

Menopause is associated with faster increases in insulin resistance in women with HIV

Rebecca A. Abelman^a, Yifei Ma^a, C. Christina Mehta^b, Qian Yang^b,
Fan Xia^a, James B. Brock^c, Maria L. Alcaide^d, Anjali Sharma^e,
Michelle Floris-Moore^f, Elizabeth Topper^g, Kathleen M. Weber^h,
Seble G. Kassayeⁱ, Deborah Gustafson^j, Carl Grunfeld^a, Cecile D. Lahiri^b
and Phyllis C. Tien^a

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Background: Switching to an integrase strand transfer inhibitor (INSTI) during the menopausal transition has been associated with accelerated increases in visceral obesity, a risk factor for insulin resistance. Whether switching to an INSTI modifies the association of HIV and menopause with insulin resistance is unknown.

Methods: From 2006 to 2019, 389 nonpregnant women with HIV (WWH) [133 who switched to an INSTI (INSTI+); 256 who did not switch (INSTI–)] and 334 women without HIV from the Women's Interagency HIV study without diabetes or hepatitis C virus were included in the analysis. Mixed effect models evaluated the change in insulin resistance estimated through log HOMA-IR by HIV status by menopausal phase. We then compared trajectories by INSTI group. Menopausal phase was determined by anti-Müllerian hormone, a biomarker of ovarian reserve.

Results: Compared to women without HIV, INSTI+ WWH in premenopause had nonstatistically significant faster annual increases in HOMA-IR [difference in slope: 7.03%; 95% confidence interval (CI): –4.99 to 20.58] whereas INSTI– WWH had nonstatistically significantly faster annual decreases [–1.01% (95% CI: –7.34 to 5.75)]. In late perimenopause, INSTI+ and INSTI– had 4.87% (95% CI: –3.59 to 14.06) and 4.38% (95% CI: –3.10 to 12.44) nonstatistically significantly faster annual increases in HOMA-IR, respectively. In menopause, INSTI+ and INSTI– WWH had 9.18% (95% CI: 1.60 to 17.33) and 11.28% (95% CI: 3.27 to 19.91) statistically significant faster annual increases in HOMA-IR than women without HIV. There was no statistically significant difference between INSTI+ and INSTI– in any menopausal phase.

Conclusion: Regardless of switching to an INSTI or not, WWH in late perimenopause and menopause have faster increases in insulin resistance when compared to women without HIV. Diabetes screening and prevention in midlife WWH is imperative.

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^aDepartment of Medicine, University of California San Francisco, San Francisco, CA, ^bDivision of Infectious Diseases, Department of Medicine, Emory University School of Medicine, Atlanta, GA, ^cDepartment of Medicine, University of Mississippi Medical Center, Jackson, MS, ^dDepartment of Medicine, Miller School of Medicine, Miami, FL, ^eDepartment of Medicine, Albert Einstein College of Medicine, Bronx, NY, ^fDepartment of Medicine, University of North Carolina School of Medicine, Chapel Hill, NC, ^gDepartment of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, ^hHektoen Institute of Medicine, Chicago, IL, ⁱDepartment of Medicine, Georgetown University Medical Center, Washington, DC, and ^jDepartment of Neurology, State University of New York Downstate Health Sciences, NY, USA.

Correspondence to Rebecca A. Abelman, MD, University of California, San Francisco, VAHCS, Infectious Disease Section, 111W, 4150 Clement Street, San Francisco, CA 94121, USA.

Tel: +1 415 221 4810 x23613; e-mail: Rebecca.abelman@ucsf.edu

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Introduction

Women with HIV (WWH) are at higher risk for insulin resistance and diabetes than women without HIV [1,2]. The cause of this HIV-associated risk is likely multifactorial, including increased immune activation, environmental and behavioral exposures, an obesogenic environment, and certain antiretroviral therapy (ART) medications [2–4]. In the contemporary era, integrase strand transfer inhibitors (INSTIs) have been implicated in weight gain in people with HIV, particularly in women [5–7], and has thus been investigated as a driver of insulin resistance and diabetes. However, whether INSTIs increase diabetes risk and if this is exacerbated in WWH has been equivocal [2,7–11]; some studies have demonstrated an increased risk in insulin resistance and diabetes development with INSTI use, likely mediated by weight gain, whereas others have suggested null or decreased risk when compared to other antiretroviral medications [8–10,12–15].

