

# Weight and Body Mass Index Change After Switching to Integrase Inhibitors or Tenofovir Alafenamide Among Women Living with HIV

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## Abstract

Weight and body mass index (BMI) change was assessed among women after switch to integrase inhibitors (INSTIs) and/or tenofovir alafenamide (TAF). From 2006 to 2019, 1,458 women living with HIV enrolled in the Women's Interagency HIV Study and on antiretroviral therapy (ART) with  $\geq 1$  study visit before and after switching to INSTIs and/or TAF were included. Weight and BMI were compared pre- and postswitch to INSTI (by class and type) and/or TAF using multivariable linear mixed effects models; all models were also stratified by preswitch presence or absence of obesity (BMI  $\geq 30$  vs.  $< 30$  kg/m<sup>2</sup>). Mean age preswitch was  $47 \pm 6$  years, 64% were black, mean CD4 =  $475 \pm 201$  cells/mm<sup>3</sup>, 56% had HIV RNA  $< 200$  copies/mL, 36% switched to TAF but not INSTI, 60% to INSTI but not TAF, and 3.5% to TAF+INSTI. Time from pre- to postswitch was  $12.8 \pm 11.8$  months. The INSTI-only group but not TAF groups had small but significant increases in weight and BMI: mean 79.2–80.6 kg and 30.2–30.7 kg/m<sup>2</sup>,  $p$ 's  $< .001$ , respectively, with congruent findings by INSTI type ( $p$ 's  $\leq .01$ ). In stratified (preswitch BMI) analyses, only nonobese subgroups experienced increases in weight and BMI across all ART treatment groups ( $p$ 's  $< .05$ ). Significant, although small-to-medium, increases in weight and BMI occurred among nonobese women who switched to INSTIs and/or TAF over short follow-up. Given long-term health consequences of obesity particularly as a low-grade inflammatory condition, identifying women at highest risk of ART-associated weight gain is imperative.

**Keywords:** HIV, women, integrase inhibitors, tenofovir alafenamide, body weight, body mass index

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## Introduction

**P**ERSONS LIVING WITH HIV (PLWH) are increasingly overweight (body mass index, BMI, 25.0–29.9 kg/m<sup>2</sup>) or obese (BMI ≥30 kg/m<sup>2</sup>) either at HIV diagnosis or within 2–3 years of antiretroviral therapy (ART) initiation.<sup>1–5</sup> Obesity contributes to adverse health outcomes including cardiovascular disease, diabetes mellitus (DM), and hypertension.<sup>6</sup> Integrase strand transfer inhibitor (INSTI)-containing ART regimens are the recommended first-line treatment of ART-naïve PLWH due to virologic efficacy and tolerability.<sup>7</sup> Despite excellent safety profiles and low side effect rates in Phase III clinical trials, data from randomized controlled trials and observational studies after widespread use of INSTIs in more diverse populations have shown increases in weight and BMI<sup>8–18</sup> particularly with dolutegravir<sup>9–11,14,16,18</sup> and among black and Hispanic women.<sup>9,11</sup>

Recently, we showed that women switching to or adding an INSTI to their ART regimen in the pretenofovir alafenamide (TAF) era were more likely to experience clinically significant (≥7%) weight gain than women remaining on non-INSTI ART for an 18-month period: 22% versus 14%, with congruent findings across additional adiposity measures.<sup>19</sup> New evidence suggests that the nucleoside reverse transcriptase inhibitor (NRTI) TAF either alone<sup>20</sup> or in combination with INSTIs<sup>18,21</sup> is also associated with weight gain; however, the effect of switching to TAF on body weight remains unclear, particularly among women. We assessed changes in body weight and BMI among women living with HIV (WLWH) on ART who switched to an INSTI and/or TAF.

## Methods

We utilized data collected from WLWH enrolled in the Women's Interagency HIV Study (WIHS) between 2006 and 2019. As previously described, WIHS is the largest ongoing longitudinal cohort study of WLWH and at-risk HIV-seronegative women in the United States.<sup>22,23</sup> WIHS participants undergo semiannual study visits with clinical and medication history assessment through standardized survey instruments and physical examinations including height and weight measurements for BMI assessment (height/weight<sup>2</sup>). Ten WIHS sites were included: San Francisco, CA; Chicago, IL; Brooklyn, NY; Bronx, NY; Washington, DC; Chapel Hill, NC; Miami, FL; Birmingham, AL/Jackson, MS combined site; Atlanta, GA; and Los Angeles, CA.

