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Premature and early menopause among US women with or at risk for HIV

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Availability of data and material: Access to individual-level data from the MACS/WIHS Combined Cohort Study Data (MWCCS) may be obtained upon review and approval of a MWCCS concept sheet. Links and instructions for online concept sheet submission are on the study website (http://mwccs.org/).

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Abstract

Objective: Little is known about the prevalence and treatment of premature and early menopause among people with HIV. We described premature and early menopause and subsequent hormonal treatment in a longitudinal cohort of women living with or at risk for HIV in the US.

Methods: Data from the Women's Interagency HIV Study between 2008 and 2020 were analyzed to describe premature and early menopause among cohort participants under the age of 51.

Results: Of 3,059 eligible women during the study period, 1% (n=35) underwent premature menopause before age 41, 3% (n=101) underwent menopause between ages 41 and 46, and 21% (n=442) underwent menopause between ages 46 and 50, inclusive. Of participants who experienced menopause before age 41, between age 41 and 45, and between ages 46 and 50, 51%, 24%, and 7% (respectively) received either menopausal hormone therapy or hormonal contraception.

Conclusion: These findings suggest that disparities in receipt of recommended hormone therapy for premature and early menopause may contribute, in part, to evident health disparities, such as cardiovascular disease, osteoporosis, and overall mortality. They also suggest a substantial need for education among people experiencing early menopause and their providers, with the goal of improving access to hormone therapy based on guidelines to address health disparities and minimize future health consequences.

Keywords

HIV; premature menopause; early menopause; menopausal hormone therapy

Introduction

While the average age of non-surgical menopause in the United States (US) is 51 years, 1–2% of people who menstruate experience premature menopause, or cessation of menstruation before age 40. An additional 3–5% experience early menopause, which occurs between 41 and 45 years [1, 2]. Hypoestrogenism, a result of premature or early menopause, increases the risk of vasomotor symptoms [3], osteoporosis and bone fracture [4–6], cardiovascular disease [7–9], and all-cause mortality [9, 10]. For these reasons, US and international professional organizations recommend continuous exogenous estrogen replacement either in the form of systemic menopausal hormone therapy (MHT) or combined hormonal contraceptives from the onset of premature or early menopause until approximately age 51 [11, 12]. Though population-level data on uptake of MHT among premature and early menopausal people in the US is limited, expert opinion [12, 13] and data from Sweden [14], Canada [15], and the US [16] suggest that prescription of MHT following both surgical and non-surgical premature and early menopause is underutilized.

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Descriptions of the prevalence and treatment of premature and early menopause among people living with or at risk for HIV are limited. Prior analyses of the Women's Interagency HIV Study (WIHS), a large cohort study of women with or at risk for HIV, have demonstrated that the median age of menopause does not differ by HIV status, although women with HIV often have episodes of prolonged amenorrhea without ovarian failure [17, 18]. In a smaller cohort in Brazil, severe immunodeficiency (CD4 count <50 cells/mm^3) from HIV was associated with early menopause [19]. Hormonal support is indicated for people experiencing premature or early menopause with HIV or at risk for HIV. However, concerns about drug-drug interactions with HIV treatment may make healthcare providers reluctant to prescribe MHT to people with HIV [20].

The purpose of this study was to describe premature and early menopause in a longitudinal cohort of women living with or at risk for HIV in the US. Secondarily, we examined the prevalence of MHT and hormonal contraception among women with premature and early menopause to determine if women receive guideline-based hormone support.

Methods

Recruitment, retention, and participant characteristics of the WIHS, a geographically diverse multicenter cohort of women with or at risk for HIV, are described elsewhere [21]. Since 1994, women aged 25 to 60 years have been recruited in four waves and then participated in biannual study visits. Women were generally considered at risk for HIV at enrollment if they had at least one high-risk exposure in the preceding five years. High-risk exposures were defined as a sexually transmitted infection diagnosis, sex with six or more men or sex without a condom with three or more men, trading sex, sex with a man with HIV, injection drug use, use of crack cocaine, cocaine, heroin, or methamphetamine, or having a partner who had any of these high-risk exposures [21]. Women consented to the use of their data as part of their overall WIHS participation, and the institutional review board at University of North Carolina at Chapel Hill approved this secondary data analysis.

