HIV-Infected Women Gain More Weight than HIV-Infected Men Following the Initiation of Antiretroviral Therapy

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Abstract

Background: Obesity is prevalent among HIV-infected individuals on antiretroviral therapy (ART). Cross-sectional studies have suggested that HIV-infected women are more likely to be overweight than men, but observational studies evaluating sex differences in body mass index (BMI) increases following ART initiation are conflicting.

Materials and Methods: We pooled data from three randomized clinical trials of ART initiation in persons with HIV in the United States. BMIs were compared between 760 women and 3041 men to test whether BMI changes in the first 96 weeks following initiation of ART differed by sex at birth. Linear regression estimated the relationship between sex and change in BMI from pre-ART initiation to week 96.

Results: After 96 weeks, women gained an average of 1.91 kg/m² (95% confidence interval [CI] 1.64–2.19), men gained an average of 1.39 kg/m² (95% CI 1.30–1.48); p for sex difference <0.001; the sex difference persisted within each pre-ART initiation BMI subgroup. After adjusting for pre-ART initiation age, CD4+ count, HIV-1 viral load, race/ethnicity, study, and ART regimen, mean BMI change for women was 0.59 kg/m² (95% CI 0.37–0.81) more than for men (p < 0.001). Statistical interactions were observed between sex and both pre-ART CD4+ count and HIV-1 viral load and suggest that for subgroups with higher viral load and lower CD4+ at baseline, the estimated BMI changes in women are even larger than the average estimated difference.

Conclusions: HIV-1-infected women experienced a significantly greater increase in BMI following ART initiation than men. These differences are a problem of clinical significance to women living with HIV.

Keywords: HIV, BMI, sex differences, obesity

Background

Despite improvements in survival with antiretroviral therapy (ART),1–4 life expectancy for those living with HIV is still lower compared with age-matched HIV-uninfected individuals.1 Non-HIV-related events such as cardiovascular disease (CVD) and diabetes are more prevalent in ART-treated HIV-infected persons compared to age-matched HIV-uninfected individuals.4–13 Obesity is an independent risk factor for CVD and obese individuals living in the United States are nearly twice as likely to experience CVD, even after adjustment for other traditional risk factors.14 Cross-sectional studies reveal a high prevalence of obesity among HIV-infected individuals15–17 and research has noted increases in weight gain after ART initiation, with up to 20% of patients moving into an overweight or obese body mass index (BMI) category within 2 years of ART initiation.18 Importantly, short-term gains in BMI following ART initiation have been directly linked to increases in the long-term risk of both CVD and diabetes.19

Several cross-sectional studies have suggested that HIV-infected women are more likely to be overweight or obese than HIV-infected men.14,20,21 However, observational cohort studies evaluating differences in BMI increases following
ART initiation in men and women have yielded conflicting results. These observational studies evaluated patients on a variety of ART regimens that are no longer preferred, and may not reflect the current experience.

In this study, we pooled data from three randomized controlled trials of treatment-naïve participants initiating ART with modern regimens in the United States, to assess changes in BMI over 96 weeks and explore the relationship between sex and changes in BMI.

Materials and Methods

Parent studies

We accessed participant-level data from three Phase 3, AIDS Clinical Trials Group (ACTG) ART initiation trials in treatment-naive persons, in which BMI data were collected. We included data from ACTG A5142 (NCT#00050895, enrolled 2003–2004);26 A5202 (NCT#00118898, enrolled 2005–2007),27 and A5257 (NCT#00811954, enrolled 2009–2011).28

ACTG 5142 randomized 757 participants to one of three class-sparing regimens: lopinavir/ritonavir and two nucleoside reverse transcriptase inhibitors (NRTIs) (lamivudine plus zidovudine, stavudine, or tenofovir disoproxil fumarate [TDF]), efavirenz and two NRTIs, or lopinavir/ritonavir and efavirenz.26 A5202 included 1858 participants randomized to atazanavir/ritonavir or efavirenz combined with either abacavir/lamivudine or TDF/emtricitabine (FTC); and A5257 included 1809 participants randomized to atazanavir/ritonavir, darunavir (DRV)/ritonavir, or raltegravir (RAL) combined with TDF/emtricitabine.

