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Regional Adipose Tissue and Elevations in Serum Aminotransferases in HIV-Infected Individuals

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Abstract

Background—The association of fat distribution with alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevations is not well-defined in HIV-infected individuals. Obesity is associated with hepatic steatosis, and ALT is a marker of steatosis in the general population.

Methods—Cross-sectional analysis of 1119 HIV-infected and 284 control subjects. Hepatitis C virus (HCV) RNA testing determined HCV infection. Magnetic resonance imaging measured regional adipose tissue volume.

Results—After adjustment for demographic and lifestyle factors, visceral adipose tissue (VAT) was positively associated with ALT in HIV/HCV-coinfected subjects (+9.8%, 95% confidence interval [CI]: 2.8 to 17.6), HIV-monoinfected subjects (+8.0%, 95% CI: 4.2 to 12.1), and controls (+5.9%, 95% CI: 2.0 to 10.1). In contrast, lower trunk subcutaneous adipose tissue (SAT) was negatively associated with ALT in HIV/HCV-coinfected subjects (−14.3%, 95% CI: −24.7 to −4.2) and HIV-monoinfected subjects (−11.9%, 95% CI: −18.4 to −5.3); there was a trend toward an association in controls (−7.1%, 95% CI: −22.7 to 5.9). Estimated associations between regional adipose tissue and AST were small and did not reach statistical significance.

Conclusions—More VAT and less lower trunk SAT are associated with elevated ALT, which likely reflects the presence of steatosis. There was little association with AST. HCV infection and having more VAT or less lower trunk SAT are independently associated with elevated ALT in HIV infection. Study regarding the association between VAT, trunk SAT, HCV, and progression of steatosis and fibrosis is needed in HIV-infected individuals.

Keywords

adipose tissue; aminotransferase levels; hepatitis C virus; HIV; lipodystrophy

In HIV-infected individuals, the use of specific antiretroviral (ARV) drugs^{1–5} and the presence of opportunistic infections (OIs)⁶ have been associated with abnormalities in serum aminotransferases, that is, alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Concurrent viral hepatitis infection, including hepatitis C virus (HCV) and hepatitis B virus (HBV), has been associated with further worsening of aminotransferase levels in HIV-infected patients started on antiviral drugs associated with hepatotoxicity.^{2,4,5,7}

Few studies have examined the association of body fat distribution with serum aminotransferase levels in HIV-infected individuals, however. In large epidemiologic studies in the general population, ALT has been shown to be a key marker of nonalcoholic fatty liver disease (NAFLD).^{8–10} NAFLD, which can progress to nonalcoholic steatohepatitis (NASH) and cirrhosis, is a leading cause of chronic liver disease in the United States and Europe.^{11,12} Obesity, particularly visceral obesity, is thought to be a key risk factor.^{13,14} Lipoatrophy has also been associated with hepatic steatosis (or fatty liver) in patients with acquired and inherited lipodystrophies.¹⁵ Subcutaneous lipoatrophy, with the lower body affected more than the upper trunk, is the predominant body fat change observed in HIV infection.^{16,17} Small studies in HIV-infected patients have demonstrated an association between clinically diagnosed lipodystrophy and increased liver fat content¹⁸ and steatosis,¹⁹ but the contribution of lipoatrophy versus lipohypertrophy has not been differentiated.

Herein, we examine the association of magnetic resonance imaging (MRI)–measured regional adipose tissue volume with ALT and AST levels in a cohort of HIV/HCV-coinfected subjects, HIV-monoinfected subjects, and controls with neither HIV nor HCV infection.

METHODS

Between June 2000 and September 2002, 1183 HIV-infected persons and 297 controls were enrolled in the study of Fat Redistribution and Metabolic Change in HIV Infection (FRAM) study. The FRAM study was cross-sectional. One of the primary aims of the FRAM study was to understand the association of regional adipose tissue distribution in HIV infection with metabolic outcomes, including serum amino-transferases; ALT has been suggested as a marker of steatosis in the general population. HIV-infected participants were selected from randomly ordered coded lists of patients seen in 16 HIV or infectious disease clinics or cohorts during 1999. Of the 1183 HIV-infected participants, 30% (n = 350) were women. Control subjects were recruited from 2 centers of the Coronary Artery Risk Development in Young Adults (CARDIA) study.^{20,21} CARDIA subjects were originally recruited as a sample of healthy 18- to 30-year-old white and African American men and women from 4 cities in 1985 to 1986 for a longitudinal study of cardiovascular risk factors, with population-based recruitment in 3 cities and recruitment from the membership of a prepaid health care program in the fourth city. Participants in the CARDIA study were stratified for the 2 races and genders in each center. The recruitment and data collection procedures for the entire cohort have been described elsewhere.²² HIV-infected participants in FRAM study were nationally representative of HIV-infected patients in care,²² and control participants were representative of the general population.²⁰ Institutional review boards at all participating sites approved the study protocol and consent process.

FRAM study participants were asked about their physical activity, alcohol intake, smoking, illicit drug use, and adequacy of food intake using standardized instruments.^{23–26} Medical

history was also assessed. Research associates interviewed HIV-infected participants and reviewed medical charts to determine the dates of use of individual ARV medications.