Participants were eligible for this analysis if they were classified as experiencing menopause before the age of 51 at one or more visits where comprehensive menopause data were collected (October 2008-September 2020). Premature menopause was defined as report of 1) cessation of menses for > 12 months before the age of 41 in the absence of hormonal contraceptives or hysterectomy, without subsequent report of return of menses, or 2) bilateral oophorectomy (surgical menopause), before the age of 41. Early menopause was defined using the same criteria but between ages 41–45. Women who experienced menopause between age 46 and age 50 were also included in this analysis, as they were considered to have experienced the earliest normal menopause and thus were most similar to women experiencing early or premature menopause.

Reproductive aging category (premenopausal, early perimenopausal, late perimenopausal, post-menopausal) was assigned at each visit using the Stages of Reproductive Aging Workshop criteria based on menstrual history [22]. Participants who were not assigned a reproductive aging category at a given visit were assigned to the reproductive aging category of their previous visit. A set of clinically relevant rules were established by multiple team

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members (AK, AE, BB) for participants with inconsistent reproductive aging categories across visits, shown in Supplemental Table 1. Remaining inconsistent visits were examined and modified by a board-certified OBGYN (AK) on a case-by-case basis.

Participants who reported using hormonal contraceptives, including oral contraceptives, implants, Depo Provera, and hormonal IUDs, in the past six months at all visits between October 2008 and September 2020 were excluded from the analysis, as reproductive aging category could not be assigned based on menstrual history alone. Current substance use was defined as self-reported use in the past six months. Hormonal contraceptive use, MHT use, and vaginal estrogen use were determined by self-reported use of hormones and by categorizing self-reported prescription drug use. Visits where a participant had reported previously undergoing hysterectomy without bilateral oophorectomy, or where status of bilateral oophorectomy was undetermined, were also excluded because reproductive aging category could similarly not be determined due to lack of menses post-hysterectomy.

Demographic information of participants was collected via questionnaire at the first visit at which amenorrhea was reported. We identified sexual and physical trauma [23], mental health conditions [24], and substance use [25, 26] as factors that might both worsen menopausal symptoms and affect the choice of treatment with MHT or other medications. Childhood trauma was defined as self-reported physical violence or sexual abuse before the age of 18. Recent trauma was defined as any self-reported sexual abuse, emotional abuse, or physical violence in the past six months. Depressive symptoms was defined as Center for Epidemiological Studies-Depression Scale score ≥16 [27]. Use of antidepressants and antipsychotics was determined by categorizing self-reported prescription drug use. For each type of substance use, including heavy drinking (seven or more drinks/week), smoking, using cannabis, and using illicit drugs (crack, cocaine, heroin, other injected drugs, or prescription drugs in a way not prescribed), “ever use” was defined as any self-reported use prior to or during enrollment in the WIHS.

We identified autoimmune disease [28], cardiovascular disease [29], hypertension [30], liver disease [31], kidney disease [32], diabetes [33, 34], and cancer [35] as comorbid medical conditions that affect experiences with menopause or recommendations for hormone therapy. Autoimmune disease included any self-report of lupus, Sjogren’s, multiple sclerosis, Graves, or Hashimoto’s. Cardiovascular disease was defined as any self-reported previous diagnosis of or hospitalization for angina, congestive heart failure, stroke, or myocardial infarction, or any surgery to open blocked blood vessels. Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, self-reported hypertension, or use of anti-hypertensive medications at any point prior to or during enrollment in the WIHS. Liver disease was defined as AST to Platelet Ratio Index (APRI) >0.5 or Fibrosis-4 (FIB-4)>1.5 for more than one visit prior to amenorrhea. Kidney disease was defined as estimated glomerular filtration rate (eGFR)<60 for more than one visit prior to the study period. Diabetes was defined as self-reported use of anti-diabetic medication, two fasting glucose levels >= 126 mg/dL, or fasting glucose ≥ 126 mg/dL and a concurrent hemoglobin A1C level of 6.5% or greater when not pregnant at any point prior to or during enrollment in the WIHS. Cancer included self-reported and registry-matched cases.

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Comorbidities were considered prevalent at the time of menopause diagnosis if a participant had reported them before or at the time of first menopausal visit. Comorbidities were considered prevalent during premature or early menopause if they were reported at least once at or after the first menopausal visit and the last visit before the participant turned 51. For comorbidities experienced during menopause, both the proportion of participants experiencing the comorbidity and the proportion of visits where participants experienced the comorbidity were calculated.

Results

Of the 3,059 unique women who had at least one WIHS visit between October 2008 and September 2020 and for whom reproductive aging category could be determined, a total of 578 (19%) experienced menopause before the age of 51 (Supplemental Figure 1). Of these, 35 (1% of all women; 6% of those who experienced menopause before 51) underwent premature menopause, 101 (3% of all women;17% of those who experienced menopause before 51) underwent early menopause, and 442 (14% of all women; 76% of those who experienced menopause before 51) underwent menopause between the ages of 46 and 50. Of all women who underwent menopause before age 51, only 4% had surgical menopause.

