

# Altered Lipid Profile in Treated HIV Patients with Increased Visceral Adiposity: Association with More Severe CVD Risk Parameters and Response to Tesamorelin (TH9507), a Growth Hormone-Releasing Factor (GRF) Analogue

Julian Falutz<sup>1</sup>, Jean-Claude Mamputu<sup>2</sup>, Christian Marsolais<sup>3</sup>, Diane Potvin<sup>4</sup>, Monika Zoltowska<sup>5</sup>, Graziella Souhbar<sup>6</sup>, Donald Kotler<sup>7</sup>, and Steven Grinspoon<sup>8</sup>

<sup>1</sup>Montreal General Hospital, McGill University Health Centre, Montreal, Canada; <sup>2</sup>Theratechnologies Inc., Montreal, Canada; <sup>3</sup>St. Luke's Roosevelt Hospital Center, Columbia University College of Physicians and Surgeons, New York, NY, USA; <sup>4</sup>Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA.

Corresponding author:  
Julian Falutz, MD  
Phone: (514) 934-8095  
Fax: (514) 937-1424  
julian.falutz@mcgill.ca

## ABSTRACT

**Background:** Increased visceral adipose tissue (VAT) is common among HIV patients treated with antiretroviral therapy (ART) and has been shown to improve with tesamorelin therapy. Visceral adiposity is associated with dyslipidemia in HIV patients, but it is unknown if the presence of an atherogenic lipid profile (ALP) is associated with greater degree of insulin resistance and progression of metabolic abnormalities. Furthermore, although triglycerides (TGs) decrease with tesamorelin therapy, it is unknown whether the effect is different in patients with ALP. We determined the response of HIV patients with and without ALP to tesamorelin or placebo in a pooled population of 2 randomized phase 3 studies.

**Methods:** 816 ART-treated HIV patients with increased waist circumference (WC) at baseline were randomized in 2 studies to receive tesamorelin 2 mg (n=550) or placebo (n=266) sc daily for 26 weeks. The primary endpoint was the % change from baseline in computerized tomographic (CT) scan-determined VAT. Secondary endpoints included changes in lipids. An ALP(+) pattern was defined as TGs≥75<sup>th</sup> percentile (≥6.1 mmol/L) plus HDL-cholesterol (HDL-C)≤25<sup>th</sup> percentile (≤0.8 mmol/L) while an ALP(-) pattern included patients with TGs≤median (≤1.4 mmol/L) plus HDL-C≥median (≥1.5 mmol/L) at baseline. Data were analyzed using ANCOVA.

**Results:** At baseline, mean age of the combined cohorts was 47±7 (SD) yrs, WC 105±9 cm, and BMI 29±4 kg/m<sup>2</sup>. An ALP(+) pattern occurred in 78 (10%) patients, while 154 (19%) had an ALP(-) pattern. ALP(+) patients had greater VAT, insulin, total cholesterol/HDL cholesterol (TC/HDL-C), and TGs than ALP(-) patients in both the tesamorelin and placebo groups (p<0.05). Among patients receiving placebo, those with ALP(+) had a progressive increase in insulin (1.9±26.6 (SE) vs. -64.1±18.0 pmol/L, p=0.017) and HOMA (0.7±1.1 vs. -2.4±0.8, p=0.02) compared to ALP(-) patients at Week 26. Tesamorelin treatment resulted in a similar decrease in VAT in both ALP(+) and ALP(-) patients. No significant differences in the changes in TC/HDL-C were found between ALP(+) and ALP(-) patients receiving tesamorelin. However, TGs decreased significantly more in ALP(+) vs. ALP(-) patients: -1.0±0.3 vs. -0.1±0.2 mmol/L, respectively, p=0.01.

**Conclusion:** ALP is associated with greater progression of critical metabolic variables in HIV patients with abdominal fat accumulation. Tesamorelin effectively reduces VAT in patients both with and without an ALP(+) pattern and decreases elevated TGs to a greater degree in ALP(+) patients.

## INTRODUCTION

HIV-infected patients on ART often develop body composition changes and metabolic abnormalities, including abdominal fat accumulation, hyperglycemia and dyslipidemia, which may increase cardiovascular (CV) risk.<sup>1-3</sup>

Atherogenic dyslipidemia, which is defined as elevated TGs and concomitant low HDL-C level, is associated with insulin resistance, metabolic syndrome and increased CV risk in the non-HIV population.<sup>4</sup>

Here we report baseline body composition and metabolic parameters in patients with and without atherogenic lipid profile (ALP) as well as changes in those parameters following 26 weeks of treatment with tesamorelin or placebo in a pooled population of 2 randomized phase 3 studies.