Height and weight were measured. Using standardized protocols, body composition was measured using regional anthropometry, including waist and hip circumferences, and by MRI. MRI scans were segmented using image analysis software (Tomovision Inc., Montreal, Quebec, Canada).^{16,27,28} The volume of each tissue for the space between 2 consecutive slices was calculated by means of a mathematic algorithm.²⁹ Using these methods, we quantified adipose tissue volume in the leg, lower trunk (abdomen and back), upper trunk (chest and back), arm, and abdominal viscera.

Blood was drawn and sent to a central laboratory (Covance) for determination of CD4 cell counts and HIV RNA levels by polymerase chain reaction (PCR) in HIV-infected participants and for determination of AST and ALT levels in HIV-infected and control participants. For women, the upper limit of normal (ULN) for ALT and AST was 34 U/L, and for men, the ULN was 43 U/L for ALT and 34 U/L for AST, based on age-specific normal ranges provided by Covance laboratory. Stored serum samples were tested centrally for HCV RNA level by branched DNA (bDNA) using the Bayer Versant HCV RNA 3.0 assay (Bayer HealthCare-Diagnostics, Tarrytown, NY) and for hepatitis B surface antigenemia using the Auszyme monoclonal enzyme immunoassay (Abbott Laboratories, Abbott Park, IL) on all FRAM study participants.

Among the FRAM study HIV-infected participants, 1149 had available ALT or AST measurements and known HCV status (by HCV RNA). An additional 30 participants with an OI or malignancy within the same or previous calendar month as the examination were excluded because they may have had acute changes in fat. Among the control participants, 292 had available ALT or AST measurements; those with known HCV infection ($n = 5$) or HIV infection ($n = 3$) were excluded. Therefore, 1119 HIV-infected and 284 control participants were included in the analysis.

ALT and AST levels were compared between HIV/HCV-coinfected, HIV-monoinfected, and control participants using the Mann-Whitney U test.

Multivariable linear regression analysis was first conducted using stepwise regression to examine the association of HIV status with ALT and AST after adjustment for potential confounding factors. This analysis was restricted to those between the ages of 33 and 45 years ($n = 594$ HIV-infected participants), because the control population did not include participants outside this age range. Gender, age, ethnicity, HIV status, and HCV status (by HCV RNA level) were forced to be included in the model, and other candidates were included with a criterion of $P \leq 0.05$ for entry and retention. Interactions between gender, HIV/HCV status, and other factors in the model were assessed and included in models if they had a P value < 0.05 . Because we saw substantially stronger effects of HIV/HCV coinfection on ALT and AST levels compared with HIV monoinfection, HIV/HCV-coinfected and HIV-monoinfected participants were compared separately with controls. Because of their skewed distribution, ALT and AST were log-transformed in all linear regression analyses; results were back-transformed to produce estimated percentage effects of each factor. Confidence intervals (CIs) were determined using the bias-corrected accelerated bootstrap method,²⁹ with the P value defined as that minus the highest confidence level that still excluded 0; this was necessary because the error residuals seemed to be non-Gaussian.

Non-HIV-related candidate variables tested in the multivariable models included MRI measurements of adipose tissue volume from 5 anatomic sites (plus total SAT and total fat), diabetes (defined as fasting glucose ≥ 126 mg/dL or hypoglycemic medication use), current lipid-lowering medication use, tobacco use, alcohol intake, adequate food intake, level of

physical activity, and current illicit drug use (marijuana, speed, heroin, crack, cocaine [which is distinguished from crack in our self-administered questionnaire when participants are asked whether they have used other forms of cocaine that are not crack, including powder, freebase, and coca paste], and combination use of crack and cocaine). The linearity assumption for continuous predictors was also tested. The 5 adipose tissue sites considered were visceral, lower trunk, upper trunk, arm, and leg. Measurements were normalized by dividing by height-squared, analogous to body mass index (BMI), and summaries were back-transformed to 1.75 m of height. Because of their skewed distribution, the adipose tissue measures were also log-transformed.

A second set of multivariable regression analyses were stratified by HIV and HCV status to examine the associations of adipose tissue depots with ALT and AST. These models controlled for gender, age, and ethnicity, with other candidates tested as described previously.

Finally, multivariable regression analyses were performed only among HIV-infected subjects to determine the factors independently associated with ALT and AST levels in HIV infection. In addition to the predictors listed previously, these models included HIV RNA level ($\log_{10}$) and CD4 cell count ($\log_2$) at the time of study visit as well as hepatitis B surface antigen (HBsAg) status. Other candidates related to HIV-infection included AIDS diagnosis by a CD4 count <200 cells/ μL or OI, HIV duration (from self-reported date of HIV diagnosis), days since last OI, and HIV risk factors. In multivariable models controlling for the previous factors that were independent predictors, we evaluated current use and duration of each individual ARV drug and ARV class: nucleoside reverse transcriptase inhibitor (NRTI; which included stavudine, zidovudine, lamivudine, didanosine, zalcitabine, and abacavir), nonnucleoside reverse transcriptase inhibitor (NNRTI; which included efavirenz, nevirapine, and delavirdine), protease inhibitor (PI; which included indinavir, lopinavir/ritonavir, nelfinavir, amprenavir, saquinavir, and ritonavir), and highly active antiretroviral therapy (HAART), as previously defined.¹⁵ We also performed exploratory analyses to examine the association of BMI and anthropometry measures (ie, waist and hip circumference) in place of MRI-measured regional adipose tissue.

