

FAT GAINS OCCUR AFTER ART WITHOUT CHANGES IN METABOLIC RATE OR CALORIC INTAKE

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ABSTRACT

Background: Increases in weight and fat gains with antiretroviral treatment (ART) are serious problems in people with HIV (PWH), but the pathogenesis is poorly understood. Some have suggested changes in resting metabolic rate (RMR) and/or caloric intake are responsible, but no data exists. We examined changes in RMR, oxygen consumption (V_{O2}), and dietary intake and associations with changes in weight and body composition after ART initiation.

Methods: ART-naïve PWH were prospectively enrolled and underwent a comprehensive clinical and laboratory assessment at baseline and at 6 and 12 months after ART initiation. Fasting RMR/V_{O2} and body composition were measured by indirect calorimetry and whole-body DXA, resp. Nutrient intake was assessed by a registered dietician via 24-hour dietary recalls x3 at each time point and analyzed using dietary analysis software. Changes in variables and associations were assessed using linear mixed effects models.

Results: 30 PWH were enrolled (mean age: 31 yrs, 77% male, 74% black; mean baseline CD4 444 cells/mm³; HIV RNA 267,148 copies/mL, BMI 28.6 kg/m², RMR 1420 kcal/day, V_{O2} 205 mL/min, 1690 total kcal average daily intake). All but 1 initiated an integrase inhibitor-based regimen (53% DTG, 37% TAF). By 6 and 12 months, all but 3 and 1 participant, respectively, had an HIV RNA <200 copies/mL. At both time points, there was a significant increase in mean weight, total fat and trunk fat (6 mo/12 mo: +3.8/+10.2 kg, +2.4/+4.6 kg, +1.6/+3.4 kg, resp; all P<0.05), but a nonsignificant increase in total lean body mass (+1.7/+2.7 kg, P=0.09/0.71). Over the study period, there were no significant changes in RMR, V_{O2} or dietary intake (kcal, total fat, saturated fat, fiber, protein, total sugars, fructose, branched-chain amino acids, or arginine) (all P>0.70). All body composition changes were significant after adjusting for sex, baseline HIV RNA and RMR (or V_{O2}) at both time points except for lean body mass at 12 months.

Conclusions: Significant increases in weight and fat gains were seen after ART initiation, despite a lack of significant changes in RMR, V_{O2} or diet. All body composition changes except for lean body mass at 12 months were significant after adjusting for RMR or V_{O2}. These data do not support the hypothesis that changes in RMR or caloric intake are responsible for increases in weight and fat gains after ART initiation in PWH.

BACKGROUND

- Weight gain and fat accumulation (particularly visceral and ectopic fat) occur frequently after antiretroviral therapy (ART) initiation in people with HIV (PWH) and is a substantial threat to the success of modern treatment; however, the etiology is poorly understood.
- Researchers have hypothesized that changes in metabolic demands, energy requirements and/or dietary intake that occur after ART initiation may be responsible for this phenomenon.
- Support for this comes from a study published early in the HIV epidemic showing a correlation between HIV RNA and resting energy expenditure.
- Resting energy expenditure (aka resting metabolic rate (RMR)) is a highly accurate, non-invasive metabolic assessment to evaluate a person's daily calorie (i.e. energy) requirements in order to maintain basic body functions while in a state of rest.
- To date, however, resting energy expenditure (commonly referred to as resting metabolic rate (RMR)) has not been investigated in PWH before and after ART initiation.

OBJECTIVES

- To assess changes in body composition after ART initiation
- To assess metabolic rate in PWH prior to ART and changes in metabolic rate after ART initiation
- To assess dietary intake in PWH prior to ART and changes in dietary intake after ART initiation
- To determine if changes in body composition after ART initiation are related to changes in metabolic rate and/or dietary intake

