Review: Clinical Trial Outcomes

CLINICAL INVESTIGATION

Tesamorelin for the treatment of excess abdominal fat in HIV-infected individuals with lipodystrophy

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Metabolic and morphologic abnormalities in persons with HIV remain common contributors to stigma and morbidity. Increased abdominal circumference and visceral adiposity were first recognized in the late 1990s, soon after the advent of effective combination antiretroviral therapy. Visceral adiposity is commonly associated with metabolic abnormalities including low HDL-cholesterol, raised triglycerides, insulin resistance and hypertension, a constellation of risk factors for cardiovascular disease and diabetes mellitus known as 'the metabolic syndrome'. Medline and conference abstracts were searched to identify clinical research on factors associated with visceral adiposity and randomized studies of management approaches. Data were critically reviewed by physicians familiar with the field. A range of host and lifestyle factors, as well as antiretroviral drug choice, were associated with increased visceral adiposity. Management approaches included treatment switching. Supraphysiological doses of recombinant HGH and the hGHRH tesamorelin both significantly and selectively reduce visceral fat over 12–24 weeks; however, the benefits are only maintained if dosing is continued. In summary, the prevention and management of visceral adiposity remains a substantial challenge in clinical practice.

Keywords: bone mineral density • ectopic fat • HIV • lipodystrophy • neurocognitive impairment • quality of life • tesamorelin • VAT

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Body composition changes have been an important component of the clinical manifestations of HIV-seropositive subjects since the onset of the epidemic. The documented changes in their manifestations recapitulate the extraordinary changes in the clinical picture of HIV disease observed over the past 30 years.

Three distinct paradigms in body composition changes parallel the evolution of clinical HIV syndromes. The first morphological complication described in untreated patients was the AIDS wasting syndrome, characterized by excessive loss of both lean and fat mass, which consisted mainly of the loss of subcutaneous fat (SAT); there was some evidence that visceral adipose tissue (VAT) [1] may have been relatively increased even prior to the availability of effective treatments [2]. The AIDS wasting syndrome occurred frequently in patients with advanced disease, and contributed independently to morbidity and mortality (mainly driven by opportunistic infections) [3]. It still occurs today in untreated patients, particularly in resource -limited countries where AIDS is still called the 'slim disease', and in currently treated patients not responding to highly active antiretroviral (ARV) therapy (HAART).

Soon after the introduction of HAART, patients' body composition changed rapidly. Many patients developed distinct body shape changes affecting fat tissues uniquely. This second paradigm of body composition changes was referred to by various names including the HIV/HAART lipodystrophy syndromes and

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consisted of peripheral lipoatrophy (loss of SAT) and central lipohypertrophy (increase in VAT [1] and, less commonly, other ectopic fat depots). These fat mass changes were often associated with metabolic abnormalities including dyslipidemia and glucose homeostasis alterations [4]. From the very first description of lipodystrophy it became apparent that its individual components overlapped significantly with manifestations of the metabolic syndrome, a constellation of abnormalities that lead to an increased risk of cardiovascular disease (CVD), type II diabetes mellitus (T2DM) and overall mortality in the general population. This was the early sign of a new clinical syndrome characterized by a series of HIV-associated non-AIDS conditions, namely cardiovascular, bone, liver, and renal diseases, as well as nondementing cognitive dysfunction and other noncommunicable diseases.

We are now facing a third-related HIV syndrome mainly characterized by an overlap between the increasing numbers of aging HIV subjects and the increase in proportion of older subjects occurring in the general population. More middle-aged and older adults are contracting new HIV infections, and more people living with HIV disease are living for longer due to medical treatment advances [5–8]. It is predicted that by 2015, more than 50% of HIV-infected people in North America will be older than 50 years [9]. The morphological changes observed in HIV aging patients are characterized by a progressive increase in VAT [10], in parallel with a progressive loss of SAT and of fat-free mass, as generally occurs in aging individuals.

These three paradigms, although historically described in distinct decades, may characterize the clinical picture of the same HIV-infected patient getting access to era-specific HIV care and aging with HIV infection.

What is clear, is that in ARV-treated HIV-infected individuals a progressive increase in VAT is expected over time. Therefore the treatment of excess abdominal fat in patients with lipodystrophy and aging with HIV infection is a relevant clinical issue.

This paper will review the clinical use of tesamorelin (Egrifta®; Theratechnologies; Montreal, Canada), a hGRF (somatoliberin) analog, recently approved in the USA for the management of excess abdominal fat in HIV-infected patients with lipodystrophy.

Methods for assessing VAT

VAT consists of adipose tissue distributed in the three body cavities: intrathoracic, intra-abdominal and intrapelvic. However, most authors refer to VAT as synonymous to intra-abdominal adipose tissue, with a radiological range from 5 cm below L4–L5 to the slice corresponding to the superior border of the liver [11–15].

The easily and reliably measured waist circumference (WC) is recommended for the routine clinical assessment of central adiposity, despite the use of several intra- and inter-ethnic cut-points, as it correlates well with directly measured VAT [16]. However, the sensitivity and specificity of using the WC to diagnose a specific amount of VAT is uncertain.