All analyses were conducted using the SAS system, version 9.1 (SAS Institute Inc., Cary, NC).

RESULTS

Among the 1119 HIV-infected subjects, the 247 (22%) with HCV infection were older, more often African American, and more likely to have a history of injection drug use (Table 1). Current smoking was reported more often in HIV/HCV-coinfected subjects, but recent alcohol consumption was reported less often. BMI was similar between HIV/HCV-coinfected and HIV-monoinfected subjects. HIV/HCV-coinfected subjects had higher HIV RNA levels and lower CD4 cell counts than HIV-monoinfected subjects. Among the control subjects, the distribution by gender and African American or white race was similar by design. Control subjects had a similar median age as HIV-monoinfected subjects but a higher median BMI.

Association of HIV and HCV With ALT and AST Levels

HIV/HCV-coinfected subjects had higher median ALT (43 vs. 25 U/L) and AST (51 vs. 27 U/L) levels than HIV-monoinfected subjects (Fig. 1). HIV-monoinfected subjects had higher median ALT (25 vs. 21 U/L) and AST (27 vs. 22 U/L) levels than controls. After adjustment for demographic and lifestyle factors as well as regional adipose tissue, HIV/HCV coinfection and HIV monoinfection remained associated with higher ALT levels and AST levels than controls (Table 2). The effect of HIV monoinfection on ALT was attenuated after adjustment (-11% ; $P < 0.001$), whereas the effect of HIV/HCV coinfection on ALT was not attenuated ($+3\%$; $P = 0.085$). The effect of HIV monoinfection on AST was attenuated after adjustment

(−5%; $P = 0.026$), with a similar attenuation in HIV/HCV coinfection (−6%; $P = 0.18$) that did not reach significance. Sensitivity analysis, excluding those subjects with hepatitis B surface antigenemia, found little change in the results. We also performed sensitivity analysis that included only African Americans and whites (to match the ethnic composition of the control group) and found little change in the results.

Association of Regional Adipose Tissue With ALT and AST by HIV and HCV Status

Visceral adipose tissue (VAT) was positively associated with ALT levels, whereas lower trunk subcutaneous adipose tissue (SAT) was negatively associated with ALT levels after adjustment for demographic and lifestyle factors in each of the 3 groups: HIV/HCV-coinfected subjects, HIV-monoinfected subjects, and controls (Table 3). The association between lower trunk SAT and ALT levels in controls did not reach statistical significance, however. Leg SAT trended in the same direction as lower trunk SAT in all 3 groups but was weaker (data not shown). In HIV-monoinfected subjects, upper trunk SAT was also associated with higher ALT levels. In controls and HIV/HCV-coinfected subjects, upper trunk SAT showed weaker positive associations with ALT levels, but these did not reach statistical significance. By contrast, VAT, lower trunk SAT, and upper trunk SAT showed little association with AST levels in the 3 groups, and none of the associations reached statistical significance.

As illustrated in Figure 2, increasing VAT and upper trunk SAT were associated with higher ALT, whereas increasing lower trunk SAT was associated with lower ALT in all 3 groups. There were no statistically significant differences in slope between the HIV-monoinfected, HIV/HCV-coinfected, and control groups for the fat depots studied, however.

Demographic, Lifestyle, and HIV-Related Factors Associated With ALT and AST in HIV

After multivariable adjustment in separate models for ALT and AST among HIV-infected subjects, HCV infection and hepatitis B surface antigenemia remained associated with higher ALT and AST (Table 4). Female gender and current smoking were associated with lower ALT and AST. Increasing age was associated with lower ALT but showed little or no association with AST. We observed a possible HCV-by-age interaction for ALT ($P = 0.053$), however. In HIV/HCV-coinfected subjects, age was associated with a 16% reduction in ALT per decade, whereas in HIV-monoinfected subjects, age was associated with a 5.2% reduction per decade. Diagnosis of diabetes was associated with higher ALT but showed little apparent association with AST.

Among HIV-related factors, a higher HIV viral load was associated with higher ALT and AST; a higher CD4 cell count was associated with lower ALT and AST, but the association between CD4 cell count and ALT did not reach statistical significance. Current ritonavir use was associated with lower ALT and AST, whereas zidovudine and efavirenz use was associated with lower AST and, possibly, lower ALT. In contrast, saquinavir use was associated with higher ALT and AST. Stavudine use was associated with 9% higher ALT in univariate analysis ($P = 0.041$), but this effect was attenuated after multivariable adjustment (5%; $P = 0.25$); by contrast, ritonavir and saquinavir use remained strongly associated with ALT, even after controlling for stavudine. Didanosine use showed little association with ALT in univariate (0%; $P = 0.996$) or multivariate (−1.3%; $P = 0.81$) analysis. Similarly, stavudine and didanosine showed little or no association with AST.

Because regional adipose tissue is not measured clinically, we also analyzed whether BMI and anthropometry measures had similar associations. BMI was associated with higher ALT (+1.6% per kg/m^2 increase, 95% CI: 0.7 to 2.5; $P < 0.0001$). Consistent with our findings with regional adipose tissue depots, waist circumference was associated with higher ALT (+1.5% per 1-cm increase, 95% CI: 1.0 to 2.0; $P < 0.0001$), whereas hip circumference was associated

with lower ALT (-1.1% per 1-cm increase, 95% CI: -1.7 to -0.5 ; $P = 0.002$). Also, as expected from our findings with regional adipose tissue, there was little association of BMI or waist or hip circumference with AST (data not shown).