## SUBJECTS AND METHODS

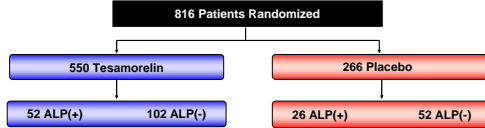
### OBJECTIVES:

The objectives of the current sub-analyses were to define a particularly high risk group of patients, with known long-term cardiovascular disease (CVD) risks, within an already high-risk group of patients (the entire cohort of HIV patients with excess abdominal fat), and to determine biologic characteristics of that group at baseline and after 6 months of treatment with tesamorelin. An ALP(+) pattern was defined as TGs≥75<sup>th</sup> percentile plus HDL-C≤25<sup>th</sup> percentile,<sup>5</sup> while an ALP(-) pattern included patients with TGs≤median plus HDL-C≥median at baseline.

### STATISTICAL ANALYSES:

VAT was analysed using an ANCOVA on natural log of (VAT at Week 26/VAT at Baseline) as the dependent variable with natural log of VAT at baseline, Treatment (tesamorelin, placebo), Study (first or second pivotal study), ALP (+, -) and Treatment-by-ALP interaction included in the model. For lipids, the Week 26 change-from-baseline was the dependent variable with lipid at baseline, Treatment, Study, Lipid-Lowering-Treatment use (yes, no), ALP, and treatment-by-ALP interaction included. ANCOVA models similar to that for lipids were used for the other parameters (fat, glucose, insulin, HOMA-IR), but without Lipid-Lowering-Treatment included. For all analyses, ALP(+) vs. ALP(-) comparisons within each treatment were presented. A type one error of 5% was used and no adjustment for multiplicity of testing was performed.

### PATIENT DISPOSITION:

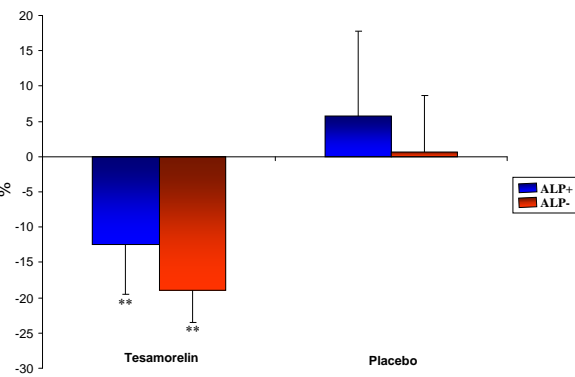


## RESULTS

Parameters	Tesamorelin		Placebo	
	ALP(+) (N=52)	ALP(-) (N=102)	ALP(+) (N=26)	ALP(-) (N=52)
Age (years)	47±7*	50±6	49±7	48±8
CD4 (cells/mm <sup>3</sup> )	603±327	581±263	582±309	549±275
BMI (kg/m <sup>2</sup> )	29.9±3.2	29.6±3.8	30.0±3.6	29.5±2.8
Waist circumference (cm)	105±9	105±10	107±10	104±6
Systolic BP (mmHg)	126±14	125±13	123±12	124±13
Diastolic BP (mmHg)	78±7	80±8	80±7	79±8
VAT (cm <sup>2</sup> )	218±94*	176±79	231±101*	160±62
Trunk Fat (kg)	14.8±5.0	15.9±5.4	15.7±6.2	16.0±4.2
% Trunk fat/total fat	69.0±6.7*	65.4±8.3	67.3±6.9*	63.0±8.2
% Trunk fat/limb fat	283.3±107.3*	235.2±92.7	256.3±89.9	209.3±86.8
Fasting Glucose (mmol/L)	5.68±0.93*	5.35±0.75	5.65±0.73	5.48±1.22
Fasting Insulin (pmol/L)	307±438*	99±69	174±102*	119±117
HOMA-IR	11.12±15.28*	3.41±2.71	6.31±3.93	4.65±6.12
Triglycerides (mmol/L)	6.10±4.93*	1.39±0.43	5.16±1.76*	1.49±0.39
HDL-C (mmol/L)	0.77±0.15*	1.52±0.36	0.78±0.16*	1.51±0.33
Total-C (mmol/L)	5.03±1.11	4.95±0.89	4.95±0.96	5.04±0.78
Total-C/HDL-C	6.74±1.87*	3.37±0.68	6.54±1.60*	3.44±0.71
Non-HDL-C (mmol/L)	4.26±1.09*	3.43±0.79	4.17±0.90*	3.53±0.74
Triglycerides/HDL-C	8.66±8.24*	0.96±0.37	7.18±3.98*	1.04±0.35

