Changes in Fat Density After ART Initiation

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BACKGROUND

- Adipose tissue (AT) quality (density) and quantity (area) can both be measured using computed tomography (CT).
- AT quality and quantity may independently contribute to metabolic health, as function/quality can vary at any given quantity.
- People living with HIV (PLWH) have multiple virus- and antiretroviral therapy (ART)-specific risk factors for AT dysfunction, in addition to traditional contributors such as obesity.

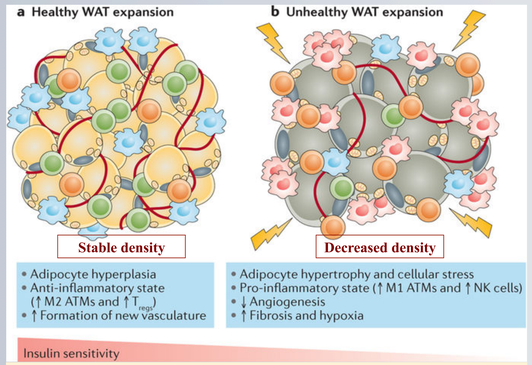


Figure 1: Metabolically healthy vs unhealthy AT expansion.[1]

- With "healthy" AT expansion (hyperplasia), adipocytes maintain the same size and density.
- With "unhealthy" expansion (hypertrophy), adipocytes become lipid engorged, of poorer quality, and less dense.
- We previously demonstrated that CT-quantified, abdominal subcutaneous AT (SAT) density reflects biopsy-quantified SAT adipocyte size in PLWH on ART, and that AT quantity increases following ART initiation.

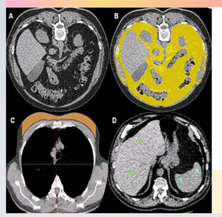
STUDY POPULATION & PURPOSE

- ACTG A5257 randomized ART-naïve, adult PLWH to raltegravir (RAL) or ritonavir-boosted atazanavir (ATV/r) or darunavir (DRV/r), each with tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC).
- Participants in A5260s, the metabolic sub-study of A5257, had L4-L5 single slice CT scans at weeks 0 and 96 (W0 and W96), from which visceral AT (VAT) and SAT density were measured.
- A5260s participants with W0 and W96 CT scans and W96 HIV-1 RNA <50 copies/mL were included in this analysis (n=288).
- We explored changes in AT density after ART initiation and associations with immuno-metabolic parameters.

STATISTICAL METHODS

- Linear regression models compared W0, W96 and 96-week changes in SAT and VAT density (in Hounsfield units, HU), adjusting for AT area and clinical and demographic parameters.
- Partial Spearman's correlations adjusting for AT area assessed relationships between AT density/immuno-metabolic parameters.
- Signed-rank test determined statistical significance.

CT METHODS[2]



- CT scan images were read centrally at the University of Colorado by a reader blinded to treatment arm.
- AT was identified by a mean attenuation of -190 to -30 HU (**more negative=lower density**).
- VAT was distinguished from SAT by tracing along the facial plane of the internal abdominal wall.

Figure 2: A=prior to AT isolation, B=omental and mesenteric AT, C=SAT, D=intra-hepatic and intra-splenic VAT.

RESULTS

Table 1: Baseline Participant Characteristics*

Age (years)	36 (28, 45)
Black race or Hispanic ethnicity	51%
Male Sex	89%
History of smoking	56%
BMI (kg/m^2)	25 (22, 28)
CD4$^+$ T lymphocyte count (cells/mm^3)	344 (193, 455)
HIV-1 RNA (log10 copies/mL)	4.5 (4.0, 5.1)

*Percent or median (interquartile range).

Table 2: SAT and VAT Density (HU)⌘

	W0	W96	P value*
SAT density	-99 (-104, -87)	-102 (-106, -93)	<0.001
VAT density	-80 (-89, -66)	-84 (-92, -71)	<0.001
DRV/r (n=74)			
SAT density	-96 (-104, -84)	-100 (-105, -92)	<0.001
VAT density	-77 (-86, -64)	-80 (-89, -70)	0.003
ATV/r (n=75)			
SAT density	-100 (-105, -87)	-102 (-106, -91)	0.060
VAT density	-80 (-89, -67)	-84 (-91, -70)	0.004
RAL (n=79)			
SAT density	-101 (-105, -89)	-102 (-109, -95)	0.006
VAT density	-82 (-90, -68)	-86 (-94, -75)	<0.001
Men (n=204)			
SAT density	-98 (-104, -86)	-101 (-105, -92)	<0.001
VAT density	-80 (-89, -66)	-83 (-91, -71)	<0.001
Women (n=24)			
SAT density	-103 (-107, -96)	-106 (-110, -101)	0.046
VAT density	-80 (-89, -67)	-88 (-93, -76)	<0.001

⌘Median (interquartile range), *within-group. No statistically significant differences between groups except SAT density by sex p=0.03.

