Tesamorelin Improves Fat Quality Independent of Changes in Fat Quantity

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Background

- Adipose tissue (AT) quality (density) and quantity (area) can both be measured using computed tomography (CT).
- AT quality may affect AT health independently of AT quantity, as function can vary at any given quantity.
- Adults living with HIV have multiple risk factors for AT dysfunction, including virus- and antiretroviral therapy-specific contributors.
- Tesamorelin, a growth hormone-releasing hormone analogue, reduces visceral AT (VAT) area in some adults living with HIV and central adiposity[1], but its effect on VAT density is unknown.
- We hypothesized that, among persons experiencing a reduction in VAT area on tesamorelin therapy, VAT density would increase, potentially reflecting an improvement in AT quality.

Study Design

- Participants were selected from two completed, randomized (2:1) trials of tesamorelin vs placebo for the treatment of central adiposity in adults living with HIV.
- Included participants had a clinical response to tesamorelin[2] (defined as a VAT decrease ≥8% over 26 weeks, ≈70% of tesamorelin-treated participants) or were randomized to placebo.
- Week 0 and 26 abdominal (L4-L5) CT scans were re-analyzed for VAT and subcutaneous AT (SAT) density (in Hounsfield Units, HU) by a central lab (University of Colorado) blinded to treatment arm.
- Biomarker concentrations were available from previous analyses.
- Paired t tests and linear regression models assessed 26-week, between-group differences in fat density changes.

Figure 1: Adipocyte Hypertrophy vs Hyperplasia

- Healthy adipocytes are small and well-differentiated, with a modest lipid droplet.
- AT depots can expand through **hyperplasia:** (new, same-sized adipocytes, density stays stable) or **hypertrophy:** (adipocytes become lipid engorged, density decreases).

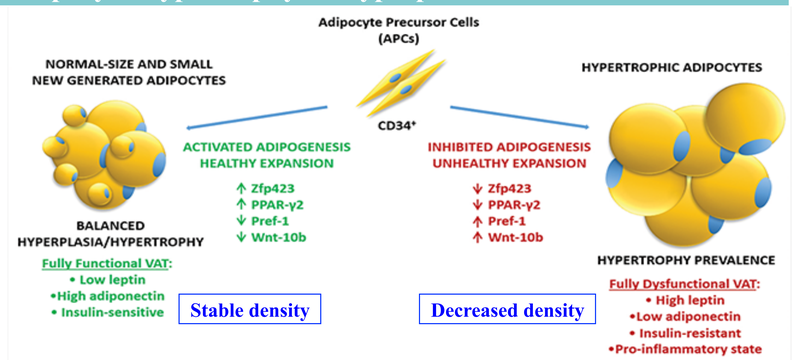
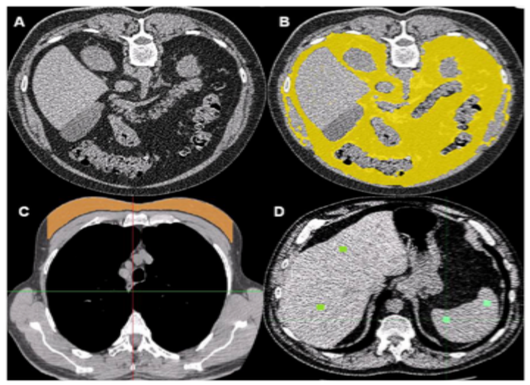


Figure 1: Healthy AT expansion through mixed hyperplasia/hypertrophy (left) vs unhealthy expansion via primarily hypertrophy (right).

Figure 2: CT-Quantified AT Density[1]



- Available, analyzable, paired scans (baseline and week 26) were re-analyzed using a semi-automatic segmentation image analysis program (Exelis Visual Information Solutions, Boulder, CO).
- 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=L4-L5 prior to fat isolation, B=omental and mesenteric fat, C=SAT, D=intra-hepatic and intra-splenic VAT.

