The HIV lipodystrophy syndrome includes subcutaneous lipoatrophy, with the lower body affected more than the upper body. Particular antiretroviral drugs, especially thymidine analogues, are the major cause of lipoatrophy (which is not reversible\(^1\)), whereas accumulation of visceral adipose tissue (VAT) is not linked to specific drugs\(^1\). Although lipoatrophy and VAT accumulation are not linked, they can occur in the same patient. Dyslipidaemia is induced by HIV itself, specific antiretroviral drugs, lipoatrophy and VAT accumulation, as well as the usual dietary and genetic factors in the absence of HIV infection\(^1\).

The synergistic effects of the HIV-related factors, particularly in those with both lipoatrophy and VAT accumulation, make the dyslipidaemia worse and harder to treat, and some of the same factors induce insulin resistance. These metabolic complications might increase the risk of cardiovascular disease, and the changes in body composition are also distressing\(^2\) and could reduce therapy adherence\(^3\).

**Basis of discovery**
Administration of growth hormone 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 growth hormone\(^4\)\(^-\)\(^6\). However, direct therapy with growth hormone could be associated with insulin resistance and other adverse effects linked to excess growth hormone, perhaps because it leads to sustained levels of growth hormone, rather than the fluctuating levels provided by the normal pulsatile secretion of the endogenous hormone\(^6\)\(^-\)\(^8\). So, treatment with growth hormone-releasing hormone (GHRH) — a peptide that acts on the pituitary somatotroph cells to stimulate the synthesis and pulsatile release of endogenous growth hormone — was investigated as an alternative strategy, with the intention of restoring a more physiological pattern of growth hormone activity\(^5\)\(^-\)\(^8\).

**Drug properties**
Although initial studies supported the potential of GHRH for treating visceral fat accumulation in HIV-associated lipodystrophy\(^9\), the pharmacokinetic properties of GHRH were not well suited for further development, partly owing to its rapid degradation by the protease dipeptidyl peptidase 4 (DPP4). To address this issue, synthetic analogues of GHRH modified with hydrophobic chains were investigated\(^9\). This led to the discovery of tesamorelin (originally known as TH9507), which consists of a synthetically produced 44 amino acid sequence of human GHRH with a hexenoyl moiety attached to the tyrosine residue at the amino terminus\(^8\)\(^-\)\(^10\). In preclinical studies, tesamorelin was found to be resistant to deactivation by DPP4, and markedly increased plasma levels of growth hormone and insulin-like growth factor 1 (IGF1) after daily dosing\(^9\).

**Clinical data**
The safety and efficacy of tesamorelin (2 mg administered by subcutaneous injection once a day) was investigated in two randomized, double-blind, placebo-controlled studies involving HIV-infected patients with lipodystrophy and excess abdominal fat\(^10\)\(^-\)\(^12\). Key inclusion criteria included a waist circumference ≥95 cm and a waist-to-hip ratio ≥0.94 for men, and a waist circumference ≥94 cm and a waist-to-hip ratio ≥0.88 for women\(^10\)\(^-\)\(^12\). Patients were on a stable antiretroviral regimen for at least 8 weeks before randomization\(^10\)\(^-\)\(^12\).

The two trials, which involved 412 patients and 404 patients, consisted of a 26-week main phase and a 26-week extension phase\(^10\)\(^-\)\(^12\). In the main phase, patients were randomized in a 2:1 ratio to either tesamorelin or placebo\(^10\)\(^-\)\(^12\). The primary end point was the percentage change from baseline in VAT, as assessed by computed tomography\(^10\)\(^-\)\(^12\). Secondary end points included changes in patient-reported outcomes related to body image, triglyceride levels, ratio of total cholesterol to high-density lipoprotein (HDL) cholesterol and IGF1 levels\(^10\)\(^-\)\(^12\). In the double-blind extension phase, 381 patients in the tesamorelin groups who completed the 26-week main phase were re-randomized to receive 2 mg tesamorelin or placebo for a further 26 weeks in order to assess maintenance of VAT reduction and to gather longer-term safety data\(^10\)\(^-\)\(^12\).

In a pooled analysis of the two trials\(^13\), after 26 weeks, VAT decreased by 24 cm\(^2\) in patients receiving tesamorelin compared with an increase of 2 cm\(^2\) in patients receiving placebo, representing a treatment effect of −15.4%. Tesamorelin improved patient and physician ratings of abdominal profile, and patients receiving tesamorelin showed significant decreases in triglyceride levels (−37 mg per dl compared with an increase of 6 mg per dl with placebo) and cholesterol to HDL ratio (−0.18 compared with 0.18 with placebo)\(^13\). Mean levels of IGF1 also increased in patients receiving tesamorelin compared with those receiving placebo\(^13\).

