The Effect of Menopausal Status, Age, and Human Immunodeficiency Virus (HIV) on Non-AIDS Comorbidity Burden Among US Women

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Menopause may impact the earlier onset of aging-related comorbidities among women with versus without human immunodeficiency virus (HIV). We found that menopausal status, age, and HIV were independently associated with higher comorbidity burden, and that HIV impacted burden most in the pre-/perimenopausal phases.

Keywords. women with HIV; HIV and aging; HIV and menopause; non-AIDS comorbidities; comorbidity burden.

Women with human immunodeficiency virus (HIV) (WWH) are living longer and an increasing number are reaching menopause. From 2014 to 2018, HIV diagnoses increased by 5% among women aged 55 years and older [1]. In this growing population of aging WWH, unique biological and psychosocial factors may affect the senescence process, including the menopausal transition and development of non-AIDS comorbidities (NACMs).

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Menopause is characterized by estrogen depletion, resulting from aging-related declines in ovarian reserve, and is associated with an increased risk of cardiovascular disease (CVD), osteoporosis, and other NACMs [2]. Women with HIV may experience menopause earlier and with greater symptom intensity than the general female population; however, studies are inconsistent and inconclusive [3]. HIV-related inflammatory effects on the neuroendocrine axis have the potential to impact menopause timing and severity [4, 5]. Further, the menopausal transition among WWH may also be affected by antiretroviral exposure and a high prevalence of substance use, viral coinfections, and socioeconomic hardship in this population [6].

Leveraging the Women's Interagency HIV Study (WIHS), we previously showed that WWH versus women without HIV had a higher burden of 10 aging-related NACMs overall and specifically among those aged 40–49 and 60 years and older, and had a significantly earlier incidence of NACMs [7, 8]. Mechanisms by which menopause may affect the natural history of aging-related NACMs among WWH remain largely unknown; thus, we evaluated whether HIV modifies the effects of age and menopausal status on comorbidity burden.

METHODS

We analyzed data from the WIHS, the largest prospective, multisite US cohort of women with and without HIV. Participants underwent semiannual in-depth assessment of medical history, physical examination, and biospecimen collection [7]. Focusing on the menopausal transition, we included women aged 26–59 years with 2 or more study visits from 2009 (when >80% of WWH used antiretroviral therapy) through the end of observation (30 March 2018).

The primary outcome was comorbidity burden, defined as the number of prevalent NACMs per participant as of the last observation out of 10 total assessed (hypertension, dyslipidemia, diabetes, non-AIDS cancer, psychiatric illness, cardiovascular, kidney, lung, liver, and bone disease). Non-AIDS comorbidities were ascertained using up to 3 data sources: (1) self-reported diagnosis or medication, (2) clinical measurement, and/or (3) laboratory evidence, as previously described [7]. At last observation, participants were categorized by age (<40, 40–49, 50–59 years) and by menopausal status based on participant responses to detailed questions on menstrual cycles (ie, regularity and timing of periods) according to the Stages of Reproductive Aging Workshop (STRAW) +10 principal criteria as premenopausal (ie, reproductive), perimenopausal (ie, menopausal transition characterized by irregular menstrual cycles), or postmenopausal (ie, beginning the day after no menstrual period in >12 months) [9]. Among those who

were postmenopausal, surgical menopause was ascertained by participant-reported bilateral oophorectomy. HIV serostatus was determined at study entry and, if negative, at each subsequent visit; seroconverters were excluded.

Linear regression evaluated the effects of HIV serostatus, categorized age, and menopausal status on prevalent comorbidity burden. Model 1 (unadjusted) included these terms plus all possible interaction terms derived from the HIV × age × menopausal status 3-way interaction. To incorporate potential confounders of menopausal status on comorbidity burden, model 2 (covariate-adjusted) included all model 1 variables plus race (non-Hispanic Black or White, Hispanic, other), body mass index (BMI; ≥30 or <30 kg/m^2), and smoking status (current, former, never) at last observation.