Among the 2,164 unique women with HIV who had at least one WIHS visit between October 2008 and September 2020, a total of 445 (21%) experienced menopause before the age of 51. Of these, 27 (1% of all women with HIV; 6% of women with HIV who experienced menopause before 51) underwent premature menopause, 87 (4% of all women with HIV; 20% of women with HIV who experienced menopause before 51) underwent early menopause, and 331 (15% of all women with HIV; 74% of women with HIV who experienced menopause before 51) underwent menopause between the ages of 46 and 50.

Many women who experienced premature or early menopause reported prevalent conditions at the time of menopause diagnosis, also shown in Table 1. These included HIV (77% overall; under 41: 77%; 41–45: 86%; 46–50: 75%), cardiovascular disease (under 41: 29%; 41–45: 32%; 46–50: 39%), hypertension (under 41: 77%; 41–45: 65%; 46–50: 74%), and liver disease (under 41: 31%; 41–45: 49%; 46–50: 47%). Prevalent conditions at the time of menopause diagnosis did not differ by age at diagnosis.

Additionally, women who underwent premature or early menopause reported trauma, mental health conditions, and substance use exposures between the time of menopause and age 51 that could affect symptom management (Table 2). These included depressive symptoms (under 41: 69%; 41–45: 67%; 46–50: 54%) and sexual or physical trauma (under 41: 6%; 41–45: 17%; 46–50: 10%). Many women also report heavy alcohol use, tobacco use, cannabis use, and illicit drug use during this time.

51%, 24%, and 7% of participants who experienced menopause before age 41, between ages 41 and 45, and between ages 46 and 50, respectively, received either MHT or hormonal contraception (Table 2). Use of MHT or hormonal contraception was reported at 18%, 11%, and 4% of study visits before the age of 51 in each of these groups.

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Discussion

In a population of women in the US with or at risk for HIV, approximately 1% of women underwent premature menopause before reaching 41 years of age and 3% of women underwent early menopause between 41 and 45 years of age. Among those who experienced premature and early menopause, any hormone use was reported at only a small minority of visits between the onset of menopause and age 51. Given the low prevalence of hormone use among premature and early menopausal women in this cohort, many in this group are at increased risk of osteoporosis and fracture [4–6], cardiovascular disease [7–9], and other adverse health outcomes [10] after long periods of hypoestrogenism.

The reported prevalence of early and premature menopause in our study is similar to previously reported findings from the US in the National Health and Nutrition Examination Survey and the Study of Women Across the Nation [1, 2]. They are significantly lower than those reported from a cross-sectional sample of Canadian women living with HIV [36]. This may be due, in part, to our ability to use longitudinal data to assign women with prolonged amenorrhea to a premenopausal status if menses resumed. To our knowledge, there are no prior studies of hormone use among all premature and early menopausal people in the US for comparison. However, in Canadian and US samples of women undergoing premature surgical menopause, approximately half received any hormonal medication, although the duration of therapy was short, often one year or less [15, 16]. Initiation of hormonal medications was less frequent in our sample, though the relatively short duration may be similar given the low percentage of visits where hormone use was reported, suggesting even greater unmet need. Notably, participants in the Canadian study had higher income than participants in the WIHS, and participants in the US study were majority white compared to the WIHS's majority Black population. It remains unclear whether this observed disparity is driven primarily by differences in approaches to surgical versus non-surgical premature or early menopause or by differences in access to hormone therapy driven by demographic or other characteristics.

There are a variety of reasons that women with or at risk for HIV may be undertreated for premature or early menopause. First, the WIHS sample is majority Black and low income with many women reporting current or past substance use, all of which likely contribute to disparities in access to health care [37, 38]. Those who do have access to care may experience hesitancy to prescribe MHT from providers. Though interactions between MHT and HIV medications do not affect the efficacy of HIV treatment and are not contraindications to MHT, many providers may be hesitant to prescribe because of potential interactions with older classes of antiretrovirals [20, 39]. Additionally, providers may perceive some relative contraindications as absolute, such as hypertension, especially in the presence of other medical conditions or substance use, both of which are common in this study population [40]. Some premature or early menopausal people may also decline hormone therapy even when it is recommended due to medication burden or concerns about side effects [41, 42]. Also, it is possible that menopause in this population is not recognized by providers, as amenorrhea may be attributed to substance use or other illness. Lastly, our data were collected beginning in 2008, six years after the Women's Health Initiative (WHI) randomized trial for hormone therapy in healthy postmenopausal women was stopped early

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due to adverse outcomes [43]. Though hormone use for premature and early menopause was not the focus of the WHI, studies of the aftermath of the trial stoppage suggest that the negative media attention from the study did result in substantially decreased hormone use in younger age groups [44, 45].