In particular, older antiretroviral medications have been associated with increases in insulin resistance [3]. In a prior study in the Women's Interagency HIV Study (WIHS), WWH had a higher median homeostasis model assessment of insulin resistance (HOMA-IR) than women without HIV, and WWH who had been exposed to older ART medications, particularly nucleoside reverse transcriptase inhibitors (NRTIs), were found to have higher rates of insulin resistance than their counterparts [2]. In this study, being in postmenopause was also associated with insulin resistance, likely due to increases in visceral adiposity.

Menopause, characterized by the cessation of menses due to the depletion of ovarian follicles, has been associated with increases in visceral adiposity and concomitant metabolic derangements in women without HIV [16–18]. We have previously found that in WWH who were exposed to older ART regimens, HIV appeared to blunt the accelerated increases in BMI and waist circumference, a marker of visceral adiposity, across the transition to menopause [19]. We also found that in a contemporary cohort of women, WWH who switched to an INSTI in late perimenopause and menopause had accelerated increases in waist circumference [20], suggesting that certain ART medications may alter the trajectory of metabolic changes that occur across the menopausal transition. However, whether there are resultant cardiometabolic consequences is unknown.

To address this knowledge gap, we conducted a longitudinal retrospective analysis to evaluate whether switching to an INSTI across the menopausal transition was associated with alterations in insulin resistance trajectories compared to WWH who did not switch and to demographically similar women without HIV. To determine menopausal phase, we used anti-Müllerian hormone (AMH), a biomarker of ovarian reserve.

Methods

Study design

We conducted a longitudinal study of WWH and demographically similar women without HIV enrolled in the WIHS (now part of the MACS-WIHS Combined Cohort Study, or MWCCS). Full details of WIHS recruitment, retention, and demographics have been published elsewhere [21,22]. Women were seen every 6 months for survey administration, biospecimen collection, and physical exam, including anthropometry. Fasting specimens for HOMA-IR were collected annually.

For this analysis, we included women with available HOMA-IR measurements within the Sex-specific Predictors, Pathways, and Cardiometabolic Effects (SPPACE) INSTI sub-study of the WIHS that spanned 2006–2019. This study included WWH who switched to an INSTI, WWH who were not previously exposed to an INSTI, and demographically similar women without HIV who were enrolled in the study during the study period. Women were considered part of the INSTI group if they switched to or added an INSTI and remained on the same INSTI regimen for at least 1 year. Except for INSTI switch, inclusion criteria were the same for all WWH. Further details including additional inclusion criteria of the SPPACE INSTI sub-study have been published previously [20,23].

Women were divided into three distinct groups: WWH who switched to an INSTI (INSTI+), WWH who did not switch to an INSTI (INSTI–), and women without HIV. The INSTI switch visit was the first study visit at which a participant reported INSTI use. The index visits for INSTI– and women without HIV were selected to reflect similar calendar time periods to the switch visit [24]. AMH levels were then used to determine menopausal phase for women at each visit.

For our analysis, we excluded women who did not have a HOMA-IR value prior to the switch visit, who had diabetes at baseline, who had unclear hysterectomy or bilateral oophorectomy status, or who had a history of hepatitis C virus (HCV antibody positive) due to its association with insulin resistance [4,25].

Study measurements

Menopausal phase was determined using predicted AMH at each visit, as has been described previously [19,20,26]. After measuring serial AMH measures within the WIHS, we previously created prediction models for AMH declines to undetectable levels (<0.08 ng/ml). Using these predicted models, we categorized menopausal phase as follows: premenopause, defined as at least 5 years before AMH became undetectable; early perimenopause, defined as 0 to less than 5 years before an undetectable AMH; late perimenopause, defined as 0 to up to 5 years

after AMH became undetectable; and menopause, defined as greater than 5 years after AMH became undetectable [19,26].

