Poster 695

Predictors of Severe Weight/Body Mass Index Gain Following Antiretroviral Initiation

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ABSTRACT

Background: Excessive weight gain following antiretroviral therapy (ART) is common and may predispose individuals to HIV-associated metabolic syndrome, sometimes leading to ART discontinuation and/or poor adherence. The objective of this study is to understand predictors of severe weight/body mass index (BMI) gain in individuals initiating ART.

Methods: This was a retrospective analysis of the ACTG A5257 study, where ART-naïve HIV-infected individuals were randomized to one of 3 regimens: atazanavir/ritonavir (ATV/r), darunavir/ritonavir (DRV/r), or raltegravir (RAL) each in combination with tenofovir disoproxil fumarate/emtricitabine. Severe weight/BMI gain outcomes over 96 weeks were defined two ways: (1) percent weight increase ≥ 10%; (2) an upward change in BMI category. Among those underweight at baseline, only those who were overweight or higher at follow-up were included in both outcomes. Logistic regression was used to examine the association between participant characteristics and severe weight/BMI gain.

Results: The study population (N=1,809) was 76% male, largely black non-Hispanic (41.9%) and white non-Hispanic (34.1%), with a mean baseline weight of 79 kg and BMI of 26 kg/m^2. Over 96 weeks, the average weight increased by 3.8 kg and BMI by 1.3 kg/m^2. Those with severe weight gain had a mean increase of 14.9 kg (N=373), and those with severe BMI gain had a mean increase of 4.4 kg/m^2 (N=361). The odds of severe weight gain were 1.55 times higher for black non-Hispanic compared to white non-Hispanic individuals (95% CI: 1.10 to 2.20; p=0.013). The odds of severe weight gain were 2.52 times higher for every 1 log (10-fold) higher in baseline HIV-1 RNA (95% CI: 2.00 to 3.16; p<0.0001), and 1.28 times higher for every 100 cell/mm^3 lower in baseline CD4+ count (95% CI: 1.18 to 1.39; p<0.0001). Results were similar for severe BMI. Results also suggested that treatment with protease inhibitors vs RAL may be protective against severe weight/BMI gain. The odds of severe weight gain were significantly lower for ATV/r vs RAL (OR: 0.72 [95% CI: 0.53 to 0.99]; p=0.043), while odds of severe BMI gain were significantly lower for DRV/r vs RAL (OR: 0.73 [95% CI: 0.53 to 0.99]; p=0.041).

Conclusions: Predictors of severe weight/BMI gain in this population included black race, higher baseline disease severity, and use of RAL. Understanding factors predisposing individuals to unhealthy weight gain may help better manage metabolic complications of HIV.

BACKGROUND

- Overweight/obesity has manifested itself as an important health issue in the HIV-infected population.[1]
- While wasting was more commonly associated with HIV infection earlier in the epidemic, the prevalence of overweight/obesity has been increasing and becoming closer to that of the general population.[1-3]
- Weight gain has been found to be associated with a higher risk of CVD and diabetes after ART initiation depending on baseline BMI.[4,5]
- Severe weight gain has been shown to occur for some individuals after ART initiation, shifting them into higher BMI categories.[3,6]

OBJECTIVE

In HIV-infected, ART-naïve participants from the A5257 study, we examine potential demographic and clinical risk factors associated with severe weight/BMI gain after therapy initiation.

METHODS

Study Design

- This retrospective cohort study was conducted using data from the AIDS Clinical Trials Group (ACTG) A5257 clinical trial.
- A5257 was a phase III randomized clinical trial comparing the virologic efficacy and tolerability of three non-nucleoside reverse transcriptase inhibitor (NNRTI) sparing antiretroviral regimens comprised of Tenofovir Disoproxil Fumarate/Emtricitabine (TDF/FTC) plus Atazanavir/Ritonavir (ATV/r), Darunavir/Ritonavir (DRV/r), or Raltegravir (RAL).
- Participants were excluded if they had diabetes mellitus, known CVD, untreated hypothyroidism/hyperthyroidism, or were using statins or other hypolipemic agents.
- 1,809 participants were included in the study sample.

