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Regional fat deposition and cardiovascular risk in HIV infection: The FRAM study

J.E. Lake, M.D.[1], **D. Wohl, M.D.**[2], **R. Scherzer, Ph.D.**[3,4], **C. Grunfeld, M.D. Ph.D.**[*,3,4], **P.C. Tien, M.D. M.P.H.**[3,4], **S. Sidney, M.D. M.P.H.**[5], and **J.S. Currier, M.D. M.Sc.**[1]

[1]University of California Los Angeles, Los Angeles, CA, US

[2]University of North Carolina, Chapel Hill, NC, US

[3]Department of Veterans Affairs Medical Center, San Francisco, CA, US

[4]University of California San Francisco, San Francisco, CA, US

[5]Kaiser Permanente, Oakland, CA, US

Abstract

HIV-infected individuals are at increased risk for cardiovascular disease (CVD) and lipodystrophy, but the relationship between regional adipose tissue (AT) depots and CVD risk is not well-described. We determined regional AT volumes and CVD risk in an analysis of 586 HIV-infected and 280 control FRAM study subjects using whole-body magnetic resonance imaging (MRI) and the Framingham Risk Score (FRS). Median FRS and FRS >10% were higher in HIV than control men (4.7% vs. 3.7%, p=0.0002; 16% vs. 4%, p<0.0001). HIV and control women had similarly-low FRS (1.1% vs. 1.2%, p=0.91). In controls, total AT and all regional AT depots showed strong positive correlations with FRS (p<0.001) in men, and weaker positive correlations in women. Greater visceral AT (VAT) and lower leg subcutaneous AT (SAT) volumes were associated with elevated FRS in HIV subjects, with a trend for upper trunk SAT. Controls in the lowest quartile of leg SAT had the lowest FRS (1.5%), whereas HIV with similarly-low leg SAT had the highest FRS (4.0%, p<0.001 vs. controls). Increased VAT is associated with CVD risk, but the risk is higher in HIV-infected individuals relative to controls at every level of VAT. Peripheral lipoatrophy (as measured by leg SAT) is associated with striking increased CVD risk in HIV-

[*]carl.grunfeld@ucsf.edu .

Sites and investigators: University Hospitals of Cleveland (Barbara Gripshover, MD); Tufts University (Abby Shevitz, MD (deceased) and Christine Wanke, MD); Stanford University (Andrew Zolopa, MD); University of Alabama at Birmingham (Michael Saag, MD); John Hopkins University (Joseph Cofrancesco, MD and Adrian Dobs, MD); University of Colorado Heath Sciences Center (Lisa Kosmiski, MD and Constance Benson, MD); University of North Carolina at Chapel Hill (David Wohl, MD and Charles van der Horst, MD*); University of California at San Diego (Daniel Lee, MD and W. Christopher Mathews, MD*); Washington University (E. Turner Overton, MD and William Powderly, MD); VA Medical Center, Atlanta (David Rimland, MD); University of California at Los Angeles (Judith Currier, MD); VA Medical Center, New York (Michael Simberkoff, MD); VA Medical Center, Washington DC (Cynthia Gibert, MD); St Luke's-Roosevelt Hospital Center (Donald Kotler, MD and Ellen Engelson, PhD); Kaiser Permanente, Oakland (Stephen Sidney, MD); University of Alabama at Birmingham (Cora E. Lewis, MD).

FRAM 2 data coordinating center: University of Washington, Seattle (Richard A. Kronmal, PhD, Mary Louise Biggs, PhD, J. A. Christopher Delaney, Ph.D., and John Pearce).

Image reading centers: St Luke's-Roosevelt Hospital Center: (Steven Heymsfield, MD, Jack Wang, MS and Mark Punyanitya). Tufts New England Medical Center, Boston: (Daniel H. O'Leary, MD, Joseph Polak, MD, Anita P. Harrington).

Office of the Principal Investigator: University of California, San Francisco, Veterans Affairs Medical Center and the Northern California Institute for Research and Development: (Carl Grunfeld, MD, PhD, Phyllis Tien, MD, Peter Bacchetti, PhD, Michael Shlipak, MD, Rebecca Scherzer, PhD, Mae Pang, RN, MSN, Heather Southwell, MS, RD)

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infected patients, even after controlling for VAT, whereas low leg SAT is associated with low CVD risk in controls.