Women who were 55 years or older and who reported hysterectomy or oophorectomy were categorized as postmenopausal. In women less than 55 years of age, the menopausal status of women with a history of hysterectomy or oophorectomy was determined using the last measured AMH value after hysterectomy or oophorectomy as described previously [20].

The primary outcome was the HOMA-IR, which is an indirect measurement of insulin resistance and is calculated using the formula $(\text{insulin} \times \text{glucose})/405$ with insulin measured in $\mu\text{IU}/\text{ml}$ and glucose measured in mg/dl [27]. We selected HOMA-IR because it has been widely used in large epidemiologic studies to estimate insulin resistance and has been standardly used across the studies in the MWCCS. A cutoff of greater than 2 has been used mostly in general population epidemiologic studies to define insulin resistance, but cutoffs vary depending on the specific population characteristics. For our population of WWH, we therefore examined HOMA-IR as a continuous measure.

Covariates included race/ethnicity (white, Black, Hispanic, or other), smoking status (never, current, or former), alcohol consumption [abstain, light (>0 –7 drinks/week), moderate (>7 –12 drinks/week), heavy (>12 drinks/week)], depressive symptoms [Center for Epidemiological Studies Depression (CESD) scale >16 [28]], hypertension (defined by SBP ≥ 140 mmHg, DBP ≥ 90 mmHg, or use of antihypertensive medication), and chronic kidney disease (defined as EGFR <60 ml/min/ 1.73 m^2 using CKD-EPI), and waist circumference (cm) due to its known association with insulin resistance [29]. HIV-related parameters included CD4⁺ T-cell count (nadir and current), HIV RNA (detectable vs. undetectable, <48 copies/ml until 2011 then <20 copies/ml), and current use of ART (yes/no).

Statistical analysis

Sociodemographic and clinical characteristics were summarized using median [interquartile range (IQR)] for continuous variables and percentage (frequency) for categorical variables at the index visit. We compared each characteristic by group using χ^2 tests or Fisher's exact tests for categorical variables and either t tests or Mann-Whitney tests for continuous variables, wherever appropriate. Statistical tests with a p -value of 0.05 were considered significant for all analyses.

We then assessed the change in insulin resistance over time using linear mixed models with a random intercept and random time effect for each participant. HOMA-IR was log transformed to better approximate normality. We fitted each model with a $\text{time} \times \text{group}$ and a $\text{time}^2 \times$

group interaction in addition to the main effect of time, assuming a nonlinear longitudinal trajectory. The $\text{time}^2 \times \text{group}$ interaction was excluded if it was not statistically significant, as this suggested fitting a linear trend was appropriate. None of the $\text{time}^2 \times \text{group}$ interactions reached statistical significance so a linear trend was used for all models.

Analyses included the visit preceding the index visit and at least one visit after the index visit. Models first evaluated the change in insulin resistance estimated through log HOMA-IR across 5 years of follow-up as a function of study group and time-varying menopausal phase. The models were stratified by the menopausal phase at the index visit. In each model, we adjusted for baseline age, menopausal phase at each visit, and the covariates specified above at each visit. Time intervals of 1 year were used as HOMA-IR was collected annually. HOMA-IR values were back-transformed with coefficients presented in percentages. Given some participants only had one AMH test preceding the index visit, each menopausal phase used the preceding phase as the reference (e.g. the reference for the late perimenopausal phase was early perimenopause). As tenofovir alafenamide (TAF) has been associated with weight gain in WWH [5], we then performed a sensitivity analysis among those who were on tenofovir disoproxil fumarate (TDF). Analyses were conducted using SAS 9.4 (SAS Institute, Cary, North Carolina, USA).