RESULTS

Among 2716 women (1931 WWH; 785 without HIV), the median age was 48 (quartile [Q] 1–Q3, 41–54) years, 65% were non-Hispanic Black, 51% had a BMI of 30 kg/m^2 or greater, and 38% reported current smoking at last observation. Hormonal contraceptive or hormone replacement therapy use as of last observation was reported in 5.6% and 2.7% of women, respectively. Overall, 923 (34%) women were premenopausal, 411 (15%) perimenopausal, and 1382 (51%) postmenopausal. Of postmenopausal women, 303 (22%) reported surgical menopause including 7, 71, and 225 participants aged less than 40, 40–49, and 50–59 years, respectively. Mean (standard deviation) NACM burden was 3.1 (2.0) among all women and increased significantly across pre- versus peri- versus postmenopausal women (1.9 [1.5] vs 2.9 [1.9] vs 3.9 [2.0], respectively; $P < .0001$).

The prevalence of postmenopausal status increased with each successive age group, comprising 9% (44/517), 30% (295/978), and 85% (1043/1221) of women aged less than 40, 40–49, and 50–59 years, respectively. Comparing WWH with women without HIV, postmenopausal status was 10% versus 6% ($P = .0939$), 34% versus 21% ($P = .0004$), and 86% versus 85% ($P = .9706$) among women aged less than 40, 40–49, and 50–59 years, respectively. In an unadjusted model, HIV did not significantly modify the effects of age and menopausal status on prevalent comorbidity burden (3-way interaction, $P = .5999$).

In covariate-adjusted analyses, menopausal status, age, and HIV were independently associated with higher comorbidity burden. The estimated mean (95% confidence interval [CI]) NACM burden among pre-, peri-, and postmenopausal women overall was 2.26 (2.03–2.48), 2.83 (2.62–3.04), and 3.41 (3.18–3.65), respectively, and was higher in successive age groups. Across all age and menopause strata, the estimated mean difference (95% CI) in NACM burden was +.32 (.08–.56) comparing women with versus without HIV, and across all age and HIV strata was +.57 (.29–.86) or +1.16 (.86–1.46) comparing peri- or postmenopausal with premenopausal women, respectively.

Comparing WWH with women without HIV, the estimated mean difference (95% CI) in NACM burden stratified by age less than 40, 40–49, and 50–59 years was +.22 (−.13 to .58), +.50 (.18–.84), and +.52 (−.60 to 1.63) among premenopausal women; +.52 (−.26 to 1.31), +.43 (−.10 to .95), and +.47 (−.22 to 1.17) among perimenopausal women; and −.22 (−1.39 to .95), +0.25 (−.25 to 0.75), and +.18 (−.07 to .43) among postmenopausal women, respectively (Table 1; adjusted 3-way interaction, $P = .9580$).

DISCUSSION

In this hypothesis-generating analysis of a diverse cohort of US women with and without HIV, we observed that menopausal status, age, and HIV were independently associated with a higher burden of NACMs. While HIV did not significantly modify the effects of menopausal status and age on prevalent comorbidity burden, there were trends toward a higher burden of NACMs among WWH versus women without HIV, especially for perimenopausal women aged less than 40 years and pre- and perimenopausal women aged 40–59 years. These findings, if confirmed in larger studies, would have important clinical implications for optimizing NACM screening and prevention strategies for aging WWH.

We previously demonstrated that the burden of aging-related NACMs was significantly higher among WWH versus women without HIV, and that HIV may accelerate comorbidity development beginning in the third decade of life [7, 8]. The current analysis builds on these findings to suggest that the disparate NACM burden occurring among WWH may concentrate more in the pre- and perimenopausal phases than in the postmenopausal period. We also observed that postmenopausal status was more common among WWH than women without HIV younger than 50 years old, corroborating other studies reporting earlier menopause in HIV [3] and suggesting a potentially compounded risk of premature multimorbidity among WWH. Our data suggest that the impact of menopausal status on NACM burden may be greater than the impact of HIV (Table 1), thus underscoring menopause as a key research priority area for aging women.

