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Body Composition Changes Over the Menopausal Transition in Women With and Without Human Immunodeficiency Virus

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Background.   Women are at risk for weight gain during the transition to menopause, but few have examined the contribution of menopause to weight gain in women with human immunodeficiency virus (WWH).

Methods.   From 2000 to 2013, participants (621 WWH; 218 without HIV [WWOH]) from the Women's Interagency HIV Study were categorized by menopausal phase using serial measures of anti-Müllerian hormone (AMH). Multivariable linear mixed models examined the association of menopausal phase with body mass index (BMI) and waist circumference (WC) trajectory, stratified by HIV status.

Results.   In models controlled for chronologic age, the estimated effects (95% confidence interval) of menopausal phase on annual rate of BMI change across early perimenopause, late perimenopause, and menopause, respectively, compared to premenopause were −0.55% (−.80 to −.30), −0.29% (−.61 to .03), and −0.67% (−1.12 to −.20) in WWH, whereas estimated effects were 0.43% (−.01 to .87) and 0.15% (−.42 to .71) across early and late perimenopause, respectively, and −0.40% (−1.24 to .45) across menopause in WWOH. The estimated effects on rate of WC change were negative across early perimenopause (−0.21% [−.44 to .03]) and menopause (−0.12% [−.5 to .26]) and positive across late perimenopause (0.18% [−.10 to .45]) in WWH, and positive across all 3 menopausal phases in WWOH, but these effects were not statistically significant.

Conclusions.   In WWH, the menopausal transition was associated with BMI and WC trajectories that were mostly in a negative direction and opposite from WWOH after adjusting for age, suggesting that HIV blunts weight gain during the menopausal transition.

Keywords.   menopause; HIV; BMI; weight gain; waist circumference.

Weight gain is of increasing concern for people with human immunodeficiency virus (PWH) in the contemporary era of antiretroviral therapy (ART) [1]. Chronologic aging also contributes to weight gain in adults, regardless of human immunodeficiency virus (HIV) status. Obesity and visceral adiposity have been associated with a greater risk of comorbidities including diabetes, fatty liver disease, and cardiovascular disease in both PWH and people without HIV. Some suggest that weight gain in PWH confers a greater risk of metabolic disease than in people without HIV [2, 3].

Women may be particularly vulnerable to weight gain during the transition to menopause. Studies of women in the general population have demonstrated an increase in body mass index (BMI) and central and total adiposity during the menopausal transition [4–6]. Whether women with HIV (WWH) are similarly at risk is unclear.

Menopause occurs due to the complete depletion of ovarian follicles, and thus loss of estrogen production. Estrogen depletion has been associated with immune activation [7–9], as has HIV infection [10–12], and adipose tissue may modulate immune response [13, 14]. Recent studies in WWH show that menopause is associated with greater immune activation [15] and comorbidity burden [16, 17] compared with their premenopausal counterparts.

Those studies, however, relied primarily on self-report to characterize the menopausal phase. Prolonged amenorrhea can also occur in the setting of chronic illness [18], limiting the efficacy of self-report of menopausal status among WWH. Anti-Müllerian hormone (AMH), a biomarker of ovarian reserve, has been incorporated into the Stages of Reproductive Aging Workshop (STRAW) + 10 criteria as an adjunct for estimating menopausal phase [19]. AMH may be

particularly useful in large epidemiologic studies because levels are independent of menstrual cycle phase and strongly predict age at final menstrual period among WWH [20].

Using longitudinal data from the Women's Interagency HIV Study (WIHS), we examined the influence of menopausal phase on the trajectory of BMI and waist circumference (WC), a surrogate marker of visceral adiposity in WWH and women without HIV (WWOH). Serial AMH values were used to categorize women into the premenopausal, early perimenopausal, late perimenopausal, and postmenopausal phase at each study visit, reflecting the years leading up to, during, and after menopause.

METHODS

Study Design

The WIHS (now part of the ongoing Multicenter AIDS Cohort Study (MACS)/WIHS Combined Cohort Study) is a multicenter prospective cohort that enrolled WWH and demographically similar WWOH who had HIV risk factors during 4 recruitment waves (1994–1995, 2001–2002, 2011–2012, and 2013–2015) from 10 cities in the United States (US) [21]. Study details have been published previously [22]. Women were seen every 6 months for anthropometry, biospecimen collection, and survey administration.