Study Data

- Demographic data used for these analyses included race/ethnicity, sex, and age at entry.
- Baseline laboratory values included CD4+ (in 100 cells/mm^3) and HIV-1 RNA count (in log$_{10}$ copies/mL)
- Weight (in kg) and BMI (in kg/m^2) were collected at study entry and week 96.
- Confounding variables collected at study entry included smoking, drinking, illicit drug use, income status, and insurance status.

- *Definition of Outcomes*:
  1) **Severe weight gain**: ≥ 10% increase in weight over 96 weeks for those with at least normal baseline BMI (18.5-24.9 kg/m^2). Individuals who were underweight (BMI < 18.5 kg/m^2) at baseline and became overweight (25.0-29.9 kg/m^2) or higher at follow-up with a weight increase ≥ 10% were also included.
  2) **Severe BMI gain**: Increase of one or more BMI categories over 96 weeks for those with at least normal baseline BMI. Individuals who were underweight at baseline and became overweight or higher at follow-up were also included.

Statistical Analysis

- Logistic regression modeling was used to examine predictors of both severe weight/BMI increases via univariate models examining individual associations and multivariable models including all predictors adjusting for potential confounding.
- In addition to a complete case analysis, multiple imputation analyses using the fully conditional specification approach were conducted to account for missing covariate data
- Receiver operating characteristic (ROC) curves were used to compare the predictive accuracy of the various models.

RESULTS

Population characteristics

- Participants were predominantly male (76%) and black non-Hispanic (41.9%), with age ranging from 18 to 76 years and averaging 37 years (Table 1).
- The study population had a mean baseline weight of 79 kg and baseline BMI of 26 kg/m^2.
- The distribution of clinical BMI categories at baseline was **3.4% underweight** (BMI < 18.5 kg/m^2), **47.1% normal** (BMI 18.5-24.9 kg/m^2), **30.5% overweight** (BMI 25-29.9 kg/m^2), **15.8% obese** (BMI 30-39.9 kg/m^2), **2.8% morbid obese** (BMI 40-49.9 kg/m^2), and **0.4% super obese** (BMI ≥ 50 kg/m^2).
- On average over 96 weeks, weight increased for the study population by 3.8 kg and BMI increased by 1.3 kg/m^2, with the prevalence of overweight/obesity increasing to **35.5% overweight**, **19.6% obese**, **3.6% morbid obese**, and **1.1% super obese**.

Table 1. Demographic and baseline characteristics of A5257 study population

Baseline Characteristics	A5257 (*N = 1,809*)
Sex [N (%)]	
Male	1,374 (76%)
Female	435 (24%)
Race [N (%)]	
White non-Hispanic	615 (34%)
Black non-Hispanic	757 (42%)
Hispanic	390 (22%)
Other	43 (2%)
Baseline BMI (kg/m^2) [N (%)]	
<18.5	61 (3%)
18.5-24.9	852 (47%)
25-29.9	552 (31%)
≥30.0	344 (19%)
Baseline Weight (kg) [Mean (SD)]	78.6 (18.4)
Baseline BMI (kg/m^2) [Mean (SD)]	26.1 (5.9)
Age (years) [Mean (SD)]	37 (11)
Baseline HIV-1 RNA (log$_{10}$ copies/mL) [Mean (SD)]	4.6 (0.7)
Baseline CD4+ (100 cells/mm^3) [Mean (SD)]	3.1 (1.9)

Table 2. Demographic and baseline characteristics of A5257 study population across severe weight/BMI outcomes