Imaging techniques are the most precise and reliable methods for a qualitative and quantitative VAT analysis. Computed tomography (CT) and, especially, the gold standard technique MRI, provide methods to noninvasively estimate VAT safely and accurately [16–20]. The MRI VAT measurements have been reported as either area values (cm^2) obtained from a single image, or as volume values (cm^3) derived using tissue area measurements from multiple images. Several MRI techniques and automatic or semi-automated analyses of VAT have been reported [17,21–24].

Imaging of VAT by CT and MRI, usually at the L3–L4 level, although acknowledged as the 'gold standard', is not recommended for screening purposes and is reserved for research settings. An important limitation of the use of imaging modalities to quantify intra-abdominal fat, is the lack of consensus regarding how much fat is too much, associating specific amounts of intra-abdominal fat with risks of specific complications.

Most studies suggest that a VAT in the range of 50–100 cm^2 is associated with a low risk of CVD events [25]. An increased risk of glucose homeostasis abnormalities, dyslipidemia and CVD end points generally occurs with VAT greater then 130–150 cm^2 [25,26]. Clinically, most patients with central adiposity are routinely diagnosed by the patient's noting an increased abdominal girth, with confirmation by an experienced practitioner. However, the accuracy of this method is unknown given the difficulty to differentiate clinically between increased abdominal girth due to SAT from that due to increased VAT. Correlation exists between single-slice CT measurement of VAT and anthropometric measurements in HIV-positive patients with central fat accumulation [27]. In non-obese HIV-negative men, the correlation between VAT measured by MRI and WC is high, with similar correlations reported in HIV-positive subjects [28].

Dual-energy X-ray absorptiometry (DXA) scans, in addition to determining bone mineral density, accurately quantify trunk fat and peripheral fat [29]. A recommendation has been made to adopt the standard that a greater than 20% loss of extremity fat from baseline, while on specific ARVs, is suggestive of drug-associated lipoatrophy. However, DXA scans are not recommended for the routine diagnosis of lipoatrophy. There are no published norms correlating specific amounts of DXA-derived trunk fat with clinical outcomes. What can be considered as increased amounts of trunk fat likely

varies with BMI [30]. Furthermore, DXA scans cannot differentiate VAT from abdominal SAT, although DXA-derived trunk fat correlates well with both CT and MRI-derived VAT [31], and predicts clinical outcomes [32]. Recent studies suggest that new algorithms in use by DXA scanners may give a closer approximation of VAT by trunk fat quantification [33].

Bioelectrical impedance analysis (BIA) provides a safe and low-cost estimate of total body water and total body fat-free mass. The multisegmental BIA approach may be used to assess limb fat and total body fat, but has limited applicability with regards to VAT, and its output may be influenced by other regional changes in fat such as lipoatrophy or obesity [34,35]. More recently, a modified regional BIA technique has been used to estimate VAT, which correlated significantly with VAT by CT (r = 0.88) [36].

Pathophysiology of excess VAT in patients with HIV infection

An increase in the VAT compartment in HIV patients is generally associated with the use of HAART. However, Kotler *et al.* published the results of a retrospective analysis comparing anthropometrically determined body composition parameters in a cohort of seronegative controls and HIV-positive persons, including both untreated and treated patients, who were evaluated before and after 1996, representing the index year of HAART introduction [2]. There were no significant differences in VAT-related parameters in HIV patients during the two time periods, and the use of protease inhibitor (PI) or non-PI HAART had little impact on fat distribution. However, there were marked differences between HIV patients and controls suggestive of either loss of SAT or a relative increase in VAT in the HIV-infected patients, which was related to the amount of total body fat. Gender and HIV-RNA levels also independently predicted increased VAT, the latter suggesting that HIV replication either directly or indirectly contributes to change in VAT. Uncontrolled HIV replication is associated with an inflammatory state and abnormal levels of inflammatory markers [37]. However, the ongoing low level of HIV replication occurring in otherwise successfully treated patients may serve as a chronic inflammatory stimulus. The resulting inflammatory response may contribute to the development of serious non-AIDS-related events [38]. Obesity also has a significant inflammatory component and in HIV-negative subjects increased VAT, regardless of etiology, is associated with abnormal inflammatory markers [39]. In HIV-negative patients with chronic inflammatory conditions, VAT may be increased, as confirmed in persons with rheumatoid arthritis [40].

Soon after the general introduction of HAART in the mid-1990s some patients noted the development of distinct body shape changes. The most common site for abnormal fat accumulation in treated HIV patients is the VAT compartment but excess fat has also been detected in the dorsocervical, hepatic, cardiac, intrathoracic and subcutaneous regions, which may also contribute to the metabolic abnormalities [41–44]. Increased fat also occurs in the intermuscular [45] and intramyocellular [46] compartments, affecting glucose homeostasis. The development of excess VAT is associated with exposure to several of the PI class of ARVs, plus efavirenz, a non-nucleoside reverse transcriptase inhibitor (NNRTI) [47,48]. Several of the first-generation PI drugs have been closely associated with central lipohypertrophy. This association is less certain with the more recently approved PIs, although an increase in DXA-derived trunk fat is often noted following HAART initiation.