WLWH were included if they were previously receiving ART ≥6 months with a non-INSTI non-TAF-based regimen and switched to either an INSTI, TAF, or an INSTI+TAF. For inclusion in our data set, participants needed at least one visit before and after the switch with weight and BMI assessment. We used separate linear mixed effects models to compare body weight and BMI pre- and postswitch for each postswitch treatment group (INSTIs only, TAF only, and INSTI+TAF) controlling for relevant covariates.

For INSTIs, we conducted additional analyses by INSTI type, including dolutegravir, elvitegravir, and raltegravir. Self-reported and clinical covariates of interest available across WIHS during this time period were included in the regression analyses: age at preswitch, race/ethnicity, education, annual income, employment and marital status, current

smoking, alcohol, and illicit drug use, hepatitis C infection status (determined by hepatitis C antibody and/or hepatitis C RNA), hypertension (systolic blood pressure ≥140, diastolic blood pressure ≥90, self-report, or use of antihypertensive medications), DM (self-report, use of antidiabetic medication, or any of fasting glucose ≥126 or HgbA1C >6.5%), preswitch ART regimen, preswitch HIV RNA (copies/mL), CD4<sup>+</sup> T cell count (preswitch and nadir; cells per mm<sup>3</sup>), Center for Epidemiologic Studies Depression Scale (CES-D) score, menopausal status, duration of ART, and previous diagnosis of AIDS (clinical diagnosis or CD4<sup>+</sup> <200 cells/mm<sup>3</sup>). INSTI-only and TAF-only groups had sufficient sample sizes to perform sensitivity analyses limited to those participants with HIV RNA viral load <200 copies/mL. Interaction between preswitch BMI and treatment was assessed.

We next examined the effects of each group stratified by preswitch obesity status (<30 and ≥30 kg/m<sup>2</sup>). Multivariable regression analysis was performed for each BMI subgroup in the INSTI-only and TAF-only groups. Models were fitted using R software v3.5.2 with alpha = 0.05. Effect sizes were computed using Cohen's *d* methodology (effects, small = 0.2; medium = 0.5; large = 0.8).<sup>24</sup> Institutional Review Boards at all participating WIHS sites approved the study protocol; this analysis was reviewed and approved by the WIHS Executive Committee.

## Results

Of the 3,567 WLWH active in WIHS between 2006 and 2019, 1,458 (41%) met criteria for inclusion. Of these women, 878 (60%) switched to an INSTI-only regimen (35% dolutegravir, 40% raltegravir, and 25% elvitegravir), 529 (36%) switched to TAF only, and 51 (3.5%) switched to INSTI+TAF (96% dolutegravir). Mean time from preswitch to postswitch visit was 12.8 months (standard deviation, SD = 11.8). Overall, women had a mean age of 47 years (SD = 6), 64% identified as black, non-Hispanic, 36% had less than a high school education, 50% had annual income ≤\$12,000, 38% reported current smoking, and there were no significant differences in these characteristics by treatment group, see Table 1.

Women had high rates of comorbid disease, including 42% with preswitch obesity, 41% with hypertension, and 19% with DM. With regard to HIV disease, 56% had HIV RNA viral load ≤200 copies/mL with mean CD4 475 cells/mm<sup>3</sup> (SD = 201) at the preswitch visit, and 36% had a prior diagnosis of AIDS. All of the women in the INSTI-only and INSTI+TAF groups were INSTI-naïve compared with 512 (96.8%) of women in the TAF-only group. Fifty-seven percent of women who switched to INSTI or INSTI+TAF were previously taking a protease inhibitor (PI-based) regimen compared with 34% of women who were on a PI regimen when switched to TAF (*p* < .001); otherwise, there were no significant clinical differences between groups (Table 1).