We included participants from these studies if they had pre-ART initiation and week 96 BMI data, were enrolled in a research site in the United States (applicable to A5142 only), started ART, had matching sex at birth and current gender identity (an indication that participant was not transgender), and did not become pregnant during follow-up. Patients with active opportunistic infections were excluded from the parent studies; however, 20% of participants in the parent studies had AIDS diagnoses at study entry. Table 1 displays the pre-ART characteristics of the included subjects. Women, compared to men, were slightly older (mean of 40.5 years vs. 37.7 years). Women also had a higher mean BMI before starting ART (28.4 vs. 25.2 kg/m²). The mean pre-ART CD4+ count did not differ between the sexes (260 vs. 261 cells/mm³). Before starting ART, women had slightly lower HIV-1 viral loads, mean of 4.54 log₁₀ copies/mL in women compared to 4.74 log₁₀ copies/mL in men. Women were more likely to be black and men were more likely to be white. Finally, the proportion of women who enrolled to each trial varied: women represented 18% of participants in A5142, 17% in A5202, and 24% in A5257. Each of these observed differences between sexes is a typically observed difference (version 9.4).

Results

Analysis sample derivation and baseline characteristics

Of the 4422 participants enrolled in the parent studies, 3801 had pre-ART and week 96 BMIs and met other inclusion criteria. The primary reasons for exclusion were missing data or loss to follow-up (568), but a total of 53 individuals were excluded by study design. Twenty were enrolled in a research site outside of the United States, 22 did not start study ART, 11 did not have matching sex at birth and current gender identity, and 28 became pregnant during follow-up. Patients with active opportunistic infections were excluded from the parent studies; however, 20% of participants in the parent studies had AIDS diagnoses at study entry. Table 1 displays the pre-ART characteristics of the included subjects. Women, compared to men, were slightly older (mean of 40.5 years vs. 37.7 years). Women also had a higher mean BMI before starting ART (28.4 vs. 25.2 kg/m²). The mean pre-ART CD4+ count did not differ between the sexes (260 vs. 261 cells/mm³). Before starting ART, women had slightly lower HIV-1 viral loads, mean of 4.54 log₁₀ copies/mL in women compared to 4.74 log₁₀ copies/mL in men. Women were more likely to be black and men were more likely to be white. Finally, the proportion of women who enrolled to each trial varied: women represented 18% of participants in A5142, 17% in A5202, and 24% in A5257. Each of these observed differences between sexes is a typically observed difference within ART-naive study samples and does not represent novel or unanticipated differences.

BMI observed data

After 96 weeks, women had both larger absolute and relative changes in BMI than men (mean of 1.91 kg/m² vs. 1.39 kg/m² or mean increase of 7.65% vs. 5.92%). The mean observed difference in absolute BMI increases between women and men is 0.52 kg/m² (95% confidence interval [CI 0.29–0.75]); p for sex difference <0.001. Most of the weight change observed over 96 weeks occurred within the first year of follow-up: the magnitude of the change in BMI from baseline to week 48 (mean of 1.53 kg/m² or 6.2% for women vs. 1.15 kg/m² or 4.9% for men) was more than half of the magnitude of change from baseline to week 96.

Table 2 displays the observed mean change in BMI by pre-ART initiation BMI category (underweight, normal, overweight, and obese). The significant sex difference was seen within each pre-ART initiation BMI subgroup.

BMI modeling

In single characteristic modeling, we found that age, baseline CD4+ count, baseline HIV-1 viral load, race/ethnicity,
study, and study treatment group were each significantly associated with the absolute increase in BMI after 96 weeks of ART. After adjusting for these variables, mean BMI change for women was on average 0.59 kg/m² (95% CI 0.37–0.81) more than for men (p < 0.001) (Table 3).

Outcome of change to a worse BMI category

We defined change to a worse BMI category as the change in BMI category from underweight to overweight or obese, or from normal to overweight or obese, or change from overweight to obese in the first 96 weeks following the initiation of ART. While similar proportions of women and men moved to a worse BMI category (23.16% and 24.17%, respectively), we found that among participants moving to a worse BMI category, women gained more weight than men (mean absolute increase in BMI of 5.57 [95% CI 5.07–6.07] for women vs. 4.03 [95% CI 3.85–4.21] for men).