DISCUSSION

In our large cohort of HIV-infected individuals and controls, we found that, regardless of HIV or HCV status, VAT was associated with higher ALT levels. Conversely, less lower trunk SAT was associated with higher ALT levels, particularly in HIV-infected individuals; upper trunk SAT was associated with statistically significantly higher ALT levels in HIV-monoinfected individuals. In contrast, there was little association between any regional adipose tissue depot and AST level. We also found that female gender was associated with lower levels of ALT and AST, a finding consistent with physiologic differences between men and women.^{30,31}

As expected, among HIV-infected individuals, HCV coinfection was associated with higher aminotransferase levels; however, we also observed that HIV infection was associated with higher aminotransferase levels than controls even after multivariable adjustment that included ARV drugs and adipose tissue.

Few, if any, studies have demonstrated an association between subcutaneous fat and ALT level in HIV infection. In non-HIV-infected individuals, subcutaneous lipatrophy has been associated with steatosis and other metabolic outcomes, including insulin resistance and hypertriglyceridemia.¹⁵ Another study of elderly non-HIV-infected patients also found that lower midhigh subcutaneous fat was associated with increased triglycerides.³² HIV infection has been associated with subcutaneous fat loss.^{16,17,33–36} Using whole-body MRI to measure regional adipose tissue, we previously demonstrated in our cohort that subcutaneous fat loss seems particularly marked in the lower trunk and leg compared with other subcutaneous fat regions of the body.^{16,17} We found that less lower trunk SAT was associated with higher ALT levels.

Conversely, we found that more upper trunk SAT was associated with higher ALT levels in HIV-monoinfected individuals, suggesting that upper trunk SAT may be a metabolically important central fat depot similar to VAT. The association between upper trunk SAT and ALT in controls was also in a similar direction but did not reach statistical significance. We previously demonstrated an independent association of upper trunk SAT and VAT with insulin resistance in HIV-infected individuals and controls.³⁷

The associations between VAT and ALT in HIV-infected individuals are similar to those found in our controls and in other studies in the general population,^{38,39} where VAT has been associated with steatosis and higher ALT levels. These findings are not surprising, because we previously found little association of HIV-specific factors with VAT in our cohort.^{16,17} HCV infection also seems to have little effect on VAT.⁴⁰

Our observation, however, that VAT and lower trunk SAT remained independently associated with higher ALT in HIV/HCV-coinfected individuals is noteworthy. Our findings suggest that the combined presence of HCV infection and increased VAT or decreased lower trunk SAT in HIV-infected individuals may be associated with hepatic injury beyond what would be expected with HCV coinfection alone. Particularly concerning is that ALT is likely a marker of steatosis, which seems to be linked to fibrosis progression in HCV-monoinfected patients.^{41,42}

Because measurement of regional adipose tissue is not routinely performed clinically, we evaluated the association of BMI (a surrogate marker of obesity), waist circumference (a surrogate marker of visceral obesity), and hip circumference (a surrogate marker of lower body

fat) with ALT and AST in our multivariable model. We found that BMI was an independent predictor of higher ALT in HIV-infected participants, as was waist circumference. Hip circumference, conversely, was an independent predictor of lower ALT, consistent with our observation of an association between lower trunk SAT and ALT. Measurement of BMI and waist and hip circumference over time may be of clinical utility in patients at risk for liver disease, particularly HIV/HCV-coinfected subjects with obesity or peripheral lipoatrophy.

Our study also highlights the importance of studying the separate factors associated with ALT and AST. Most studies in HIV infection have used the presence of abnormal ALT or AST to define hepatotoxicity. Despite the associations with ALT, we found little association of regional adipose tissue (and BMI and anthropometry) with AST. In addition, we observed little association of diabetes status with AST levels; in contrast, having diabetes was associated with higher ALT levels. Some have postulated an association between diabetes and steatosis in HIV-infected individuals.⁴³ These observations suggest that ALT may be a potentially useful marker of steatosis in HIV-infected patients.

Among the HIV-related factors, higher HIV viral load and lower CD4 cell counts were associated with higher ALT and AST, although the association between CD4 cell count and ALT did not reach statistical significance. Higher ALT and AST in the presence of advanced or uncontrolled HIV disease may be attributable to OIs affecting the liver, including uncontrolled viral hepatitis infection as a result of immuno-suppression. Among the ARV drugs, current use of saquinavir was most associated with elevations in serum aminotransferases. Another study found that saquinavir used in conjunction with zidovudine was associated with severe hepatotoxicity.⁴ We found that current zidovudine use was associated with lower serum aminotransferases, however. Because our study is observational and cross-sectional, it is possible that patients who developed elevations in their aminotransferases may have been discontinued from ARV drugs such as zidovudine; therefore, only those who tolerated the drug continued to take the medication at the time of our analysis. We also note that most (77%) zidovudine use in our study was low dose.