Table 1 shows CT- and DXA-determined VAT changes in treatment-naive HIV patients initiating HAART. Although an increase in DXA-derived trunk fat may represent a 'return-to-health phenomenon', Table 1 does not show a consistent pattern of increase in trunk fat with different ARVs associated with minimal or no changes in VAT, which could then possibly be interpreted to represent such a phenomenon. In addition, there are no data to suggest that untreated patients with elevated HIV RNA have lower than normal VAT. The increase in VAT occurring with some HAART regimens, patients with normal baseline VAT, and especially if it is progressive, may well predispose patients to adverse metabolic outcomes. Overall, it is premature to conclude that current HAART regimens are either not associated with trunk adiposity, or that this early increase merely represents a non-ARV-related epiphenomenon.

The pathophysiology of HIV/HAART associated abdominal obesity is complex and of multifactorial etiology including factors related to pre-HIV exposure body composition, HIV effects and ARV-associated sequelae. PI and NNRTI activate adipocyte nuclear transcription factors with downstream effects leading to lipohypertrophy [49].

Serum markers of chronic inflammation persist despite effective HAART [38,50]. In a prospective study of HIV patients and controls, WC increased more rapidly in untreated HIV patients versus controls [51]. This finding may be related to HIV inflammation and aging. Other aging-related factors may also contribute to lipohypertrophy. VAT is increased in hypogonadism [52], which occurs in untreated HIV patients and persists in treated patients [53]. The growth hormone (GH) axis is abnormal in both untreated and treated HIV patients [54]. GH deficiency in the general population is associated both with increased VAT and CVD risk factors [1,55].

Table 1. Antropometric changes in HIV patients starting highly active antiretroviral therapy.

Study (year)	HAART			BL				Arm 1		Arm 2		Arm 3		Ref.
	Backbone	Comparators	Duration (weeks)	n (m:f)	Age (ys)	CD4	$Log_{10}V_L$	CT	DXA	CT	DXA	CT	DXA	
Jemsek *et al.* (2006)	AZT + 3TC	ATV vs EFV	48	210 (145:55) BMI-23.5	30	325	4.75	ATV BL: 54 cm^2 F/U: +40%	ATV BL: 5.9 kg F/U: +4%	EFV BL: 57 cm^2 F/U: +22%	EFV BL: 6.3 kg F/U: +2%	–	–	[109]
Carr *et al.* (2008)	TDF + 3TC	TPV/r-100 vs TPV/r-200 vs LPV/r	48	140 (104:36) BMI-23.1	35	230	5.00	TPV/r-100 BL: 72 cm^2 F/U: -8%	TPV/r-100 BL: 7.5 kg F/U: -4%	TPV/r-200 BL: 63 cm^2 F/U: -14%	TPV/r-200 BL: 7.9 kg F/U: -2%	LPV/r BL: 71 cm^2 F/U: -4%	LPV/r BL: 6.1 kg F/U: +12%	[25]
McComsey *et al.* (2009)	3TC + D4T	ATV vs ATV/r	96	200 (143:57)	35	200	5.00	ATV BL: na F/U: +33%	ATV BL: 9.9 kg F/U: +15%	ATV/r BL: na F/U: +32%	ATV/r BL: 8.7 kg F/U: +18%	–	–	[110]
Moyle *et al.* (2009)	TDF + FTC	ATV/r vs LPV/r	96	224 (153:71) BMI-23.6	36	264	5.00	ATV/r BL: 85 cm^2 F/U: +15%	ATV/r BL: na F/U: +33%	LPV/r BL: 85 cm^2 F/U: +10%	LPV/r BL: na F/U: +32%	–	–	[111]
Boothby *et al.* (2009)	EFV	AZT+3TC vs TDF+FTC	24	32 (16:16) BMI-25.1	34	210	4.85	AZT + 3TC BL: 39 cm^2 F/U: +73%	AZT + 3TC BL: 8.1 kg F/U: +1%	TDF + FTC BL: 56 cm^2 F/U: +28%	TDF + FTC BL: 6.7 kg F/U: +21%	–	–	[112]
McComsey *et al.* (2011)†	ABC/3TC or TDF/ FTC	ATV/r vs EFV	96	269 (228:41)	38	233	4.60	ATV/r BL: 84 cm^2 F/U: +27%	ATV/r BL: 9.4 kg F/U: +36%	EFV BL: 84 cm^2 F/U: +12%	EFV BL: 9.4 kg F/U: +21%	–	–	[113]
McComsey *et al.* (2011)†	ATV or EFV	ABC/3TC vs TDF/FTC	96	269 (228:41)	38	233	4.60	ABC/3TC BL: 84 cm^2 F/U: +15%	ABC/3TC BL: 9.4 kg F/U: +28%	TDF/FTC BL: 84 cm^2 F/U: +12%	TDF/FTC BL: 9.4 kg F/U: +25%	–	–	[113]
Rockstroth *et al.* (2011)†	TDF/FTC	RAL vs EFV	156	112 (99:13)	37	230	4.94	–	RAL BL: 11.0 kg F/U: +21%	–	EFV BL: 10.0 kg F/U: +38%	–	–	[114]

†Data extracted from conference poster or oral presentation.