Women were included in the current analysis if they had at least 1 detectable AMH level prior to an undetectable (UD) AMH, had their last detectable AMH after the year 2000, their first UD AMH from 2000 through 2014, and body composition data for at least 2.5 years after reaching UD AMH. We selected women whose first UD AMH was in 2000 or later to minimize ongoing effects of certain ART that have been associated with body composition changes (eg, thymidine nucleoside reverse transcriptase inhibitors). Of the 841 women who met the inclusion criteria, 2 were excluded because they reported hysterectomy or oophorectomy within 2 years of the entry visit.

Study Measurements

AMH was tested serially using the Beckman Gen II AMH enzyme-linked immunosorbent assay (ELISA) (Beckman Coulter) and beginning in 2017, the Beckman Automated DxI AMH ELISA (lower limit of detection <0.08 ng/mL). Serum samples stored at −80°C were run in duplicate for the Beckman Gen II manual ELISA (inter- and intra-assay coefficients of variation <15%) and in singlicate for the automated ELISA (interassay coefficient of variation <7.4%). Values were calibrated to the new AMH values because the automated ELISA tended to read lower than the manual ELISA [23–25].

We categorized menopausal phase as follows: premenopause, defined as ≥5 years before AMH became UD; early perimenopause, 0 to <5 years before reaching UD AMH; late perimenopause, 0–5 years after UD AMH; and menopause,

>5 years after UD AMH. The 4 menopausal categories were based upon the STRAW + 10 criteria [19]. A 5-year period was used to define the late perimenopausal phase based upon an average of 4.2 years from the estimated date of having UD AMH to the estimated date of the final menstrual period as previously defined in the WIHS [15]; this was observed among women in our analysis whose self-report of menstrual flow over time indicated an estimated final menstrual period date with high certainty.

The primary outcomes were annual rates of change in BMI (kg/m^2) and WC (cm) measured by clinicians who were trained and certified. We excluded study visits where participants reported being pregnant or on hormonal therapy.

Covariates included race/ethnicity (white, African American, Hispanic, or other), smoking status (never, current, or former), alcohol use (abstainer, light [>0–7 drinks/week], moderate [>7–12 drinks/week], heavy [>12 drinks/week]), depression (Center for Epidemiological Studies Depression scale [CES-D] score >16) [26], hepatitis B surface antigen positive (yes/no), and hepatitis C virus RNA detectable (yes/no). Lipid levels and diabetes were not included as covariates because BMI is a known contributing factor. HIV-related parameters were nadir and last CD4 cell count, HIV RNA (detectable, or >80 copies/mL vs undetectable), and current ART use.

Statistical Analysis

Sociodemographic and clinical characteristics were summarized using median (interquartile range [IQR]) for continuous variables, and percentage (frequency) for categorical variables at the first visit of UD AMH. We compared each characteristic by HIV status using χ^2 tests for categorical variables and either t tests or Mann-Whitney tests for continuous variables, where appropriate.

Using the new calibrated values, we employed a linear mixed effects tobit regression model of log-transformed AMH using SAS Proc NLMIXED to impute AMH values at visits where there was not a measured AMH level [20, 27]. We then used these imputed AMH values to determine the first visit and age with UD AMH.

Because AMH changes gradually over time, we modeled rates of change in AMH per year using slopes rather than comparing average levels within each menopausal phase category. To do this, we defined interaction terms of phase with time to allow the effect of time to vary within different menopausal phases. We then used these terms in multivariable linear mixed models with random intercepts and slopes to estimate the effect of each menopausal phase on the rate of change (per year) in BMI or WC. The outcomes in the models were log-transformed BMI and WC, and fitted coefficients were back-transformed to obtain estimated percentage change per year at different ages and the effects of menopausal phase on those rates of change. We included chronologic age as a linear spline with knots every

5 years between 30 and 55, resulting in 7 age ranges from <30 to >55 years that were allowed to have different slopes in the models. To control for chronologic aging, both age and interactions of menopausal phases with time (with premenopausal as the reference) were included in the same model. The coefficients of menopausal phases therefore estimated how much menopausal phase modified the effect of chronologic aging alone. We then fitted separate models that added each of the covariates to the model with age and phase, estimating its effect on the rate of change by using the woman's cumulative years spent in each level of the covariate from study entry up to each BMI or WC measurement. In the case of missing values, we carried forward the most recent nonmissing value to allow the accumulation process to continue. In the multivariable models with the covariates, we also controlled for women's age at first visit, race/ethnicity, study wave, and study site. Separate models were constructed for WWH and WWOH because of strong evidence for differing effects of menopausal phase. All analyses were conducted using the SAS system, version 9.4 (SAS Institute).