The cross-sectional design of our study did not allow us to make causal inferences regarding the effect of factors such as regional adipose tissue and ARV therapy on liver enzyme levels over time. Although we adjusted for many potential determinants of ALT and AST levels, we cannot exclude the possibility of residual confounding. In addition, with regard to the association between diabetes and ALT and AST levels, we found that 9 subjects reported taking oral hypoglycemic medications for HIV lipodystrophy and not diabetes. Because there were so few subjects using these medications for HIV-related lipodystrophy, we did not perform sensitivity analyses. These 9 subjects (who were all HIV-monoinfected) had ALT values that were similar to the rest of our HIV-monoinfected cohort (both with a median of 25 U/L), however.

Because we did not have liver histology data, we cannot directly demonstrate that the higher ALT is associated with histologic steatosis or if the higher ALT observed, for example, in HIV/HCV-coinfected subjects with higher VAT is associated with more severe histologic disease and more rapid fibrosis progression. Finally, we did not obtain HCV genotype data in our cohort. Although HCV genotype 3 infection has been associated with steatosis, the prevalence of HCV genotype 3 infection in the United States remains low.

We conclude that regional adipose tissue, particularly more VAT and less lower trunk SAT, is associated with higher ALT levels in HIV-infected individuals. The association of adipose tissue with ALT is likely a reflection of hepatic steatosis. In HIV/HCV-coinfected individuals, HCV infection itself and having more VAT or less lower trunk SAT independently contribute to elevations in ALT. Given the data linking steatosis to progression to fibrosis in HCV

infection, future studies need to investigate the role of VAT, trunk and leg SAT, and HCV infection on steatosis and fibrosis progression in HIV-infected individuals. In the clinical setting, obesity and lipodystrophy, particularly in the HIV-infected patient, need to be considered in the differential diagnosis of unexplained ALT elevations.

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References

1. Sulkowski MS, Mehta SH, Chaisson RE, et al. Hepatotoxicity associated with protease inhibitor-based antiretroviral regimens with or without concurrent ritonavir. *AIDS* 2004;18:2277–2284. [PubMed: 15577540]
2. den Brinker M, Wit FW, Wertheim-van Dillen PM, et al. Hepatitis B and C virus co-infection and the risk for hepatotoxicity of highly active antiretroviral therapy in HIV-1 infection. *AIDS* 2000;14:2895–2902. [PubMed: 11153671]
3. Martinez E, Blanco JL, Arnaiz JA, et al. Hepatotoxicity in HIV-1-infected patients receiving nevirapine-containing antiretroviral therapy. *AIDS* 2001;15:1261–1268. [PubMed: 11426070]
4. Sulkowski MS, Thomas DL, Chaisson RE, et al. Hepatotoxicity associated with antiretroviral therapy in adults infected with human immunodeficiency virus and the role of hepatitis C or B virus infection. *JAMA* 2000;283:74–80. [PubMed: 10632283]
5. Sulkowski MS, Thomas DL, Mehta SH, et al. Hepatotoxicity associated with nevirapine or efavirenz-containing antiretroviral therapy: role of hepatitis C and B infections. *Hepatology* 2002;35:182–189. [PubMed: 11786975]
6. Schneiderman DJ, Arenson DM, Cello JP, et al. Hepatic disease in patients with the acquired immune deficiency syndrome (AIDS). *Hepatology* 1987;7:925–930. [PubMed: 2820858]
7. Aceti A, Pasquazzi C, Zechini B, et al. Hepatotoxicity development during antiretroviral therapy containing protease inhibitors in patients with HIV: the role of hepatitis B and C virus infection. *J Acquir Immune Defic Syndr* 2002;29:41–48. [PubMed: 11782588]
8. Clark JM, Diehl AM. Defining nonalcoholic fatty liver disease: implications for epidemiologic studies. *Gastroenterology* 2003;124:248–250. [PubMed: 12512048]
9. Clark JM, Brancati FL, Diehl AM. The prevalence and etiology of elevated aminotransferase levels in the United States. *Am J Gastroenterol* 2003;98:960–967. [PubMed: 12809815]
10. Ioannou GN, Weiss NS, Boyko EJ, et al. Elevated serum alanine aminotransferase activity and calculated risk of coronary heart disease in the United States. *Hepatology* 2006;43:1145–1151. [PubMed: 16628637]
11. Browning JD, Szczepaniak LS, Dobbins R, et al. Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. *Hepatology* 2004;40:1387–1395. [PubMed: 15565570]
12. Bedogni G, Miglioli L, Masutti F, et al. Prevalence of and risk factors for nonalcoholic fatty liver disease: the Dionysos nutrition and liver study. *Hepatology* 2005;42:44–52. [PubMed: 15895401]
13. Ruhl CE, Everhart JE. Determinants of the association of overweight with elevated serum alanine aminotransferase activity in the United States. *Gastroenterology* 2003;124:71–79. [PubMed: 12512031]
14. Thomas EL, Hamilton G, Patel N, et al. Hepatic triglyceride content and its relation to body adiposity: a magnetic resonance imaging and proton magnetic resonance spectroscopy study. *Gut* 2005;54:122–127. [PubMed: 15591516]
15. Garg A. Lipodystrophies. *AmJ Med* 2000;108:143–152. [PubMed: 11126308]
16. FRAM Study Investigators. Fat distribution in men with HIV infection. *J Acquir Immune Defic Syndr* 2005;40:121–131. [PubMed: 16186728]