Results

Baseline characteristics

Of the 2063 women enrolled in the SPPACE INSTI sub-study, 1026 did not have HOMA-IR values prior to switch, 14 had unclear hysterectomy or oophorectomy status, 137 had hepatitis C antibody positivity, and 166 had diabetes at baseline and thus were excluded from the analysis. Those excluded were slightly older (median age of 48 vs. 46 years), had slightly lower CD4⁺ nadirs (median 344 vs. 413 cells/ μl), nominally higher mean viral loads (26 vs. 21 copies/ml), slightly lower median BMIs (29.3 vs. 29.9 kg/m^2), and were more likely to be menopausal (results not shown). Of the 723 included participants, 389 were WWH (133 INSTI+ and 256 INSTI–) (Table 1). The majority of women identified as Black (66%) and non-Hispanic (76%). At the index visit, 40% were premenopausal, 10% were in early perimenopause, 23% were in late perimenopause, and 27% were menopausal. Women without HIV were more likely to drink alcohol and be current cigarette smokers. Women in the INSTI+ group were older than the INSTI– WWH and women without HIV (median age 50 vs. 46 vs. 44 years) and had higher median HOMA-IR values (2.05 vs. 1.83 vs. 1.68). Among WWH, those in the INSTI+ group were more likely to have viral suppression

Table 1. Demographics and clinical characteristics by integrase strand transfer inhibitor group at the index visit.

N (%) [median (IQR)]	INSTI+ (n = 133)	INSTI- (n = 256)	WWOH (n = 334)	P value ^b
Age (years)	50 (43–56)	46 (40–53)	44 (36–51)	<0.0001
Race/ethnicity				
White	26 (20%)	61 (24%)	56 (17%)	0.063
Black	89 (67%)	151 (59%)	236 (71%)	
Other ^a	18 (14%)	44 (17%)	42 (13%)	
Hispanic	27 (20%)	73 (29%)	71 (21%)	0.073
Menopausal phase				
Premenopause	31 (23%)	94 (37%)	163 (49%)	<0.0001
Early perimenopause	9 (6.8%)	29 (11%)	37 (11%)	
Late perimenopause	36 (27%)	61 (24%)	67 (20%)	
Menopause	57 (43%)	72 (28%)	67 (20%)	
Waist circumference (cm)	92.5 (85.7–111)	91.5 (83.4–103)	98.2 (86.6–109)	0.046
Current smoking	42 (32%)	78 (31%)	140 (45%)	0.0008
Drinking				
Abstainer	68 (52%)	157 (62%)	118 (38%)	<0.0001
1–7 drinks/week	54 (42%)	77 (30%)	121 (39%)	
8–12 drinks/week	1 (0.8%)	7 (2.8%)	22 (7.1%)	
>12 drinks/week	7 (5.4%)	13 (5.1%)	49 (16%)	
Depression (CESD score)	6 (2–16)	7 (2–16)	8 (3–16)	0.360
Hypertension	59 (44%)	86 (34%)	117 (35%)	0.091
Chronic kidney disease	19 (15%)	26 (10%)	7 (2.5%)	<0.0001
HOMA-IR	2.05 (1.32–3.68)	1.83 (1.09–3.09)	1.68 (0.96–2.81)	0.026
HIV-related factors				
Undetectable HIV RNA	80 (63%)	115 (51%)	–	0.031
CD4 ⁺ T cells (cells/ μ l)	715 (554–853)	617 (450–832)	944 (636–1160)	<0.0001
Current tenofovir disoproxil fumarate (TDF) use	37 (28%)	214 (84%)	–	
Current Tenofovir alafenamide (TAF) use	50 (38%)	7 (2.7%)	–	
Current efavirenz use (EFV)	4 (3.0%)	68 (27%)	–	
Prior DDI, D4T, and AZT use	16 (12%)	17 (6.6%)	–	

Column percents may not add up to 100% due to rounding. Missing values were excluded when calculating frequencies/percentages. CESD, Center for Epidemiological Studies-Depression scale; IQR, interquartile; INSTI, integrase strand transfer inhibitor.

^aIncludes Asian, Pacific Islander, Native American, Alaskan and other study participants.

^bP value from Pearson χ^2 test, Wilcoxon rank-sum test or Fisher's exact test.

