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# Epidemiology, Assessment, and Management of Excess Abdominal Fat in Persons with HIV Infection

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## Abstract

**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 and metformin, both of which have shown benefit for insulin-resistant individuals with isolated fat accumulation. Testosterone supplements may also have benefits in a subset of individuals. Supra-physiological doses of recombinant human growth hormone and the growth hormone releasing hormone analog 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. (AIDS Rev. 2010;12:3-14)**

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## Key words

**Visceral adiposity. Lipodystrophy. HIV. Metabolic syndrome. Metformin. Tesamorelin.**

## Introduction

Outcomes for people in developed countries with HIV infection have dramatically changed with the availability of effective combination antiretroviral treatment

(cART). HIV has become a chronic, manageable infection and management of persons with HIV has refocused on the adverse effects of HIV infection, immune restoration syndromes, and off-target effects of antiretroviral medications. Many common, prevalent diseases of aging appear increased in prevalence and earlier in onset in persons with HIV infection than in the uninfected population.

Soon after the benefits of cART were observed, the FDA warned against glucose intolerance and diabetes mellitus (DM) risk in patients receiving protease inhibitors (PI)<sup>1</sup> and patient networks began reporting morphologic abnormalities, notably increased abdominal

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circumference<sup>2</sup>. Subsequently, case reports and small case series suggested an increase incidence of cardiovascular (CV) events in patients with HIV receiving cART<sup>3,4</sup>. Despite improvements in the convenience of administration and the metabolic safety profile of cART, concerns about morphologic change, CV risk, and DM remain prevalent.

Our understanding of CV risk and the pathogenesis of atherosclerosis has also changed. Beyond lifestyle and genetic factors, immune activation and inflammation have been recognized as important factors in the pathogenesis of atherosclerosis. Similarly, the adipocyte has shifted from being a passive storage cell for triglycerides to a secretory organ of adipokines such as leptin<sup>5</sup>, adiponectin, and inflammatory factors such as tumor necrosis factor alpha<sup>6</sup>. The role of central adiposity and visceral adipose tissue (VAT) in CV and DM risk has been recognized independently and through the metabolic syndrome<sup>7-10</sup>.

Visceral adiposity is both a highly stigmatizing clinical event in persons with HIV and a risk factor for future disease. Subjects with HIV infection have higher VAT than HIV-negative controls with the same body mass index (BMI)<sup>11</sup>. Additionally, HIV infection, elevated VAT, and elevated C-reactive protein are significantly associated, linking HIV and VAT to inflammatory events<sup>12</sup>.

The goal of this review is to summarize recent data regarding HIV infection and accumulation of central adiposity and, specifically, visceral fat, and to discuss clinical issues regarding the routine evaluation of VAT as well as preventive and therapeutic approaches.

## Methods for assessing visceral adipose tissue

Lipohypertrophy may include fat accumulation in the abdominal cavity (VAT), dorso-cervical fat pad, breasts, and other lipomas. Waist circumference independently contributes to CV risk and DM risk<sup>13</sup>. It is also recognized in definitions of the metabolic syndrome as being relevant to CV and DM risk. A range of waist circumference values have been suggested by groups such as the International Diabetic Federation (IDF), who define central obesity as waist circumference > 94 cm for Caucasian men and > 80 cm for Caucasian women, with ethnicity specific values for other groups<sup>14</sup>, and the National Cholesterol Education Program (NCEP), which defines abdominal obesity as waist circumference > 102 cm for men and > 88 cm for women<sup>15</sup>. However, as persons with HIV commonly have lower subcutaneous adipose tissue (SAT), simple abdominal

circumference measurements may underestimate the amount of harmful VAT<sup>16</sup>.

Visceral adipose tissue consists of adipose tissue distributed in the three body cavities: intrathoracic, intraabdominal, and intrapelvic. However, most authors refer to VAT as synonymous to intraabdominal adipose tissue, with a radiological range from 5 cm below L4-L5 to the slice corresponding to the superior border of the liver<sup>17-21</sup>.

Imaging techniques are the most precise and reliable methods for a qualitative and quantitative VAT analysis. Computed tomography (CT) and, especially, magnetic resonance imaging (MRI), the gold standard technique, provide methods to non-invasively estimate VAT safely and accurately<sup>22-26</sup>. The MRI VAT measurements have been reported as either area values (cm<sup>2</sup>) obtained from a single image, or as volume values (cm<sup>3</sup>) derived using tissue area measurements from multiple images. Several MRI techniques and automatic or semi-automated analyses of VAT have been reported<sup>22,27-31</sup>.