Keywords

HIV; fat redistribution; lipoatrophy; visceral fat; cardiovascular risk

Introduction

HIV-infected patients are at increased risk of cardiovascular disease (CVD), a finding independently linked to both HIV infection and antiretroviral therapy (ART) (J. S. Currier et al., 2003; De Socio et al., 2008; Dolan et al., 2005; Friis-Moller et al., 2003; Hadigan et al., 2003; Kotler, 2008; Lee et al., 2004; Stein et al., 2001; Triant, Lee, Hadigan, & Grinspoon, 2007). Metabolic disturbances such as insulin resistance, pro-atherogenic lipid profiles, and changes in subcutaneous and visceral fat distribution are common in HIV-infected patients both on and off ART, and may contribute to this increased risk of CVD (Bacchetti et al., 2005; J. Currier et al., 2008; De Socio et al., 2008; Dolan et al., 2005; El-Sadr et al., 2005; Fat distribution in women with HIV infection," 2006; Grunfeld et al., 1989; Grunfeld et al., 1992; Grunfeld et al., 2007; Hadigan et al., 2003; Lee et al., 2004; Mulligan et al., 2006; Nieves et al., 2003; Snijder et al., 2005; Stein et al., 2001; Tien et al., 2003; Wohl et al., 2008). Sex differences in lipid abnormalities and preferential sites of fat distribution have been reported (Bacchetti et al., 2005; J. Currier et al., 2008; Fat distribution in women with HIV infection," 2006; Galli et al., 2003; Wohl et al., 2008), but the specific contribution of regional adipose tissue (AT) deposition to CVD risk in HIV infection has not been defined.

We previously demonstrated differences in lipid profiles, insulin resistance, and regional fat depots between HIV-infected and control men and women in the Study of Fat Redistribution and Metabolic Change in HIV Infection (FRAM) (Bacchetti et al., 2005; J. Currier et al., 2008; Fat distribution in women with HIV infection," 2006; Grunfeld et al., 2007; Wohl et al., 2008). HIV infection was associated with insulin resistance, increased triglycerides, and decreased low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol in both sexes. In both HIV-infected and control subjects, greater visceral adipose tissue (VAT) and upper trunk subcutaneous adipose tissue (SAT) were associated with insulin resistance. Greater VAT was associated with lower HDL in HIV-infected subjects and controls, and greater upper trunk SAT was associated with lower HDL in control men.

The associations between AT depots and triglyceride levels were more complex. Greater VAT was associated with higher triglycerides in most groups. Among controls, greater upper trunk SAT in women and greater lower trunk SAT in men were also associated with higher triglycerides. In contrast, greater leg SAT was associated with lower triglycerides in most groups. Together, these findings suggest that the increased risk of CVD seen in HIV infection may partially be mediated by changes in regional fat deposition, and that the contribution of individual CVD risk factors to overall risk may vary between men and women.

The aim of this analysis was to determine the association between regional AT distribution and 10-year Framingham Risk Scores (FRS) among HIV-infected and control men and women in the FRAM study. While previous studies have used FRS to examine the CVD risk profile in HIV-infected cohorts (Aboud et al.; Friis-Moller et al.; Rossi et al., 2009), no nationally representative study has examined the association of magnetic resonance imaging (MRI)-quantified regional adipose tissue with CVD risk.

Methods

The FRAM study analyzed 1,480 HIV-infected men and women representative of patients in care in the US between 2000-2004. It was the first large scale, objective, and quantitative analysis (via MRI) of total body, regional subcutaneous, and visceral adipose tissue abnormalities and their relationships to metabolic disturbances in HIV-infected patients. Controls for the FRAM study are comprised of subjects from the Visceral Fat and Metabolic Rate in Young Adults (VIM) sub-study of the Coronary Artery Risk Development in Young Adults (CARDIA) study of CVD risk in the general population.

Details regarding FRAM participant and control selection, sample characteristics, and data analysis tools have previously been published (Tien et al., 2006). In summary, our population represents 1,183 HIV-infected persons and 297 controls from the first FRAM examination. HIV-infected subjects were recruited from June 2000-September 2002 from 16 geographically diverse HIV/Infectious Disease clinics or cohorts, and are believed to provide a representative cross-section of HIV-infected patients in care at that time (Tien et al., 2006). Control men and women were participants in the Visceral Fat and Metabolic Rate in Young Adults (VIM) sub-study of the population-based CARDIA study (Friedman et al., 1988). All controls were consented for participation in the FRAM study during routine CARDIA follow-up visits in 2000. Subjects were excluded if they had known contraindications to MRI scanning or were: unable or unwilling to provide informed consent, less than 18 years of age, pregnant, or planning to become pregnant in the subsequent three months. Informed consent was obtained from all participants in accordance with guidelines for human experimentation of the U.S. Department of Health and Human Services and the institutional review board of each participating institution.