METHODS

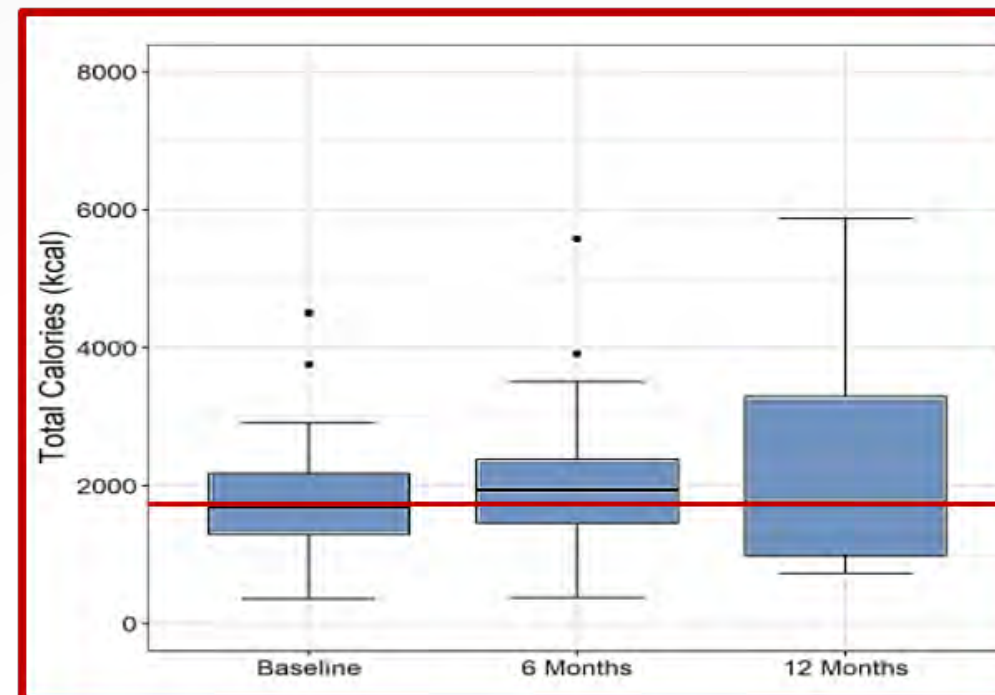
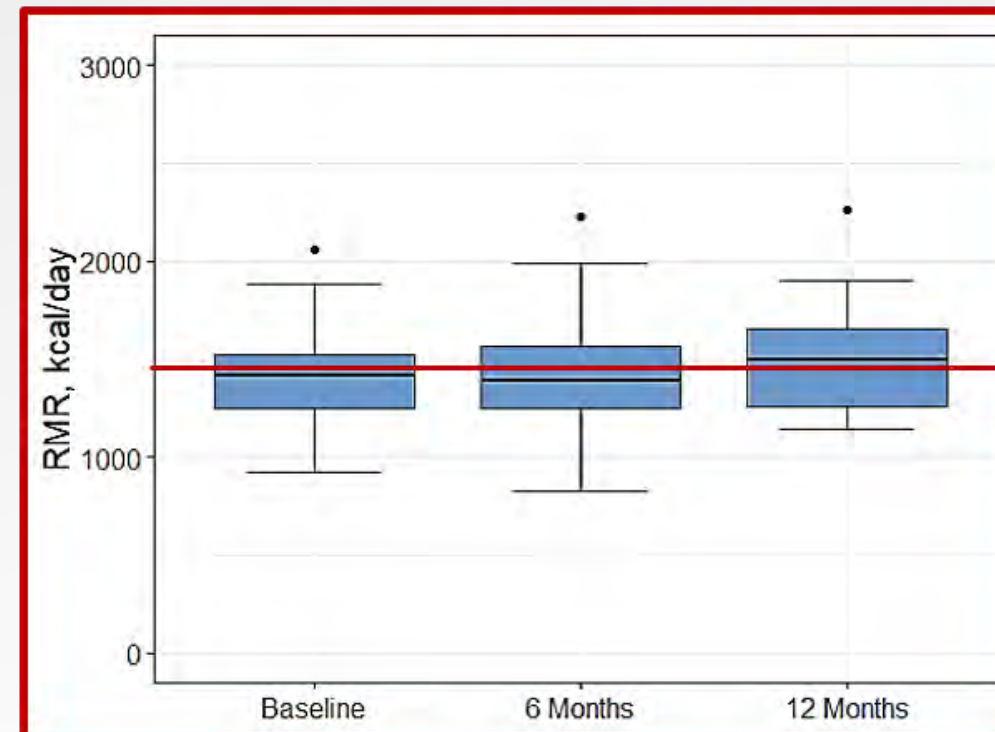
- STUDY DESIGN / STUDY POPULATION**
 - Prospective, observational, single-site (Cleveland) cohort study in which ART-naïve PWH were enrolled pre-treatment and followed longitudinally after ART initiation.
 - Participants were assessed at baseline (prior to ART treatment) and at 6 and 12 months after ART initiation.
- STUDY ASSESSMENTS**
 - Clinical and Laboratory Evaluation:** height, weight, HIV RNA, CD4
 - Metabolic Rate:** oxygen consumption (V_{O2}) was measured in a resting state via indirect calorimetry to generate a RMR (following ≥12-hr fast and ≥20 min rest).
 - Body Composition:** whole-body dual-energy absorptiometry (DXA) was used to measure total body fat, trunk fat, and lean body mass.
 - Dietary intake:** dietitians assessed dietary intake via 24-hour food recalls (average of 3 at each time point), and data were then analyzed using dietary analysis software.
- STATISTICAL ANALYSIS**
 - Appropriate two-sample and three-sample tests were used to assess changes over time.
 - Linear mixed-effects multilevel regression models were used to assess variables associated with changes in outcomes measures.
 - P<0.05 considered significant for all analyses.