Characteristics	Severe Increase in Weight		Severe Increase in BMI	
	Yes	No	Yes	No
Overall [N(%)]	373 (23.3)	1227 (76.7)	361 (22.7)	1231 (77.3)
Treatment [N(%)]				
ATV/r	114 (21.6)	415 (78.4)	117 (22.3)	408 (77.7)
RAL	144 (26.5)	399 (73.5)	136 (25.1)	405 (74.9)
DRV/r	115 (21.8)	413 (78.2)	108 (20.5)	418 (79.5)
Sex [N(%)]				
Male	269 (22.1)	947 (77.9)	260 (21.4)	953 (78.6)
Female	104 (27.1)	280 (72.9)	101 (26.7)	278 (73.3)
Race/Ethnicity [N(%)]				
White non-Hispanic	98 (17.9)	450 (82.1)	94 (17.2)	453 (82.8)
Black non-Hispanic	178 (26.9)	484 (73.1)	163 (24.9)	492 (75.1)
Hispanic	90 (26.0)	256 (74.0)	99 (28.6)	247 (71.4)
Other	5 (12.2)	36 (87.8)	4 (9.8)	37 (90.2)
HIV-1 RNA Level [N(%)]				
< 100,000 copies/mL	154 (13.9)	952 (86.1)	177 (16.1)	921 (83.9)
≥ 100,000 copies/mL	219 (44.3)	275 (55.7)	184 (37.2)	310 (62.8)
CD4+ Level [N(%)]				
≥ 350 cells/mm^3	86 (13.1)	569 (86.9)	97 (14.9)	555 (85.1)
< 350 cells/mm^3	287 (30.4)	658 (69.6)	264 (28.1)	676 (71.9)
HIV-1 RNA Level (log$_{10}$ copies/mL) [Mean (SD, range)]	5.1 (0.7, 3.1-6.6)	4.5 (0.7, 2.4-6.3)	4.9 (0.7, 2.8-6.6)	4.5 (0.7, 2.4-6.3)
CD4+ Level (cells/mm^3) [Mean (SD, range)]	198 (181, 3-889)	340 (183, 2-1610)	216 (182, 3-795)	333 (187, 2-1610)
Age (years) [Mean (SD, range)]	39 (11, 18-76)	38 (11, 18-72)	39 (11, 18-76)	37 (11, 18-74)
BMI (kg/m^2) [Mean (SD, range)]	25.2 (5.6, 15.6-64.2)	26.5 (6.0, 15.2-61.5)	26.2 (5.5, 15.6-49.7)	26.0 (5.6, 15.2-49.7)
Weight (kg) [Mean (SD, range)]	75.5 (17.6, 42.5-169.6)	79.8 (18.7, 37.6-194.5)	78.2 (17.3, 42.5-163.7)	78.4 (17.8, 37.6-163.7)

Table 3. Crude and adjusted logistic regression models predicting severe weight increase from week 0 to week 96 in the ACTG A5257 study population

	Crude		Adjusted			
			Complete Case Analysis		Imputed Data Analysis	
Covariate	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value
Treatment						
RAL	--	--	--	--	--	--
ATV/r	0.76 (0.57, 1.01)	0.0574	0.77 (0.54, 1.12)	0.1751	0.72 (0.53, 0.99)	0.0427
DRV/r	0.77 (0.58, 1.02)	0.0705	0.81 (0.56, 1.17)	0.2512	0.74 (0.54, 1.01)	0.0555
Sex						
Males	--	--	--	--	--	--
Females	1.31 (1.01, 1.70)	0.0454	1.24 (0.84, 1.83)	0.2876	1.35 (0.97, 1.89)	0.0742
Race/Ethnicity						
White Non-Hispanic	--	--	--	--	--	--
Black Non-Hispanic	1.69 (1.28, 2.23)	0.0002	1.74 (1.17, 2.58)	0.0058	1.55 (1.10, 2.20)	0.0129
Hispanic	1.61 (1.17, 2.23)	0.0038	1.13 (0.71, 1.79)	0.6034	0.99 (0.67, 1.48)	0.9757
Other	0.64 (0.24, 1.67)	0.3588	0.78 (0.27, 2.32)	0.6593	0.50 (0.17, 1.45)	0.2021
Age (years)	1.01 (0.998, 1.02)	0.1252	1.01 (0.996, 1.03)	0.1597	1.01 (0.99, 1.02)	0.2859
Baseline BMI (kg/m^2)	0.96 (0.94, 0.98)	0.0004	0.99 (0.96, 1.02)	0.5408	0.98 (0.96, 1.01)	0.1767
Baseline HIV-1 RNA (log$_{10}$ copies/mL)	3.45 (2.84, 4.19)	<.0001	2.89 (2.20, 3.80)	<.0001	2.52 (2.00, 3.16)	<.0001
Baseline CD4+ (100 cells/mm^3)	0.62 (0.58, 0.67)	<.0001	0.80 (0.73, 0.89)	<.0001	0.78 (0.72, 0.85)	<.0001