Overall, women switching to INSTIs alone had a significant increase in body weight and BMI, from a preswitch mean of 79.2 (SD = 24.7) to 80.6 kg (SD = 24.7) postswitch and 30.2 (SD = 8.7) to 30.7 kg/m<sup>2</sup> (SD = 8.8) (*p*'s < .001), respectively; however, the effect sizes were small: Cohen's *d* = 0.26 and 0.21, respectively. The same pattern was seen when examining each INSTI separately: dolutegravir [pre–post weight 80.9 (SD = 25.7) to 81.4 kg (SD = 24.2), BMI 30.6 (SD = 8.9) to 31.0 kg/m<sup>2</sup> (SD = 8.7)]; raltegravir [pre–post

TABLE 1. DEMOGRAPHIC, BEHAVIORAL, AND CLINICAL CHARACTERISTICS AT THE WOMEN'S INTERAGENCY HIV STUDY VISIT BEFORE SWITCHING TO AN INTEGRASE STRAND TRANSFER INHIBITOR AND/OR TENOFOVIR ALAFENAMIDE FROM ANTIRETROVIRAL THERAPY, STRATIFIED BY PRESWITCH BODY MASS INDEX

Variable, N (%) or mean (SD)	INSTI only		TAF only		INSTI+TAF				
	All, N=878	BMI <30, N=510	BMI ≥30, N=368	All, N=529	BMI <30, N=304	BMI ≥30, N=225	All, N=51	BMI <30, N=26	BMI ≥30, N=25
Age in years	47 (6.5)	49 (6)	46 (6.5)	45 (6)	45 (5.5)	45 (5.5)	50 (6)	50.5 (6)	50 (4)
Education <high school	302 (34)	168 (33)	127 (36)	199 (38)	121 (40)	76 (34)	20 (39)	11 (42)	9 (39)
Race/ethnicity									
White, non-Hispanic	122 (14)	90 (18)	28 (8)	48 (9)	32 (11)	16 (7)	7 (14)	3 (12)	4 (17)
Black, non-Hispanic	557 (63)	295 (58)	252 (72)	344 (65)	179 (59)	163 (73)	34 (67)	18 (69)	15 (65)
Hispanic	176 (20)	143 (22)	59 (16)	120 (23)	83 (27)	36 (16)	9 (18)	5 (20)	3 (13)
Other	23 (3)	12 (2)	10 (3)	17 (3)	10 (3)	7 (3)	1 (2)	0 (0)	1 (4)
Annual household income ≤\$12,000	451 (51)	273 (54)	168 (48)	252 (48)	150 (49)	100 (45)	20 (39)	10 (38)	9 (39)
Currently employed	312 (36)	162 (32)	142 (41)	205 (39)	112 (37)	93 (42)	18 (35)	8 (31)	9 (39)
Married	255 (29)	152 (30)	98 (28)	166 (31)	94 (31)	71 (32)	11 (22)	7 (27)	3 (13)
Currently smoking	332 (38)	217 (43)	109 (31)	204 (39)	142 (47)	61 (27)	22 (43)	13 (50)	9 (39)
Recent alcohol use >7 drinks/week	74 (8)	46 (9)	28 (8)	56 (11)	39 (13)	17 (8)	4 (8)	2 (8)	2 (9)
Marijuana use	161 (18)	104 (20)	55 (16)	77 (15)	52 (17)	25 (11)	13 (25)	8 (31)	5 (22)
Crack, cocaine, and/or heroin use	58 (7)	48 (9)	10 (3)	42 (8)	37 (12)	5 (2)	6 (12)	3 (12)	3 (13)
Hepatitis C infection status <sup>a</sup>	161 (18)	109 (21)	47 (13)	100 (19)	73 (24)	26 (12)	9 (18)	6 (23)	3 (13)
Hypertension	381 (43)	199 (39)	173 (50)	198 (37)	87 (29)	109 (49)	22 (43)	10 (38)	12 (52)
Diabetes mellitus	175 (20)	84 (16)	88 (25)	95 (18)	42 (14)	52 (23)	12 (24)	5 (19)	6 (26)
Current CD4 count, cells/mm <sup>3</sup>	487 (209)	423 (195)	577 (208)	449 (189)	394 (182)	508 (179)	501 (209)	429 (241)	502 (197)
Nadir CD4 count, cells/mm <sup>3</sup>	209 (124)	177 (118)	244 (142)	224 (113)	203 (100)	263 (114)	239 (174)	215 (177)	270 (176)
HIV RNA ≤200 copies/mL	494 (56)	276 (54)	218 (59)	295 (56)	161 (53)	134 (60)	32 (63)	16 (62)	16 (64)
Prior AIDS diagnosis	348 (40)	215 (42)	125 (36)	160 (30)	98 (32)	60 (27)	17 (33)	10 (38)	7 (30)
Integrase inhibitor type									
Dolutegravir	305 (35)	170 (33)	130 (37)	n/a	n/a	n/a	49 (96)	25 (96)	22 (96)
Raltegravir	350 (40)	228 (45)	111 (32)	n/a	n/a	n/a	1 (2)	1 (4)	0 (0)
Elvitegravir	223 (25)	112 (22)	108 (31)	n/a	n/a	n/a	1 (2)	0 (0)	1 (4)
Prior or current ART anchor drug <sup>b</sup>									
NNRTI	173 (20)	104 (20)	69 (20)	157 (30)	100 (33)	57 (26)	7 (14)	4 (15)	3 (13)
PI	507 (58)	298 (58)	195 (56)	178 (34)	83 (27)	95 (43)	27 (53)	11 (42)	14 (61)
Others	198 (23)	108 (21)	85 (24)	194 (37)	121 (40)	70 (32)	17 (33)	11 (42)	6 (26)