RESULTS

Pre-Treatment Cohort Characteristics (N=30)	
Sociodemographics	
Age, years	27.8 (21.7, 38.7)
Male sex	23 (77%)
Cisgender male	22 (73%)
Black race	22 (73%)
Hispanic ethnicity	2 (6.7%)
Current smoking	11 (37%)
Current alcohol use	22 (73%)
Clinical Data	
BMI, kg/m ²	24.7 (20.9, 35.8)
BMI categories	
Underweight (<18.5, kg/m ²)	1 (3.3%)
Normal (≥18.5–<25, kg/m ²)	16 (53.3%)
Overweight (≥25–<30, kg/m ²)	3 (10%)
Obese (≥30, kg/m ²)	10 (33.3%)
HIV Variables	
HIV duration, months	1.9 (1.3, 3.8)
CD4+ cell count, cells/mm ³	415 (274, 578)
CD4+ <200 cells/mm ³	3 (10%)
HIV RNA, copies/mL	79,503 (27,294, 277,942)
HIV RNA >100k copies/mL	12 (40%)
Treatment	
Integrase inhibitor	28 (93%)
Dolutegravir	16 (53%)
Elvitegravir	8 (27%)
Bictegravir	4 (13%)
Tenofovir alafenamide	12 (40%)

N.B. Variables shown as median (Q1, Q3) or no. (%)