Participants in both studies underwent: whole-body MRI for regional fat volume analysis (Gallagher et al., 1998); cholesterol subsets including fasting (>eight hours) direct LDL, HDL, and triglycerides; and fasting blood glucose. Blood specimens were analyzed in a single, centralized laboratory (Covance, Indianapolis, Indiana). For the purpose of comparison, the age of HIV-infected subjects was restricted to 33–45 years old to match the age range of controls. 586 HIV-infected FRAM subjects (408 male, 178 female) met this criterion and were included in the age-restricted analyses. AT volumes were normalized in all analyses by dividing by height squared, with summaries back-transformed to 1.75 m of height.

Ten-year CVD risk was estimated by the Framingham Risk Equation using the Anderson method (Anderson, Wilson, Odell, & Kannel, 1991), which was developed to accurately estimate risk for persons 30-74 years of age. These sex-specific risk calculations are based on age, total and HDL cholesterol levels, diastolic blood pressure, presence of diabetes, smoking status, and presence of left ventricular hypertrophy on electrocardiography (set to zero in this analysis as data unavailable). The equation estimates the 10-year risk for CVD events including angina pectoris, coronary insufficiency, myocardial infarction (including silent and unrecognized myocardial infarction), and death from coronary heart disease (sudden or non-sudden). In sensitivity analyses, we also evaluated an alternative version of the Framingham risk equation using systolic instead of diastolic blood pressure; the two versions were found to be highly correlated in this population (r=0.98), and results were similar. Sufficient data was available to calculate FRS for all 586 HIV-infected subjects and 280 control subjects. AT volumes were available for 519 HIV-infected and 260 control subjects; demographic and clinical characteristics were similar in those with and without MRI data.

Characteristics of HIV-infected participants and controls were compared and tested for statistical significance using the Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables. Spearman rank correlation coefficients were calculated to assess associations between AT depots and FRS. Associations of AT depots with FRS were compared between HIV and control subjects using tests of interaction. AT depots were quartiled using cut-offs from the control group (performed separately by sex) to facilitate comparison of similar quantities of AT. We did not adjust for body mass index (BMI), as BMI is influenced by fat volume, the phenomenon being studied.

We examined the association of quartiled VAT and leg SAT with FRS in separate linear regression models for HIV-infected and control participants. Because of its skewed distribution, FRS was log-transformed; results were back-transformed to produce estimated percentage differences in FRS attributable to each AT depot. Additionally, we tested the interaction of HIV status with each AT depot in a single model that combined HIV-infected and control participants.

All analyses were conducted using the SAS system, version 9.2 (SAS Institute, Inc., Cary, NC).

Results

A sex-stratified comparison of demographic and clinical characteristics between HIV-infected and control groups is presented in Table 1. A detailed characterization of FRAM participants has previously been described (Tien et al., 2006). Among the HIV-infected subjects analyzed, median age was 40 years (IQR 37-43) for men and 39 years (IQR 36-42) for women. HIV-infected men were predominantly Caucasian (57%), whereas HIV-infected women were more likely to be African-American (55%). In keeping with the design of the CARDIA study, there were similar numbers of Caucasian and African-American subjects among controls.

As previously reported, smoking was statistically significantly more common in HIV-infected participants than controls ($p<0.001$ for men and women) (J. Currier et al., 2008; Wohl et al., 2008). The overall prevalence of diabetes (defined as fasting glucose ≥126 mg/dL or current use of hypoglycemic agents) was low (HIV vs. control men: 5% vs. 2%, $p=0.15$; women: 9% vs. 5%, $p=0.18$).

HIV-infected men had lower total SAT, regional SAT, and VAT volumes compared with controls (Table 1). In HIV-infected women, total SAT volume and most SAT depots were smaller than in controls. An exception was upper trunk SAT, which was not lower in HIV-infected compared with control women (5.9 L vs. 5.2 L, $p=0.21$). VAT was also not lower in HIV-infected compared with control women (1.3 L vs. 1.1 L, $p=0.055$).