(62.5 vs. 51%) and to be on TAF than the INSTI– group (38 vs. 2.7%). INSTI+ WWH were less likely to be on efavirenz (3.0 vs. 26.6%) but had higher rates of older NRTI use (12 vs. 6.6%). Among the INSTI+ women, 22% were on raltegravir, 38% were on elvitegravir, and 31% were on dolutegravir at the switch visit.

In the evaluation of baseline characteristics and demographics by menopausal phase, median HOMA-IR increased from premenopause to menopause (Supplementary Table 1, <http://links.lww.com/QAD/D699>). TDF use also increased across menopausal phases.

Associations of menopausal phase with insulin resistance by INSTI status

Figure 1a–d shows the change in insulin resistance by INSTI group for each menopausal phase at the time of switch, adjusting for sociodemographic and clinical factors including waist circumference. Figures demonstrate the absolute changes in HOMA-IR over time.

In premenopause, when compared to women without HIV, WWH in the INSTI+ group had faster annual increases in HOMA-IR (difference in slope: 7.03%; 95% CI: –4.99 to 20.58), whereas women in the INSTI–

group had annual decreases (–1.01%; 95%CI: –7.34 to 5.75), but the differences were not statistically significant for either comparison (Fig. 1a). There was also no statistically significant difference when comparing INSTI+ and INSTI–.

In early perimenopause, when compared to women without HIV, the INSTI+ group had nonstatistically significant annual decreases (–8.10%; 95%CI: –19.97 to 5.53) and INSTI– had nonstatistically significant faster annual increases in HOMA-IR (3.68%; 95% CI: –7.80 to 16.59) (Fig. 1b). There was also no statistically significant difference when comparing INSTI+ and INSTI–.

In late perimenopause, when compared to women without HIV, INSTI+ and INSTI– women had 4.87% (95% CI: –3.59 to 14.06) and 4.38% (95% CI: –3.10 to 12.44) annual increases in HOMA-IR, respectively, but the difference was not statistically significant for either group (Fig. 1c). There was also no statistically significant difference between INSTI+ and INSTI–.

In menopause, when compared to women without HIV, the INSTI+ group had 9.18% (95% CI: 1.60 to 17.33) and INSTI– women had 11.28% (95% CI: 3.27 to 19.91)