RESULTS

Table 1 shows the characteristics of the 839 participants by HIV status at the first UD AMH visit. Overall, median age at UD AMH was 46 years and more than half identified as African American. Median age was 36 years (IQR, 33–39 years) at the entry visit and 54 years (IQR, 51–58 years) at the last visit. Among the WWH, median CD4 count (cells/µL) was 435 (IQR, 281–604) at entry, 424 (IQR, 262–642) at the first UD AMH visit, and 583 (IQR, 337–839) at the last visit; the percentage with undetectable HIV RNA was 18%, 58%, and 77%, respectively.

BMI and WC Trajectories in Relation to Chronologic Age and Ovarian Age
Figure 1 shows the relationship of chronologic age and earlier and later age at first UD AMH with the trajectory of BMI (Figure 1A) and WC (Figure 1B) by HIV status. Ages 42 and 49 years were selected as the 10th and 90th percentiles of age at UD AMH. BMI in WWOH appeared to progressively increase with chronologic age until age 50, then decline regardless of earlier or later age at first UD AMH. By contrast, BMI in WWH at first UD AMH at an earlier age remained flat with chronologic age and, in those with UD AMH at a later age, appeared to increase slowly. WC in WWH and WWOH appeared to progressively increase over time especially beginning at perimenopause until age 55, regardless of earlier or later age at first UD AMH, but the increase after age 50 appeared more steep in WWH than WWOH.

Heterogeneity of effect was assessed using a multiplicative interaction term between HIV and menopausal phase in the unadjusted models. For both the BMI and WC models, we found a statistically significant interaction between HIV status

Table 1. Demographic and Clinical Characteristics of the 839 Women at the First Predicted Anti-Müllerian Hormone Undetectable Visit

Characteristic	Women With HIV (n = 621)	Women Without HIV (n = 218)	P Value[a]
Age at undetectable AMH, y, median (IQR)	46 (44–47)	46 (44.5–48)	.13
Race/ethnicity			
White	86 (14)	21 (9.6)	.33
African American	353 (57)	132 (61)	
Hispanic	164 (26)	56 (26)	
Other[b]	18 (2.9)	9 (4.1)	
Study enrollment wave			
1994–1995	440 (71)	145 (67)	.10
2001–2002	174 (28)	73 (34)	
2011–2012	7 (1.1)	…	
Study site			
Bronx	149 (24)	63 (29)	.35
Brooklyn	105 (17)	42 (19)	
Chicago	96 (15)	20 (9)	
Washington, DC	90 (15)	32 (15)	
Los Angeles	100 (16)	32 (15)	
San Francisco	81 (13)	29 (13)	
Smoking			
Never smoker	142 (24)	28 (13)	.001
Current smoker	180 (47)	130 (63)	
Former smoker	173 (29)	49 (24)	
Alcohol consumption			
Abstainer	357 (60)	93 (45)	.001
Light (1–7 drinks/wk)	180 (31)	74 (36)	
Moderate (8–12 drinks/wk)	15 (2.5)	13 (6.3)	
Heavy (>12 drinks/wk)	39 (6.6)	25 (12)	
Depressive symptoms (CES-D score), median (IQR)	10 (3–22)	9 (5–21)	.94
Active HCV infection	148 (24)	37 (17)	.11
Hepatitis B surface antigenemia	15 (2.4)	2 (0.9)	.39
HIV-related factors			
Undetectable HIV RNA	357 (58)	…	
CD4+ count, cells/µL, median (IQR)	424 (262–642)	…	
ART use	443 (71)	…	
Thymidine NRTI[c]	185 (30)	…	
First-generation PI[d]	54 (10)	…	
Efavirenz	105 (19)	…	

Data are presented as No. (%) unless otherwise indicated. Missing values were excluded when calculating frequencies/percentages.

Abbreviations: AMH, anti-Müllerian hormone; ART, antiretroviral therapy; CES-D, Center for Epidemiological Studies Depression Scale; DC, District of Columbia; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IQR, interquartile range; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

[a]P value from Pearson χ² test, Wilcoxon rank-sum test, or Fisher exact test.

[b]Includes Asian, Pacific Islander, Native American, Alaska Native, and other study participants.

[c]Zidovudine, n = 121 (20%); didanosine, n = 35 (6%); stavudine, n = 45 (7%).