Framingham risk score in HIV-infected participants vs. controls

Levels of CVD risk by FRS (Table 2) were higher in HIV-infected men compared with control men (median 4.7% vs. 3.7%, $p=0.0002$), but were similar in HIV-infected and control women (1.1% vs. 1.2%, $p=0.91$). The prevalence of 10-year CVD risk >10% was also higher in HIV-infected men than control men (16% vs. 4%, $p<0.0001$), but was again similarly-low in HIV-infected and control women (3% vs. 1%, $p=0.25$). The prevalence of 10-year CVD risk >20% was 2% in HIV-infected men vs. 0% in control men ($p=0.12$). None of the women had 10-year CVD risk >20%, regardless of HIV status.

Pre-existing CVD was self-reported by 4% of both HIV-infected men and women at study entry compared with 6% pre-existing CVD in control participants. Although CVD was an

exclusion criterion for enrollment into the CARDIA study in 1985 (when participant ages ranged from 18-30), participants who developed CVD between 1985 and VIM sub-study enrollment in 2000 were not excluded from participating in either the sub-study or as a FRAM control. When HIV-infected subjects with pre-existing CVD were excluded from the analysis, median FRS were essentially unchanged (men 4.8%, women 1.1%), and higher rates of CVD risk >10% persisted in HIV-infected men compared to controls ($p<0.0001$). Additionally, the increased level of risk by FRS was not merely due to the higher prevalence of smoking in HIV-infected participants. Among non-smokers, the median FRS score was 2.8% (IQR: 1.1-5.3) in HIV-infected and 1.9 (0.9-3.6) in control participants ($p = 0.0012$), and the prevalence of FRS > 10% was 7% and 2% ($p=0.0063$).

Associations of adipose tissue volumes with Framingham risk score

In control men, statistically significant positive correlations were seen between FRS and percent AT, VAT, and total SAT ($p<0.0001$), as well as with individual fat depots (Table 3). FRS showed weaker but still positive associations with AT in control women, with a statistically significant association seen only for VAT ($r=0.26$, $p=0.0035$).

In contrast, percent AT and total SAT showed little association with FRS in HIV-infected men and women (Table 3), while VAT showed a strong positive association with FRS in both HIV-infected men and women ($r=0.34$, $p<0.0001$). Upper trunk SAT was associated with FRS in HIV-infected women ($r=0.16$, $p=0.049$), with a similar trend in control women. The association between upper trunk SAT and FRS in HIV-infected men was much weaker than in control men, and did not reach statistical significance. Most notably, a negative association of leg SAT with FRS was observed in HIV-infected men ($r=-0.13$, $p=0.015$), a reversal of the relationship seen in controls ($r=+0.30$, $p=0.0003$). A weak negative association with leg SAT was also seen in HIV-infected women.

AT depot associations with FRS were weaker in HIV-infected men compared with control men ($p\leq0.0007$, by tests for HIV-by-AT depot interactions in all depots). These associations also appeared to be weaker in HIV-infected women compared with control women, although the differences did not reach statistical significance. An exception was seen for VAT, with statistically significant associations with FRS seen in both HIV-infected ($r=0.34$, $p<.0001$) and control women ($r=0.26$, $p=0.0035$).

Lipoatrophy and Framingham risk score

We examined the association of VAT and leg SAT with FRS. Figures 1a and 1b show the median FRS by quartile of VAT and leg SAT. Quartiles were created using cutoffs from the control group (performed separately for men and women) to facilitate comparison of similar quantities of AT between HIV-infected and control subjects. A linear relationship was seen between FRS and VAT in controls, with the lowest FRS values seen in subjects with the smallest VAT volumes (1^{st} quartile). FRS were highest in participants with the largest VAT volumes (4^{th} quartile) in both HIV-infected (median 4.6%) and control subjects [median 3.4%, HIV vs. control (men and women combined) $p=0.055$, Figure 1a]. However, FRS were higher at every level of VAT in HIV-infected subjects compared to controls, with the most striking difference in the first VAT quartile (first quartile: 3.4% vs. 1.3%, $p<0.0001$; second quartile: 2.8% vs. 2.1%, $p=0.021$; third quartile: 4.0% vs. 2.7%, $p=0.051$).