Table 4. Crude and adjusted logistic regression models predicting severe BMI increase from week 0 to week 96 in the ACTG A5257 study population

	Crude		Adjusted			
			Complete Case Analysis		Imputed Data Analysis	
Covariate	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value
Treatment						
RAL	--	--	--	--	--	--
ATV/r	0.85 (0.64, 1.13)	0.2739	0.91 (0.64, 1.30)	0.6156	0.83 (0.62, 1.13)	0.2381
DRV/r	0.77 (0.58, 1.03)	0.0737	0.78 (0.54, 1.12)	0.1745	0.73 (0.53, 0.99)	0.0414
Sex						
Males	--	--	--	--	--	--
Females	1.33 (1.02, 1.74)	0.0347	1.11 (0.76, 1.62)	0.5779	1.14 (0.83, 1.58)	0.4085
Race/Ethnicity						
White Non-Hispanic	--	--	--	--	--	--
Black Non-Hispanic	1.60 (1.20, 2.12)	0.0012	1.56 (1.07, 2.29)	0.0218	1.48 (1.06, 2.08)	0.0217
Hispanic	1.93 (1.40, 2.67)	<.0001	1.44 (0.93, 2.23)	0.1011	1.44 (0.99, 2.10)	0.0555
Other	0.52 (0.18, 1.50)	0.2260	0.68 (0.22, 2.10)	0.5050	0.48 (0.16, 1.43)	0.1851
Age (years)	1.01 (0.999, 1.02)	0.0653	1.01 (0.99, 1.02)	0.3956	1.01 (0.995, 1.02)	0.2407
Baseline BMI (kg/m^2)	1.01 (0.99, 1.03)	0.5888	1.04 (1.01, 1.07)	0.0106	1.03 (1.00, 1.05)	0.0375
Baseline HIV-1 RNA (log$_{10}$ copies/mL)	2.32 (1.94, 2.77)	<.0001	2.11 (1.64, 2.73)	<.0001	1.79 (1.44, 2.22)	<.0001
Baseline CD4+ (100 cells/mm^3)	0.69 (0.64, 0.74)	<.0001	0.83 (0.76, 0.92)	0.0002	0.79 (0.73, 0.86)	<.0001

Figure 1. ROC curve from complete case analysis predicting severe weight gain

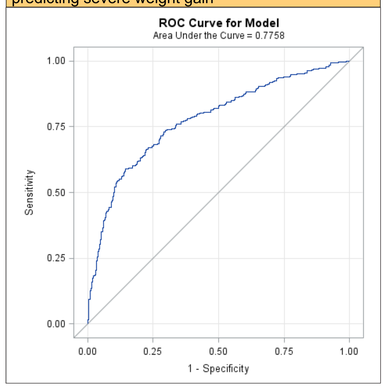
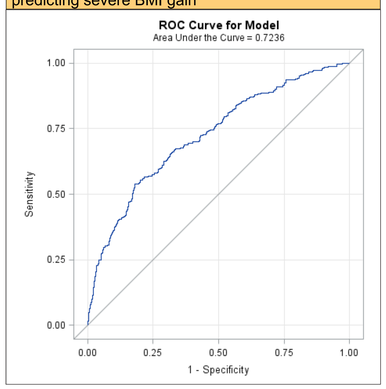