The menopausal transition is increasingly recognized as an event with substantial biopsychosocial effects on a woman's health and disease trajectory. Longitudinal CVD studies have suggested that cardiometabolic changes occurring during menopause may be intensified beyond chronological aging, highlighting the menopausal transition as a critical window for CVD risk assessment in women [2]. In disentangling the effects of chronological versus reproductive aging among WWH, it is important to consider that HIV-specific virologic,

Table 1. Estimated Mean Non-AIDS Comorbidity Burden at Last Observation in the Women's Interagency HIV Study by HIV Serostatus, Age, Menopausal Status Adjusted for Race, Body Mass Index, and Smoking Status

			Estimated Mean NACM Burden (95% CI)			
Age	HIV Serostatus	Sample Size (Pre-, Peri-, Postmenopausal), n	Premenopausal (n = 923)	Perimenopausal (n = 411)	Postmenopausal (n = 1382)	*P*
<40 years	Women with HIV	241, 40, 32	1.89 (1.64, 2.13)	2.33 (1.79, 2.88)	2.48 (1.87, 3.09)	.0687
	Women without HIV	156 36, 12	1.66 (1.37, 1.95)	1.81 (1.23, 2.38)	2.70 (1.69, 3.71)	.0519
40–49 years	Women with HIV	318, 144, 235	2.56 (2.35, 2.77)	3.32 (3.03, 3.61)	3.57 (3.32, 3.81)	<.0001
	Women without HIV	160, 61, 60	2.06 (1.76, 2.35)	2.89 (2.44, 3.34)	3.32 (2.86, 3.77)	<.0001
50–59 years	Women with HIV	36, 97, 788	2.95 (2.38, 3.52)	3.56 (3.20, 3.92)	4.30 (4.15, 4.46)	<.0001
	Women without HIV	12, 33, 255	2.43 (1.46, 3.40)	3.09 (2.48, 3.69)	4.12 (3.89, 4.36)	.0008

Linear regression was performed for NACM burden with HIV serostatus, categorized age, menopausal status, and all interaction terms included in the model, as well as race, body mass index, and smoking status: age, $P < .0001$; HIV serostatus, $P = .0083$; menopausal status, $P < .0001$; race, $P < .0001$; body mass index, $P < .0001$; smoking status, $P < .0001$; age × HIV, $P = .7275$; age × menopausal status, $P = .0722$; menopausal status × HIV, $P = .3522$; HIV × age × menopausal status, $P = .9580$.
Abbreviations: HIV, human immunodeficiency virus; NACM, non-AIDS comorbidity.

immunologic, and sociobehavioral factors likely influence both processes [10]. Younger age at final menstrual period has been associated with smoking, chronic HCV, HIV-1 viremia, and prior clinical AIDS [4]. These findings, along with our current and prior data [7, 8], suggest that both HIV-related and traditional risk factors impact the menopausal transition and associated NACM risk.

Importantly, menopausal status as ascertained by existing tools (eg, the STRAW +10 or the Study of Women's Health Across the Nation [SWAN] criteria, etc) may inadequately capture the unique sociobiological experience of aging WWH. Ovarian reserve, assessed by anti-Müllerian hormone (AMH) levels, has been shown to be reduced among premenopausal WWH versus age-matched peers [5], predictive of the menopausal transition among WWH [4], and associated with oxidative stress, immune activation, and subclinical CVD in perimenopausal WWH [5, 11, 12]. Specifically, WWH with reduced ovarian reserve (undetectable AMH) had a higher prevalence of coronary atherosclerotic plaque than premenopausal WWH with detectable AMH [12]. These data suggest that innovative tool development, perhaps including measurement of AMH or related hormonal and/or immunologic biomarkers, may be clinically useful in screening pre-/perimenopausal WWH at risk of early reproductive and natural aging and premature NACM development.

Our analysis was limited by a moderately small sample size and participant self-report of menopausal status, which limited our ability to accurately determine if participants were experiencing menopause versus irregular periods due to other medical conditions. Strengths included our focus on a critically understudied topic in HIV science, use of data from a well-curated women's cohort, and evaluation of menopausal status on overall NACM burden. In conclusion, our results suggest that disparate NACM burden among WWH may concentrate in the pre- and perimenopausal phases and therefore the optimal timing to initiate NACM risk assessment and intervention may precede menopause in these women. Larger, prospective studies among WWH well characterized by menopause status are needed to better understand how HIV affects this reproductive transition, including timing, severity, risk factors, and implications for aging-related comorbidity development, so that timely NACM identification and risk modification can be offered to those uniquely at risk.

Notes

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