Because leg SAT, a depot strongly affected by HIV-associated lipoatrophy (Saint-Marc et al., 2000), showed a negative association with FRS in HIV-infected but not control subjects, we examined this association further. In controls, FRS were lowest in the first (i.e., lowest) quartile of leg SAT (median 1.6%), and higher in those with greater amounts of leg SAT (medians 2.4-3.0%). In contrast, median FRS were highest in HIV-infected subjects with the

smallest quantity of leg SAT (median 4.1%). Within the lowest quartile of leg SAT, FRS in HIV-infected subjects were significantly higher than in controls ($p<0.0001$). There was little difference in median FRS between HIV-infected and control participants in the upper three quartiles of leg SAT.

We then modeled the association of quartiled VAT and leg SAT with FRS while simultaneously controlling for both AT depots (Table 4). The overall association of VAT volume with FRS was stronger in controls than in HIV-infected participants ($p=0.0080$). In controls, each quartile of VAT was associated with progressively higher FRS, with differences between quartiles reaching statistical significance for VAT Q3 (97% higher FRS compared with Q1, $p=0.0018$) and Q4 (163% higher vs. Q1, $p<0.0001$). In HIV-infected participants, being in the highest quartile (Q4) was associated with 44% higher FRS compared with being in the lowest quartile ($p=0.0090$).

The association of leg SAT with FRS was found to have qualitatively different associations in HIV-infected and control subjects after adjusting for VAT ($p=0.0008$). In controls, there was a suggestion of higher FRS for those in the second quartile (41% higher vs. Q1, $p=0.10$), but the overall association was flatter in the higher quartiles. By contrast, HIV-infected participants with leg SAT in the second, third, and fourth quartiles had *lower* FRS relative to those with leg SAT in the lowest (1^{st}) quartile.

Discussion and conclusions

In our cohort, 10-year FRS were higher among HIV-infected men than control men, whereas HIV-infected and control women had similar and low CVD risk scores. The percentage of HIV-infected men with 10-year FRS >10% was four-fold higher than controls, and may be partially driven by the higher rates of smoking and lower HDL values in HIV-infected compared to control men.

Our study is the first to show an independent association of specific, regional, AT depots with 10-year CVD risk. Our novel finding of associations between AT depots and FRS suggests AT aberrations may mediate CVD risk in the setting of HIV infection. Increased VAT and lower leg SAT were associated with higher FRS in both HIV-infected men and women in our cohort, with some differences seen between the sexes. HIV-infected men tended to have less VAT and SAT than controls, whereas HIV-infected women had more VAT and upper trunk SAT than controls. Because increased VAT is known to be associated with a pro-atherogenic lipid profile (Nieves et al., 2003) and was associated with lower HDL and elevated triglycerides in HIV-infected and control FRAM participants (J. Currier et al., 2008; Wohl et al., 2008), the association of VAT with increased FRS was not unexpected.

In contrast, while SAT depots were positively correlated with FRS in controls, a striking finding in our HIV-infected participants was the negative correlation of leg SAT with FRS, an association that was stronger in men than women. This negative correlation was driven by an increase in FRS among those with the lowest leg SAT volumes, reflecting the severity of lipoatrophy in these subjects (Bacchetti et al., 2005; Fat distribution in women with HIV infection," 2006; Kosmiski et al., 2008). Nearly 50% of HIV-infected men and one-third of HIV-infected women had leg SAT volumes in the lowest decile of leg SAT for controls (Kosmiski et al., 2008), and, while leg SAT is known to be the most common site of fat loss in HIV-infected men and women (Bacchetti et al., 2005; Fat distribution in women with HIV infection," 2006; Tien et al., 2003), the high prevalence of severe lipoatrophy in our HIV-infected cohort was surprising. Lower leg SAT has been shown to be associated with elevated triglyceride levels in both HIV-infected men and women (J. Currier et al., 2008; Wohl et al., 2008), and associations between lipoatrophy and other CVD risk factors have been suggested. However, an independent association of specific, regional AT depots with

10-year CVD risk has not previously been shown. Yim et al recently found femoral-gluteal SAT to be inversely associated with insulin and TG, but the associations weakened after controlling for VAT (Yim, Heshka, Albu, Heymsfield, & Gallagher, 2008). What is particularly novel in our cohort is the association of decreased leg SAT with higher CVD risk in HIV-infected participants that persisted after controlling for VAT.