[d]Saquinavir, n = 12 (2%); indinavir, n = 14 (2.5%); nelfinavir, n = 26 (5%); amprenavir, n = 2 (0.4%).

and the early perimenopause (both $P < .001$) and menopause phases (both $P < .001$), but not late perimenopause (both $P > .10$). All of the multivariable models showed similar
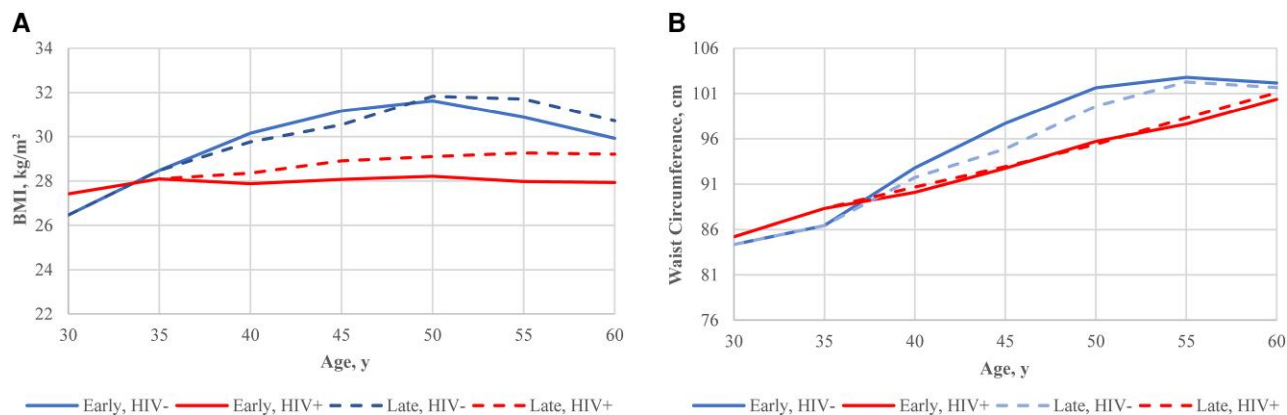
Figure 1. Relationship of chronologic age, and earlier (42 y) and later age (49 y) of reaching undetectable anti-Müllerian hormone (AMH) with the trajectory of body mass index (BMI; *A*) and waist circumference (*B*) for women with human immunodeficiency virus (HIV+) and those without human immunodeficiency virus (HIV−). Earlier and later age were the 10th and 90th percentiles of age when an undetectable AMH was reached. The fitted curves are from the models shown in Table 2.

findings (result not shown). Therefore, we constructed separate models by HIV status.

In models including both menopausal phase and chronologic age in WWH, we observed a −0.55%, −0.29%, and −0.67% effect on the annual rate of BMI change in the early perimenopause, late perimenopause, and menopause phase, respectively, compared to premenopause. That is, we estimated the percentage increase in BMI per year was lower by 0.55 during early perimenopause than it would be at the same age if the woman were still in the premenopause phase. By contrast, WWOH had a 0.43% and 0.15% effect on the annual rate of BMI change in the early and late perimenopause phases, respectively, and a −0.40% effect in the menopausal compared to premenopausal phase (Table 2).

When we examined the association of menopausal phase and chronologic age with WC, in WWH, we observed a −0.21%, 0.18%, and −0.12% effect on the annual rate of WC change in the early perimenopause, late perimenopause, and menopause phase, respectively, compared to premenopause. By contrast, in WWOH, we observed a 0.35%, 0.48%, and 0.06% effect on the annual rate of change across the 3 menopausal phases, respectively, compared to the premenopause phase (Table 2).

Adjusted Associations of Menopausal Phase With BMI and WC Change
After adjustment for chronologic age, race/ethnicity, wave of enrollment, and clinical site, the estimated effects on annual rate of BMI change remained negative and statistically significant (−0.61%, −0.37%, and −0.81%, respectively) in all 3 menopausal phases in WWH, and the effects in WWOH were statistically nonsignificant (0.40%, 0.10%, and −0.46%, respectively) but in a positive direction in the early and late perimenopausal phases (Supplementary Table 1). When we adjusted for additional factors that might be associated with BMI change (smoking, alcohol use, depression, viral hepatitis, and

HIV-associated factors), there was little change in the association of menopausal phase in WWH and WWOH.