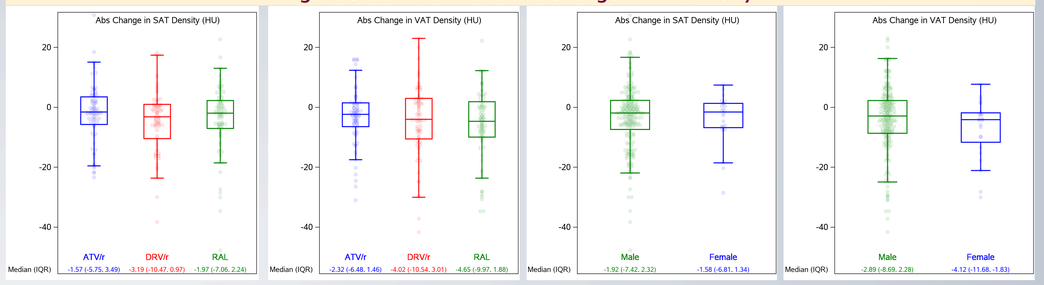
Table 3: Regression Estimates for Absolute Change in AT Density*⌘

	SAT		VAT	
	Estimate (SE)	P value	Estimate (SE)	P value
Treatment arm (PI vs RAL)	1.3 (1.4)	0.34	2.4 (1.5)	0.11
W0 AT area	0.02 (0.01)	<0.0001	0.05 (0.01)	<0.001
Female vs male sex	-4.8 (2.4)	0.045	-4.0 (2.4)	0.10
Black non-Hispanic**	-0.8 (1.6)	0.63	0.7 (1.8)	0.69
Hispanic**	-1.9 (1.8)	0.31	-3.5 (1.9)	0.07
No smoking history	2.4 (1.4)	0.07	1.8 (1.4)	0.23
Age (years)	-0.1 (0.1)	0.16	-0.1 (0.1)	0.25
W0 $\log_{10}$ HIV-1 RNA (copies/mL)	-2.3 (1.1)	0.04	-2.7 (1.2)	0.02
W0 CD4$^+$ T lymphocyte count (cells/mm^3)	0.0 (0.0)	0.85	-0.0 (0.0)	0.68

*Median (interquartile range). ⌘PI arms pooled. **Compared to white, non-Hispanic. SE=standard error.

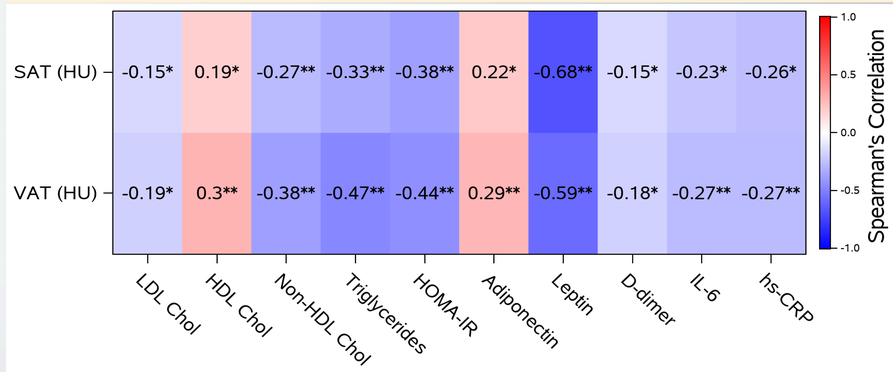
RESULTS

Figure 3: 96-Week Absolute Change in AT Density.



Significant* (p<0.05) within-group decreases in VAT and SAT density were observed in all treatment arms and for both men and women.
*except ATV/r p=0.06

Figure 4: Relationships between AT density and cardiometabolic and inflammatory biomarkers at W96.



Relationships between VAT and SAT density and biomarkers persisted after after adjusting for baseline CD4$^+$ T lymphocyte count, HIV-1 RNA and AT area.

CONCLUSIONS

- **In adult PLWH, VAT and SAT density decreased over 96 weeks of ART with ATV/r, DRV/r or RAL, each with TDF/FTC.**
- **Coupled with increased VAT and SAT quantity (previously demonstrated), this suggests unhealthy adipocyte hypertrophy following ART initiation.**
- **Female sex and higher W0 HIV-1 RNA were associated with greater decreases in AT density.**
- **Observed relationships between AT density and circulating markers of adipose tissue function, insulin resistance, lipid dysregulation and systemic inflammation were independent of AT quantity and HIV disease severity, highlighting the importance of understanding AT function as a moderator of comorbid disease in PLWH.**

Acknowledgements and References

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[1]Nat Rev Drug Discov. 2016 Sep;15(9):639-60. [2]J Gerontol A Biol Sci Med Sci 2014;69:109-17.