It is currently unknown whether the excess risk of HIV-associated atherosclerosis varies by sex. However, there is growing evidence that women with HIV may experience more excess cardiovascular events than men with HIV. Triant and colleagues reported higher rates of acute myocardial infarction in HIV-infected women compared to control women, but similar rates in HIV-infected and control men after controlling for risk factors other than sex (Triant et al., 2007). In addition, recent data from FRAM2 (a follow-up evaluation of the original FRAM participants) suggests that while men had greater absolute carotid intima-medial thickness (cIMT) than women, the magnitude of positive association between HIV infection and cIMT was greater for women than men (Grunfeld et al., 2009).

In the age range we examined, FRS did not appear to be increased for HIV-infected women vs. controls, and the 10-year risk for both groups was low. The Women's Interagency HIV Study (WIHS) also observed similar predicted CVD risk between HIV-infected and control women, and the predicted CVD risk in HIV-infected men from the Multicenter AIDS Cohort Study (MACS) appeared higher than for control men, although in both studies the 10-year predicted CVD risk was greater than observed in the FRAM study (Kaplan et al., 2007). Long-term, longitudinal follow-up is necessary to assess whether HIV-infected women will experience cardiovascular events at a rate greater than predicted by the current FRS estimates, but is beyond the scope of this cross-sectional analysis and would require a much larger numbers of subjects. However, given the data above, it is possible that leg SAT atrophy may contribute more to CVD risk in HIV-infected men with this abnormality, whereas increased VAT and upper trunk SAT volumes may be the predominant AT changes associated with CVD risk in HIV-infected women.

Given the excess CVD risk seen in men with HIV and the growing body of data suggesting heightened risk in women with HIV, a strong argument exists for early cardiovascular screening and intervention in HIV-infected patients, including those patients with lower FRS scores. Identifying sex differences in cardiovascular risk should be part of a comprehensive effort to improve risk identification, develop novel risk stratification tools, and individualize intervention strategies in HIV-infected men and women.

Limitations of our study include its cross-sectional design, and therefore our ability to provide evidence of an association between regional AT depot trends and CVD events. FRS has not been used to predict events in an HIV-infected population; however, it still has merit both in its provision of a relative estimate of risk, and in its association with site-specific AT volume, as we have shown here.

As previously reported (Bacchetti et al., 2005; J. Currier et al., 2008; Fat distribution in women with HIV infection," 2006; Tien et al., 2006; Wohl et al., 2008), most FRAM participants were ART-experienced (on ART at the time of exam: men 81%, women 71%; on ART ever: 92% men, 85% women), and our study was not designed to discern the effects of long-term or past exposure on current risk. Differences in CVD risk factors between HIV-infected subjects and controls is another limitation of this study, as minimizing differences between the groups is critical to accurately assessing the contribution of HIV-specific covariates. In our cohort, the higher prevalence of smoking in HIV-infected participants contributed to differences seen in FRS.

Despite these limitations, we have quantitatively demonstrated associations between regional AT depots and 10-year FRS amongst participants in the FRAM study. The risk differences described varied notably between HIV-infected participants and controls, and within HIV-infected subjects when stratified by sex. Future studies are needed to further our understanding of these associations, including those addressing sex-specific differences in the relationship between regional fat deposition and cardiovascular risk.

In HIV-infected subjects, increased VAT, upper trunk SAT, and decreased leg SAT are associated with 10-year CVD risk. Particularly striking is the negative association of leg SAT with FRS seen in HIV-infected subjects but not controls, and the degree to which CVD risk score correlated with severity of lipoatrophy. HIV-infected men had significantly higher FRS than age-matched controls, while women had similarly-low scores irrespective of HIV status. Our findings suggest that AT depot abnormalities may independently contribute to CVD risk in HIV-infected subjects, an observation that warrants further study. Heightened screening for CVD in patients with lipoatrophy and/or visceral fat accumulation should be considered to help prevent cardiovascular events for both HIV-infected men and women.