The relatively high cost of whole-body scans for MRI and the exposure to radiation for CT led to the use of single-slice studies for this application<sup>32</sup>. Some studies have reported a good correlation between VAT area measured in a single slice and VAT volume measured by using multiple slices<sup>33,34</sup>, whereas others have not<sup>35</sup>. The cut-off point to define visceral obesity has been suggested as 130 cm<sup>2</sup> in men and 110 cm<sup>2</sup> for women<sup>36</sup>. The coefficients of variation for VAT measurements by MRI are ~ 9 to 18%<sup>37-40</sup> and by CT are ~ 2%<sup>41</sup>. The lower coefficient of variation of CT is usually ascribed to a shorter image acquisition time, and CT is thus less vulnerable to image artifacts produced by peristaltic gastrointestinal tract movement<sup>42</sup>.

Abdominal ultrasound measurement has also been reported to provide good and reproducible calculations for VAT, suggesting ultrasonography as a promising technique based upon low cost and easy application. It has been found that pre-peritoneal and subcutaneous fat depositions, as measured by ultrasonography, correlated positively with the visceral fat area measured by CT ( $r = 0.746$ ) with a coefficient of variation of less than 6%<sup>43-46</sup>. Reproducibility across operators, machines, and sites limit the application of ultrasound in clinical studies.

Dual-energy X-ray absorptiometry (DXA) systems provide whole-body and regional estimates of fat mass, and the DXA technique is a widely used method owing to its ease of use, availability, and low radiation exposure. The advantages of DXA include good accuracy

and reproducibility. Disadvantages of DXA include a small amount of radiation, the scanning bed or stretcher has an upper weight limit, and the whole-body field-of-view cannot accommodate large individuals. A DXA provides estimates of trunk and limb fat and as such does not provide sufficient information to reliably evaluate VAT<sup>47,48</sup>.

Bioelectrical impedance analysis (BIA) provides a safe and low-cost estimate of total body water and total body fat-free mass. The multi-segmental BIA approach may be used to assess limb fat and total body fat, but has limited applicability with regards VAT, and its output may be influenced by other regional changes in fat such as lipoatrophy or obesity<sup>49,50</sup>. More recently, a modified regional BIA technique has been used to estimate VAT, which correlated significantly with VAT by CT ( $r = 0.88$ )<sup>51</sup>.

Correlation exists between single-slice CT measurement of VAT and anthropometric measurements in HIV-positive patients with central fat accumulation<sup>52</sup>. Both waist circumference and waist-to-hip ratio (WHR) correlated with VAT in men but not in women. In nonobese men, the correlation between VAT measured by MRI and waist circumference is also high ( $r = 0.77$ )<sup>48</sup>, with similar correlations reported in HIV-positive subjects<sup>53</sup>.

## The prevalence of central adiposity in HIV populations

An initial lack of objective definitions of lipoatrophy and lipohypertrophy hindered objective evaluation of morphologic changes. Thinning of the arms and legs may result in the appearance of abdomen prominence, and, with increased waist circumference, extremities may appear to be smaller. Furthermore, central fat accumulation is common in the general population and an increase in weight, abdominal girth, and VAT is a normal component of aging in the general population<sup>54</sup>. A subsequent case definition of lipodystrophy excluded isolated central adiposity from the definition<sup>55</sup>.

Initial prevalence studies were cross-sectional in nature and typically lacked objective assessments. The larger prevalence studies reported central adiposity in 30-62% of cART recipients<sup>56-60</sup>. Studies published to March, 2007 involving more than 100 patients and reporting subjective outcomes relating to central fat accumulation found prevalence estimates ranging from 13 to 58% (median 30%) of HIV-positive patients<sup>61</sup>. A recent cross-sectional French study, with more than 2,000 HIV-positive patients, showed that a waist circumference indicative of abdominal adiposity by IDF

and NCEP ATP III definitions<sup>15,16</sup> is a common and increasing problem. Increased waist circumference was more common in women than men, and its prevalence was higher in recent recipients of cART. The prevalence of abdominal adiposity was 24-53% in women and 13-29% in men who started cART before 2005, and 43-77% in women and 12-38% in men who started cART after 2005, according to IDF and NCEP ATP III definitions, respectively<sup>62</sup>.

The Fat Redistribution and Metabolic Change in HIV Infection (FRAM) study, a cross-sectional study, examined fat changes in men and women based on concordance between the patient's self-report of a decrease or increase over the previous five years and a researcher's assessment. Approximately 30% of men and 50% of women with HIV had abdominal adiposity. In the FRAM study, MRI measurements of VAT and SAT showed HIV-positive men<sup>63</sup> and women<sup>64</sup> had more fat loss than HIV-negative controls in peripheral and central depots. Among HIV-positive men, peripheral lipoatrophy was more frequent than in controls (38.3 vs. 4.6%;  $p < 0.001$ ), whereas central adiposity was less frequent (40.2 vs. 55.9%;  $p = 0.001$ ), and the presence of central adiposity was not positively associated with peripheral lipoatrophy (OR: 0.71; 95% CI: 0.47-1.06;  $p = 0.10$ )<sup>63</sup>. Among HIV-positive women, peripheral lipoatrophy was more frequent than in controls (28 vs. 4%;  $p < 0.001$ ), whereas central lipohypertrophy was similar (62 vs. 63%), and those with central lipohypertrophy were less likely to have peripheral lipoatrophy (OR: 0.39; 95% CI: 0.20-0.75;  $p = 0.006$ ) than those without central lipohypertrophy. On MRI, HIV-positive women with clinical peripheral lipoatrophy had less SAT in peripheral and central sites and less VAT than HIV-positive women without peripheral lipoatrophy. Compared with controls, HIV-positive women had less SAT in the legs, regardless of the presence or absence of lipoatrophy; however, those without lipoatrophy had more VAT and upper-trunk SAT than controls<sup>64</sup>. The lack of correlation between central adiposity and limb fat loss argues for separate processes for determining peripheral lipoatrophy and central adiposity<sup>63,64</sup>.