17. Study of Fat Redistribution and Metabolic Change in HIV Infection (FRAM). Fat distribution in women with HIV infection. *J Acquir Immune Defic Syndr* 2006;42:562–571. [PubMed: 16837863]
18. Sutinen J, Hakkinen AM, Westerbacka J, et al. Increased fat accumulation in the liver in HIV-infected patients with antiretroviral therapy-associated lipodystrophy. *AIDS* 2002;16:2183–2193. [PubMed: 12409740]
19. Marks KM, Petrovic LM, Talal AH, et al. Histological findings and clinical characteristics associated with hepatic steatosis in patients coinfecting with HIV and hepatitis C virus. *J Infect Dis* 2005;192:1943–1949. [PubMed: 16267765]
20. Friedman GD, Cutter GR, Donahue RP, et al. CARDIA: study design, recruitment, and some characteristics of the examined subjects. *J Clin Epidemiol* 1988;41:1105–1116. [PubMed: 3204420]
21. Hughes GH, Cutter G, Donahue R, et al. Recruitment in the Coronary Artery Disease Risk Development in Young Adults (CARDIA) study. *Control Clin Trials* 1987;8(4 Suppl):68S–73S. [PubMed: 3440391]
22. Tien PC, Benson C, Zolopa AR, et al. The Study of Fat Redistribution and Metabolic Change in HIV Infection (FRAM): methods, design, and sample characteristics. *Am J Epidemiol* 2006;163:860–869. [PubMed: 16524955]
23. Friedman GD, Cutter GR, Donahue RP, et al. CARDIA: study design, recruitment, and some characteristics of the examined subjects. *J Clin Epidemiol* 1988;41:1105–1116. [PubMed: 3204420]
24. Sidney S, Jacobs DR Jr, Haskell WL, et al. Comparison of two methods of assessing physical activity in the Coronary Artery Risk Development in Young Adults (CARDIA) study. *Am J Epidemiol* 1991;133:1231–1245. [PubMed: 2063831]
25. Hoegerman GS, Lewis CE, Flack J, et al. Lack of association of recreational cocaine and alcohol use with left ventricular mass in young adults. The Coronary Artery Risk Development in Young Adults (CARDIA) study. *J Am Coll Cardiol* 1995;25:895–900. [PubMed: 7884094]
26. Hill JO, Sidney S, Lewis CE, et al. Racial differences in amounts of visceral adipose tissue in young adults: the CARDIA (Coronary Artery Risk Development in Young Adults) study. *Am J Clin Nutr* 1999;69:381–387. [PubMed: 10075320]
27. Gallagher D, Belmonte D, Deurenberg P, et al. Organ-tissue mass measurement allows modeling of REE and metabolically active tissue mass. *Am J Physiol* 1998;275(2 Pt 1):E249–E258. [PubMed: 9688626]
28. Gallet B, Pulik M, Genet P, et al. Vascular complications associated with use of HIV protease inhibitors. *Lancet* 1998;351:1958–1959. [PubMed: 9654285]
29. Shen W, Wang Z, Tang H, et al. Volume estimates by imaging methods: model comparisons with visible woman as the reference. *Obes Res* 2003;11:217–225. [PubMed: 12582217]
30. Keefe EB, Dieterich DT, Han SH, et al. A treatment algorithm for the management of chronic hepatitis B virus infection in the United States: an update. *Clin Gastroenterol Hepatol* 2006;4:936–962. [PubMed: 16844425]
31. Prati D, Taioli E, Zanella A, et al. Updated definitions of healthy ranges for serum alanine aminotransferase levels. *Ann Intern Med* 2002;137:1–10. [PubMed: 12093239]
32. Snijder MB, Visser M, Dekker JM, et al. Low subcutaneous thigh fat is a risk factor for unfavourable glucose and lipid levels, independently of high abdominal fat. The Health ABC Study. *Diabetologia* 2005;48:301–308. [PubMed: 15660262]
33. Mallal SA, John M, Moore CB, et al. Contribution of nucleoside analogue reverse transcriptase inhibitors to subcutaneous fat wasting in patients with HIV infection. *AIDS* 2000;14:1309–1316. [PubMed: 10930144]
34. Mallon PW, Miller J, Cooper DA, et al. Prospective evaluation of the effects of antiretroviral therapy on body composition in HIV-1-infected men starting therapy. *AIDS* 2003;17:971–979. [PubMed: 12700446]
35. Mulligan K, Anastos K, Justman J, et al. Fat distribution in HIV-infected women in the United States: DEXA substudy in the Women's Interagency HIV Study. *J Acquir Immune Defic Syndr* 2005;38:18–22. [PubMed: 15608519]
36. Saint-Marc T, Partisani M, Poizot-Martin I, et al. A syndrome of peripheral fat wasting (lipodystrophy) in patients receiving long-term nucleoside analogue therapy. *AIDS* 1999;13:1659–1667. [PubMed: 10509567]