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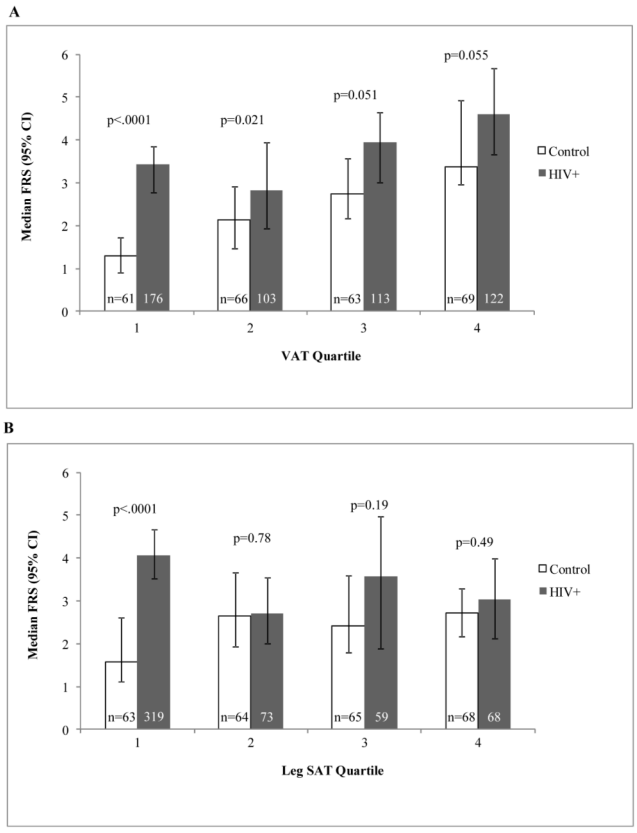

Figure 1.
Framingham risk score levels by (A) VAT and (B) leg SAT quartile in HIV-infected and control subjects (Quartile 1=lowest AT volumes)

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Table 1

Characteristics of HIV-infected and control subjects, stratified by sex

	MEN			WOMEN		
	HIV (AR)	**Control**	**P-value***	**HIV (AR)**	**Control**	**P-value***
N	408	147		178	133	
Age (y)	40.0 (37.0, 43.0)	40.0 (37.0, 43.0)	0.93	39.0 (36.0, 42.0)	42.0 (37.0, 44.0)	**0.0002**
Race: Caucasian	232 (57%)	81 (55%)	**0.043** **	58 (33%)	66 (50%)	**0.043** **
African American	124 (30%)	66 (45%)		98 (55%)	67 (50%)	
Other	52 (13%)	0		22 (12%)	0	
Current Smoker	182 (45%)	31 (21%)	**<.0001**	89 (50%)	17 (13%)	**<.0001**
Glucose	92 (87, 99)	92 (87, 99)	0.55	89 (83, 97)	88 (84, 93)	0.69
DM status***	21 (5%)	3 (2%)	0.15	15 (9%)	6 (5%)	0.18
Systolic BP (mmHg)	115 (107, 123)	117 (112, 127)	**0.002**	108 (99, 119)	113 (106, 124)	**0.001**
Diastolic BP (mmHg)	80 (72, 85)	80 (73, 86)	0.42	72 (66, 81)	78 (69, 83)	**0.006**
CHD or CVD****	17 (4%)	0	**0.009**	7 (4%)	0	**0.022**
Total Cholesterol (mg/dL)	191 (154, 227)	202 (178, 234)	**0.002**	190 (159, 228)	192 (177, 215)	0.23
HDL Cholesterol (mg/dL)	38 (31, 46)	46 (39, 57)	**<.0001**	48 (39, 58)	53 (45, 62)	**0.001**
Non-HDL Cholesterol (mg/dL)	148 (115, 181)	151 (129, 185)	0.17	138 (107, 171)	138 (119, 165)	0.64
LDL Cholesterol (mg/dL)	104 (75, 129)	124 (104, 156)	**<.0001**	103 (78, 134)	117 (97, 139)	**0.004**
Triglycerides (mg/dL)	170 (108, 294.0)	108 (63, 160)	**<.0001**	132 (89, 205)	81 (64, 118)	**<.0001**
BMI (kg/m^2)	24 (22, 27)	27 (25, 30)	**<.0001**	26 (22, 32)	28 (23, 33)	0.13
SAT Total (L)	10.1 (7.0, 14.9)	14.7 (11.5, 19.0)	**<.0001**	25.3 (16.0, 36.8)	30.4 (20.0, 41.9)	**0.021**
Leg (L)	2.9 (2.0, 4.3)	4.6 (3.8, 5.8)	**<.0001**	7.3 (5.1, 10.8)	10.5 (7.6, 14.0)	**<0.0001**
Arm (L)	1.0 (0.8, 1.3)	1.1 (0.9, 1.4)	**0.017**	1.8 (1.2, 2.5)	2.3 (1.5, 3.0)	**0.004**
Upper Trunk (L)	2.5 (1.7, 3.5)	3.1 (2.4, 4.2)	**<.0001**	5.9 (3.3, 8.8)	5.2 (2.9, 8.1)	0.21
Lower Trunk (L)	3.3 (2.0, 5.3)	5.9 (4.2, 7.6)	**<.0001**	9.7 (5.7, 13.3)	10.9 (7.1, 15.5)	**0.020**
VAT (L)	1.4 (0.7, 2.6)	2.0 (1.2, 3.0)	**0.001**	1.3 (0.6, 2.3)	1.1 (0.5, 2.0)	0.055