To address underutilization of MHT among women with or at risk for HIV infection, our findings support the inclusion of premature and early menopause care in guidelines specifically for people living with HIV. These guidelines should clarify confusion about potential hormone interaction with HIV medication and misunderstandings regarding WHI findings, as in the recent comprehensive recommendations from King *et al* [39]. Additionally, expanding partnerships between primary HIV care providers and providers with expertise in menopausal care would help ensure that people experiencing premature and early menopause could receive hormone treatment when appropriate.

This study has several limitations. Ascertainment of menopausal history was based on menstrual history alone. Thus, though women were excluded if they reported hysterectomy or consistent use of hormonal contraception throughout the entire study period, some potentially premenopausal women whose resumption of menses was not captured during the study period may have been included. It is also possible that some women experienced prolonged amenorrhea due to other medical conditions or medications rather than menopause. Additionally, even though the WIHS is a large cohort, premature and early menopause are both rare outcomes; therefore, the sample size of this study is small. Lastly, use of hormonal contraception and hormonal therapy were all determined by self-report [21].

Conclusion

The prevalence of premature (1%) and early menopause (3%) in a cohort of women living with or at risk for HIV is similar to those reported in broader US samples. However, very few, if any, of the women in our sample who experienced premature or early menopause received consistent hormone therapy until the age of 51. Among a group that already bears a significant burden of chronic disease by the time they enter premature or early menopause, treatment disparities for premature and early menopause may contribute in part to worsening health disparities in cardiovascular disease, osteoporosis, and overall mortality. They also suggest a substantial need for education among people experiencing early menopause and their providers, with the goal of improving access to hormone therapy based on guidelines to address health disparities and minimize future health consequences.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Participant demographic characteristics, prevalent comorbidities and substance use at the time of menopause diagnosis[a] and during menopause[b], Women's Interagency HIV Study, 2008–2020.[c]

	Menopause before 41 N=35 *N (%) or Median [IQR]*	**Menopause 41–45 N=101** *N (%) or Median [IQR]*	**Menopause 46–50 N=442** *N (%) or Median [IQR]*
Demographic characteristics at the time of menopause diagnosis			
Age	37 [36,39]	44 [42,45]	49 [48,50]
Race			
Black	31 (89)	73 (72)	276 (62)
White	3 (9)	20 (20)	97 (22)
Other[d]	1 (3)	8 (8)	69 (16)
Hispanic	4 (11)	17 (17)	94 (21)
Completed high school	19 (54)	56 (55)	272 (62)
Employed	14 (40)	21 (21)	127 (29)
Average annual household income			
<$12,000	20 (57)	63 (63)	260 (59)
$12,001-$18,000	6 (17)	14 (14)	56 (13)
>$18,000	9 (26)	23 (23)	123 (28)
Health insurance	34 (97)	85 (84)	387 (88)
Menopause characteristics			
Surgical menopause[e]	1 (3)	6 (6)	15 (3)
Hysterectomy	0 (0)	5 (5)	13 (3)
Prevalent conditions at the time of menopause diagnosis			
Childhood trauma	6 (17)	13 (13)	97 (22)
BMI ≥30 (kg/m^2)	22 (63)	52 (51)	204 (46)
HIV	27 (77)	87 (86)	331 (75)
AIDS	9 (26)	31 (31)	144 (33)
Autoimmune disease[f]	1 (3)	9 (9)	35 (8)
Cardiovascular disease[g]	10 (29)	32 (32)	173 (39)
Hypertension[h]	27 (77)	66 (65)	327 (74)
Any liver fibrosis[i]	11 (31)	49 (49)	206 (47)
Kidney disease[j]	7 (20)	16 (16)	80 (18)
Diabetes	7 (20)	15 (15)	94 (21)
Cancer	4 (11)	11 (11)	28 (6)
Prevalent mental health conditions during menopause			
Depressive symptoms	24 (69)	68 (67)	240 (54)
Recent trauma	2 (6)	17 (17)	42 (10)
Antidepressants	6 (17)	29 (29)	87 (20)