3TC: Lamivudine; ABC: Abacavir; ATV: Atazanavir; AZT: Azidothymidine; BL: Baseline; CT: Computerised tomography; D4T: Stavudine; DXA: Dual-energy X-ray absorptiometry; EFV: Efavirenz: f: Female; FTC: Emtricitabine; F/U: Follow up; HAART: Highly active antiretroviral therapy; LPV: Lopinavir; m: Male; na: Not applicable; r: Ritonavir; RAL: Raltegravir; TDF: Tenofovir; TPV: Tipranavir; V_L: HIV viral load; ys: Years.

Consequences of VAT changes

A recent scientific statement from the American Heart Association underlines that there is a clear association between excess adiposity and adverse health consequences, including CVD and diabetes [56]. Reduction in adiposity is associated with improvement in obesity-related comorbidities. Abdominal obesity and general obesity are associated with cerebrovascular disease (odds ratio [OR]: 1.22–2.37), coronary heart disease (OR: 1.21–3.25), and all-cause mortality (OR: 1.9–2.42) [56].

Excess fat is associated with metabolic abnormalities; high levels, specifically, of VAT are characterized by the most severe metabolic abnormalities [56].

The metabolic and morphologic changes observed in persons with HIV infection receiving combined ARV therapy (cART) show considerable overlap with diagnostic criteria for the metabolic syndrome [57,201], which lead to an increased risk of CVD and diabetes mellitus in the general population.

Observational studies suggest an increased risk of CVD among HIV-positive patients compared with the general population [58] and an increased risk of myocardial infarction in HIV-positive persons with each year of HAART exposure, particularly to the PI class [59,60]. Traditional CV risk factors, such as smoking, dyslipidemia, and impaired glucose tolerance are more common among HIV-positive patients and contribute significantly to CV events [61]. The contribution of emerging CV risk biomarkers to risk in HIV is less established.

Silent plaque imaging assessed by coronary artery calcium (CAC) score, a sensitive marker of atherosclerosis, is associated with total coronary atherosclerotic disease burden.

An observational cross-sectional study of 372 HIV-positive patients receiving cART found a CAC score of >10 in 134 patients (36%), with a median CAC score of 50 (range 10–1243). Lipoatrophy alone (OR: 3.82; 95% CI: 1.11–13.1), fat accumulation alone (OR: 7.65; 95% CI: 1.71–37.17) and mixed lipodystrophy phenotypes (OR: 4.36; 95% CI: 1.26–15.01) were strongly associated with the presence of CAC after adjusting for age, sex, hypertension, and cumulative exposure to ARV therapy [62].

Recent data from a study evaluating the relationship between visceral adiposity measurements and coronary artery disease (CAD) detected by CT angiography demonstrated that VAT is independently related to coronary atherosclerosis after adjustment for CV risk variables in the non-HIV population. In particular, patients with a VAT area greater than 145 cm^2 have been shown to have a threefold (95% CI: 1.3–6.3) CAD risk compared with those with lower values [26].

Data linking VAT to CV risk in HIV-infected patients have become available during the past 4 years. In a study involving HIV-infected men without history or symptoms of CAD, VAT was positively related to the CAC score [63]. This finding was confirmed in a prospective, observational study of patients receiving ARV therapy in which VAT was significantly associated with absolute CAC progression [64]. Mean VAT in patients with CAC progression was 177 cm^2, whereas the value was 122 cm^2 in patients with unchanged CAC. Of note, 76% of patients with CAC progression showed >15% yearly progression, a threshold associated with increased risk of myocardial infarction in the general population.

As in the general population, in HIV-positive individuals there is an independent relationship of upper trunk and VAT with insulin resistance [44].

A recent paper from McCutchan *et al.* explored the relationships between HIV-associated neurocognitive disorder and metabolic variables in 130 participants of the CHARTER cohort research. Case definitions of cognitive status were analyzed both with Frascati criteria for HAND [65] and with automated global deficit scores. A multivariate regression model was built to model neurocognitive impairment as a function of demographic, medical, and metabolic predictors of interest including BMI and average mid-WC. Central obesity, but not more generalized increases in BMI, was associated with a higher prevalence of neurocognitive impairment in HIV-infected persons [66].

An important recent study looking at the association between regional body composition and mortality in HIV-infected patients showed that increased VAT and decreased limb muscle were independently associated with elevated 5-year mortality risk in a full multivariate model analysis including skeletal muscle and adipose tissue, simultaneously [67]. Patients in the highest tertile of VAT were reported to have a odds of death 2.1-fold higher compared with patients with the lowest VAT tertile. Lower limb fat was not statistically associated with mortality in unadjusted or adjusted analyses.

