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Relationships Between Hepatic Steatosis and Frailty Differ by HIV Serostatus

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Abstract

Background: Frailty is associated with obesity-related comorbidities, but the relationship with nonalcoholic fatty liver disease (NAFLD) in people with HIV has been incompletely described. Our objective was to assess the associations between NAFLD and frailty.

Methods: Cross-sectional and longitudinal analysis of men in the Multicenter AIDS Cohort Study. NAFLD was defined as a liver/spleen ratio, <1.0 on abdominal computed tomography scans; frailty was defined by the frailty phenotype as having 3 of the following: weakness, slowness, weight loss, exhaustion, and low physical activity.

Results: Men without (n = 200) and with HIV (n = 292) were included. NAFLD prevalence was 21% vs 16% and frailty 12% vs 17%, respectively. Among men with NAFLD, frailty was more prevalent in men without HIV (21% vs 11%). In multivariate analysis, NAFLD was significantly associated with frailty after controlling for significant variables. Men without HIV and NAFLD had 2.6 times higher probability [95% confidence interval (CI): 1.2– to 5.7] of frailty relative to men with neither HIV nor NAFLD. This association was not seen in men with HIV. The probability of frailty was higher among men without HIV with NAFLD (27% vs 10% in men without NAFLD) but lower among men with HIV with NAFLD (14% vs 19% in men without NAFLD). No significant relationships were found in longitudinal analyses.

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Conclusions: NAFLD was independently associated with frailty among men without HIV but not men with HIV, despite increased prevalence of frailty among men with HIV. The mechanisms of the muscle–liver–adipose tissue axis underlying NAFLD might differ by HIV serostatus.

Keywords

HIV; NAFLD; frailty

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD), now encompassed under the umbrella of metabolic-associated steatotic liver disease or MASLD, is one of the most important causes of liver disease with an estimated prevalence of 25% in the United States.[1] The prevalence of NAFLD in people with HIV (PWH) is estimated to be 25%–50%,[2–4] and it is associated with future development of metabolic syndrome and cardiovascular disease.[5,6] The higher prevalence of "lean NAFLD" [NAFLD in a patient with body mass index (BMI) <25 kg/m^2] in PWH compared with the general population may suggest the potential for differences in the pathogenesis of NAFLD and complications in people with and without HIV.[4,7] In addition, data suggest that inflammation and progression to fibrosis in PWH is more rapid than people without HIV.[8,9]

As PWH live longer, a greater prevalence of age-related challenges arises. PWH are more vulnerable to poor health and higher risk of age-related health problems, despite viral suppression and immune recovery.[10,11] These HIV-associated, non-AIDS conditions share many similarities with frailty and aging-associated inflammation.[10] Frailty represents the cumulative effects of age-related deterioration in multiple physiological systems with disruption of homeostasis, resulting in greater vulnerability to stressors and exposure to detrimental health-associated outcomes.[12,13] Aging is a major contributor to frailty due to aging-associated changes, such as reduced physical activity, and deterioration of body functions.[12,14] Chronic, low-grade inflammation triggered by genetic susceptibility, central obesity, and increased gut permeability, is an important contributor to the pathogenesis of metabolic disorders and strongly associated with frailty.[15]

In NAFLD, excessive caloric intake, genetic predisposition, and chronic inflammation lead to the disruption of the triangular crosstalk among the adipose tissue, skeletal muscle, and liver, resulting in ectopic fat accumulation and fatty infiltration within skeletal muscle, defined as myosteatosis.[16] This can lead to progressively diminished muscle mass strength and function, or sarcopenia.[16] Reduced hand grip strength has been associated with NAFLD in the general population and PWH.[17,18] In addition, studies have shown that older participants with NAFLD are at higher risk of age-related disorders, such as cognitive impairment, than those without NAFLD.[13] In addition to the frailty phenotype, individual components of sarcopenia, reduced grip strength, and deterioration of body function can lead to adverse clinical outcomes.[12,16,19,20]

Frailty involves loss of muscle mass (sarcopenia) and decreased energy, with resulting weight loss, declines in strength, exercise tolerance, performance speed, and physical activity.[14] In 2007, the Multicenter AIDS Cohort Study (MACS) began assessing the

components of frailty at each study visit for all participants. Previous analyses from the MACS have shown that both HIV and its duration are predictors of frailty-like manifestations in men. The associations between frailty and hepatic steatosis/fibrosis in PWH have only been assessed in a 1 European cohort, and a control group of people without HIV was not included.[21] The objective of our study was to assess associations between NAFLD and components of frailty, and to determine whether there are differences by HIV serostatus. We hypothesized that participants with HIV and NAFLD will have higher prevalence of frailty compared with men without HIV, independent of traditional risk factors.