After adjustment for chronologic age, race/ethnicity, wave of enrollment, and clinical site, in WWH, the effects on annual rate of change in WC in the early perimenopausal and menopausal phases were steeper and statistically significant (−0.40% and −0.42%, respectively), whereas the effect on WC trajectory during the late perimenopausal phase was attenuated (−0.05%) and nonstatistically significant (Supplementary Table 1). In WWOH, the effect on annual rate of WC change was attenuated after adjustment (0.27% and 0.36% in the early and late perimenopause phases, respectively) and nonstatistically significant, whereas WC reversed direction (−0.08%) in the menopausal phase and was nonstatistically significant compared to the premenopausal phase. When we adjusted for additional factors that might be associated with WC change, there was little change in the association of the menopausal phase in WWH and WWOH (Supplementary Table 1).

Behavioral and Clinical Factors Associated With BMI and WC Change
In multivariable models examining the estimates of factors associated with BMI change over time, in WWH, current smoking (−0.37% [95% confidence interval{CI}, −.58% to −.16%]), heavy alcohol use (−0.88% [95% CI, −1.28% to −.47%]), CD4 count <200 cells/µL (−0.48% [95% CI, −.69% to −.27%]), presence of viral hepatitis (−0.35% [95% CI, −.54% to −.15%]), and detectable HIV RNA (−0.84% [95% CI, −1.00% to −.68%]) were statistically significantly associated with BMI change in a negative direction, whereas ART use was associated with BMI change in a positive direction (0.36% [95% CI, .19%–.53%]). In WWOH, light alcohol use was associated with BMI change in a negative direction (−0.39% [95% CI, −.69% to −.09%]) whereas heavy alcohol use (0.52% [95% CI, .07%–.98%]) and presence of viral

Table 2. Effects of Early Perimenopause, Late Perimenopause, and Menopause on the Annual Rate of Change in Body Mass Index and Waist Circumference, Compared to Premenopause, in Women With or Without Human Immunodeficiency Virus, After Adjustment for the Effects of Chronologic Age (Also Shown)

Characteristic	BMI Women With HIV		BMI Women Without HIV		Waist Circumference Women With HIV		Waist Circumference Women Without HIV	
Menopausal phase (Ref: premenopause)								
Early perimenopause	−0.55% (−.80% to −.30%)	**<.001**	0.43% (−.01% to .87%)	.053	−0.21% (−.44% to .03%)	.084	0.35% (−.06% to .76%)	.092
Late perimenopause	−0.29% (−.61% to .03%)	.072	0.15% (−.42% to .71%)	.616	0.18% (−.10% to .45%)	.206	0.48% (−.02% to .97%)	.060
Menopause	−0.67% (−1.12% to −.20%)	**.005**	−0.40% (−1.24% to .45%)	.361	−0.12% (−.50% to .26%)	.534	0.06% (−.64% to .75%)	.871
Chronologic age, y								
<30	−0.26% (−.90% to .39%)	.434	2.49% (1.47%–3.51%)	**<.001**	0.24% (−2.19% to 2.72%)	.849	1.43% (−.33% to 3.23%)	.111
30–<35	0.48% (.21%–.76%)	**.001**	1.49% (1.03%–1.95%)	**<.001**	0.70% (.21%–1.19%)	**.005**	0.50% (−.21% to 1.22%)	.168
35–<40	0.19% (.02%–.36%)	**.033**	0.88% (.59%–1.18%)	**<.001**	0.52% (.32%–.72%)	**<.001**	1.22% (.87%–1.56%)	**<.001**
40–<45	0.53% (.29%–.77%)	**<.001**	0.40% (−.01% to .81%)	.058	0.55% (.32%–.77%)	**<.001**	0.6% (.21%–.98%)	**.003**
45–<50	0.62% (.29%–.97%)	**<.001**	0.47% (−.11% to 1.07%)	.110	0.63% (.35%–.91%)	**<.001**	0.58% (.08%–1.09%)	**.023**
50–55	0.50% (.05%–.96%)	**.028**	−0.08% (−.86% to .70%)	.834	0.51% (.15%–.87%)	**.006**	0.16% (−.49% to .8%)	.632
>55	0.63% (.07%–1.20%)	**.027**	−0.25% (−1.23% to .75%)	.630	0.68% (.23%–1.15%)	**.003**	−0.19% (−1.00% to .62%)	.641

Data in parentheses indicate the 95% confidence interval. Values in bold are statistically significant at *P* < .05.

Abbreviations: BMI, body mass index; HIV, human immunodeficiency virus.

hepatitis (0.56% [95% CI, .20%–.91%]) were associated with BMI change in a positive direction.