The studies addressing non-antiretroviral factors of central adiposity in HIV-positive patients are also hampered by the lack of a consensus definition and by differences in the design and populations studied. Non-antiretroviral factors reported to be associated with a higher risk for central adiposity in HIV-positive persons are older age<sup>60,65</sup>, female gender<sup>59,60,65</sup>, white race<sup>60</sup>, higher body fat<sup>60</sup>, less exercise<sup>59</sup>, and lower CD4<sup>+</sup> cell count<sup>60,66</sup>.

## Consequences of visceral adipose tissue in HIV-positive patients

The metabolic and morphologic changes observed in persons with HIV infection receiving cART show considerable overlap with diagnostic criteria for the metabolic syndrome, a constellation of abnormalities<sup>14,15</sup> that lead to an increased risk of CV disease and DM in the general population.

Recent epidemiological data collected from the Data Collection on Adverse Events of Anti-HIV Drugs (DAD) study shows an increasing prevalence of the metabolic syndrome over six years from 2000 to 2007<sup>67</sup>.

Observational studies suggest an increased risk of CV disease among HIV-positive patients compared with the general population<sup>68</sup> and an increased risk of myocardial infarction in HIV-positive persons with each year of cART exposure, particularly to the PI class<sup>69,70</sup>. Traditional CV risk factors, such as smoking, dyslipidemia, and impaired glucose tolerance, are more common among HIV-positive patients and contribute similarly to CV events<sup>71</sup>. The contribution of emerging CV risk biomarkers to risk in HIV is less established.

Silent plaque imaging assessed by coronary calcium score (CAC) is associated with total coronary atherosclerotic disease burden. The CAC score is a strong predictor of subsequent CV disease and recently it has been shown that slowing the coronary artery calcification process will translate into a reduced risk of events (as previously demonstrated with regression of luminal stenosis in angiographic trials)<sup>72</sup>. An observational cross-sectional study of 372 HIV-positive patients receiving cART found a CAC score > 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 ART<sup>73</sup>. The prospective extension of this study, analyzing predictors of progression of CAC in 132 patients who underwent two sequential CT scans (median follow-up time of 333 days), showed that CAC progression was independently related to older age, higher LDL, higher CD4<sup>+</sup> lymphocytes, and greater VAT<sup>74</sup>.

Thus, increased VAT in HIV-positive patients is associated with surrogate markers of CV disease and atherosclerosis progression.

Both DM and insulin resistance (IR) are more prevalent in the HIV-positive population<sup>75</sup> and these

changes in glucose homeostasis are associated with CV risk<sup>76,77</sup>.

In antiretroviral-naïve, HIV-positive patients with or without coinfection with hepatitis C virus, the prevalence of IR is about 12%<sup>78,79</sup>. As with the general population, in HIV-positive individuals there is an independent relationship of upper trunk and visceral adipose tissue with IR<sup>80</sup>.

Relative growth hormone deficiency has been described in patients with HIV-associated central fat accumulation<sup>81</sup>. Among HIV-positive patients, reduced pulse height and overnight growth hormone concentrations are most strongly associated with increased visceral adiposity<sup>81-83</sup>. Reduced growth hormone secretion is independently associated with dyslipidemia, higher glucose and C-reactive protein among HIV-positive patients with abdominal fat accumulation<sup>84</sup>.

Central adiposity and increased VAT diminishes health-related quality of life through erosion of self-esteem and decreased social functioning<sup>85</sup>. Patient dissatisfaction about body image may lead to anxiety and depression as well as sexual dysfunction<sup>86-88</sup>. Dissatisfaction with body shape may unfavorably impact adherence to cART<sup>89</sup>.