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	Menopause before 41 N=35 ***N (%) or Median [IQR]***	**Menopause 41–45 N=101** ***N (%) or Median [IQR]***	**Menopause 46–50 N=442** ***N (%) or Median [IQR]***
Antipsychotics	4 (11)	15 (15)	36 (8)
Premenopausal substance exposures			
Ever heavy drinking[j,k]	10 (29)	44 (44)	188 (43)
Ever smoking	19 (54)	72 (71)	358 (81)
Ever marijuana use	15 (43)	48 (48)	213 (48)
Ever illicit drug use	9 (26)	40 (40)	215 (49)
Prevalent substance exposures during menopause			
Current smoking	16 (46)	55 (54)	250 (57)
Current heavy drinking[j]	10 (29)	26 (26)	95 (21)
Current cannabis use	14 (40)	24 (24)	109 (25)
Current illicit drug use	6 (17)	20 (20)	117 (26)

[a] Either: 1) postmenopausal before the age of 51 while not taking hormonal contraception nor having undergone neither hysterectomy nor bilateral oophorectomy; or 2) having undergone bilateral oophorectomy before the age of 51, regardless of hormonal contraception use or history of hysterectomy.

[b] A comorbidity was considered prevalent during early menopause if it was present at or after the time of premature menopause diagnosis and before a participant turned 51.

[c] WIHS participants were eligible for inclusion in this study if they attended at least one WIHS visit between October 2008 and September 2020 in which reproductive aging stage was determined. Participants were excluded from the study if they met any of the following criteria: (a) Participant reported using hormonal contraception for all visits between 29 and 50; (b) Participant reported having previously undergone hysterectomy but not double oophorectomy, or status of oophorectomy was undetermined, prior to October 2008.

[d] Includes American Indian, Alaskan Native, Asian, Native Hawaiian, Pacific Islander, and multi-racial, as well as any self-identified “other” racial category.

[e] Participant underwent bilateral oophorectomy, with or without hysterectomy.

[f] Any self-reported lupus, Sjogren’s, multiple sclerosis, Graves, or Hashimoto’s.

[g] Any self-reported previous diagnosis of or hospitalization for angina, congestive heart failure, stroke, or myocardial infarction, or any surgery to open blocked blood vessels.

[h] Systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, self-reported hypertension, or use of anti-hypertensive medications at any point prior to or during enrollment in the WIHS.

[i] AST to Platelet Ratio Index (APRI) >0.5 or Fibrosis-4 (FIB-4)>1.5 for more than one visit prior to amenorrhea.

[j] Estimated glomerular filtration rate (eGFR)<60 for more than one visit prior to the study period. Diabetes was defined as self-reported use of anti-diabetic medication, two fasting glucose levels >= 126 mg/dL, or fasting glucose ≥ 126 mg/dL and a concurrent hemoglobin A1C level of 6.5% or greater when not pregnant at any point prior to or during enrollment in the WIHS.

[k] ≥7 drinks/week.

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Table 2.

Prevalence of hormonal medication use during menopause by participant and by visit, Women's Interagency HIV Study, 2008–2020.

	Menopause before 41 *N (%)*		Menopause 41–45 *N (%)*		Menopause 46–50 *N (%)*	
	Participant[a] (N=35)	Visits (N=255)	Participant[b] (N=101)	Visits (N=775)	Participant[c] (N=442)	Visits (N=1,548)
Hormone use						
Vaginal estrogen[d]	0 (0)	0 (0)	16 (16)	134 (17)	3 (1)	25 (2)
Menopausal hormone therapy[e]	5 (14)	10 (4)	16 (16)	49 (6)	29 (7)	57 (4)
Hormonal contraception[f]	13 (37)	37 (15)	10 (10)	34 (4)	2 (0)	2 (0)
Any oral hormones[g]	18 (51)	47 (18)	24 (24)	82 (11)	30 (7)	59 (4)

[a]Median [interquartile range] of visits between premature menopause before age 41 and age 51 was 5 [2,9].

[b]Median [interquartile range] of visits between premature menopause between ages 41 and 45 and age 51 was 5 [2,9].

[c]Median [interquartile range] of visits between premature menopause between ages 46 and 50 and age 51 was 2 [1,4].

[d]Self-reported use of prescription drug that was classified as vaginal estrogen.

[e]Self-reported use of hormone therapy or self-reported use of prescription drug that was classified as hormonal therapy

[f]Self-reported use of oral contraceptives, implants, Depo Provera, or hormonal IUDs or self-reported use of a prescription drug that was classified as hormonal contraception. [8]

[g]Includes hormone therapy and hormonal contraceptives.