Current, refers to within the past week; recent, refers to within 6 months of the most recent WIHS visit.

<sup>a</sup>HCV infection status is determined through a combination of HCV antibody and RNA testing.

<sup>b</sup>For INSTI groups, indicates ART anchor drug participants were switched from; for TAF-only group, includes ART anchor drug participants were already receiving.

ART, antiretroviral therapy; BMI, body mass index; INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; SD, standard deviation; TAF, tenofovir alafenamide; WIHS, Women's Interagency HIV Study.

TABLE 2. CHANGE IN BODY WEIGHT AND BODY MASS INDEX IN WOMEN SWITCHING TO AN INTEGRASE STRAND TRANSFER INHIBITOR AND/OR TENOFOVIR ALAFENAMIDE

	Preswitch weight, kg(SD)	Postswitch weight, kg (SD)	p <sup>a</sup>	Preswitch BMI (SD)	Postswitch BMI (SD)	p
INSTI only (n=878)	79.2 (24.7)	80.6 (24.7)	<.0001	30.2 (8.7)	30.7 (8.8)	<.0001
Preswitch BMI <30 kg/m <sup>2</sup> (n=510)	64.4 (10.0)	66.5 (11.8)	<.0001	24.7 (3.3)	25.5 (4.1)	<.0001
Preswitch BMI ≥30 kg/m <sup>2</sup> (n=368)	100.9 (23.8)	100.9 (24.4)	.087	38.1 (7.9)	38.2 (8.4)	.097
TAF only (n=529)	78.7 (23.5)	78.8 (23.7)	.989	30.0 (8.3)	30.1 (8.4)	.697
Preswitch BMI <30 kg/m <sup>2</sup> (n=304)	63.8 (9.5)	64.2 (9.9)	.019	24.6 (3.2)	24.8 (3.4)	.013
Preswitch BMI ≥30 kg/m <sup>2</sup> (n=225)	99.3 (21.4)	98.3 (22.9)	.062	37.5 (7.2)	37.2 (7.9)	.13
INSTI+TAF (n=51)	79.9 (22.4)	82.3 (21.8)	.647	30.7 (8.8)	31.6 (8.2)	.75
Preswitch BMI <30 kg/m <sup>2</sup> (n=26)	63.2 (12.0)	68.6 (16.0)	.014	24.1 (3.7)	26.1 (5.1)	.013
Preswitch BMI ≥30 kg/m <sup>2</sup> (n=25)	98.7 (15.1)	96.0 (18.0)	.129	38.3 (6.4)	37.0 (7.0)	.126

<sup>a</sup>p-Values calculated by two-sample two sided *t* test.

INSTI, integrase strand transfer inhibitor; BMI, body mass index; TAF, tenofovir alafenamide; SD, standard deviation.

weight 74.6 (SD=22.0) to 76.4 kg (SD=22.7) and BMI 28.6 (SD=7.7) to 29.3 kg/m<sup>2</sup> (SD=7.9)]; elvitegravir [pre–post weight 84.0 (SD=26.2) to 86.0 kg (SD=27.3) and BMI 32.0 (SD=9.5) to 32.7 kg/m<sup>2</sup> (SD=9.8)], Cohen’s *d* all <0.3.

By contrast, there was no significant change in either body weight or BMI in women switching to TAF only or INSTI+TAF (Table 2). There was significant interaction be-

tween preswitch BMI and treatment for all groups in both weight and BMI change analyses (*p*’s <.05).