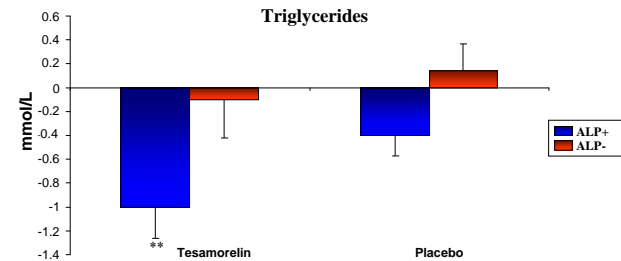
**Table 1.** Baseline characteristics by treatment Group. Data are mean ± SD. \* p<0.05 (within-group difference). An ALP(+) pattern occurred in 78 (10%) patients, while 154 (19%) had an ALP(-) pattern. Aside from the increased TGs and decreased HDL-C levels, ALP(+) patients had increased levels of biologic features known to increase CVD risk, including VAT, fasting insulin, HOMA-IR, and TC/HDL-C ratio.

## VAT



**Figure 1.** Changes from baseline in VAT by treatment group at Week 26. Data are mean ± SEM. Tesamorelin was equally effective in the ALP(+) vs. ALP(-) groups (p=0.11), \*\* p<0.01 vs. placebo in either the ALP(+) or ALP(-) group.

## RESULTS



**Figure 2.** Changes from baseline in triglyceride levels by treatment group at Week 26. Data are mean ± SEM. \*\*, p=0.01 for tesamorelin ALP(+) vs. tesamorelin ALP(-).

Parameters	Tesamorelin		Placebo	
	ALP(+) (N=52)	ALP(-) (N=102)	ALP(+) (N=26)	ALP(-) (N=52)
Trunk Fat (kg)	-0.73±0.29	-1.14±0.20*	0.01±0.40	0.66±0.28
% Trunk Fat/Total Fat	-1.10±0.32*	-1.44±0.22*	0.32±0.44	-0.24±0.31
% Trunk Fat/Limb Fat	-15.52±4.34*	-18.64±3.03	8.01±6.00	-9.20±4.26
HDL-C (mmol/L)	-0.02±0.04	-0.00±0.03	-0.00±0.05	-0.06±0.03
Total-C (mmol/L)	-0.09±0.11	-0.07±0.08	-0.03±0.15	0.16±0.11
Total-C/HDL-C	-0.01±0.18	-0.20	-0.21±0.21	0.02±0.14
Non-HDL-C (mmol/L)	0.00±0.11	-0.10±0.07	0.05±0.14	0.19±0.10
Fasting glucose (mmol/L)	0.24±0.10	0.09±0.07	0.14±0.16	-0.10±0.11
Fasting Insulin (pmol/L)	33.60±18.14	-33.79±12.30	12.91±26.59	-64.09±17.97
HOMA-IR	1.50±0.74	-1.33±0.50	0.69±1.08	-2.43±0.77

**Table 2.** Changes from baseline in other body composition, lipid and glucose parameters at Week 26. Data are mean ± SEM. \*, p<0.01 for tesamorelin vs. placebo in either the ALP(+) or ALP(-) groups. Changes in fasting glucose levels were not significantly different between ALP(+) and ALP(-) patients in either treatment group. Insulin levels and HOMA-IR significantly increased from baseline in ALP(+) patients compared to ALP(-) patients at Week 26. However, no significant differences in these parameters were observed between tesamorelin-treated patients and placebo in either the ALP(+) or ALP(-) groups.

## CONCLUSION

ALP(+) patients had more elevated VAT compared to ALP(-) patients at baseline. Tesamorelin effectively reduces VAT in both patients with and without an ALP pattern and decreases elevated TGs to a greater degree in ALP(+) patients. ALP is associated with greater progression of critical metabolic variables in HIV patients with abdominal fat accumulation.

### REFERENCES

1. Grinspoon S, Carr A. *N Engl J Med*. 2005;352:48-62.
2. Badier C, Metzger J-B, Corcos C, et al. *Clin Infect Dis*. 2001;32:130-9.
3. Wyszynski D.E., Watersworth D.M., Barber P.J., et al. *Am J Cardiol*. 2005;95:194-8.