37. Grunfeld, C.; Rimland, D.; Gibert, C., et al. Insulin resistance is independently associated with VAT and upper trunk SAT in controls and HIV infection. Presented at: Eighth International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV; San Francisco. 2006.
38. Burgert TS, Taksali SE, Dziura J, et al. Alanine aminotransferase levels and fatty liver in childhood obesity: associations with insulin resistance, adiponectin, and visceral fat. *J Clin Endocrinol Metab* 2006;91:4287–4294. [PubMed: 16912127]
39. Stranges S, Dorn JM, Muti P, et al. Body fat distribution, relative weight, and liver enzyme levels: a population-based study. *Hepatology* 2004;39:754–763. [PubMed: 14999694]
40. Tien PC, Bacchetti P, Gripshover B, et al. Association between hepatitis C virus coinfection and regional adipose tissue volume in HIV-infected men and women. *J Acquir Immune Defic Syndr* 2007;45:60–65. [PubMed: 17356466]
41. Hourigan LF, Macdonald GA, Purdie D, et al. Fibrosis in chronic hepatitis C correlates significantly with body mass index and steatosis. *Hepatology* 1999;29:1215–1219. [PubMed: 10094967]
42. Adinolfi LE, Gambardella M, Andreana A, et al. Steatosis accelerates the progression of liver damage of chronic hepatitis C patients and correlates with specific HCV genotype and visceral obesity. *Hepatology* 2001;33:1358–1364. [PubMed: 11391523]
43. Mynarcik DC, McNurlan MA, Steigbigel RT, et al. Association of severe insulin resistance with both loss of limb fat and elevated serum tumor necrosis factor receptor levels in HIV lipodystrophy. *J Acquir Immune Defic Syndr* 2000;25:312–321. [PubMed: 11114831]

APPENDIX

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FIGURE 1. Median ALT and AST levels in the 1119 HIV-infected and 284 control subjects included in the analysis by HIV and HCV status.

FIGURE 2.

Multivariable association of regional adipose tissue depots with ALT levels by HIV and HCV status. Effect sizes are displayed per doubling of depot along with P values. A, Association of VAT with ALT. B, Association of upper trunk SAT with ALT. C, Association of lower trunk SAT with ALT. All fat depots are height-normalized.

TABLE 1

Demographic and Clinical Characteristics by HIV and HCV Status

n	HIV ⁺ /HCV ⁺ 247	HIV ⁺ /HCV ⁻ 872	Control 284
Gender			
Female	35%	28%	48%
Male	65%	72%	52%
Age [y], median (IQR)	45 (41 to 50)	41 (36 to 48)	41 (37 to 43)
Race			
White	28%	54%	52%
African American	59%	34%	48%
Hispanic	9%	10%	
Other	4%	2%	
Current smoking	62%	37%	16%
Alcohol use			
0 drinks/wk	41%	25%	22%
<1 drinks/wk	23%	31%	28%
1 to 7 drinks/wk	22%	30%	35%
>7 drinks/wk	14%	14%	16%
BMI [kg/m ²], median (IQR)	24.6 (21.8 to 27.7)	24.6 (22.4 to 27.8)	27.4 (24.0 to 31.5)
Leg SAT [L], median (IQR)	4.2 (2.7 to 6.3)	3.3 (2.1 to 5.6)	6.1 (4.3 to 10.0)
Lower trunk SAT [L], median (IQR)	4.8 (2.7 to 8.6)	3.9 (2.4 to 6.9)	7.1 (4.6 to 11.8)
Arm SAT, L, median (IQR)	1.2 (0.9 to 1.8)	1.1 (0.8 to 1.6)	1.4 (1.0 to 2.2)
Upper trunk SAT [L], median (IQR)	2.9 (1.9 to 5.1)	3.0 (2.0 to 4.7)	3.6 (2.4 to 5.6)
VAT [L], median (IQR)	1.3 (0.6 to 2.2)	1.7 (0.8 to 3.0)	1.5 (0.7 to 2.6)
HBsAg ⁺	2%	7%	1%
HIV risk factors			
Heterosexual	7%	19%	
IDU	63%	8%	
MSM	14%	56%	
Other	16%	17%	
Duration HIV [y], median (IQR)	9.1 (5.7 to 12.2)	7.6 (5.1 to 11.4)	
Log ₁₀ HIV RNA, median (IQR)	2.8 (2.6 to 4.3)	2.6 (2.6 to 4.0)	
Undetectable HIV RNA	43%	53%	
Current CD4 count [cells/ μ L], median (IQR)	293 (184 to 452)	376 (227 to 561)	
Current use of HAART	71%	78%	

Subjects with recent OIs or missing ALT and AST levels were excluded.

IDU indicates injection drug user; IQR, interquartile range; MSM, men who have sex with men.

TABLE 2

Association of HIV/HCV Coinfection and HIV Mono-infection With ALT and AST Levels

	HIV ⁺ /HCV ⁺ vs. Control		HIV ⁺ /HCV ⁻ vs. Control	
	% Effect (95% CI)	<i>P</i>	% Effect (95% CI)	<i>P</i>
ALT				
Unadjusted	106 (76 to 139)	<0.0001	25 (15 to 35)	<0.0001
Adjusted	108 (75 to 148)	<0.0001	14 (3.1 to 25)	<0.010
AST				
Unadjusted	127 (103 to 155)	<0.0001	26 (18 to 34)	<0.0001
Adjusted	121 (97 to 150)	<0.0001	21 (14 to 29)	<0.0001

Outcomes analyzed are log-transformed ALT and AST levels, with results back-transformed to the original scale.

