

WOMEN GAIN MORE WEIGHT THAN MEN FOLLOWING INITIATION OF ANTIRETROVIRAL THERAPY



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BACKGROUND

- Cross-sectional studies reveal a high prevalence of obesity among HIV-infected individuals.
- A number of studies have noted increases in weight gain after ART initiation with up to 20% of persons (or PLWH) moving into a deleterious BMI category within 2 years of ART initiation in one study.
- Short-term gains in body mass index [BMI] have been directly linked to increases in the long-term risk of both cardiovascular disease and diabetes.
- Three AIDS Clinical Trials Group [ACTG] U.S.-based randomized trials (A5142, A5202 and A5257) assessed changes in BMI in treatment-naïve individuals initiating ART and provide an opportunity to examine the relationship between sex and changes in BMI after randomized ART initiation with scientific rigor.

OBJECTIVE

- To evaluate whether BMI changes in the first 96 weeks following initiation of ART therapy differ by sex.
- Outcome to evaluate objective above:
 - Between sex differences in the absolute changes in BMI from baseline (time of ART initiation), to week 96, and percent of women obese/overweight/normal BMI before and after ART.

METHODS

- Retrospective, cross-protocol, pooled analysis using data captured under ACTG randomized clinical trials A5142, A5202, and A5257.
- Multivariable linear regression to evaluate the relationship between sex and change in BMI from baseline to 96 weeks.
- Models adjusted for the following demographic and clinical covariates: sex, age, race/ethnicity, baseline CD4+ cell count, baseline HIV RNA level, clinical trial, and ART regimen.
- Subgroup analysis was performed within the A5257 study in order to adjust for additional potentially prognostic baseline covariates available only within this one clinical trial, including socio-economic status (SES), alcohol and illicit drug use, smoking, and history of metabolic syndrome.
- Note: Sex analyzed as sex at birth (transgender persons excluded). To be included in the analysis participants needed to a) start ART, b) have observed BMI assessment just prior to ART initiation (baseline) and at their week 96 study assessment, c) be enrolled in the United States, d) not become pregnant before BMI assessment at 96 weeks (for women only).

RESULTS

Table 1: Baseline characteristics	Women (n=760)	Men (n=3041)	Total (n=3801)	p-value
Age (years), mean	40.5	37.7	38.3	<0.001
Body Mass Index (kg/m ²), mean	28.4	25.2	25.9	<0.001
BMI category				<0.001
Underweight (< 18.5 kg/m ²)	37 (5%)	89 (3%)	126 (3%)	
Normal (18.5 – 24.9 kg/m ²)	245 (32%)	1557 (51%)	1802 (47%)	
Overweight (25.0 – 29.9 kg/m ²)	223 (29%)	1007 (33%)	1230 (32%)	
Obese (>= 30.0 kg/m ²)	255 (34%)	388 (13%)	643 (17%)	
Race/ethnicity				<0.001
White, non-Hispanic	127 (17%)	1320 (43%)	1447 (38%)	
Black, non-Hispanic	439 (58%)	951 (31%)	1390 (37%)	
Hispanic	180 (24%)	669 (22%)	849 (22%)	
Other (including missing/unknown)	14 (2%)	101 (3%)	115 (3%)	
CD4+ cell count (mm ³), mean	260.2	261.2	261.0	0.9
Plasma HIV-1 viral load (log ₁₀ copies/mL), mean	4.54	4.74	4.70	<0.001
Randomized clinical trial source (enrollment and 96 week follow-up) [ART regimens]				<0.001
ACTG A5142 (Jan 2003 – Feb 2006) [EFV+NRTIs vs. LPV/r+NRTIs vs. EFV+LPV/r]	104 (14%)	465 (15%)	569 (15%)	
ACTG A5202 (Sep 2005 – Sep 2009) [EFV vs. ATV/r + ABC/3TC vs. TDF/FTC]	267 (35%)	1325 (44%)	1592 (42%)	
ACTG A5257 (May 2009 – June 2013) [TDF/FTC + ATV/r vs. TDF/FTC + DRV/r vs. TDF/FTC + RAL]	389 (51%)	1251 (41%)	1640 (43%)	

RESULTS

Table 2: Mean Body Mass Index (BMI in kg/m²) change

	n (%)	Women (n=760)	Men (n=3041)	Sex difference	p-value (t-test)
Overall Observed (i.e. unadjusted)					
Thru week 48	3801 (100%)	1.53	1.15	0.38	0.002
Thru week 96	3801 (100%)	1.91	1.39	0.52	<0.001
Overall Model-based (i.e. adjusted) thru week 96				0.59	<0.001
Observed By Pre-ART Initiation BMI Category, thru week 96					
Underweight (< 18.5)	126 (3%)	3.51	2.12	1.4	0.016
Normal (18.5 – 25)	1802 (47%)	2.37	1.68	0.69	0.003
Overweight (25 – 30)	1230 (32%)	1.71	1.04	0.67	<0.001
Obese (≥ 30)	643 (17%)	1.42	0.99	0.43	<0.001