Statistical interactions between sex and baseline CD4+ count and HIV-1 viral load

We observed significant two-way statistical interactions between sex and each of pre-ART CD4+ count and HIV-1 viral load such that for subgroups with higher viral load and lower CD4+ count at baseline, the estimated BMI changes in women are even larger than the average estimated difference. Figure 1a and b illustrate the distribution of observed BMI changes.
changes over time by sex, and separately by baseline RNA subgroup and CD4 cell count subgroup. Figure 2 illustrates the statistical interactions by showing the estimated sex differences for absolute BMI change to week 96 at various baseline CD4+ and viral load levels. For instance, at CD4 cell count of 260 and HIV-1 viral load of 4.7 log10 copies/mL (i.e., at the observed means for these laboratory values within the study sample), the estimated sex difference was 0.62 kg/m², which was similar to the overall sex effect of 0.59 kg/m² estimated in the main effects only multivariable model. However, for those with more advanced HIV disease characteristics—for example, with CD4 cell count of 120 and HIV viral load of 5.2, women gain an excess of 1.12 kg/m² in BMI more than men over the 96-week follow-up period. For those with less advanced HIV disease characteristics, the estimated sex difference is smaller.

### Sensitivity analysis

A sensitivity analysis was performed among participants who were virologically suppressed at weeks 48 and 96. Overall, 3091 (81%) of 3801 participants were virologically suppressed at both week 48 and 96. This subgroup was representative of the entire BMI analysis sample. The mean observed difference in absolute BMI changes between women and men in this virologically suppressed subgroup was 0.52 kg/m² (95% CI 0.20–0.85).

### Subgroup analysis

A subgroup analysis was performed within the A5257 study to adjust for SES defined by highest education attained, binge alcohol drinking, illicit drug use, smoking status, and history of metabolic syndrome. Participants of the subgroup analysis comprised 43% of the overall BMI analysis and the observed BMI sex difference was 0.59 (95% CI 0.19–0.99) within this subgroup. Overall, the subgroup was fairly representative to the full sample, but differed in the following aspects: (1) type of ART (TDF/FTC + ATV/r was more commonly used than TDF/FTC + DRV/r and TDF/FTC + RAL); (2) higher baseline CD4 cell count and lower baseline HIV-1 viral load; (3) larger proportion of women (24%); and (4) more non-white participants (66%). Both the unadjusted and adjusted sex difference estimate for BMI was 0.59 kg/m² (for factors included in main effects model). Importantly, this difference in BMI changes by sex was not modified by SES, alcohol or illicit drug use, and metabolic syndrome.

A significant statistical interaction between smoking status and sex was observed (p = 0.03). Among non-smokers, the adjusted sex difference on BMI change to week 96 was estimated as 0.86 kg/m². This sex difference estimate was attenuated among both former smokers (0.52 kg/m²) and current smokers (−0.04 kg/m²). Current smokers of either sex (38% of participants) gained, on average, the smallest amount of any subgroup defined by sex and smoking status (observed data): there was a mean of 0.83 kg/m² weight gain among currently smoking men, and mean of 0.93 kg/m² weight gain among currently smoking women.

### Discussion/Conclusions

In this pooled analysis of 3801 individuals initiating ART in randomized clinical trials, we found that HIV-1-infected women experienced a significantly greater increase in BMI following ART initiation than men. This effect was independent of age and ART regimen, and remained after controlling for pre-ART CD4 count and HIV-1 viral load. A large part of the BMI increase occurred in the first 48 weeks following initiation of ART, and we found significant interactions between sex and baseline CD4+ count and HIV-1 viral load such that the estimated BMI increases in women with higher baseline viral loads and CD4+ counts were even greater. From subgroup analysis where additional characteristics were available, we found that the estimated sex difference was not modified by SES, alcohol or illicit drug use, or the metabolic syndrome, but current or former smoking status mitigated the estimated sex difference on BMI change.

Although similar proportions of women and men moved to a worse BMI category, we found that among participants moving to a worse BMI category, women gained more weight.
than men. Evaluating changes in both BMI category change and absolute BMI change by sex was an essential exercise because sex differences could have been missed or underestimated if either of these endpoints had been evaluated in isolation.