## Changes in visceral adiposity with antiretroviral therapy initiation and switch

Advanced, untreated HIV infection is associated with proatherogenic dyslipidemia, including low HDL and raised triglycerides<sup>90</sup>, together with raised resting energy expenditure, weight loss, and cachexia<sup>91,92</sup>. Commencement of effective antiretroviral therapy is associated with a restoration to health in the depleted compartments, including a rise in lean mass and trunk and limb fat<sup>93</sup>. Use of antiretroviral regimens containing the thymidine analog reverse transcriptase inhibitors zidovudine (AZT) and stavudine (d4T) is associated with subsequent subcutaneous and limb fat loss<sup>93</sup>. Metabolic changes precede body composition changes and appear at best only partially correlated with morphologic abnormalities<sup>94,95</sup>. The prospective ACTG384/5005s study noted that while individuals showed diverse patterns of fat gain and loss over 64 weeks after initiation of cART, the changes tended to occur in the same direction. Changes in waist and hip circumferences correlated positively ( $r = 0.62$ ;  $p < 0.001$ ). In this study, the proportion of subjects with WHR more than 0.95 (men) or 0.90 (women) was 34% at baseline and 47% at week 64 ( $p = 0.003$ ). In those



who developed increased WHR, 76% had increased waist circumference<sup>96</sup>.

The impact of specific drug choices on body composition is incomplete, particularly with regard to visceral adiposity, but has been investigated using a variety of techniques in comparative studies of nucleoside reverse transcriptase inhibitors (NRTI), PI, and “class-sparing” regimens. The data point to differences between drugs within the same class and across classes as well as an influence over baseline health status, such as CD4<sup>+</sup> cell count and BMI, on changes in body composition.

### **Comparisons between nucleoside reverse transcriptase inhibitors**

Thymidine analog-based regimens are associated with subcutaneous and peripheral limb fat loss relative to thymidine-sparing<sup>93</sup> and NRTI-sparing therapy<sup>97</sup>.

The FIRST and ABCDE studies documented differences between d4T and abacavir (ABC) based regimens. In the FIRST study, which used anthropometry, the didanosine (ddI) plus d4T arm saw declines in both waist and hip circumferences, the decline being more rapid for the hip circumference, resulting in the WHR actually increasing. An opposite effect was seen with the ABC plus lamivudine (3TC) arm, with both circumferences increased, but more slowly for the waist circumference, resulting in a declining WHR<sup>98</sup>.

In the ABCDE study, fewer ABC recipients were clinically assessed as having lipo-accumulation (10.7 vs. 24.7% with d4T;  $p = 0.023$ ). The ABC recipients had greater weight increases to week 96 (4.7 vs. 2.25 kg), reflecting a marked decline in limb fat seen in the d4T group. A significantly smaller increase in the WHR was observed in the ABC group as compared to the group receiving d4T (1.2 vs. 4.5%;  $p = 0.002$ ). This difference was driven by a significant increase in waist girth in both arms accompanied by an increase in hip girth only in the ABC arm<sup>99</sup>.

Nonrandomized data from a large cohort followed by anthropometric measurements support the assertion that thymidine analog-based regimens are associated with waist circumference increases whereas ABC is not<sup>100</sup>.

Studies GS903 and GS934 each lacked baseline morphology assessments. In GS934, among patients who had DXA scans at weeks 48 and 96, limb fat was lower and declining in the AZT/3TC arm and rose in the tenofovir (TDF)/emtricitabine (FTC) arm. Through 96 weeks, patients receiving TDF/FTC had a significantly greater

median increase from baseline in weight of 2.7 kg compared with 0.5 kg in patients receiving ZDV/3TC ( $p < 0.001$ ). Truncal fat by DXA at week 96 was higher with TDF/FTC (10.4 kg) compared with AZT/3TC (8.6 kg) ( $p = 0.053$ )<sup>101</sup>.

### **Comparison between protease inhibitors**

The BASIC trial study randomized 120 ARV-naïve patients to saquinavir/ritonavir (SQV/r) 2,000/100 mg daily, or atazanavir/ritonavir (ATV/r) 300/100 mg daily, both combined with TDF/FTC. The ATV/r subjects experienced significant increases from baseline in lean body mass, limb fat, SAT, and VAT, with a significantly greater increase in limb fat ( $p = 0.03$ ) and VAT ( $p = 0.04$ ) in the ATV/r arm compared with the SQV/r arm<sup>102</sup>. Similar observations were seen in the CASTLE lipodystrophy substudy. Total weight as well as limb, subcutaneous and visceral fat increased in both groups. Changes in subjects' body composition were influenced by baseline CD4<sup>+</sup> cell count, BMI, and randomized group. In low BMI ( $< 22 \text{ kg/m}^2$ ) patients, ATV/r resulted in significantly greater gain in SAT and VAT compared to lopinavir/ritonavir (LPV/r). A trend to greater limb fat gain was also seen in the subjects with ATV/r compared to LPV/r. In patients with advanced HIV disease (CD4<sup>+</sup> cell counts  $< 50 \text{ cells/mm}^3$ ) ATV/r resulted in a significantly greater gain in limb fat and SAT compared to LPV/r. In higher BMI ( $> 27 \text{ kg/m}^2$ ) patients, trends to greater gains in SAT and limb fat were seen with LPV/r compared to ATV/r<sup>103</sup>. These data suggest that both PI choice and baseline characteristics influence observed body composition changes.