In unadjusted analyses stratified by preswitch BMI, across all treatment groups, only nonobese WLWH experienced significant increases in both body weight and BMI, (*p*’s ≤.01) (Table 2); among nonobese women, the effect size of the weight and BMI increase was small for the INSTI-only (Cohen’s *d*=0.34 and 0.32) and TAF-only groups (Cohen’s *d*=0.09 and 0.12) but moderate for the INSTI+TAF group (Cohen’s *d*=0.53 and 0.54, respectively) (Fig. 1). In multivariable regression analyses, weight gain remained significant for the women in the INSTI-only group overall and in the INSTI-only subgroup with baseline BMI <30 kg/m<sup>2</sup> (*p*’s <.01); however weight gain was no longer significant among women with BMI <30 kg/m<sup>2</sup> in the TAF-only group (*p* >.1). There were no changes in overall and BMI stratified results after conducting sensitivity analyses limited to women with baseline HIV RNA viral load <200 copies/mL or when limited to women who were INSTI naive.

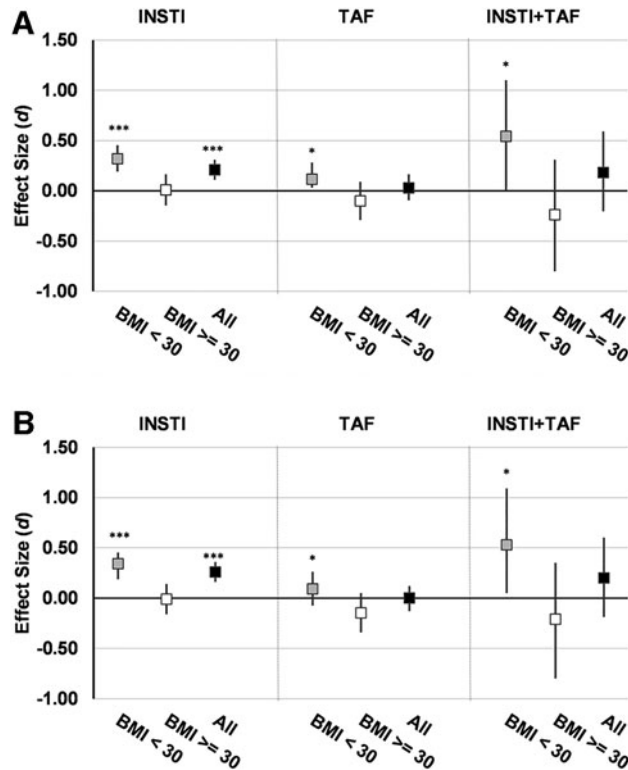


FIG. 1. Effect size of body weight (A) and BMI change (B) by Cohen’s *d* is shown by treatment group (INSTI, only;TAF, only; INSTI+TAF) overall and stratified by baseline BMI (<30 and ≥30 kg/m<sup>2</sup>). \**p*<.05, \*\*\**p*<.0001. BMI, body mass index; INSTI, integrase strand transfer inhibitor; TAF, tenofovir alafenamide.

## Discussion

Switching to an INSTI and/or TAF-containing regimen was associated with small but significant increases in body weight and BMI for 1–2 years in WLWH who were nonobese before switch, and the effect size was strongest among women switching to both INSTI+TAF. Women who were obese before switch showed minimal (if any) weight or BMI change after the switch.

Multiple studies have shown that INSTI use in the pre-TAF era (in treatment-naïve and experienced persons) is associated with body weight and BMI gain, and this effect is augmented in women.<sup>8,11–13</sup> Furthermore, there is growing evidence that TAF may be compounding the INSTI weight gain effect, although the largest studies to date were conducted in treatment-naïve individuals.<sup>17,18</sup> In the ADVANCE trial, naïve participants randomized to receive dolutegravir-based ART (with either tenofovir disoproxil fumarate, TDF, or TAF) had greater increases in body weight at 48 weeks compared with standard of care (efavirenz and TDF), and this effect was greatest for those receiving TAF (vs. TDF) and in women versus men.<sup>18</sup>

In a pooled analysis of eight randomized clinical trials of treatment-naïve persons initiating ART, TAF was associated

with greater weight gain at 96 weeks compared with any other NRTI.<sup>17</sup> Studies of ART initiation, however, are confounded by the “return to health” phenomenon that occurs during rapid virologic suppression.<sup>2,25</sup>