METHODS

Study Population

The MACS, now part of the MACS–Women's Inter-agency HIV Study Combined Cohort Study (MACS/WIHS Combined Cohort Study), was a prospective cohort study of men who have sex with men with and without HIV in 4 US cities: Baltimore/Washington, DC; Chicago; Los Angeles; and Pittsburgh.[22] Participants were followed on a semi-annual basis for a standardized interview, clinical evaluations, laboratory tests, and storage of specimens for the biorepository. The complete study design of the MACS has previously been described.[22]

Participants enrolled in a MACS cardiovascular ancillary study, CVD2, were included. Complete methodological details of this subcohort have been previously described.[23,24] From January 2010 to August 2013, men aged 40–71 years enrolled in the MACS underwent computed tomography (CT) imaging. Exclusion criteria for the subcohort were weight >300 pounds, history of cardiac surgery, or history of coronary angioplasty or stent placement. Among the subcohort participants, 829 had adequate visualization of the liver and spleen on noncontrast cardiac CT. Men who consumed 3 or more alcoholic drinks per day or were infected with hepatitis C or hepatitis B virus were excluded.

Frailty and Physical Function Assessments

Frailty measurements, including gait speed and grip strength, were performed at each visit. Gait speed (m/s) was determined using the faster of two 4-m gait speed assessments at a "normal, comfortable pace." Grip strength (kg) was calculated using a Jamar dynamometer, as the average of 3 attempts. Frailty was based on the MACS modified Fried frailty phenotype components: (1) weakness (grip strength, <20th percentile of men without HIV), (2) slowness (time to walk 4 meters, < 1 m/s), (3) unintentional weight loss of ≥10 pounds since the last visit, (4) exhaustion ("yes" to question "During the past 4 weeks did you have difficulty completing your work or activities due to your physical health?"), and (5) low physical activity ("yes" to question "Does your health limit you from vigorous activities such as running, lifting heavy objects, participating in strenuous sports?"). Participants were categorized as nonfrail (<3 components) or frail (3 or more components).[14,19,25] These procedures were standardized across all study sites. For the longitudinal analysis, participants were considered to have developed frailty if at subsequent visits they had (1) ≥2

visits meeting ≥3 frailty-related phenotype criteria or (2) 1 visit meeting ≥3 criteria and 2 subsequent visits meeting 1–2 criteria, as previously defined.

Hepatic Steatosis and Adipose Tissue Measurements

Multidetector row CT scanning was performed on each participant, and each scan was reviewed by a single reader who was blinded to all demographic and clinical data. NAFLD was defined as a liver attenuation/spleen attenuation ratio <1.0 on noncontrast CT, as previously described.[26] Visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) area and density were measured from a single CT slice in the space between the fourth and fifth lumbar vertebrae.[27]

Covariates

Additional participant-level covariates were obtained at the time of the CT scan. Age, race, alcohol and drug use history, medication use, and clinical diagnosis history were assessed by self-report unless otherwise defined. Antiretroviral therapy (ART) use and duration and concomitant medication use were confirmed through medical record review. Depression was defined as Center for Epidemiologic Studies Depression Scale Score ≥16. Height and weight were measured using standardized procedures and used to calculate BMI in kg/m^2. Insulin resistance was calculated using the homeostatic model assessment (HOMA) equation [HOMA-IR = fasting insulin (mU/mL) × fasting glucose (mmol/L)/22.5].[28] Diabetes was defined as self-report or use of antidiabetic medications. Metabolic syndrome was defined according to National Cholesterol Education Program III criteria.[29] Hypertension was defined as resting blood pressure.>130/90 mm Hg, self-report of hypertension, or use of antihypertensive medication.

Glucose, high-density lipoprotein cholesterol, and triglyceride levels were measured from fasting blood samples. Among men with HIV, longitudinal data collected at study visits included HIV-1 RNA levels, $CD4^+$ T-lymphocyte counts/mm^3 (CD4), and duration of ART use.

Statistical Analysis

Continuous variables were presented as medians and interquartile ranges (IQR), and categorical variables as percentages. Comparisons of continuous variables between men with and without HIV were performed using the Wilcoxon rank-sum test and for categorical variables using the χ^2 test. Hepatic fibrosis was estimated using the FIB-4 using the formula [age (years) × AST]/[platelet count (10^9/L) × $ALT^{1/2}$]. Multivariate Poisson regression with robust variance estimates assessed cross-sectional relationships between NAFLD and frailty. Significant variables in univariate analyses were included in the final model. The final regression models were adjusted for HIV serostatus, age, race/ethnicity, SAT density, smoking status, alcohol use, FIB-4 >3.25, history of depression, physical activity level (by the International Physical Activity Questionnaire), and study site. The final model for frailty included a NAFLD*HIV interaction. The hazard for developing frailty in men with vs without NAFLD was assessed with multivariate complementary log–log regression models. Men with frailty at the initial visit were excluded from this analysis. Models were adjusted for HIV serostatus, study site, age, race/ethnicity, alcohol use, smoking status, and

depression. Associations between gait speed and grip strength with NAFLD were assessed with linear regression, adjusting for HIV status, age, race/ethnicity, VAT density, presence of metabolic syndrome, HOMA-IR below or ≥2.5, smoking status, alcohol use, and physical activity level. Multiple imputations by chained equations was used to handle missing data across variables.

