

ORIGINAL RESEARCH

# THE GROWTH HORMONE RELEASING HORMONE ANALOGUE, TESAMORELIN, DECREASES MUSCLE FAT AND INCREASES MUSCLE AREA IN ADULTS WITH HIV

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**Abstract:** *Background:* Tesamorelin, a growth hormone-releasing hormone analogue, decreases visceral adipose tissue in people living with HIV, however, the effects on skeletal muscle fat and area are unknown. *Objectives:* The goals of this exploratory secondary analysis were to determine the effects of tesamorelin on muscle quality (density) and quantity (area). *Design:* Secondary, exploratory analysis of two previously completed randomized (2:1), clinical trials. *Setting:* U.S. and Canadian sites. *Participants:* People living with HIV and with abdominal obesity. Tesamorelin participants were restricted to responders (visceral adipose tissue decrease  $\geq 8\%$ ). *Intervention:* Tesamorelin or placebo. *Measurements:* Computed tomography scans (at L4-L5) were used to quantify total and lean density (Hounsfield Units, HU) and area (centimeters<sup>2</sup>) of four trunk muscle groups using a semi-automatic segmentation image analysis program. Differences between muscle area and density before and after 26 weeks of tesamorelin or placebo treatment were compared and linear regression models were adjusted for baseline and treatment arm. *Results:* Tesamorelin responders (n=193) and placebo (n=148) participants with available images were similar at baseline; most were Caucasian (83%) and male (87%). In models adjusted for baseline differences and treatment arm, tesamorelin was associated with significantly greater increases in density of four truncal muscle groups (coefficient 1.56-4.86 Hounsfield units; all  $p < 0.005$ ), and the lean anterolateral/abdominal and rectus muscles (1.39 and 1.78 Hounsfield units; both  $p < 0.005$ ) compared to placebo. Significant increases were also seen in total area of the rectus and psoas muscles (0.44 and 0.46 centimeters<sup>2</sup>;  $p < 0.005$ ), and in the lean muscle area of all four truncal muscle groups (0.64-1.08 centimeters<sup>2</sup>;  $p < 0.005$ ). *Conclusions:* Among those with clinically significant decrease in visceral adipose tissue on treatment, tesamorelin was effective in increasing skeletal muscle area and density. Long term effectiveness of tesamorelin among people with and without HIV, and the impact of these changes in daily life should be further studied.

**Key words:** Muscle quality, sarcopenia, frailty, IGF-1, visceral adipose tissue.

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## Introduction

Due to the successes of antiretroviral therapy, persons living with human immunodeficiency virus infection (PLWH) are living longer (1) and experiencing conditions commonly associated with aging (i.e., cardiovascular disease (2-4), neurocognitive dysfunction (5, 6), physical function impairments (7, 8), and falls (7, 9)). Although multiple factors contribute to the development of these disease processes, an accumulation of visceral adipose tissue (VAT) may play a central role (10-12). VAT accumulation is associated with HIV (4), antiretroviral therapy (4, 6, 12), and diet and physical activity (6, 12), and may contribute to the low-level, chronic inflammatory state persistent in HIV infection despite virologic suppression. Indeed, several studies have shown strong associations between VAT or central adiposity and cardiovascular disease (10), neurocognitive dysfunction (6, 11), and frailty (13) among PLWH.

VAT tends to accumulate with increasing age (14, 15). The deposition of this ectopic adipose tissue in organs including the

liver, epicardium, and skeletal muscle has been associated with organ-specific disease development including liver steatosis and fibrosis (16), myocardial infarction (17), and physical function limitations (18) or falls (18). The combination of age-associated and HIV-associated VAT accumulation may accentuate the effects of organ-specific diseases and frailty among people aging with HIV. Furthermore, therapeutic options to reverse VAT accumulation are limited (19).