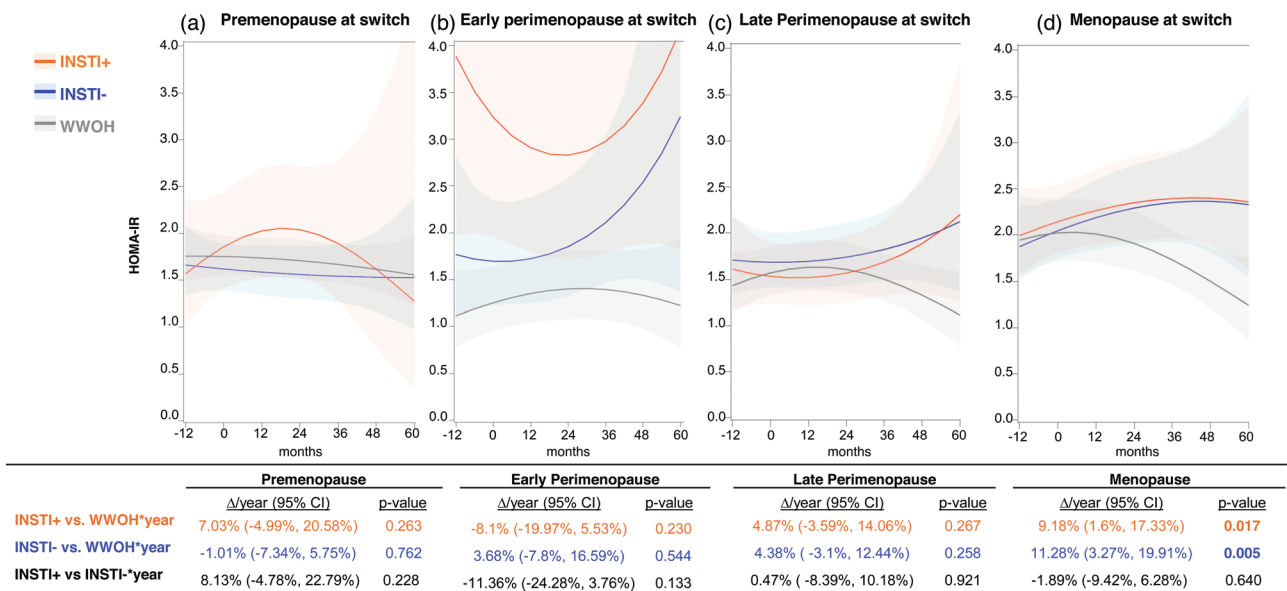


Fig. 1. Change in HOMA-IR by menopausal phase by integrase strand transfer inhibitor status.

statistically significantly faster annual increases in HOMA-IR (Fig. 1d). There was no statistically significant difference between INSTI+ and INSTI-.

Sensitivity analysis among those on tenofovir disoproxil fumarate

When limited to just those on a TDF-containing regimen, the trajectories appeared similar and were in the same direction (Supplementary Table 2, <http://links.lww.com/QAD/D700>). When comparing INSTI+ to INSTI-, there was no statistically significant difference between groups across all menopausal phases.

Discussion

We found that WWH in late perimenopause and especially menopause had a faster increase in insulin resistance compared to women without HIV. Notably, this increase was independent of visceral obesity as assessed by waist circumference. Our findings suggest that during the menopausal transition, WWH are at greater risk for faster increases in insulin resistance, which could increase the risk for type 2 diabetes, and it is not related to the use of INSTIs.

The association of treated HIV and menopause with greater HOMA-IR is suggested by our prior studies in WWH who had been exposed to older ART regimens. In an early study in WIHS, we found that HIV and menopause were independently associated with greater HOMA-IR, but most were on protease inhibitor-based regimens and the proportion reporting menopause was low [2]. In this more contemporary cohort of WWH, we found that INSTI+ women had faster increases in waist

circumference in late perimenopause and menopause, a finding that was not seen in the INSTI- group [20]. Interestingly, in this study, we did not find commensurate INSTI-associated changes in insulin resistance. Rather, it was menopausal WWH who distinctly demonstrated increases in insulin resistance, whereas menopausal women without HIV had stable levels of insulin resistance followed by declines. The latter findings are consistent with the literature in the general population, which has not found menopause-associated changes in insulin resistance after adjustment for chronologic age [17,30]. Taken together, our findings suggest that there is neither a direct effect of INSTI on insulin resistance nor an indirect effect through visceral adiposity. Additional research is needed to understand the mechanism by which menopause affects insulin resistance.

Prior studies have yielded inconclusive findings regarding the effects of INSTI use on insulin resistance and diabetes. In a meta-analysis evaluating whether INSTIs were associated with a higher risk of incident diabetes or higher rates of insulin resistance in people with HIV, the authors found that INSTI therapy was associated with a lower risk of incident diabetes, especially when compared to NNRTIs [8]. Similarly, in a large study of ART-naïve individuals, people starting an INSTI vs. an NNRTI had a small-to-null association with incident diabetes when accounting for 12-month weight gain [10]. Notably, the majority of participants in these studies were male, and in the latter study, men were more likely to be started on an INSTI than women. By contrast, a prior study by Summers *et al.* [9] in the WIHS, including predominantly midlife WWH, found that women who switched to an INSTI had greater increases in HgbA1c when compared to WWH who did not switch. Although we did not see an INSTI-associated difference in our study of women,

the Summers *et al.* analysis did not incorporate menopausal phase, which may explain this discrepancy.