The results of a previous publication from the FRAM study indicated that greater VAT and lower leg SAT were associated with elevated 10-year Framingham Risk Scores in HIV-infected men [68]. It should be noted that the unexpected negative correlation between leg SAT and 10-year Framingham Risk Scores in HIV-infected men was a reversal of the association observed in control men and, according to the authors, warrant further study.

A possible association between increased VAT and a decrease in thoracolumbar bone mineral density has been suggested but not yet substantiated [69,70].

These findings suggest that treatment strategies aimed at reducing VAT while preserving or increasing muscle mass may have an important impact on clinical outcomes for HIV-infected patients.

Taken together, the above data indicate that an increased risk of metabolic abnormalities and cardiometabolic events may occur with elevated waist girth or VAT (>130 cm^2), although there is still no consensus in the literature regarding a specific gender- and ethnic-controlled amount of VAT above which risks are increased.

Relative GH deficiency has been described in patients with HIV-associated central fat accumulation [71]. Among HIV-positive patients, reduced pulse height and overnight GH concentrations are most strongly associated with increased visceral adiposity [71–73]. Reduced GH secretion is independently associated with dyslipidemia, higher glucose and C-reactive protein among HIV-infected patients with abdominal fat accumulation [74].

Central adiposity and increased VAT diminishes health-related quality of life through erosion of self-esteem and decreased social functioning [75]. Patient dissatisfaction about body image may lead to anxiety and depression as well as sexual dysfunction [76,77]. Dissatisfaction with body shape may unfavorably impact adherence to cART [78].

Management strategies for increased VAT in HIV infection

General aspects

Management of abdominal obesity in the general population is complicated and of uncertain long-term efficacy. A reduced-calorie diet and lifestyle that includes a sustained exercise program decreases VAT in the short term, as well as the risk of T2DM and CVD. The use of weight-reducing drugs remains controversial, their ability to significantly reduce VAT and decrease CVD risk is uncertain, and toxicities are common. In GH-deficient subjects with abdominal obesity, GH replacement reduces increased VAT in the short term but follow up has not been long enough to determine whether CVD risk is also decreased.

Studies assessing the effects of exercise in HIV-positive patients with central fat accumulation indicate mixed results. Most studies suffer from limitations such as short duration, small patient numbers and variability in inclusion criteria. Case-control data suggest that diets higher in total protein and dietary fiber and performing more resistance training are associated with a lower risk of central adiposity (defined as a weight-to-hip ratio > 0.95) [79].

Once central adiposity is clinically diagnosed, several studies demonstrate benefits on central fat accumulation through a combined program of diet, aerobic exercise and progressive resistance training [80,81]. Broadly, data suggest well-supported diet and exercise regimens are worthwhile but not sufficient in the prevention and management of central adiposity in HIV-positive persons.

The management of abdominal obesity in treated HIV patients is equally challenging. Changing a PI drug possibly associated with truncal adiposity for either an NNRTI drug or one of the newer PIs has not generally been effective in reducing VAT. Two recent studies highlight this situation. In a small study, in overweight subjects (mean weight = 88 kg, mean BMI = 29 kg/m^2) on ritonavir-boosted lopinavir, those who were switched to ritonavir-boosted atazanavir showed a modest but significant reduction in VAT [82]. However, in a larger study that enrolled stable, normal-weight patients, also on ritonavir-boosted lopinavir (mean weight = 67 kg, BMI = 23 kg/m^2), those who switched to ritonavir-boosted atazanavir generally had a significant increase in VAT [83]. A reasonable explanation for the variable effects on VAT of switching to atazanavir remains speculative but may be partially related to the different baseline trunk fat content.

The insulin-sensitizing drug metformin causes a modest reduction of VAT in HIV patients, but is also associated with worsening lipoatrophy [84]. It is unknown whether metformin may be effective in patients with abdominal obesity and glucose homeostasis abnormalities but without peripheral lipoatrophy. A recent small study using recombinant leptin decreased VAT significantly [85]. In a study of testosterone replacement in hypogonadal HIV males with confirmed abdominal obesity, the DXA-derived trunk fat decreased but the VAT did not change, highlighting the need to use accurate imaging modalities to properly assess responses to interventions [86].

Administration of GH was investigated as a potential strategy to treat visceral fat accumulation in patients with HIV lipodystrophy on the basis of its lipolytic actions and data suggesting that HIV-infected patients with visceral fat accumulation have reduced secretion of GH [71,87]. Although GH significantly decreased VAT, insulin resistance and other adverse effects linked to excess GH commonly occurred, perhaps related to the sustained, supraphysiologic GH levels, rather than the levels related to normal pulsatile secretion of endogenous GH [88–90]. Treatment with GHRH – an endogenous anterior pituitary secreted peptide that acts on the pituitary somatotroph cells to stimulate the synthesis and pulsatile release of endogenous GH – was therefore investigated as an alternative strategy, with the intention of restoring a more physiological pattern of GH activity [89,90].