In November 2010, the United States Food and Drug Administration approved tesamorelin for the treatment of excessive abdominal fat in PLWH (20). Tesamorelin is a synthetic growth hormone-releasing hormone that acts on the anterior pituitary gland to stimulate the endogenous growth hormone secretion (21). In randomized, controlled, double-blinded studies, tesamorelin decreased VAT by approximately 15% compared to placebo (22-24). In a separate study, tesamorelin reduced hepatic fat by a relative 40% (25) among PLWH with abdominal fat accumulation, compared to a 27% increase in the placebo arm. Ongoing studies are investigating the long-term safety of tesamorelin and the impact

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of tesamorelin on cognition, liver inflammation, and diabetic retinopathy in PLWH. The goals of this exploratory secondary analysis were to determine the effects of tesamorelin on muscle quality, as measured by changes in computed tomography (CT)-based trunk muscle density, a biopsy-correlated measurement of skeletal muscle fat (26), and trunk muscle area. We hypothesized that tesamorelin would increase skeletal muscle density (less fat) and skeletal muscle area, supportive of an overall improvement in muscle quality, compared to placebo.

### Methods

#### *Participants*

This analysis is a secondary, exploratory analysis of two previously completed randomized (2:1), clinical trials of tesamorelin versus placebo among PLWH with abdominal adiposity (22-24). Details of the study design and primary study outcomes have been previously published (22-24, 27). In brief, eligible participants from both studies were between 18 and 65 years of age with a CD4+ T-lymphocyte count >100 cells/ $\mu$ L, an HIV-1 RNA <10,000 copies/mL, on stable antiretroviral therapy for at least 8 weeks, and had evidence of excessive abdominal fat accumulation (defined as having waist circumference of  $\geq 95$  cm and waist to hip ratio  $\geq 0.94$  for men and  $\geq 94$  cm and waist to hip ratio  $\geq 0.88$  for women). The initial study design consisted of a primary efficacy phase of the initial studies (baseline–week 26) and a safety extension phase (week 26–52). A minimum of 8% of VAT change was considered clinically relevant (27), and PLWH with  $\geq 8\%$  in VAT reduction were thus deemed responders. Based on the initial studies, approximately 70% of PLWH with central adiposity that received tesamorelin met responder criteria. For this exploratory analysis, data were restricted to the primary efficacy phase and participants who were receiving either placebo (regardless of response) or were tesamorelin responders, as these patients would be those most likely to receive ongoing therapy in clinical practice (Supplemental Figure).

#### *Body Composition Measurement*

CT scans for VAT were obtained as part of the initial studies, with methods described elsewhere (22-24, 27). For this exploratory analysis, truncal muscle density (in Hounsfield Units, HU) and area ( $\text{cm}^2$ ) from scans at baseline and week 26 were analyzed using a semi-automatic segmentation software using an IDL platform (Exelis Visual Information Solutions, Boulder CO). Muscle groups of interest were 1) rectus abdominis, 2) anterolateral abdominal wall muscles (external and internal oblique, and transversus abdominis), 3) psoas major, and 4) paraspinal muscles (erector spinae and transversospinalis). The segmentation technique takes advantage of the unique signal CT-assessed density differences between muscle and fat and has been used in similar studies (28, 29). Lean muscle area was defined as the

muscle component with density >30 HU (30, 31). Muscle and fat segmentations were completed by a single analyst blinded to study arm; 5% of scans were re-analyzed by a second analyst. Prior studies have found a strong correlation between CT-measured muscle density and intramuscular lipid by muscle biopsy (26, 28).

#### *Laboratory Assessments*

As previously described, laboratory analyses included insulin-like growth factor-1 (IGF-1) (27).

#### *Statistical Analysis*

Change in muscle density, lean muscle density, muscle area, and lean muscle area for each muscle group between weeks 0 to 26 were compared within treatment arms using paired t-tests. Pearson correlation coefficients were used to describe associations between changes in predictors and changes in outcome variables, restricted to the tesamorelin arm. Bivariate linear regression models included the baseline value (of muscle area or density) and tested the effect of treatment arm. We then singularly tested the addition of change in VAT and change in IGF-1. To adjust for multiple analyses, a p value of <0.005 was considered statistically significant. Analysis using Stata® version 14.2 (Stata Corp LP).

### Results

Of the 272 tesamorelin-responders, evaluable CT images were available at both week 0 and 26 for 193 participants; of 201 placebo recipients, evaluable CT images were available for 148 participants (Supplemental Figure). The majority of participants were Caucasian (83%) and male (87%) with extended antiretroviral history; baseline characteristics were similar between the tesamorelin and placebo groups as detailed in Table 1. Baseline measurements of muscle density and area by study arm are shown in Table 2.