In multivariable models examining factors associated with WC change over time, in WWH, current smoking (−0.25% [−.40% to −.09%]), heavy alcohol use (−0.92% [95% CI, −1.29% to −.54%]), depression (−0.18% [95% CI, −.34% to −.03%]), and detectable HIV RNA (−0.73% [95% CI, −.88% to −.58%]) were statistically significantly associated with WC change in a negative direction over time. In WWOH, light alcohol use was statistically significantly associated with WC change in a negative direction over time (−0.35% [95% CI, −.64% to −.06%]).

DISCUSSION

Contrary to expectation, we found that in WWH, the menopausal transition was associated with annual rates of change in BMI that were lower when compared to premenopause after adjusting for chronologic age. Findings were mostly in the same unexpected direction for WC but were smaller and not statistically significant. By contrast, in WWOH, being in early and late perimenopause was associated with annual rates of BMI and WC change that were nonstatistically significantly higher when compared to premenopause after adjusting for chronologic age. Our findings suggest that the expected increases in weight gain during the menopausal transition are blunted by HIV infection and possibly the residual effects of early ART on subcutaneous adipose tissue (SAT) in a US cohort that is nationally representative of WWH.

Our findings in WWH differ from a cross-sectional study from Zanni et al of mostly virally suppressed non-US WWH on ART. That study found that obesity and a high WC (>88 cm) was associated with advanced reproductive age (defined as having UD AMH from a single measurement or no report of menses for >12 months) after adjusting for chronologic age [17]. While our study longitudinally examined BMI and WC trajectories across menopausal phases, there were also differences in study population that could explain the conflicting findings. The Zanni study included women with a median CD4 count close to 700 cells/μL and low reports of smoking, drinking, depression, and viral hepatitis. In our study, at the time of first UD AMH, slightly over half were virally suppressed, median CD4 count was <500 cells/μL, and half reported smoking and drinking. Women were also exposed to older ART regimens that could have enduring effects on SAT.

In WWOH, we found that the perimenopausal phase was associated with BMI and WC changes that are consistent with that reported in the general population. The differential effects by HIV status are corroborated by the statistically significant interaction between HIV status in the early perimenopausal and menopausal phases and the association of detectable HIV RNA with a lower annual rate of change in BMI and WC over time. Whereas studies

from the general population, including the Study of Women's Health Across the Nation by Greendale et al, have found accelerated changes in body composition during the menopausal transition [6], we found that in WWH, during late perimenopause there was a small negative effect on BMI change and there was only a small positive estimated effect on WC change. These findings suggest that there are HIV-specific factors that blunt the expected gains in BMI and WC.

Prior studies show an association of HIV infection with subcutaneous fat loss including the study of Fat Redistribution and Metabolic Changes in HIV Infection (FRAM) that used whole-body magnetic resonance imaging to measure SAT [28]. A subsequent 5-year follow-up in FRAM found that despite average gains in subcutaneous fat with chronologic age, the expected gains remained blunted in WWH compared to WWOH [29]. Similarly, WWH in the WIHS had about double the incidence of peripheral and central lipoatrophy than WWOH [30]. Taken together, HIV infection and residual effects of ART such as stavudine use on SAT could be mechanisms by which weight gain is blunted over the menopausal transition.

Strengths of our study include our ability to leverage a large, decades-long, ethnically diverse cohort that includes a nationally representative sample of WWH and to measure AMH serially to better ascertain menopausal phase in WWH who are at risk of irregular menstrual cycles. Study limitations include using surrogate markers of obesity and visceral adiposity. However, imaging modalities to quantify fat volume are not practical for large studies of weight gain trajectory. While ART use was a covariate in our models, we were not able to adjust for the use of integrase inhibitors, which have been associated with weight gain [1, 31], or specific antiretroviral drugs associated with fat loss [32–34]. Finally, US Food and Drug Administration–approved AMH assays with lower limits of sensitivity have recently become available, perhaps reducing the precision of our estimates of the timing of ovarian reserve depletion [35].

CONCLUSIONS

In WWH, the transition to menopause was associated with effects on BMI and WC trajectories that were mostly in a negative direction and opposite from WWOH, after adjusting for chronologic age. HIV infection may blunt the expected gains in weight during the menopausal transition, in women who mirror the US HIV epidemic in women. Further study is needed to understand how clinical, behavioral, and immunologic factors influence body composition during the menopausal transition in order to develop appropriate strategies to reduce adverse cardiometabolic outcomes among WWH at midlife.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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