The pharmacokinetic properties of native GHRH are not well suited for clinical development, partly owing to its rapid degradation by the protease DPP4. To address

this issue, the properties of modified analogs of native GHRH were investigated. This led to the development of tesamorelin (originally known as TH9507), a synthetically produced 44 amino acid sequence of hGHRH with a hexenoyl moiety attached to the tyrosine residue at the amino terminus (Figure 1) [91] . The N-terminal modification increases the potency and stability of tesamorelin relative to the natural peptide [92].

In *in vitro* studies, the binding affinity of tesamorelin to the GHRH receptor was roughly similar to that of unmodified hGHRH (50% inhibitory concentration 0.069 vs 0.083 nmol/l) [202], but tesamorelin was more resistant to cleavage and inactivation by DPP-IV than hGHRH [203].

Like hGHRH, tesamorelin acts on the pituitary somatotroph cells to stimulate the synthesis and release of endogenous GH [202,203] and, subsequently, increases IGF-1 and IGF-binding protein-3 levels [93]. GH interacts with specific receptors in many tissues, including muscle, fat, liver, heart, kidney and brain, to exert its pharmacodynamic effects, either directly or by the stimulation of IGF-1, insulin and free fatty acids [94]. It is thought that the major mechanism by which GH administration reduces total fat mass involves enhancement of the lipolytic activity of adipose tissue and the reduction of triglyceride (TG) accumulation [95].

In preclinical studies, tesamorelin was found to be resistant to deactivation by DPP4, and markedly increased plasma levels of GH and IGF-1 after daily dosing [91].

Clinical studies of tesamorelin

In clinical studies, daily doses of 0.5-, 1.0-, or 2.0-mg tesamorelin, given subcutaneously, significantly increased IGF-1 and GH levels within the normal range. A 12-week, randomized, double-blind, placebo-controlled study, using daily doses of 1.0- or 2.0-mg tesamorelin, was undertaken in treated HIV subjects with central fat accumulation diagnosed using anthropometrics [93]. The surrogate markers used, WC ≥ 95 cm and a WHR ≥ 0.94 in men and WC ≥ 94 cm and WHR ≥ 0.94 in women, are associated with increased VAT in seronegative individuals [96]. Mean baseline CT-determined VAT ranged from 158–190 cm^2 across the treatment groups. Subjects with impaired fasting glucose (IFG) or asymptomatic diet-controlled T2DM were enrolled, based on results showing no adverse effects of tesamorelin in patients with T2DM [97]. Trunk fat decreased by 9.2% in the 2.0-mg group ($p = 0.014$ for the 2.0-mg vs placebo group) and VAT decreased significantly by 15.7% within the 2.0-mg group ($p = 0.03$). Importantly, SAT did not change between groups. Significant treatment-associated reductions occurred in baseline elevated TG levels and in the total cholesterol–HDL-cholesterol ratio. HDL cholesterol increased significantly. No subject with baseline IFG developed T2DM and an increase in the fasting insulin and homeostasis model assessment of insulin resistance occurred only within the 2.0-mg group. Self-reported abdominal bloating and enlarged abdominal girth improved within the 2.0-mg group ($p < 0.05$).

Two large, placebo-controlled, randomized, similar but independent studies of 2.0-mg tesamorelin were subsequently undertaken using the same enrolment criteria as in the Phase II study [98,99]. The mean combined baseline VAT of the placebo and treatment groups in each study was 175 and 190 cm^2. Both studies included a 26-week primary phase followed by a 26-week extension phase during which patients on tesamorelin were rerandomized to continued tesamorelin or placebo while patients on placebo received tesamorelin [99,100]. At enrollment, 22% had IFG and 7.4% had diet-controlled T2DM. Results were reported for each study and in a pooled analysis [101] in which VAT decreased significantly by 15.4% compared with placebo. Limb fat decreased by a clinically insignificant 0.2% in the treatment compared with the placebo group. Trunk fat (by DXA) and WC also decreased significantly in the treatment compared with placebo group. IGF-1 levels increased significantly but remained generally within the physiologic range (84 ± 101%). Relative to placebo, TG and total cholesterol–HDL ratio in treated subjects decreased significantly by 12.3 and 7.2%, respectively. Overall, there were no effects on glucose-related parameters except for a 0.14% increase in glycated hemoglobin, from 5.26–5.39% in treated patients, of unknown clinical significance. Subjects on placebo experienced a decline in quality of life, whereas this remained unchanged in treated persons.

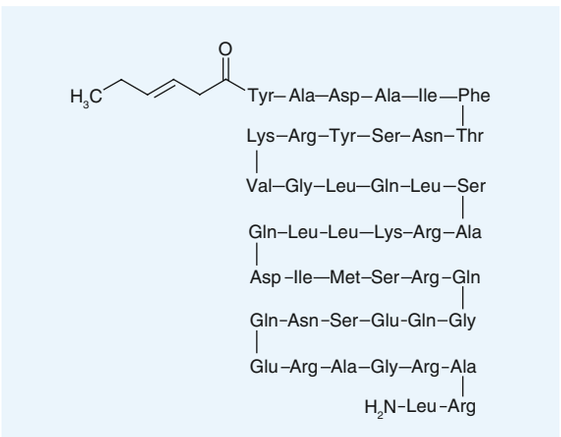

Figure 1. Structure of tesamorelin.