#### *Correlations*

Among participants in the tesamorelin arm, change in VAT correlated with change in total and lean anterolateral/abdominal and total rectus density (Table 3). Change in VAT was correlated only with change in anterolateral/abdominal area. Change in IGF-1 was not significantly correlated with change in density or area.

#### *Changes in Muscle Density*

Compared to placebo, 26 weeks of tesamorelin was associated with significantly greater increases of total muscle density (less muscle fat) within all four truncal muscle groups (rectus abdominis, anterolateral abdominal, psoas major and paraspinal muscle groups,  $p < 0.005$ ); Table 2. The largest net increase was observed within the rectus abdominis (3.5 HU) of the tesamorelin arm. Although increases were also seen in the lean component of muscle density, only differences in

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anterolateral abdominal muscles were significantly greater in the tesamorelin vs placebo arms ( $p < 0.005$ )

**Table 1**  
Baseline Characteristics

Characteristics	Tesamorelin (N = 193)	Placebo (N = 148)	P-Value
Age (years)	47.8 ( $\pm 7.3$ )	48 ( $\pm 7.6$ )	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
ART usage at baseline (%)			0.642
NRTI + NNRTI	34.7	32.4	
NRTI + NNRTI + PI	9.3	6.8	
NRTI + PI and no NNRTI	47.7	48	
NRTI alone	4.1	6.1	
Other	4.1	6.8	
CD4+ cell count (cells/mm <sup>3</sup> )	636 ( $\pm 319$ )	604 ( $\pm 270$ )	0.664
Body mass index (kg/m <sup>2</sup> )	28.9 ( $\pm 4.2$ )	28.6 ( $\pm 4.3$ )	0.337
Viral load (copies/mL)	851 ( $\pm 1,675$ )	440 ( $\pm 659$ )	0.17
Visceral adipose tissue area (cm <sup>2</sup> )	197 ( $\pm 86$ )	189 ( $\pm 85$ )	0.38
Insulin-like growth factor-1	152 ( $\pm 61.5$ )	157 ( $\pm 63$ )	0.43

Abbreviations: ART, antiretroviral therapy; NRTI, nucleoside reverse-transcriptase inhibitor; NNRTI, nonnucleoside reverse-transcriptase inhibitor; PI, protease inhibitor

Multivariate analyses adjusted for baseline values + treatment arm, and then one additional variable (change in VAT or IGF-1) are shown in Table 4. Compared to placebo, tesamorelin resulted in significantly greater increases in muscle density across all total muscle groups and in the lean anterolateral/abdominal and rectus muscle, even after adjusting for differences at baseline. After adjusting for changes in VAT, changes in total muscle density of both the rectus and paraspinal muscles remained significant, while other total and lean muscle groups were attenuated and no longer significant. Lastly, adjustment for changes in IGF-1 slightly attenuated effects, but statistically significant effects persisted across most of the total (anterolateral/abdominal, rectus, paraspinal) and the anterolateral/abdominal lean muscle component.

### Changes in Muscle Area

In unadjusted analyses, significant increases in psoas area were seen with 26 weeks of tesamorelin (0.4 cm<sup>2</sup>) compared to placebo (-0.1 cm<sup>2</sup>);  $p < 0.005$ ; Table 2. Differences across other muscle groups did not reach statistical significance. In contrast, the tesamorelin arm experienced significantly greater increases

in lean muscle area for all 4 muscle groups compared to placebo (all  $p < 0.005$ ).

In multivariate analyses adjusted for baseline values + treatment arm, tesamorelin was associated with significant increases in rectus and psoas total area (Table 4). Significant increases were seen in the lean muscle area of all four muscle groups, with effect sizes nearly double that of the total muscle component. Changes in total muscle area were independent of changes in VAT (tesamorelin resulted in significantly greater increases in total muscle area after adjusting for VAT). In contrast, adjustment for change in IGF-1 explained most of the changes in total muscle area, such that many associations were no longer significant. Lean muscle area changes remained significant after adjusting for VAT; only changes in the rectus and paraspinal lean muscles remained highly significant ( $p < 0.005$ ) after adjusting for changes in IGF-1.