Changes in Metabolic Rate and Caloric Intake Over Study Period



RESULTS

Changes in Variables Over Study Period

Variable*	Baseline (N=30)	6 months (N=29)	12 months (N=23)	P
HIV Variables				
CD4 cell count, cells/mm ³	415 (280, 578)	567 (388, 799)	639 (487, 852)	0.007
HIV <400 copies/mL	0 (0%)	26 (90%)	22 (96%)†	<0.001
Metabolic Rate				
V _{O2} , mL/min	205 (181, 220)	198 (181, 226)	216 (181, 237)	0.657
RMR, kcal/day	1,420 (1,250, 1,520)	1,387 (1,253, 1,563)	1,500 (1,260, 1,650)	0.675
Dietary Intake				
Total calories (kcal)	1,690 (1,295, 2,172)	1,933 (1,454, 2,378)	1,755 (985, 3,293)	0.938
Total fat, g	65.2 (51.6, 98.1)	71.0 (52.7, 103.4)	78.3 (39.0, 152.9)	0.887
Saturated fat, g	20.8 (17.1, 29.1)	21.2 (14.7, 32.9)	23.6 (11.4, 47.7)	0.974
Total sugar, g	87.4 (52.1, 125.9)	78.3 (54.6, 133.9)	76.2 (52.7, 129.7)	0.985
Fructose, g	22.8 (11.6, 32.5)	19.5 (11.8, 26.9)	20.8 (7.9, 26.8)	0.917
Protein, g	60.2 (48.0, 85.9)	63.0 (45.2, 92.8)	83.8 (40.3, 104.2)	0.891
Fiber, g	10.2 (8.7, 15.3)	11.9 (6.0, 17.4)	13.2 (5.2, 27.5)	0.755
Branched-chain amino acids				
Isoleucine, g	2.7 (2.0, 3.9)	2.8 (2.0, 4.0)	3.2 (1.8, 4.8)	0.940
Leucine, g	4.7 (3.6, 6.6)	4.7 (3.3, 7.1)	5.8 (3.1, 8.0)	0.952
Valine, g	3.1 (2.3, 4.3)	3.1 (2.2, 4.5)	3.6 (2.0, 5.2)	0.945
Arginine, g	3.4 (2.6, 4.6)	3.6 (2.4, 4.9)	4.7 (1.9, 6.3)	0.898

*Median (Q1, Q3) or no. (%); †1 missing. N.B. P values <0.05 are bold-faced. There were no differences in variables based on treatment: TAF vs. no TAF or DTG vs. no DTG.

Variables Associated with Changes in Body Composition

Trunk Fat†			
Variable	Coef.	SE	P
Changes to 6 mo.	1.92	0.60	0.001
Changes to 12 mo.	2.68	0.66	<0.001
Female sex	11.74	3.74	0.002
Baseline RMR	0.02	<0.01	0.001

Baseline HIV RNA included in model but was not significant.

*Models for weight and total fat were qualitatively similar to trunk fat except female sex was not significant for changes in weight.

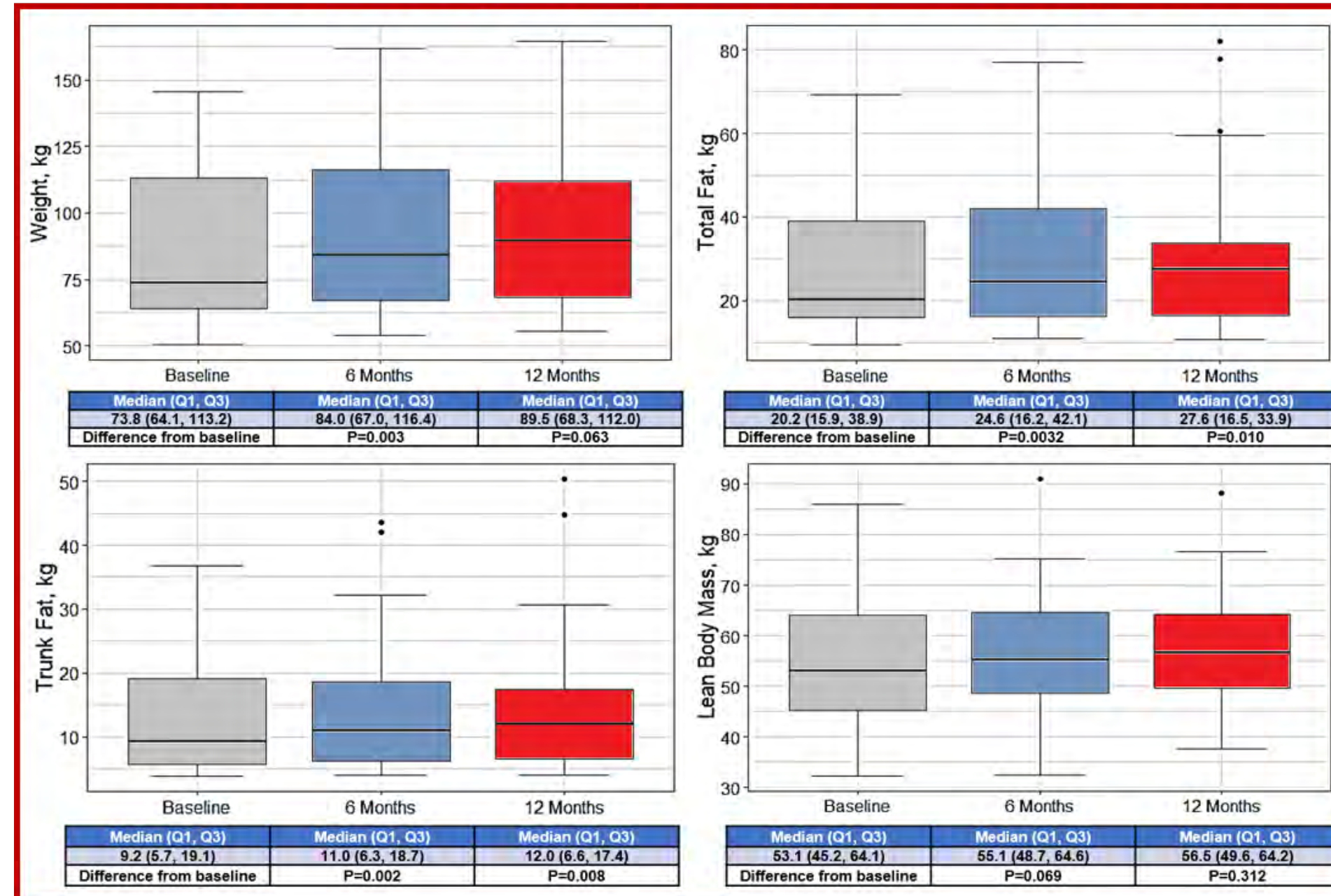
Lean Body Mass			
Variable	Coef.	SE	P
Changes to 6 mo.	1.32	0.66	0.045
Changes to 12 mo.	0.93	0.73	0.204
Baseline RMR	0.03	<0.01	<0.001