During the extension phase, treated subjects achieved an overall 17.5% reduction in VAT compared with baseline, with maintenance of the 26-weeks improvements in trunk fat, WC, TG and IGF-1. No SAT or limb fat reduction occurred with treatment at 52 weeks versus baseline. However, in subjects switched to placebo at 26 weeks both the VAT and trunk fat returned to baseline within 3 months.

Overall, musculoskeletal, local and several treatment-related adverse events were more common in the tesamorelin group, although adverse events resulting in study termination did not differ between groups [101]. Self-limited hypersensitivity reactions occurred more often in the treated group (2.9 vs 0.4%). IgG antibodies to tesamorelin occurred in 49% of treated and 3% of control patients but were unrelated to outcomes.

A *post hoc* analysis explored whether changes in VAT were associated with the metabolic effects of tesamorelin using data from the two aforementioned multicenter, randomized, placebo-controlled, double-blind Phase III studies of tesamorelin [98,100–102].

As per a consensus roundtable, a decrease of ≥8% in baseline VAT area was determined to be the minimally clinically significant amount of reduction in VAT required for proof-of-efficacy in pharmacologic studies of HIV-associated abdominal obesity [103] and was used to define 'responders', as specified *a priori* in the data analysis plan. In total, 402 (73%) of the tesamorelin subjects and 197 (74%) of the placebo subjects met criteria for perprotocol analysis at 26 weeks. The responder rate (VAT reduction ≥ 8%) was higher for tesamorelin-treated patients than for placebo recipients at 26 weeks (69 vs 33%; p <.001) and rose slightly among those who continued to receive tesamorelin for 52 weeks (72%). In total, 16 out of the 39 nonresponders at week 26 became responders by week 52. Changes in TG level (Figure 2A), fasting glucose level (Figure 2B), homeostasis model assessment of insulin resistance value (Figure 2C), and 2-h glucose following 75-g oral glucose load (Figure 2D) in responders and nonresponders to tesamorelin at 26 and at 52 weeks are shown in Figure 2 [102].

In this analysis, it was shown that, in contrast to nonresponders, responders, defined by the ≥8%