### Discussion

Prior studies have found that lower skeletal muscle density, a measure of muscle quality (18) closely related to VAT accumulation (18, 32), is associated with impairments in physical function and falls among older adults (18). We have shown that a growth hormone-releasing hormone analogue approved for reduction in VAT among PLWH with central adiposity also appears to result in significant improvements in skeletal muscle quality. Whether these increases in skeletal muscle density and area have clinically meaningful impacts in skeletal muscle function cannot be determined through this analysis, but our initial exploratory findings support known IGF-1 effects on skeletal muscle, prompt further investigation, and highlight several points of discussion.

Can one imply clinical relevance based on previously published differences in muscle density or area? Several studies (7, 33, 34) have shown associations between less dense thigh musculature with poorer lower limb performance, which may contribute to mobility impairment. Although most prior studies of muscle density and area have focused on thigh musculature, Goodpaster et al. observed that trunk muscle density (our primary outcome) was strongly correlated with thigh density ( $r = 0.65-0.77$ ;  $p < 0.01$ ) (26). Trunk muscle density has been correlated with trunk muscle strength across multiple muscle groups ( $r = 0.32-0.61$ ;  $p < 0.05$ ) (35). Adults with moderate or severe back pain had lower trunk muscle density (by 3.4 HU) and poorer score in lower extremity performance tests (chair stands, timed pace walk, and timed standing balance) compared to healthy controls (36). Anderson et al. (37) found greater paraspinal muscle density (10-12 HU) with better balance (less postural sway) in older adults (~84 years old). Lastly, among post-menopausal women randomized to hormone replacement, high-impact exercise, hormone replacement + exercise, or control for 1 year, hormone replacement with or without exercise resulted in significantly greater quadriceps muscle density (0.6-1.3 HU) compared to loss of 0.6 HU in the control

**Table 2**  
Muscle Density and Area by Study Arm at Baseline and Difference between Week 26 and Baseline

Muscle measurements	Baseline		P-Value	Difference Week 26 - Baseline		P value of Difference
	Tesamorelin (N = 193)	Placebo (N = 148)		Tesamorelin	Placebo	
Anterolateral/abdominal						
Muscle density (HU)	37.3 (10.8)	35.4 (10.6)	0.11	2.0 (4.9)	-0.6 (4.9)	<0.001
Lean muscle density (HU)	50.3 (6.2)	49.3 (5.7)	0.14	0.9 (3.2)	-0.2 (3.4)	0.002
Muscle area (cm²)	27.6 (6.2)	26.0 (6.2)	0.017	-0.2 (2.9)	0 (2.8)	0.50
Lean muscle area (cm²)	19.0 (6.3)	17.2 (6.3)	0.008	0.7 (2.8)	-0.2 (2.7)	0.003
Rectus						
Muscle density (HU)	32.5 (13.6)	30.0 (12.8)	0.089	3.5 (7.5)	-0.8 (8.6)	<0.001
Lean muscle density (HU)	49.2 (8.0)	47.7 (7.6)	0.080	1.2 (4.5)	-0.2 (5.3)	0.012
Muscle area (cm²)	9 (2.5)	8.2 (2.3)	0.005	0.4 (1.6)	0.1 (1.2)	0.055
Lean muscle area (cm²)	5.8 (2.8)	5.0 (2.6)	0.005	0.7 (1.6)	-0.1 (1.3)	<0.001
Psoas						
Muscle density (HU)	50.2 (10.3)	47.6 (9.8)	0.025	0.9 (3.9)	-0.3 (3.4)	0.004
Lean muscle density (HU)	57.6 (8.5)	55.7 (7.9)	0.033	0.2 (3.0)	-0.3 (3.0)	0.13
Muscle area (cm²)	18.7 (3.8)	17.4 (3.7)	0.002	0.4 (1.3)	-0.1 (1.0)	<0.001
Lean muscle area (cm²)	15.9 (4.0)	14.6 (3.8)	0.002	0.5 (1.3)	-0.1 (1.0)	<0.001
Paraspinal						
Muscle density (HU)	41.8 (10.9)	39.8 (10.7)	0.087	1.1 (3.8)	-0.6 (3.4)	<0.001
Lean muscle density (HU)	54.1 (6.7)	53.2 (5.8)	0.17	0.3 (2.5)	-0.1 (2.4)	0.158
Muscle area (cm²)	25.6 (4.8)	25.0 (4.8)	0.26	0.2 (1.9)	-0.2 (2.2)	0.059
Lean muscle area (cm²)	18.9 (5.9)	17.8 (6)	0.12	0.5 (2.1)	-0.4 (2.2)	<0.001

Abbreviations: HU, Hounsfield units.

group (p <0.05) (38).

