to provider bias in offering MHT and cultural differences in treatment preferences. Cultural variation in MHT use has been previously described, with white women more likely to be prescribed therapy than non-white ethnicities.[27,31] Similarly, in a previous study of mostly ACB women living with HIV who were offered MHT, up to half did not accept it.[15] We observed lower unadjusted rates of MHT use and lower rates of provider-led menopause discussions in ACB women. When menopause discussions were adjusted for, ACB descent was no longer associated with MHT use. Together, these findings suggest that differences in menopause

discussions *between cultural groups* may be driving some of the disparities in uptake. The reasons for why these conversations are not taking place is an important area of future study. These findings could reflect providers' discomfort in addressing menopause amongst certain cultural groups or cultural differences in how menopause and its treatments are perceived.[31,32] Further, ACB women may feel less at ease to discuss these personal aspects of health with providers, a reluctance that may be driven by experiences of structural racism and negative healthcare encounters in the past.[33,34] Such experiences may lead to medical mistrust which in turn influences medication necessity beliefs.[35] Moving forward, further attention should be given to better understand cultural disparities in menopausal assessment and break down barriers to menopausal care.

Our finding that those with increased symptoms would be more likely to receive MHT was expected and in keeping with guideline recommendations.[13] By contrast, early menopause was not associated with MHT despite recommendations supporting its use in this setting. Early menopause is of particular relevance because it has been described at increased frequency in cohorts of WLWH.[7,9,36] Early menopause has been associated with long term health consequences, including increased risk of fractures and cardiovascular events.[12] For this reason, expert guidelines recommend MHT in early menopause due to its observed health benefits and potential to mitigate the effects of premature hormonal decline.[10,12,13,22] For women living with HIV who already experience high rates of bone and cardiovascular disease, the benefits of MHT may be even greater for those with early menopause than in the general population.[23] Our finding of low rates of MHT use in early menopause may point to a knowledge gap for providers of this indication.

This study has limitations. Its cross-sectional nature limits our ability to draw conclusions on temporality, particularly in evaluating contraindications to MHT. Second, our analysis was not designed or powered to evaluate the impact of MHT on comorbidity risk. The risk and benefits of MHT in the context of HIV is essentially unexplored and is important given the recognized risk of multimorbidity of this group.[23,37,38] Our assessment also did not include granular data on the formulations of MHT used by women, which also influence comorbidity risk. Finally, we only assessed those women that *took* MHT not those who were *offered* it. Understanding the values, preferences, and attitudes of women living with HIV toward MHT are important avenues for future research and may benefit from qualitative assessments in this area.

Conclusion:

We present the largest evaluation of MHT use in women living with HIV thus far, adding to existing evidence that MHT is underutilized in this group. We suggest for the first time that a major barrier to use is lack of menopause discussions in clinical care, underscoring the importance of enhanced menopausal education amongst providers and women living with HIV. Although guidelines are recently available to help guide menopause care in the setting of HIV,[39-41] ongoing advocacy is needed to ensure that menopause assessments are integrated into routine clinical care for midlife women living with HIV.

Table/Figure Captions

Table 1 Baseline characteristics of perimenopausal and menopausal women living with HIV in Canada (n=464) and by menopausal hormone therapy (MHT) use ever

Figure 1 Univariable (panel a) and multivariable (panel b) analyses of factors associated with ever using menopausal hormone therapy in peri/menopausal women living with HIV (n=464). *P*-values: **<0.05; **** <0.001

Appendix, Table 1 Logistic regression analysis of factors associated with ever and current use of menopausal hormone therapy (MHT) in midlife women living with HIV (n=464) in Canada

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Table 1 Baseline characteristics of perimenopausal and postmenopausal women living with HIV in Canada (n=464) and by menopausal hormone therapy (MHT) use ever