Subjects were age restricted, and those with recent OIs were excluded. Adjusted effects models control for HIV and HCV status, gender, age, ethnicity, lifestyle factors, and regional adipose tissue.

TABLE 3
Multivariable Association of Regional Adipose Tissue With ALT and AST Stratified by HIV and HCV Status

	ALT			AST		
	% Effect	95% CI	P	% Effect	95% CI	P
HIV⁺/HCV⁺						
Log ₂ (VAT/ht ²)	9.8	2.8 to 17.6	0.010	2.1	-3.0 to 7.0	0.44
Log ₂ (upper trunk SAT/ht ²)	5.8	<i>-16.8 to 29.5</i>	0.67	-0.9	<i>-9.8 to 8.4</i>	0.84
Log ₂ (lower trunk SAT/ht ²)	-14.3	-24.7 to -4.2	0.010	-5.6	<i>-14.4 to 1.9</i>	0.16
HIV⁺/HCV⁻						
Log ₂ (VAT/ht ²)	8.0	4.2 to 12.1	0.001	1.0	-1.5 to 3.5	0.43
Log ₂ (upper trunk SAT/ht ²)	12.7	2.4 to 24.7	0.009	0.0	-4.3 to 4.4	0.99
Log ₂ (lower trunk SAT/ht ²)	-11.9	-18.4 to -5.3	<0.0001	-2.5	-6.1 to 1.2	0.18
Control						
Log ₂ (VAT/ht ²)	5.9	1.7 to 9.9	0.007	-1.5	-4.6 to 1.8	0.37
Log ₂ (upper trunk SAT/ht ²)	3.4	<i>-13.1 to 24.7</i>	0.67	-3.1	<i>-8.3 to 2.4</i>	0.26
Log ₂ (lower trunk SAT/ht ²)	-7.3	<i>-19.0 to 6.2</i>	0.28	-4.3	<i>-9.8 to 1.5</i>	0.15

Models also control for demographics and lifestyle factors. HIV-related factors are excluded from the models. Analysis is OI excluded and not age restricted.
Italicized factors did not enter into the model above but are shown controlling for other factors in the model.

TABLE 4

Association of Demographic, Lifestyle, and HIV-Related Factors on ALT and AST Among HIV-Infected Subjects After Multivariable Adjustment

	ALT			AST		
	% Effect	95% CI	P	% Effect	95% CI	P
HCV RNA⁺	101.3	79.4 to 127.4	<0.0001	104.0	83.9 to 126.7	<0.0001
Demographic factors						
Female vs. male	-21.4	-30.1 to -9.5	<0.0001	-13.1	-19.4 to -6.5	<0.0001
African American vs. white	-2.6	-12.0 to 7.3	0.60	0.5	-7.1 to 7.9	0.92
Hispanic vs. white	3.7	-8.7 to 18.7	0.57	3.3	-6.6 to 15.7	0.51
Other vs. white	-4.5	-23.4 to 26.3	0.73	-9.7	-26.7 to 24.7	0.50
Age (decade)	-7.2	-11.4 to -3.1	<0.0001	-0.1	-3.9 to 3.8	0.96
Adipose tissue						
Log ₂ (VAT/hr ²)	7.3	3.7 to 11.4	<0.0001	1.3	-1.2 to 3.9	0.30
Log ₂ (upper trunk SAT/hr ²)	12.7	2.1 to 23.9	0.015	-0.8	-5.0 to 3.6	0.70
Log ₂ (lower trunk SAT/hr ²)	-13.5	-19.4 to -7.0	<0.0001	-2.6	-6.2 to 1.1	0.17
Lifestyle and non-HIV-related						
Current smoker	-12.7	-19.5 to -5.4	0.002	-7.2	-13.6 to -0.7	0.038
Food: adequate vs. inadequate	12.0	2.4 to 22.8	0.017	9.7	1.8 to 18.5	0.013
Diabetes	19.4	5.4 to 37.5	0.003	2.8	-9.3 to 16.5	0.66
Lipid-lowering therapy	9.2	-1.7 to 20.8	0.11	10.9	0.5 to 22.4	0.033
HIV-related						
HBsAg ⁺	47.0	28.3 to 69.6	<0.0001	45.0	24.2 to 75.0	<0.0001
Current HIV viral load (log ₁₀)	6.9	1.6 to 12.1	0.003	5.3	1.1 to 10.3	0.012
Current CD4 count (log ₂)	-2.7	-6.2 to 0.5	0.11	-4.0	-7.7 to -1.0	0.006
HIV duration (y)	0.6	-0.4 to 1.6	0.21	1.0	0.2 to 1.8	0.017
Current use of ritonavir	-16.8	-23.5 to -8.3	<0.0001	-14.7	-21.1 to -7.4	<0.0001
Current use of saquinavir	24.7	7.5 to 46.5	0.004	11.1	-1.9 to 26.0	0.098
Current use of zidovudine	-7.9	-15.4 to 0.2	0.056	-11.2	-16.7 to -4.8	<0.0001
Current use of efavirenz	-6.5	-14.7 to 2.5	0.15	-8.4	-15.0 to -1.2	0.027

Italicized factors did not enter into the model above but are shown controlling for other factors in the model.