Limited data among PLWH provide some clinical relevance as well. PLWH with lipodystrophy had significantly lower median muscle density (55.0 HU; IQR 51.0-58.3) compared to PLWH without lipodystrophy (57.0 HU; IQR 55.0-59.0) and HIV-uninfected men (59.5 HU; IQR 57.3-64.8) [39]. In the Multicenter AIDS Cohort Study, men with HIV (~57 years old) on antiretroviral therapy had lower thigh muscle density (by 1 HU), compared to their HIV-uninfected peers (~54 years old), and lower thigh muscle density was correlated with greater VAT area and weaker grip strength (7). We have previously shown that antiretroviral therapy initiation was associated with a decrease in trunk muscle density (-0.87 to -2.4 HU across muscle groups) over 96 weeks [40]. Lastly, in a three month intervention of metformin with or without aerobic + resistance exercise among lipodystrophic men and women with HIV (n=25), participants in the exercise + metformin arm experienced greater increase in thigh muscle attenuation (median change 2.0; IQR 0.5, 5.0 HU) compared to metformin only arm (-1.0, IQR -3.5, 0; p=0.04) (41). In summary, the extent of change that we observed among tesamorelin responders is consistent with clinically meaningful differences

seen in other study populations.

In our analysis, changes in muscle density within the tesamorelin arm did not correlate with IGF-1 concentration. These findings were further corroborated in the multivariate analyses, where changes in muscle density remained significant across many muscle groups even after adjusting for change in IGF-1. In contrast, changes in total and lean muscle density with tesamorelin were attenuated across most of the muscle groups after adjusting for VAT. These findings suggest similar mechanisms may underlie changes in VAT and muscle density, but that the tesamorelin-related effects on muscle density are independent of IGF-1. In contrast to the muscle density findings, muscle area and lean muscle area were independent of VAT but not IGF-1 changes. Although our findings suggest that the tesamorelin effect on muscle area may be more related to the IGF-1 effects rather than the VAT reduction, our results are limited by the inclusion of VAT responders only.

Several limitations to our study should be noted: the majority of participants were male, Caucasian, with an average age less than 50, thus may not reflect the global HIV population. Similarly, the mean age of our participants is well below the typical targeted population for lean mass-directed therapies.

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**Table 3**

Pearson Correlation Coefficients Describing the Change in Body Composition or Laboratory Measures with the Change in Muscle Density or Area, Tesamorelin Arm only

	Change in Total Density (r)				Change in Lean Density (r)			
	Anterolateral/ Abdominal	Rectus	Psoas	Paraspinal	Anterolateral/abdominal	Rectus	Psoas	Paraspinal
Change in VAT	-0.205†	-0.183*	-0.058	-0.066	-0.154*	-0.081	-0.002	0.059
Change in IGF-1	0.075	0.036	-0.119	0.058	0.086	0.027	0.058	0.057
	Change in Total Area				Change in Lean Area			
	Anterolateral/ Abdominal	Rectus	Psoas	Paraspinal	Anterolateral/abdominal	Rectus	Psoas	Paraspinal
Change in VAT	0.276†	0.073	0.056	0.177	0.080	-0.022	0.014	0.070
Change in IGF-1	0.037	0.012	0.082	0.087	0.060	0.056	0.133	0.068

†p <0.005, \* p <0.01; BMI, body mass index; VAT, visceral adipose tissue; IGF-1, insulin-like growth factor-1.