	Total n=464	**No MHT use ever n=409**	**MHT use ever n=55**
Sociodemographics			
Age (years); median [IQR]	54.0 [49.5 to 58.0]	54.0 [49.0 to 58.0]	53.0 [50.0 to 59.0]
Ethnicity; n (%)			
Indigenous	86 (18.5%)	77 (18.8%)	9 (16.4%)
African/Caribbean/Black	117 (25.2%)	109 (26.7%)	8 (14.5%)
White	235 (50.6%)	200 (48.9%)	35 (63.6%)
Mixed and other ethnicities	26 (5.6%)	23 (5.6%)	3 (5.5%)
Household income; n (%)			
<$20,000	292 (62.9%)	258 (63.1%)	34 (61.8%)
≥$20,000	162 (34.9%)	141 (34.5%)	21 (38.2%)
Unknown/no answer	10 (2.2%)	10 (2.4%)	0 (0.0%)
Education; n (%)			
Less than high school	144 (31.0%)	130 (31.8%)	14 (25.5%)
More than high school	320 (69.0%)	279 (68.2%)	41 (74.5%)
Employed*; n (%)			
Employed	135 (29.1%)	120 (29.3%)	15 (27.3%)
Unemployed	325 (70.0%)	286 (69.9%)	39 (70.9%)
Unknown/no answer	4 (0.9%)	3 (0.7%)	1 (1.8%)
Smoking; n (%)			
Current	207 (44.6%)	178 (43.5%)	29 (52.7%)
Former/never	255 (55.0%)	229 (56.0%)	26 (47.3%)
Unknown/no answer	2 (0.4%)	2 (0.5%)	0 (0%)
Recreational drug use (in past 6 months); n (%)			
Yes	98 (21.1%)	86 (21.0%)	12 (21.8%)
No	365 (78.7%)	322 (78.7%)	43 (78.2%)
No answer	1 (0.2%)	1 (0.2%)	0 (0)
Menopause characteristics			
Early menopause/POI; n (%)			
Yes	79 (17.0%)	66 (16.1%)	13 (23.6%)
No	233 (50.2%)	207 (50.6%)	26 (47.3%)
Unknown/no answer	152 (32.8%)	136 (33.3%)	16 (29.1%)
Menopause symptom score (by MRS); median [IQR]	10.0 [5.0 to 17.0]	10.0 [4.0 to 17.0]	11.0 [6.0 to 21.5]
Unknown/no answer	22 (4.7%)	18 (4.4%)	4 (7.3%)
Discussed menopause with provider; n (%)			
Yes	208 (44.8%)	170 (41.6%)	38 (69.1%)
No	255 (55.0%)	238 (58.2%)	17 (30.9%)
Unknown/no answer	1 (0.2%)	1 (0.2%)	0 (0)
Type of care provider; n (%)			

Infectious Disease specialist	333 (71.8%)	292 (71.4%)	41 (74.5%)
General practitioner	80 (17.2%)	72 (17.6%)	8 (14.5%)
Other	48 (10.3%)	42 (10.3%)	6 (10.9%)
No recent visit/unknown/no answer	3 (0.6%)	3 (0.7%)	0 (0%)
Pap test within last year; n (%)			
Yes	179 (38.6%)	155 (37.9%)	24 (43.6%)
No	212 (45.7%)	184 (45.0%)	28 (50.9%)
Unknown/no answer	73 (15.7%)	70 (17.1%)	3 (5.5%)
Drug interaction between ART & MHT*; n (%)			
Yes	188 (40.5%)	165 (40.3%)	23 (41.8%)
No	276 (59.5%)	244 (59.7%)	32 (58.2%)
Contraindication to MHT; n (%)			
Yes	76 (16.4%)	66 (16.1%)	10 (18.2%)
No	386 (83.2%)	342 (83.6%)	44 (80.0%)
Unknown/no answer	2 (0.4%)	1 (0.2%)	1 (1.8%)
HIV Care			
Self-reported CD4 count; n (%)			
≥200 cells/mm^3	377 (81.2%)	330 (80.7%)	47 (85.5%)
<200 cells/mm^3	22 (4.7%)	20 (4.9%)	2 (3.6%)
Unknown/no answer	65 (14.0%)	59 (14.4%)	6 (10.9%)
Self-reported viral load; n (%)			
Undetectable	411 (88.6%)	359 (87.8%)	52 (94.5%)
Detectable	30 (6.5%)	29 (7.1%)	2 (3.6%)
Unknown/no answer	65 (14.0%)	59 (14.4%)	6 (10.9%)
ART adherence; n (%)			
≥95%	350 (75.4%)	303 (74.1%)	47 (85.5%)
<95%	81 (17.5%)	74 (18.1%)	7 (12.7%)
Unknown/no answer	33 (7.1%)	32 (7.8%)	1 (1.8%)
ART regimen; n (%)			
NNRTI-based	114 (24.6%)	99 (24.2%)	15 (27.3%)
PI-based	98 (21.1%)	86 (21.0%)	12 (21.8%)
INSTI-based	125 (26.9%)	111 (27.1%)	14 (25.5%)
Combined classes	41 (8.8%)	35 (8.6%)	6 (10.9%)
None	18 (3.9%)	18 (4.4%)	0 (0%)
Unknown/no answer	68 (14.7%)	60 (14.7%)	8 (14.5%)

IQR = interquartile range; MHT = menopausal hormone therapy; POI = premature ovarian insufficiency; MRS = menopause rating scale; ART = antiretroviral therapy; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; INSTI = integrase strand transfer inhibitor.
Data are presented as n (%) or median [interquartile range].
*Participants were considered to have a drug interaction between MHT and ART if they took one or more of the following: efavirenz, etravirine, nevirapine, unboosted atazanavir, cobicistat or ritonavir boosted regimens.