### **Nucleoside reverse transcriptase inhibitor-sparing regimens and newer regimens**

In the MEDICLAS study, the AZT/3TC plus LPV/r group experienced progressive limb fat loss, whereas abdominal fat increased, exclusively in the visceral compartment ( $+21.9 \pm 8.1 \text{ cm}^2$ ;  $p = 0.008$ ). In contrast, the nevirapine (NVP) plus LPV/r group saw a generalized increase in fat mass, supporting the role for thymidine analogs in VAT increase<sup>104</sup>. In the Abbot 613 study, the mean trunk fat increased from baseline to week 96, both in subjects randomized to LPV/r monotherapy (after a 24-week induction with additional AZT/3TC) or efavirenz (EFV) plus AZT/3TC. At week 96, the proportion of subjects with lipoatrophy was significantly lower in the LPV/r treatment group than in the EFV treatment

group (5 vs. 34%, respectively;  $p < 0.001$ ), whereas the proportion of subjects with lipohypertrophy did not differ between the two treatment groups (45 vs. 44%, respectively;  $p > 0.99$ )<sup>105</sup>. In the ACTG 5142 study, which compared three class-sparing strategies, trunk fat increased from a median of 8.2 kg (IQR: 5.0-12.2) at entry to 10.4 kg (IQR: 6.8-14.4) at week 96. There were no significant differences at weeks 48 or 96 by randomized treatment or NRTI selection in either percentage change in trunk fat or percentage of subjects with more than 20% gain in trunk fat. Similarly, in the FIRST study, the mean change in visceral tissue area from baseline was significant and sustained, with no differences between NRTI plus PI, nonnucleoside reverse transcriptase inhibitor (NNRTI) or PI plus NNRTI strategies<sup>106</sup>.

In subjects receiving raltegravir or EFV over 48 weeks in the StartMRK study, both groups saw similar increases in total, appendicular, and truncal fat by DXA<sup>107</sup>.

### **Switching antiretrovirals to reduce visceral adipose tissue**

Variable responses have been seen in changes in VAT or truncal fat following antiretroviral switch. The lack of improvement in visceral fat mass with switch suggests several possibilities. Weight gain after initiation of cART is well recognized and may represent a restoration to health phenomenon. Visceral adiposity and the metabolic syndrome are common events in the general population. Once established, visceral adiposity may be a self-sustaining event, a vicious cycle in the majority of patients. The lack of improvement in visceral fat after treatment switch may, therefore, indicate a limited role of antiretroviral drug choice in the majority of individuals with visceral adiposity.

However, benefits have been seen in selected patients. In a study of 15 patients with marked abdominal adiposity and hyperinsulinemia, decreases in VAT and improved glucose uptake by muscle were observed following switch from LPV/r to ATV/r<sup>108</sup>. A larger study, however, of PI/r to ATV/r switch, which based entry on abdominal circumference, did not show benefit<sup>109</sup>. Other PI replacement studies have seen similar outcomes. Replacement of a PI with ABC<sup>110</sup>, NVP<sup>111</sup>, or EFV<sup>111,112</sup> did not improve visceral adiposity.

Thymidine analog substitution studies involving switch of NRTI for the management of lipodystrophy have shown different outcomes on visceral adiposity. While two studies did not show any benefit<sup>113,114</sup>, in ACTG 5110 a switch from d4T or AZT to a non-thymidine

analog or to a NRTI-sparing regimen was associated with qualitatively similar improvements in thigh fat, SAT, and VAT:TAT ratio at 48 weeks. Reductions in VAT were seen in the group that switched to ABC<sup>115</sup>.

### **Exercise, diet, and oral interventions for central fat accumulation in HIV-patients**

#### **Exercise and diet**

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 WHR  $> 0.95$ )<sup>116</sup>.

Once central adiposity is established, several studies show benefits on central fat accumulation through a combined program of diet, aerobic exercise, and progressive resistance training<sup>117,118</sup>. Uncontrolled data in men demonstrated that 16 weeks of exercise leads to a 2% decrease in total body fat from baseline (1.5 kg;  $p < 0.01$ ), mostly occurring in the trunk<sup>118</sup>. Comparing exercise versus no exercise in HIV-positive women with fat accumulation, a randomized study revealed a modest reduction in waist circumference in the exercise group, but no change in total fat or VAT<sup>117</sup>. A four-month light aerobic exercise program in patients with documented fat accumulation was associated with preferential and significant loss of VAT (−12% versus baseline) and significant improvements in total and HDL cholesterol and triglycerides<sup>119</sup>.