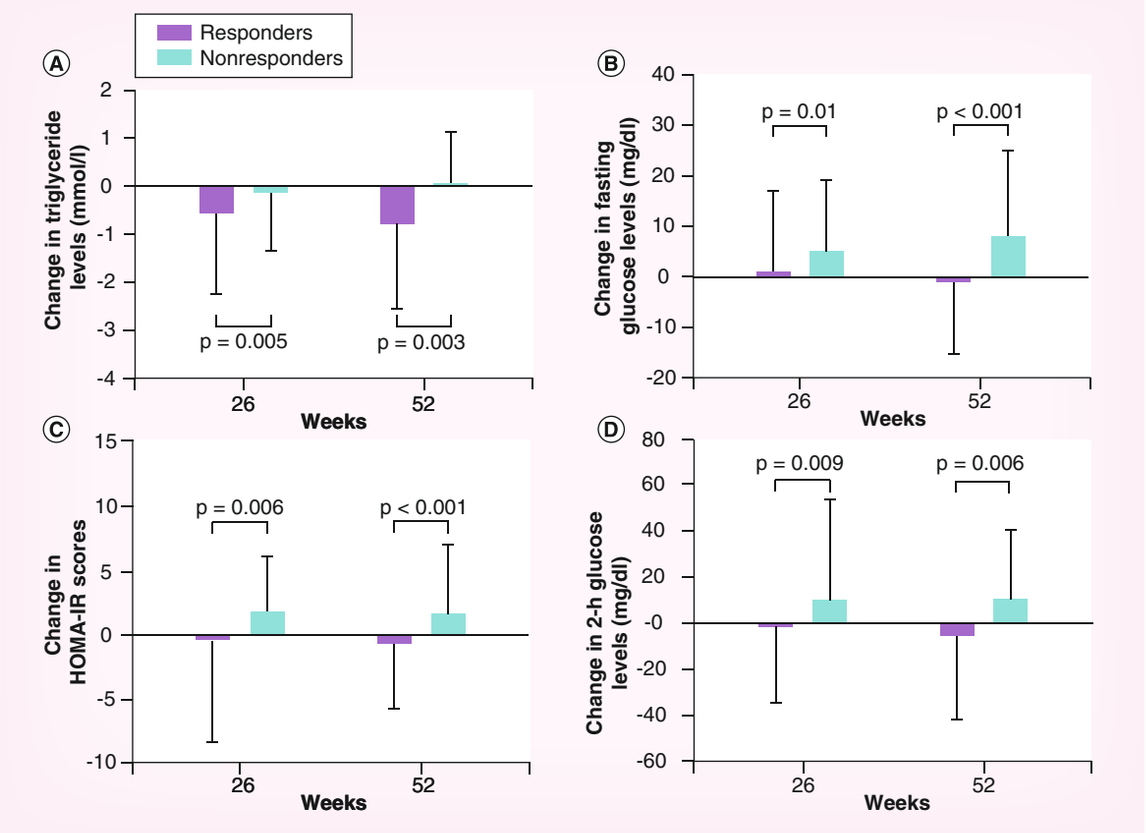

Figure 2. Changes in responders and nonresponders to tesamorelin at 26 and 52 weeks. (A) Triglyceride levels, **(B)** fasting glucose levels, **(C)** HOMA-IR values, and **(D)** 2-h glucose following 75 g oral glucose loads [110].
HOMA: Homeostasis Model of Assessment; IR: Insulin resistance.

reduction in VAT as noted above, experienced significantly greater improvements in levels of TGs and adiponectin and preservation of long-term glucose homeostasis over 52 weeks, suggesting that reduction of VAT was associated with distinct metabolic benefits in this population.

In addition to metabolic benefits, greater responses to tesamorelin in terms of VAT reduction were also associated with less distress regarding abdominal adiposity, and this may be an important benefit of therapy in patients among whom baseline body dysmorphia and related distress have been shown [104].

A separate analysis showed an association between baseline VAT and serum levels of inflammatory markers tPA and PAI-1 levels and an inverse association with serum adiponectin levels [105]. Patients receiving tesamorelin experienced a significant overall decrease in serum tPA antigen concentrations, as well as an increase in serum adiponectin. These improvements were not felt to be associated with the physiologic increase in GH as there was no association between changes in tPA levels and IGF-1, a marker for change in GH. Overall, it was felt that the beneficial effects on these inflammatory and fibrinolytic markers were related to the primary effect of tesamorelin on decreasing VAT.

These short-term studies are consistent with an overall beneficial effect of tesamorelin on decreasing elevated baseline VAT and on improving metabolic parameters associated with increased VAT. The drug was generally well tolerated. Tesamorelin was recently approved by the US FDA for the reduction of excess abdominal fat in HIV-infected patients with manifestations of HIV/ HAART lipodystrophy [106]. Careful and longer follow up will be required to clarify several important issues. A possible association between long-term exposure to supraphysiologic IGF-1 levels and an increased cancer risk has been suggested in the general population [107]. This potential risk with tesamorelin may be minimized, however, as the increased IGF-1 generally remains within the normal range. A recent analysis of GH replacement in patients with GH deficiency showed no association with malignancy if IGF-1 levels were targeted to within normal age-related ranges [108]. The FDA recommends that IGF-1 be monitored in tesamorelin-treated patients and should be discontinued if levels increase persistently by more than three standard deviations. Similarly, patients' glucose parameters should be followed and stopping treatment considered if either *de novo* impaired glucose tolerance or laboratory evidence of T2DM develops. Furthermore, long-term effects on relevant cardiometabolic parameters are unknown, as is the optimal treatment duration and options for the long-term maintenance of decreased VAT (e.g., using lower maintenance doses or cyclic treatment).

Future perspective

Abdominal adiposity is an ongoing concern in treated HIV patients and is a complication that will likely continue to occur, especially as clinically stable patients grow older. An association of increased VAT with adverse clinical outcomes is emerging. The etiology is multifactorial and an association with GH deficiency appears consistent and significant. Current options for successfully reducing the increased VAT are limited.

Executive summary

Methods for assessing visceral adipose tissue

- The gold standard to measure visceral adipose tissue (VAT) is through computerised tomography scan.

Consequences of VAT changes

- In antiretroviral-treated HIV-infected individuals a progressive increase in VAT is expected over time and is associated with increased cardiovascular risk.

Pathophysiology of excess VAT in patients with HIV infection

- Increased VAT may have multiple etiologies; HIV *per se*, chronic inflammation, antiretroviral drugs, aging and growth hormone deficiency.

Management Strategies for Increased VAT in HIV Infection

- No gold standard medical therapy exists to manage increased VAT.

Clinical studies of tesamorelin

- Tesamorelin, a synthetic GHRH analog, has recently been approved by the US FDA for the treatment of excess abdominal fat in HIV-infected patients with lipodystophy.
- Tesamorelin showed significant improvement of VAT and quality of life without worsening peripheral lipoatrophy or glucose homeostasis.

Future perspective

- The benefits are only maintained if dosing is continued; long-term benefit and potential toxicities associated with this drug are uncertain.

The most effective treatment option is tesamorelin, a synthetic 44-amino acid GH-releasing hormone analog that decreases VAT area by approximately 15% over 26 weeks of treatment and by 18% over 52 weeks. Long-term benefit and potential toxicities associated with this drug are uncertain. The association between VAT reduction and surrogate markers for CVDs and markers of chronic inflammations are needed.

Novel pharmacologic options are emerging and ongoing investigations will clarify their role in the therapeutic armamentarium.

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