Note: Continuous measures are summarized as Median (IQR).

IQR = Interquartile Range; AR = Age-Restricted

* P-value is HIV (AR) vs. controls.

** Race comparison is proportion of Caucasian vs. African-Americans

*** Diabetes defined as fasting glucose ≥126 mg/dL or self-reported insulin or hypoglycemic medication.

**** CHD or CVD defined as self-report of any of the following: heart attack, angina, stroke, or "other" indicative of CHD, e.g. quintuple bypass surgery.

Table 2

Framingham risk score in men and women by HIV status

	Framingham Risk Score (%)			CVD Risk ≥ 10%/10 years		
	Median	**IQR**	**P-value**	**n**	**%**	**P-value**
Men						
HIV+	4.7	2.8, 8.1	**0.0002**	65	16%	**<.0001**
Control	3.7	2.0, 6.4		6	4%	
Women						
HIV+	1.1	0.05, 2.6	0.91	6	3%	0.25
Control	1.2	0.6, 2.5		1	1%	

Note: analysis is age-restricted. IQR=Interquartile range

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Table 3

Associations of body composition with Framingham risk score

Spearman Correlations	% AT	VAT	SAT				
			Total	Leg	Upper Trunk	Lower Trunk	Arm
Men							
Control	**0.42** ***	**0.55** ***	**0.35** ***	**0.30** **	**0.44** ***	**0.37** ***	**0.29** **
HIV+	0.037	**0.34** ***	−0.020	**−0.13** +	0.085	0.017	−0.0091
HIV x Depot§ p-values	p<.0001	p=0.0007	p<.0001	p<.0001	p<.0001	p<.0001	p=.0006
Women							
Control	0.12	**0.26** *	0.15	0.077	0.17	0.16	0.16
HIV+	0.087	**0.34** ***	0.078	−0.040	**0.16** +	0.10	0.13
HIV x Depot§ p-values	p=0.71	p=0.71	p=0.46	p=0.12	p=0.91	p=0.55	p=0.73

Note: table contains unadjusted Spearman correlations. Analysis is age-restricted.

*** denotes p<0.0001,

** p<0.001,

* p<0.01,

+ p<0.05

§ HIV x depot interactions. P-values are from linear regression models with log-transformed Framingham score as outcome; models control for HIV status, the depot of interest, and HIV x depot interaction.

Table 4

Percent effects of VAT and leg SAT on Framingham risk score, controlling for quartiled VAT and leg SAT simultaneously.

	Control % Estimate (95%CI)	HIV-infected % Estimate (95%CI)	HIV x AT interaction
VAT			**p=0.0080**
Q2 vs. Q1	35.8 (−9.0, 102.5), p=0.13	−0.9 (−25.3, 31.4), p=0.95	
Q3 vs. Q1	97.3 (29.2, 201.2), **p=0.0018**	23.6 (−6.0, 62.4), p=0.13	
Q4 vs. Q1	163.4 (68.6, 311.5), **p<.0001**	43.6 (9.5, 88.2), **p=0.0090**	
Leg SAT			**p=0.0008**
Q2 vs. Q1	40.7 (−6.4, 111.3), p=0.10	−36.8 (−52.8, −15.4), **p=0.0021**	
Q3 vs. Q1	14.5 (−24.3, 73.2), p=0.52	−34.1 (−52.4, −8.7), **p=0.012**	
Q4 vs. Q1	−2.2 (−37.5, 53.2), p=0.92	−29.8 (−48.3, −4.7), **p=0.023**	

Note: analysis is age-restricted. FRS is log transformed; results are back transformed to produce percentage estimates.