Exercise and dietary interventions have been investigated in HIV-positive patients presenting with general obesity or metabolic syndrome. In 30 HIV-positive individuals with lipohypertrophy and a mean baseline WHR from 0.91-0.94 receiving a low-fat diet, a 12-week exercise program had no additional effect compared with stretching and relaxation on body fat, body weight, or WHR<sup>120</sup>. However, a 12-week study of a reduced-calorie diet combined with aerobic and resistance exercise in 18 HIV-positive women with general obesity led to significant reductions in waist circumference (−6.1 cm;  $p < 0.001$ ) but not WHR. The volumes of both VAT (−17%) and SAT (−15%) declined significantly, whereas VAT:SAT ratio, glucose and lipids did not change significantly<sup>121</sup>. A randomized study of observation versus intensive lifestyle intervention, comprising

weekly one-on-one counseling sessions focusing on reducing saturated fats, increasing fiber, and walking, evaluated 34 HIV-positive subjects with metabolic syndrome. At six months, subjects assigned to lifestyle intervention experienced a mean 2.6 cm decrease in waist circumference ( $p < 0.05$  versus baseline and control group), as well as significant improvements in systolic blood pressure and hemoglobin A1c, but not lipid levels, fasting glucose, or IR<sup>122</sup>.

Broadly, data suggest well supported diet and exercise regimens are worthwhile in the prevention and management of central adiposity in HIV-positive persons.

## Testosterone

A randomized, placebo-controlled, 24-week trial of 10 g testosterone gel or placebo given to 88 HIV-positive men with increased WHR ( $> 0.95$ ) or waist circumference ( $> 100$  cm) demonstrated that testosterone therapy in patients with abdominal obesity was not associated with a significantly greater reduction in visceral fat mass. However, total body, trunk, abdominal SAT, and appendicular fat mass decreased to a greater extent in the testosterone group than in the placebo group. These changes in abdominal fat mass in the testosterone-treated men were associated with greater reductions in waist circumference and WHR and in perceptions of change in abdomen size than those observed in the placebo group<sup>123</sup>.

## Antidiabetic medications

Treatment with thiazolidinediones, such as rosiglitazone or pioglitazone, has been studied in HIV-positive patients. Although some of these studies showed modest improvement in peripheral lipoatrophy upon assessment by DXA<sup>124-126</sup>, this was not confirmed in other studies<sup>127,128</sup>. Importantly, none of these studies showed a beneficial effect on VAT when assessed by MRI or CT<sup>124,125,127,128</sup>. Similarly, therapy with metformin appears to have inconsistent effects on visceral fat accumulation in HIV-positive patients<sup>129-131</sup>. One randomized, placebo-controlled study in 26 HIV-positive patients with signs of IR and evidence of truncal fat accumulation found that metformin 500 mg given twice daily significantly reduced insulin levels on oral glucose challenge<sup>129</sup>, and was associated with significant reductions in weight, waist circumference, and a trend toward reduced VAT ( $-1,115$  vs.  $1,191$  mm<sup>2</sup>;  $p = 0.08$ , a decline of approximately 7% in the metformin group).

However, there was also a decrease in mean SAT as compared to placebo treatment and the WHR did not change significantly. In another small, randomized, placebo-controlled study, which enrolled HIV-positive patients with self-reported increases in abdominal girth and with excess WHR, 24 weeks of treatment with metformin had no effect on VAT, but significantly reduced limb fat<sup>130</sup>. Taken together, these findings suggest that in treating visceral fat accumulation, metformin should be reserved for patients with impaired glucose tolerance or DM and no evidence of lipoatrophy. A recent study of combining metformin with rosiglitazone, compared with either monotherapy, in the treatment of HIV-positive patients with hyperinsulinemia and elevated WHR found no significant differences between treatment groups regarding changes in abdominal VAT<sup>131</sup>. Finally, combining metformin treatment with exercise training for three months was more effective than metformin alone in reducing median WHR and both abdominal SAT and VAT<sup>132</sup>. In the metformin-only group, VAT area had minimally increased, but decreased by 17 cm<sup>2</sup> in the metformin plus exercise group ( $p = 0.063$ ).

## Injectable therapies for visceral adiposity

Both recombinant human growth hormone (rhGH) and the growth hormone releasing hormone (GHRh) analog, tesamorelin, have been studied in HIV-positive individuals with increased waist circumference.

Growth hormone therapy is approved by the FDA but not by the European Medicines Evaluation Agency for AIDS-related wasting, where it improves muscle mass and physical performance<sup>133</sup>. Recent studies of pharmacologic doses of growth hormone have shown a consistent reduction in visceral adiposity in HIV-positive patients, but highly supra-physiologic levels of insulin-like growth factor 1 (IGF-1) and symptoms of growth hormone excess, such as glucose intolerance, fluid retention, arthralgia, and myalgia, resulted in an excess of discontinuations<sup>134,135</sup>. Of note, combination of rhGH with rosiglitazone appears to abrogate the negative effects on glucose metabolism<sup>126</sup>.

Twelve weeks of rhGH at a dose of 4 mg daily led to a 20.3% mean reduction in VAT, whereas the placebo group showed no change ( $+3.6\%$ ;  $p < 0.001$ ). The rhGH group also had a 20% reduction in trunk fat, 7.1% reduction in abdominal SAT, and 6.0% reduction in limb fat by DXA. In contrast, the placebo group showed gains in trunk fat, abdominal SAT, and limb fat (1.4, 1.6, and 2.8%, respectively;  $p < 0.001$  for each between-group difference)<sup>135</sup>.