After 52 weeks, decreases in VAT (−35 cm\(^2\)), waist circumference (−3.4 cm) and triglycerides (−48 mg per dl) and cholesterol parameters were maintained in the patients that continued to receive tesamorelin, whereas patients switched to placebo showed significant increases in VAT\(^13\). No clinically meaningful differences in glucose parameters were observed between the groups after 26 and 52 weeks\(^13\).

**Indications**
Tesamorelin is approved by the US Food and Drug Administration (FDA) for the reduction of excess abdominal fat in HIV-infected patients with lipodystrophy\(^10\).
Analysing issues in the management of VAT accumulation in HIV-infected patients with lipodystrophy is Carl Grunfeld, M.D., Ph.D., Professor of Medicine, University of California San Francisco, and Associate Chief of Staff for Research and Development, Veterans Affairs Medical Center, San Francisco, USA.

Multiple epidemiological studies have found that visceral fat levels are associated with the cardiovascular risk factors of hypertriglyceridaemia, low levels of HDL cholesterol and insulin resistance. However, whether visceral fat is a marker or a cause of the metabolic disturbances was not determined until it was shown in humans that removal of visceral fat improved insulin sensitivity, whereas removal of subcutaneous fat did not.

The approval of tesamorelin in patients with VAT accumulation and HIV lipodystrophy is the first for any drug to reduce VAT. Tesamorelin treatment reduced triglyceride levels and the cholesterol to HDL ratio, which might reduce cardiovascular risk. For HIV-infected patients with dyslipidaemia due to a combination of HIV-related factors (such as HIV itself, ritonavir and efavirenz) and factors outside of HIV (such as diet) — a group that was selected for by the inclusion criteria of visceral obesity and lipodystrophy — tesamorelin offers an additional therapeutic approach that may be needed, given the difficulty of treating hypertriglyceridaemia in HIV-infected patients. Importantly, whereas experimental treatment of similar patients with growth hormone induced insulin resistance, tesamorelin therapy did not induce any increase in fasting insulin levels.

The effects of tesamorelin are reversed after cessation, and the role of long-term therapy with tesamorelin is not yet clear. The average 15-4% reduction in visceral fat was accompanied by a clear-cut improvement in body appearance distress rating over the course of the studies, but whether that patient perception will continue in the long term is unknown. Whether the average 37 mg per dl decrease in triglyceride levels will be perceived as adequate by caregivers and patients is also unknown. These positive effects must be put into the context of a daily injection (>20% of subjects discontinued therapy in both drug and placebo arms in the trials), injection site reactions in 25% of patients and the high cost with unknown rules for insurance coverage.

The most important unknown is whether tesamorelin therapy decreases cardiovascular disease events. Given the size of the population that meets criteria for treatment and the degree of improvement in dyslipidaemia, such a study probably cannot be done. With that unknown, the manufacturer has stated that careful consideration should be given as to whether to continue tesamorelin in patients who do not show a reduction in VAT on computed tomography scans or in waist circumference.

Although the safety profile of tesamorelin in these studies looks good, as with any new drug, one cannot predict long-term safety. Tesamorelin does not induce insulin resistance, as did growth hormone therapy in similar patients, and the changes in glucose metabolism are not clinically substantial; however, a small but significant increase in haemoglobin A1c of 0.12% was seen in a group that was selected for by the inclusion criteria of visceral obesity and lipodystrophy — tesamorelin-treated group had a hazard ratio of 3.3 for developing a haemoglobin A1c of ≥6.5, the diagnostic level for diabetes. Whether the observations of worsening of glucose metabolism will offset the improvements in lipid levels remains to be seen. An additional unknown is whether the 84% increase in IGFI levels seen in patients receiving tesamorelin might have consequences, such as increased malignancy. Caution is urged in treating those with prior malignancy, and a long-term, post-marketing safety study has been requested by the FDA, as well as a study of whether tesamorelin has an impact on diabetic retinopathy.

Box 1 | The market for HIV lipodystrophy

Analysing the market for HIV lipodystrophy is Argyris Dritsela, IMS Health, London, UK.

Treatment for changes in body composition in patients with HIV has usually been provided through surgical care; that is, through liposuction and injectable fillers. The approval of tesamorelin (Egrifta; Theratechnologies/EMD Serono) by the US FDA in November 2010 now provides the first drug for the reduction of excess abdominal fat in HIV-infected patients with lipodystrophy. Tesamorelin will be commercialized in the United States by EMD Serono. Theratechnologies is seeking a partner in Europe, and the company recently announced a distribution and licensing agreement for the product in Latin America and the Middle East with Sanofi-Aventis. Analysts predict peak annual sales in excess of US$350 million. They also highlight that reimbursement will be an important factor in its market penetration, considering the initial price of $23,000 per year for a course of therapy.


Competing financial interests

C. G. declares competing financial interests; see web version for details.