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Results

Table 1: Demographic and Clinical Characteristics

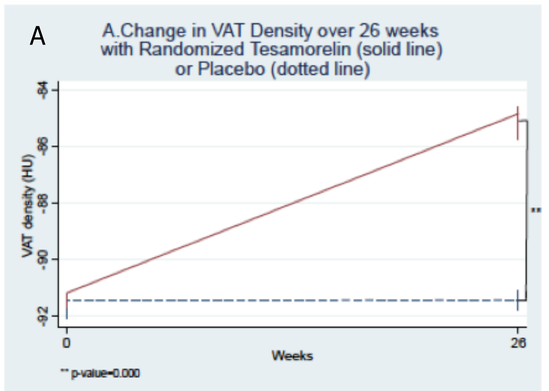
Characteristics (N = 341)	Tesamorelin (N = 193)	Placebo (N = 148)	P Value
Age (years)	47.8 (±7.3)	48 (±7.6)	0.792
Male (%)	89.1	83.8	0.149
Race (%)			0.208
White	86	78.4	
Black or African American	9.3	11.5	
Others	4.6	10.2	
Use of lipid lowering treatment (%)	52.8	43.9	0.102
Use of testosterone (%)	24.9	17.6	0.105
Body mass index at baseline (kg/m^2)	28.9 (±4.2)	28.6 (±4.3)	0.337
CD4 cell count at baseline (cells/μL)	635.6 (±318.7)	604 (±270)	0.664
CD8 cell count at baseline (cells/μL)	974.4 (±469.1)	953 (±389.2)	0.063
Time since initial HIV diagnosis (months)	171.1 (±64.1)	158 (±64.1)	0.189
Duration of ART therapy (months)	59 (±38)	53.7 (±34.5)	0.172

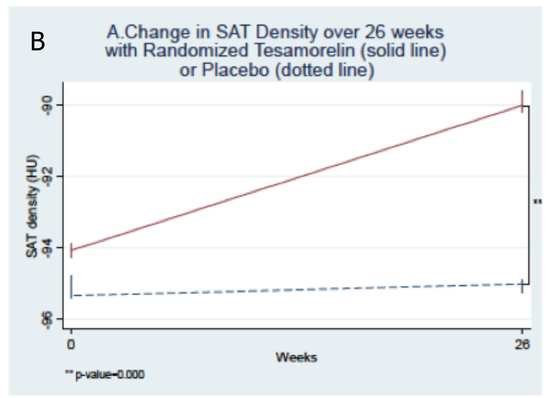
Table 2: AT Density by Randomization Arm

	Tesamorelin Responders	Placebo	P value
Baseline (HU)			
VAT density	-91	-91	0.80
SAT density	-94	-95	0.29
Unadjusted 26-week change (HU)*			
VAT density	6.2 (8.7)	0.3 (4.2)	<0.0001
SAT density	4.0 (8.7)	0.3 (4.8)	<0.0001
Adjusted 26-week change (HU)⌘**			
VAT density	2.3 (4.5, 7.3)	--	0.001
SAT density	3.5 (2.3, 4.7)	--	<0.001

*mean (standard deviation)
**adjusted for baseline AT density, baseline AT area and change in AT area
⌘HU effect size estimate and 95% confidence interval

Figure 3: 26-Week Changes in AT Density





- **Tesamorelin therapy was associated with significant increases in VAT and SAT density.**

Table 3: Partial* Correlations Between Changes in AT Density, AT Area and Inflammatory Biomarker Concentrations

	VAT HU*	P value	SAT HU*	P value	VAT area (cm^2)**	P value	SAT area (cm^2)**	P value
Adiponectin	0.19	0.02	0.21	0.02	-0.27	<0.0001	-0.20	0.001
C Reactive Protein	0.07	0.43	0.14	0.11	0.01	0.83	0.08	0.17
Plasminogen Activator Inhibitor (PAI)-1 Activity	0.01	0.92	-0.03	0.73	-0.03	0.59	-0.10	0.11
Tissue Plasminogen Activator (TPA) Activity	0.01	0.86	0.01	0.91	-0.11	0.08	0.00	0.96
Homeostatic Assessment Model of Insulin Resistance (HOMA-IR)	0.02	0.79	0.05	0.54	0.10	0.09	0.05	0.39
Insulin-like growth factor-1	0.06	0.48	0.12	0.16	-0.39	<0.0001	-0.03	0.57
VAT area (cm^2)	-0.30	<0.0001	--	--	--	--	--	--
SAT area (cm^2)	--	--	-0.21	0.01	--	--	--	--

*Adjusted for change in AT area
**Adjusted for baseline AT area

Conclusions

- **In adults living with HIV who had central adiposity and responded to tesamorelin therapy (≥8% VAT reduction over 26 weeks), VAT and SAT density increased independent of changes in fat area.**
- **Increases in AT density correlated with decreases in AT area, and these changes correlated with increases in adiponectin levels.**
- **Increased AT quality with tesamorelin therapy suggests that, among tesamorelin responders, improvements in both VAT and SAT quality may occur independent of changes in AT quantity.**

References

[1]N Engl J Med. 2007 Dec 6;357(23):2359-70. [2]Clin Infect Dis. 2012 Jun;54(11):1642-51. [3]Dietary and Hormonal Factors Involved in Healthy or Unhealthy Visceral Adipose Tissue Expansion, Adiposity - Epidemiology and Treatment Modalities. DOI: 10.5772/65927. [4]J Gerontol A Biol Sci Med Sci 2014;69:109-17.