Other smaller studies have shown similar effects<sup>136-138</sup> although a 6 mg rhGH daily dose resulted in a mean VAT decrease of 42% ( $n = 24$ ;  $p < 0.001$ ), whereas only a 15% decline in VAT was seen with 4 mg every other day ( $n = 10$ ;  $p < 0.01$ ) after 12 weeks, with trends toward further decreases after an additional 12 weeks at each dose. Tolerability was poor, however, with joint pain, muscle pain, and new onset DM observed. Body composition rebounded to or near baseline after a 12-week washout period<sup>139</sup>.

Lower, more physiological doses of rhGH have also been tested in growth hormone-deficient abdominally obese persons with HIV. In a randomized, 56-patient, double-blind, placebo-controlled trial, subjects received either rhGH or matching placebo titrated to the upper quartile of normal IGF-1 range for 18 months. The starting dose of rhGH was 2  $\mu\text{g/kg/day}$  and increased to maximum dose of 6  $\mu\text{g/kg/day}$  (average dose, 0.33 mg/day). The VAT area decreased significantly in the rhGH group compared with the placebo group (treatment effect,  $-19 \text{ cm}^2$ ; 95% CI:  $-38$  to  $-0.5 \text{ cm}^2$ ;  $p = 0.049$ ), which corresponds with a percentage change in VAT of  $-8.5\%$  in the rhGH group and  $-1.6\%$  in the placebo group. Adverse event rates were similar and lipid parameters improved, but two-hour glucose levels on glucose tolerance testing were increased by rhGH<sup>140</sup>.

Two large, 26-week, randomized studies of tesamorelin versus placebo in individuals with visceral adiposity have been performed, with crossover designs allowing both the effects of a further 26 weeks of therapy and the effects of withdrawal of therapy to be observed. In the first study, which enrolled 412 HIV-positive individuals, VAT decreased by 15.2% in the tesamorelin group and increased by 5.0% in the placebo group. Other favorable effects were seen with triglycerides decreased by 50 mg/dl with tesamorelin versus an increase of 5 mg/dl in the placebo group, and the ratio of total cholesterol to HDL cholesterol decreased by 0.31 and increased by 0.21, respectively ( $p < 0.001$  for all comparisons). Levels of total cholesterol and HDL cholesterol also improved significantly in the tesamorelin group. Levels of IGF-1 increased by 81.0% in the tesamorelin group and decreased by 5.0% in the placebo group ( $p < 0.001$ ). Adverse events did not differ significantly between the two study groups, although hypersensitivity to tesamorelin has been occasionally reported<sup>141</sup>.

At week 26 of tesamorelin, the change in VAT was  $-18.1\%$  compared to baseline. Patients who stopped tesamorelin regained VAT so that after 26 weeks off therapy VAT was  $-1.6\%$  compared to baseline<sup>142</sup>. In the

second, similar study, which enrolled 404 HIV-positive individuals, tesamorelin decreased VAT by  $-10.9\%$  ( $-21 \text{ cm}^2$ ) vs.  $-0.6\%$  ( $-1 \text{ cm}^2$ ) in the placebo group in the six-month efficacy phase ( $p < 0.0001$ ). Trunk fat ( $p < 0.001$ ), waist circumference ( $p = 0.02$ ), and WHR ( $p = 0.001$ ) improved, with no change in limb or abdominal subcutaneous fat. Insulin-like growth factor-1 increased ( $p < 0.001$ ), but no change in glucose parameters was observed. Patient rating of belly appearance distress ( $p = 0.02$ ), and physician rating of belly profile ( $p = 0.02$ ) were significantly improved in the tesamorelin vs. placebo-treated groups. The drug was well tolerated<sup>143</sup>.

The effects of tesamorelin appear to be highly specific for the visceral-fat compartment, with relatively little effect on subcutaneous fat or fat in limbs. This preferential reduction in VAT is important, given that peripheral lipoatrophy is commonly also present. The reductions in visceral adiposity observed correlated with the degree of baseline visceral adiposity, larger effects being seen among patients with more accumulation of visceral fat.

Recombinant human leptin (r-metHuLeptin) has also been evaluated in a small randomized, placebo-controlled, double-blinded, crossover study in seven HIV-positive men with lipoatrophy, serum leptin level less than 3 ng/ml, and fasting triglyceride level greater than 300 mg/dl. Compared with placebo, r-metHuLeptin therapy improved fasting insulin levels, IR (by HOMA), and high-density lipoprotein. Body weight and fat mass decreased on r-metHuLeptin, mainly due to a decrease in truncal fat but not peripheral fat or lean body mass. Measurement of VAT was not performed. In addition, r-metHuLeptin was well tolerated, and HIV control was not adversely affected<sup>144</sup>. These data suggest further investigation of leptin is warranted.