**Table 4**

Bivariate and Multivariate Linear Regression Exploring the Effects of Tesamorelin Compared to Placebo on Changes in Muscle Density (Hounsfield Units [HU]) and Muscle Area (cm<sup>2</sup>)

	Total Muscle Density (top) or Area (bottom)			Lean Muscle Density (top) or Area (bottom)		
	Coefficient (SE)			Coefficient (SE)		
	Tesamorelin Effect Compared to Placebo (baseline adjustment only)	Tesamorelin Effect, Adjusted for Baseline and Change in VAT or IGF-1		Tesamorelin Effect Compared to Placebo (baseline adjustment only)	Tesamorelin Effect, Adjusted for Baseline and Change in VAT or IGF-1	
		Δ VAT§	Δ IGF-1§		Δ VAT†	Δ IGF-1†
<i>Muscle Density (HU)</i>						
Anterolateral/abdominal	2.98 (0.51)‡	1.32 (0.58)*	2.77 (0.62)‡	1.39 (0.32)‡	0.55 (0.41)	1.29 (0.41)‡
Rectus	4.86 (0.83)‡	3.10 (1.09)‡	4.41 (1.05)‡	1.78 (0.48)‡	1.29 (0.63)*	1.59 (0.74)*
Psoas	1.56 (0.37)‡	0.74 (0.45)	1.23 (0.52)*	0.82 (0.30)†	0.40 (0.35)	0.85 (0.41)*
Paraspinal	1.97 (0.38)‡	1.58 (0.51)‡	1.93 (0.55)‡	0.51 (0.25)*	0.47 (0.33)	0.58 (0.37)
<i>Muscle Area (cm<sup>2</sup>)</i>						
Anterolateral/abdominal	-0.11(0.31)	1.23 (0.42)‡	-0.25 (0.41)	1.08 (0.31)‡	1.38 (0.37)‡	0.91 (0.38)*
Rectus	0.44 (0.15)‡	0.57 (0.20)‡	0.32 (0.19)	0.85 (0.15)‡	0.75 (0.21)‡	0.69 (0.20)‡
Psoas	0.46 (0.12)‡	0.62 (0.16)‡	0.27 (0.19)	0.64 (0.13)‡	0.66 (0.17)‡	0.38 (0.19)*
Paraspinal	0.46 (0.22)*	0.97(0.28)‡	0.24 (0.25)	0.96 (0.23)‡	1.30 (0.30)‡	0.81 (0.28)‡

\*\*\*p<0.005 †p<0.01 \* p<0.05; §multivariate model including baseline value of muscle area or density, treatment arm, and either change in visceral adipose tissue (VAT) area or change in insulin-like growth factor (IGF)-1.

We restricted this exploratory analysis to the tesamorelin responder arm, as these patients would be those most likely to receive long-term therapy in clinical practice. Whether tesamorelin would have an effect on muscle density or area without a response to VAT, whether the effects might differ in an older population with poorer muscle quality or age-associated declines in IGF-1, or whether the effects on muscle area and density persist after continuation or cessation of therapy cannot be extrapolated from these initial findings. Importantly, the Phase III clinical trials did not collect objective or subjective measures of muscle function, and thus the clinical relevance of these changes is unknown. Although the tesamorelin and placebo group were similar by demographic characteristics, the muscle area and density were significantly different at baseline in a number of muscle groups; we adjusted

these differences in baseline values in our analyses, but these baseline differences may represent other characteristics that were not accounted for. Multiple analyses were performed, increasing the likelihood that some of our findings were by chance; a lower significant p value (<0.005) was chosen to minimize chance findings. Lastly, a number of CT images were incompatible with the current digital standards or were not available. Despite these limitations, the robust sample size, and the randomized, placebo-controlled design of our initial study provides provocative preliminary findings to support future study.

In summary, among PLWH with excess abdominal fat who had a clinical response to tesamorelin, trunk muscle density and lean muscle area increased over 26 weeks. Changes in muscle density were largely independent of changes in IGF-1



and attenuated by changes in VAT while changes in muscle area were independent of VAT changes and attenuated, in part, by changes in IGF-1. The clinical relevance of these changes on measures of muscle strength and function in tesamorelin recipients remain to be established. Moreover, as cessation of the tesamorelin is typically associated with rapid VAT accumulation (23, 27), the long-term durability of changes in muscle density and area on or following cessation of tesamorelin therapy need to be established, as does the effect of longer-term tesamorelin treatment. Although our findings are too preliminary to suggest that tesamorelin might serve as therapy for impaired muscle function, future studies could investigate the additive effect of tesamorelin and exercise or other sarcopenia-reversing therapies among older adults with excess VAT, regardless of HIV serostatus.

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**Conflict of interest:** none declared by the authors

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