Figure 2. ROC curve from complete case analysis predicting severe BMI gain



RESULTS (Continued)

Severe Weight Gain

- The following significant associations were found in the final imputed data model (Table 3):
  - For every factor of 10 increase in baseline HIV-1 RNA level, the odds of severe weight gain were 2.52 times higher (95% CI: 2.00 to 3.16; p<0.0001).
  - Every additional 100 cell/mm^3 of baseline CD4+ count was associated with a 0.78 times lower odds of severe weight gain (95% CI: 0.72 to 0.85; p<0.0001).
  - The odds of a severe weight increase are 1.55 times higher for black compared to white individuals (95% CI: 1.10 to 2.20; p=0.0129).
- ATV/r was associated with a lower odds of severe weight gain compared to RAL (OR: 0.72; 95% CI: 0.53 to 0.99; p=0.0427). The results for DRV/r versus RAL were similar but not statistically significant (OR: 0.74; 95% CI: 0.54 to 1.01; p=0.0555).
- The area under the curve (AUC) value for the complete case analysis was 0.78. The results of the imputation analysis were consistent with the complete case analysis (Figure 1).

Severe BMI gain

- Results from the severe BMI models were similar to the weight gain outcome, showing associations of baseline disease severity and black non-Hispanic race/ethnicity with severe BMI gain over 96 weeks (Table 4). In addition, baseline BMI was also found to be associated with severe BMI gain.
- The odds of a severe BMI gain with DRV/r treatment was 0.73 times lower than the odds with RAL treatment (95% CI: 0.53 to 0.99; p=0.0414). ATV/r was also associated with a lower odds of severe BMI gain compared to RAL, but was not statistically significant.
- The AUC value for the complete case analysis was 0.72. The results of the imputation analysis were consistent with the complete case analysis (Figure 2).

DISCUSSION

- The ROC curves revealed that multivariable models for both severe weight and BMI outcomes had similar AUC values and reasonable predictive accuracy.
- Our study demonstrates that higher HIV-RNA levels and lower CD4+ levels appear to be strongly associated with severe increases in both BMI and weight.
- Black non-Hispanic individuals compared to white non-Hispanic individuals may have a higher odds of weight gain after therapy initiation.
- Treatment with the protease inhibitors ATV/r and DRV/r may be associated with less severe weight/BMI increases compared to treatment with the integrase inhibitor RAL.

- *Limitations*
  - 11.6% of participants in the A5257 study did not have weight/BMI follow-up measurements, however, these individuals were relatively similar concerning baseline/demographic characteristics compared to those with follow-up measurements.
  - Results may not be generalizable to the broader HIV-infected population due to the restrictive inclusion and exclusion criteria of the randomized controlled trial.

- *Strengths*
  - This study was conducted using prospectively collected clinical trial data.
  - We were able to examine associations between pre-treatment risk factors and post-ART weight/BMI gains.
  - The study had a large sample size, with a racially and ethnically diverse population of both males and females, which allowed us to examine several predictors of severe weight gain.

CONCLUSION

- Findings from this longitudinal study indicate that increased HIV disease severity before therapy initiation may be associated with severe increases in weight/BMI, suggesting that early treatment may prevent weight gain.
- In addition, certain race/ethnicity minority groups may have a proclivity for weight increases, manifesting a need for additional focus on investigating such complications in these groups.
- Understanding patient characteristics linked with extreme weight increases may help clinicians optimize treatment approaches to prevent such adverse changes in health.

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