There are conflicting reports in the literature on the relationship between sex and changes in BMI following the initiation of ART. There is a need for understanding the underlying reason for the relationship between female sex and greater BMI gain. Each ART regimen was evaluated individually rather than by class (e.g., protease inhibitors [PIs] vs. non-PIs), given prior studies have not shown differences in body composition changes in PI-based regimens compared to non-PI-based regimens. The underlying reason for the relationship between female sex and greater BMI gain is not known, but deserves further exploration.

A state of chronic inflammation and immune activation has been described in HIV and immune activation has been shown to be most robust in those with low CD4+ counts and high HIV-1 viral loads, the subgroup in which we observed

![Graphs showing BMI changes by sex and subgroups](image-url)
the greatest difference in BMI changes. This effect is seen in both resource-rich and resource-poor settings.\textsuperscript{32} Adipose tissue is increasingly recognized as an important metabolically active tissue and a source of bioactive peptides that participate in inflammation and immunity. A complex interplay of factors mediated by nuclear factor kappa-light-chain-enhancer of activated B cell signaling results in disordered inflammatory regulation.\textsuperscript{33} Adipose tissue has been demonstrated to produce over 50 cytokines\textsuperscript{34} from adipocytes, macrophages, or other cells of the monocyte lineage.\textsuperscript{35} Adipocytes induce secretion of inflammatory cytokines, including those interleukins associated with increased mortality and noninfectious morbidities in HIV-infected individuals, such as interleukin-6.\textsuperscript{36,37} Leptin, a key proinflammatory adipokine, is associated with an inflammatory state in the setting of obesity and its synthesis is increased by female sex hormones.\textsuperscript{38} We hypothesize that different states of immune activation may underlie the sex difference in BMI gain that we observed in this study. Indeed, prior studies have found that several markers of immune activation are higher in HIV-infected women than in men,\textsuperscript{39} and some markers of inflammation have been associated with greater gains in fat after ART.\textsuperscript{40,41}

There are several limitations to our study that deserve consideration. One of the ART regimens used in one of the studies, lopinavir/ritonavir, is no longer in common use in the United States. Inclusion of participants randomized to lopinavir/ritonavir and efavirenz may be viewed as a limitation, but the overall results were similar in the A5257 subgroup analysis, and this study included only modern ART regimens. Although we did not have complete data on covariates such as tobacco use, alcohol/substance abuse, physical activity, diet, or SES, we were able to perform a subgroup analysis on A5257 participants to adjust for some of these important variables (SES as defined by highest education attained, alcohol and illicit drug use, smoking, and history of metabolic syndrome). We chose to use education level as a surrogate for SES because this is the only covariate that was available. We recognize that this analysis could have benefited from a more sensitive analysis of SES if additional indicators had been available. Given the randomized nature of the three studies, it is unlikely that the unmeasured covariates would have biased our estimates. Finally, since this was a post hoc analysis with multiple comparisons, marginally significant associations should be interpreted with caution.

One additional point to consider is that, although BMI has been used in many studies and is linked to outcomes such as diabetes and other metabolic diseases,\textsuperscript{42–44} the results must be interpreted with the understanding that BMI does not allow us to differentiate between fat and lean body mass. While BMI typically correlates with the proportion of total body fat, a normal BMI may represent excess adiposity in persons with low muscle mass. Women in general have lower total muscle mass than men and BMI may therefore underestimate the sex differences in changes in adiposity following the initiation of ART. In addition, current research suggests that the location and type of fat may be important in the inflammatory response and the resultant adverse outcomes. Visceral obesity has been implicated in cardiovascular morbidity\textsuperscript{45} and further work with this cohort will investigate sex differences in the changes in regional body fat distribution after ART.

In conclusion, we found that in the setting of randomized clinical trials, HIV-1-infected women experienced a significantly greater increase in BMI following ART initiation than men. The fact that these sex differences exist, among persons who are already overweight before starting ART, suggests a problem of clinical significance to women living with HIV. Future work will explore the impact of immune activation on the observed sex differences.

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Author Disclosure Statement
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