To our knowledge, only three published studies with small sample sizes have examined the association between TAF use and weight gain in treatment-experienced persons. Gomez *et al.* compared 129 participants in Germany (>80% male) who switched to TAF from TDF with 241 remaining on TDF and found greater weight gain at 1 year with TAF versus TDF (3.17 kg ±0.21 vs. 0.55 ±0.17).<sup>21</sup> Furthermore, in 252 individuals (65% male) who switched from TDF to TAF as part of a rilpivirine-based regimen, Taramasso *et al.*<sup>20</sup> found significant body weight gain (~4 kg) 3–6 months postswitch in women and those with BMI >25 mg/kg<sup>2</sup>.<sup>20</sup> Finally, Schafer *et al.* reported a 0.45 kg/m<sup>2</sup> increase in BMI 1 year after switching from TDF to TAF in 110 patients (73% male).<sup>26</sup> A study from the observational pharmaco-epidemiology research and analysis cohort recently presented at the International AIDS Conference examined >5,000 participants (~80% male) switching from TDF to TAF and found that they gained 1.98–2.64 kg/year, with the most weight gain in those maintaining an INSTI-based regimen.<sup>27</sup>

In contrast, we only saw significant BMI increase in WLWH switching to TAF or TAF+INSTI regimens who were nonobese preswitch. These discrepant findings may be explained by different characteristics of the study populations: we assessed a large population of predominantly minority women, almost half of whom were already obese preswitch, and the effects of TAF use on BMI may not be generalizable to all PLWH.

Our findings show that women with lower BMIs may be more at risk for weight gain after a switch to INSTIs and/or TAF, and enhanced follow-up and counseling are warranted in the clinical setting after ART regimen changes. Mechanisms to explain the lack of INSTI and/or TAF-associated weight gain in already obese women remain unclear, but may be explained by the impact of obesity on antiretroviral pharmacokinetics, as obesity has been associated with decreased plasma drug exposure for dolutegravir,<sup>28</sup> raltegravir, and tenofovir.<sup>29</sup> Impact of antiretroviral pharmacokinetics on outcomes such as body weight gain and its metabolic sequelae should be further explored.

Our study had several limitations. First, although our overall sample size was large, the sample size for the INSTI+TAF subgroup was small. Although we saw the most concerning signal for weight and BMI gain in nonobese women within this treatment group, studies with larger sample sizes are needed to confirm these findings. Second, >40% of women had HIV RNA >200 copies/mL preswitch, therefore, it is possible that subsequent virologic suppression after ART switch may have contributed to weight gain in this population. However, given that our sensitivity analyses limited to women with baseline HIV RNA <200 copies/mL showed the same results, it is less likely that “return to health” played a large role in this weight gain.

Although we controlled for many relevant covariates, the potential for unmeasured confounders remains given the retrospective observational study design. Specifically, we were unable to account for other factors that impact body weight, including concurrent non-ART medications, diet, and physical activity. Third, data regarding the reason for the

switch (e.g., drug intolerance) and the exact date of switch were unavailable. Finally, our follow-up time period was short (~12 months from time of switch). Although a short follow-up period allowed us to isolate the acute impact of the drug switch on weight and BMI, additional longitudinal measures are warranted to gauge long-term effects.

## Conclusion

To conclude, we examined a large sample of geographically and racially diverse WLWH in the United States and found that switching to INSTIs and/or TAF was associated with significant short-term body weight and BMI gain, particularly in women who were nonobese at baseline and in women receiving INSTIs rather than TAF alone. WLWH are a critical population to study as they experience an incredibly high burden of non-AIDS comorbidities,<sup>30</sup> and may be at particular risk for obesity and its long-term consequences. Understanding the mechanisms and clinical consequences of ART-mediated weight gain and obesity is essential to improve the care of a growing population of women aging with HIV.

## Authors' Contributions

Conceptualization of the study was carried out by C.D.L. and L.H.R.; data curation was performed by Y.X. and K.W.; formal analysis was done by Y.X. and K.W.; writing—original draft—of the article was done by C.D.L. and L.H.R.; and writing—review and editing—was done by C.D.L., Y.X., K.W., J.A.A., A.N.S., J.O., A.B.S., P.T., D.R.G., J.M., M.A.F., D. K.-P., A.A.A., A.S., K.M.W., I.O., and L.H.R.

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