## Conclusions and summary

Increased abdominal fat accumulation, particularly VAT, is increasingly recognized in aging populations and is contributing to increased CV disease and type 2 DM. Increased VAT is commonly associated with multiple metabolic abnormalities as part of the "metabolic syndrome". Selective surgical removal of a small amount of visceral fat improves metabolic risk factors, whereas liposuction to remove considerable subcutaneous fat has little effect<sup>145,146</sup>.

HIV-positive individuals appear to commonly develop increased VAT and the metabolic syndrome after the initiation of a range of antiretroviral regimens. Increased

upper trunk and visceral fat have been shown to correlate most strongly with IR and dyslipidemia in HIV-positive patients<sup>53,80,95</sup>. Recent data in HIV-positive patients receiving cART suggest increased VAT is significantly associated with progression of coronary calcium scores<sup>73,74</sup>. The adverse effects of increased waist circumference shown in HIV-negative patients may be greater among HIV-positive patients, in whom waist circumference is made up of increased VAT with loss of SAT, as opposed to HIV-negative patients, with obesity and excess VAT and SAT. Therefore, there may be a particularly strong logic to selectively reducing VAT in the HIV population.

Diet and exercise should be considered a routine part of HIV care, with evidence supporting both a preventative role in central fat accumulation as well as therapeutic effect on central adiposity and some metabolic parameters. Data on antiretroviral drug choice, especially with current regimens, are limited although differences in effects on metabolic parameters are better defined. Some observed changes in body composition may represent restoration to health, with greater increases in fat, both visceral and subcutaneous, occurring in those with most advanced disease and lowest fat mass at baseline<sup>103</sup>. Switching between antiretrovirals does not lead to consistent improvements in VAT although selected subjects, such as those on a thymidine analog or with documented IR on a PI, may benefit. Similarly, additional agents such as metformin may benefit selected subjects with documented IR and no peripheral lipoatrophy. Testosterone supplementation has a more limited role.

Injectable therapies, rhGH, and tesamorelin appear to provide the most consistent benefits in reducing VAT and improving distress around abdominal adiposity. A dosage of rhGH 4 mg/day is associated with a 20% decline in VAT over 12 weeks, but with fluid retention side effects (myalgia, arthralgia, edema, carpal tunnel syndrome) characteristic of elevated IGF-1 levels as well as glucose intolerance<sup>135</sup>. More physiological dosing of rhGH (0.3 mg/day) is better tolerated but has only modest (–7%) effects on VAT<sup>140</sup>. Tesamorelin 2 mg/day reduces VAT by 15–18% over 26 weeks and appears well tolerated, even in diet-controlled patients with DM, and does not lead to supra-physiological exposures of IGF-1<sup>141–143</sup>. In each case, VAT appears to rebound after drug discontinuation so further work on maintenance approaches is needed.

In summary, abdominal adiposity and increased VAT are common problems in persons with HIV. They are associated with metabolic disorders and progression

of coronary artery plaques. Management options appear limited at present, although new injectable agents hold considerable promise.

## Conflict of Interests

Dr. Moyle has received research grants from Abbott, Ardea Biosciences, Bionor, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Merck, Pfizer, Theratechnologies, and Tibotec. He has received honoraria as speaker and/or advisor from Boehringer-Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Merck, Pfizer, Theratechnologies, Tibotec and ViiV Healthcare. Dr. Moutschen has received research grants and honoraria as speaker and/or advisor for Theratechnologies. Dr. Domingo has received research grants from Abbott, Gilead Sciences, GlaxoSmithKline, Pfizer, and Tibotec. He has received honoraria as speaker and/or advisor from Boehringer-Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Merck, Pfizer, Theratechnologies, and Tibotec. Dr. Guaraldi has received research grants from Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Merck, Pfizer, Boehringer-Ingelheim, Theratechnologies, and Tibotec. He has received honoraria as speaker and/or advisor from Boehringer-Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Merck, Pfizer, Theratechnologies, and Tibotec. Dr. Raffi has received honoraria for speaking engagements, advisory board membership and consultancy, as well as research grants from companies including Abbott, Boehringer Ingelheim, Gilead Sciences, GlaxoSmithKline, Merck, Pfizer, Theratechnologies, and Tibotec. Prof. Behrens has received grant support by the German Research Foundation, the Minister for Education and Research, the H.W. & J. Hector Foundation, Bristol-Myers Squibb, and Abbott. He received honoraria as speaker and/or advisor from Abbott, Boehringer-Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Merck, Pfizer, Theratechnologies and Tibotec. Dr. Reiss has received honoraria for speaking engagements, advisory board membership and consultancy, as well as research grants from companies including Boehringer Ingelheim, Hoffmann-La Roche, Merck, Tibotec, Gilead Sciences, GlaxoSmithKline, Pfizer, Bristol-Myers Squibb and Theratechnologies.

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