Menopause is associated with body composition change and concomitant metabolic derangements in the women without HIV [17,31], but whether similar effects are seen in WWH is incompletely characterized. Other general population studies have suggested that metabolic parameters begin to worsen in the perimenopausal period, such as acceleration of markers of adiposity [31], increases in lipid profiles [30], and elevated risk of metabolic syndrome development [32,33]. We have also previously found that in both women with and without HIV, late perimenopause and menopause were associated with shorter relative times to diabetes, independent of BMI [26]. In this analysis, we similarly found that HOMA-IR trajectories began to accelerate beginning in late perimenopause and spanning into menopause, and that the HIV effect was most pronounced in menopause. Although there were elevations in HOMA-IR in early perimenopause, we cannot make inferences from these data based on the small sample size; however, this may suggest a potential imprinting effect starting in the perimenopausal period. Whereas the trajectories of HOMA-IR in women without HIV began to decrease about a year after menopause, insulin resistance trajectories remained flat in WWH. Taken together, this suggests menopause may differentially impact insulin resistance in WWH.

The absence of an INSTI effect in insulin resistance among WWH may be due to sex differences in INSTI effects on adipose tissue. Prior in-vitro and in-vivo studies have found that INSTI exposure to adipose tissue leads to alterations contributing to insulin resistance and impaired insulin-mediated glucose uptake [34,35]. Building on this work, another study found that INSTI-related effects on adipocytes are altered by estrogen exposure [36], suggesting that INSTIs may impact adipose tissue and glucose uptake differentially by sex. The mechanism by which estrogen depletion in the setting of HIV might affect a possible association of INSTI with insulin resistance merits further study.

We did not find that TDF use altered HOMA-IR trajectories in WWH by menopausal phase. Prior studies have suggested that either TAF [5] or the cessation of TDF, which may have catabolic effects [37–39], contributes to the weight gain seen in WWH, which would serve as a driver of insulin resistance. For example, in a study applying diabetes predictive models to the ADVANCE cohort, an additional six cases of diabetes were predicted when comparing TAF to TDF-based regimens with an INSTI backbone at 96 weeks [3,40], likely due to weight gain. However, in our study, when limiting to those on TDF, we did not see any changes in HOMA-IR trajectories. While there was low TAF uptake in our cohort precluding an analysis among those

just on TAF, when adjusting for visceral obesity, the effects of TDF were small or null on insulin resistance levels, suggesting menopausal phase was a more important predictor of insulin resistance than tenofovir exposure.

Limitations of this study include examining INSTIs as a drug class rather than by individual agent, as there may be differential effects of INSTIs on insulin resistance and diabetes [3]. Due to attrition in longitudinal follow-up, we had fewer participants beyond 5 years, limiting our ability to evaluate longer term changes after INSTI switch. Due to the observational nature of this study, we could not determine causality, nor could we exclude that the demographic differences between the WWH and the women without HIV or other potential confounders, such as physical activity and diet, are contributing to the results seen here.

This study had several strengths. We leveraged a large geographically and racially/ethnically diverse US cohort of women with and without HIV across the reproductive lifespan. We had detailed ART characterization at the index visit as well as serial HOMA-IR and AMH measurements. This study includes women, particularly midlife WWH, who may require distinct screening or therapeutic interventions as they undergo the transition to menopause.

In conclusion, we found that WWH in late perimenopause and menopause have faster increases in insulin resistance when compared to women without HIV, and this increase was independent of switching to an INSTI or tenofovir exposure. These findings suggest that diabetes screening and prevention in midlife WWH is imperative, regardless of ART regimen.

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analysis, helped guide interpretation of the data, and assisted with writing the manuscript. C.M. helped with the interpretation of data and statistical analysis and assisted with writing the manuscript. Q.Y. helped with data interpretation and statistical analysis and assisted with writing the manuscript. F.X. helped with data interpretation and statistical analysis and assisted with writing the manuscript. J.B., M.A., A.S., M.F.M., E.T., K.W., S.K., D.G., C.G.: all contributed equally and assisted with writing the manuscript. C.L. helped develop the study question and assisted with writing the manuscript. P.T. helped develop the study question, interpreted the data, and assisted with writing the manuscript.

Conflicts of interest

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