Baseline HIV RNA and sex included in model but were not significant

N.B. Models control for study time. Coefficients represented as kg.

Baseline HIV RNA and CD4 cell counts were not significant when considered in separate models (without RMR but adjusted for sex); however, P values for changes in outcome measures were similar to above models.

Changes in Body Composition Over Study Period



N.B. There were no differences in outcome measures based on treatment: TAF vs. no TAF or DTG vs. no DTG.

SUMMARY OF RESULTS

- Weight, total body fat, and trunk fat all increased significantly at both 6 and 12 months after ART initiation. In contrast, despite a trend at 6 months, there was no significant change in lean body mass at 12 months after ART initiation.
- Dietary intake remained stable after ART initiation with no significant changes in total calories, macro-nutrients (total fat and protein), fat quality, fiber, sugar, or relevant amino acids
- Metabolic rate did not change significantly at either 6 or 12 months after ART initiation. Pre-treatment metabolic rate, however, was a significant factor associated with increases in weight, total fat, trunk fat, and lean body mass, even after adjusting for sex and HIV RNA.
- Female sex was significantly associated with increases in total fat and trunk fat (but not weight or lean body mass); however, baseline HIV RNA and CD4 cell counts were not significantly associated with changes in either weight or body composition.
- Even after adjusting for sex, baseline metabolic rate, HIV RNA, and CD4 cell counts, increases in weight, total fat, and trunk fat were still significant at 6 and 12 months after ART initiation. In contrast, increases in lean body mass were only significant at 6 months (but not 12 months) after ART initiation.

CONCLUSIONS

- This study does not support the hypothesis that changes in caloric intake or metabolic rate are responsible for increases in weight and fat accumulation after ART initiation.
- Pre-treatment metabolic rate, however, independent of HIV RNA, may play a significant role in subsequent weight gain and fat accumulation after ART initiation.
- Notably, weight gain and fat accumulation were still significant after adjusting for sex, baseline RMR, HIV RNA, and CD4 cell counts, suggesting that there are additional unidentified factors contributing to the pathogenesis.
- Continued enrollment, extended follow up, and additional investigations are on-going to further explore possible etiologies of this phenomenon.

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