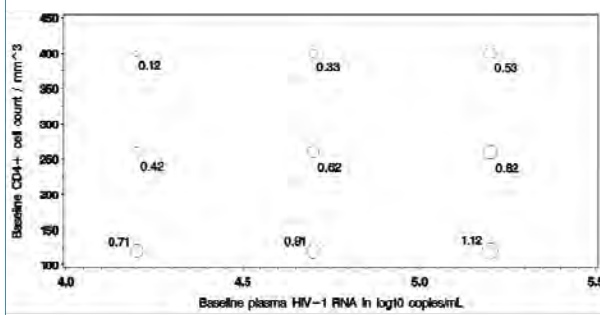
Table 3a. BMI Category Change for Women

BMI category for women (with row %)	After 96 weeks follow-up (columns)			
@ baseline (rows)	Underweight	Normal	Overweight	Obese
Underweight	9 (24%)	23 (62%)	5 (14%)	0 (0%)
Normal	4 (2%)	142 (58%)	81 (33%)	18 (7%)
Overweight	0 (0%)	31 (14%)	120 (54%)	72 (32%)
Obese	0 (0%)	2 (1%)	18 (7%)	235 (92%)

Table 3b. BMI Category Change for Men

BMI category for women (with row %)	After 96 weeks follow-up (columns)			
@ baseline (rows)	Underweight	Normal	Overweight	Obese
Underweight	30 (34%)	58 (65%)	1 (1%)	0 (0%)
Normal	14 (1%)	1033 (66%)	469 (30%)	41 (3%)
Overweight	0 (0%)	112 (11%)	671 (67%)	224 (22%)
Obese	0 (0%)	2 (<1%)	53 (14%)	333 (86%)

Figure 1: Model-based estimates of sex difference (women - men) in BMI changes to week 96 (in kg/m²), at various different CD4 cell counts and plasma HIV-1 viral loads



RESULTS

- Subgroup analysis was performed within the A5257 study in order to adjust for socio-economic status (SES) as defined by highest education attained, alcohol and illicit drug use, smoking, and history of metabolic syndrome.
- Characteristics of subgroup analysis:
 - Participants included comprised 43% of the overall BMI analysis
 - Overall BMI sex effect was similar to the full analysis
 - Subgroup overall representative to the full sample but differed in the following aspects:
 - Type of ART (TDF/FTC + ATV/r vs. TDF/FTC + DRV/r vs. TDF/FTC + RAL)
 - Higher baseline CD4 cell count and lower baseline HIV RNA
 - Larger proportion of women (24%)
 - More non-white participants (66%)
- Both the unadjusted and adjusted (for factors including in main analysis model) sex difference estimate for BMI changes to week 96 was 0.59 kg/m².
- Difference in BMI changes by sex was not modified by SES, alcohol or illicit drug use, or metabolic syndrome.
- A statistically significant 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 (women - men). 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) on average gained the smallest amount of any subgroup defined by sex and smoking status (observed data): mean of 0.83 kg/m² among currently smoking men, and mean of 0.93 kg/m² among currently smoking women.

DISCUSSION

- 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.
- The largest magnitude of the increase in BMI over 96 weeks occurred in the first 48 weeks following initiation of ART.
- We also found significant interactions between sex and both baseline CD4+ count and HIV-1 RNA such that the estimated BMI changes in women with higher baseline viral loads and CD4+ counts are even greater.
- After performing a subgroup analysis, 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 significantly obliterated or attenuated the estimated sex difference on BMI change.
- 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 RNA levels, the subgroup in which we observed the greatest difference in BMI changes.
- We hypothesize that different states of immune activation may underlie the sex difference in BMI gain which we observed in this study.

CONCLUSIONS AND FUTURE DIRECTIONS

- After adjustment for HIV disease activity, HIV-1 infected women experienced a significantly greater increase in BMI following ART initiation than men.
- The fact that these sex differences exist, even in women in the obese BMI category at baseline, suggests a problem of real clinical significance to women living with HIV.
- Future work will evaluate sex differences in changes in body composition as measured by DXA following the initiation of ART.
- We also plan to explore the impact of immune activation on the observed sex differences in BMI change.

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