RESULTS

Of 492 men included in the study, 200 were without HIV and 292 with HIV. The characteristics by HIV serostatus and NAFLD are presented in Table 1. NAFLD was found in 21.0% and 15.8% of men without and with HIV, respectively. Men with NAFLD had higher BMI, greater frequency of insulin resistance or a diagnosis of metabolic syndrome, higher VAT and SAT areas, and lower VAT and SAT density. Liver fibrosis as measured by FIB-4 was only present in 7 participants. Among men with HIV, those with NAFLD had been on ART longer and had been significantly longer on protease inhibitors.

Associations Between NAFLD and Frailty

Overall, the prevalence of frailty in men with NAFLD was 16%. Frailty was more frequent in men without HIV with NAFLD (21%) vs men with HIV (11%), despite the increase prevalence of frailty in men with HIV (17% vs 12% in men without HIV). To assess which clinical parameters were associated with frailty, we performed adjusted regressions with an HIV interaction (Fig. 1). In cross-sectional adjusted models, men with NAFLD without HIV had a 2.6-fold (95% CI: 1.2 to 5.7; $P = 0.02$) increase in the probability of frailty relative to men without HIV and without NAFLD. In men with NAFLD, the probability of frailty in men without HIV was 27% vs 14% in men with HIV. In men without NAFLD, the probability of frailty in men without HIV was 11% vs 19% in men with HIV (Table 2). As described in Figure 1, tobacco use and history of depression were also associated with an increase in the probability of frailty. High physical activity level was associated with a lower probability of frailty. No specific HIV characteristics were associated with a frailty.

In longitudinal analysis, adjusting for HIV serostatus, study site, age, race/ethnicity, alcohol use, smoking status, and depression, NAFLD was not associated with an increased risk for developing frailty (Fig. 2). Physical activity had a limited time period of data collection and could not include in longitudinal analyses. The proportional hazards assumption was violated for age, history of depression, and study site. Additional models with stratified time frames to correct this [first 3 years after baseline, and years 4–9 (max follow-up time) after baseline] were constructed. No significant differences were seen (data not shown). Age, Black race and non-White/non-Black race, tobacco use, and history of depression were associated with increased hazard of developing a frailty phenotype.

Associations Between NAFLD, Gait Speed, and Grip Strength

Linear regression estimates for gait speed and grip strength are represented in Table 3. NAFLD was not associated with either gait speed or grip strength after adjusting for HIV, age, race/ethnicity, VAT density, metabolic syndrome, HOMA-IR, smoking status, alcohol use, and physical activity levels. Only Black race was significantly associated

with slower gait speeds. High and moderate physical activity[30] and current use of alcohol were significantly associated with faster gait speeds. Weaker grip strength was significantly associated with increasing age; high and moderate physical activity and current alcohol use were significantly associated with a stronger grip strength.

DISCUSSION

In this cohort of men who have sex with men, NAFLD was associated with increased prevalence of frailty among men without HIV but not among men with HIV, despite the higher prevalence of frailty in men with HIV. These results run counter to our hypothesis and raise the possibility that there may be other biological mechanisms contributing to NAFLD and frailty in men with HIV compared with men without HIV.

Our study is the first study, to our knowledge, to compare associations between frailty and NAFLD prevalence in men with and without HIV. The increased association between NAFLD and frailty in men without HIV is consistent with current studies showing an association between NAFLD and frailty in the general population.[13,20,31] Insulin resistance and high BMI play an important role in NAFLD, all favoring an inflammatory environment with elevated levels of cytokines, particularly interleukin-6 (IL-6) and tumor necrosis factor-α, higher levels of which facilitate muscle breakdown with subsequent decreased muscle mass and strength.[32] Decreased muscle mass and sarcopenia, distinctive features of frailty, have been associated with higher risk of hepatic steatosis and fibrosis.[33] Previous published data from the MACS cohort describe differences in associations between NAFLD and inflammatory biomarkers by HIV serostatus.[34] Particularly, although men with HIV had higher tumor necrosis factor-α Receptor 2 and IL-6 levels, these markers were not associated with hepatic steatosis as they were in men without HIV. A possible explanation for this discrepancy may be that persistent inflammation associated with chronic HIV, in combination with an increased number of comorbidities, leads earlier to frailty[25] and obscures associations between frailty and hepatic steatosis without fibrosis.

The associations between frailty and hepatic steatosis/fibrosis have not been widely investigated in PWH. The only large study is an Italian cross-sectional analysis of 707 PWH with NAFLD defined by controlled attenuation parameter, rather than CT scan. Notably, this cohort had a high prevalence of steatosis (40%) and found that hepatic steatosis (OR 2.1) and hepatic steatosis with fibrosis (OR 9.2) were independent positive predictors for frailty.[21] Discrepancy with our results might be due to the ability to stratify severity of steatosis and fibrosis with controlled attenuation parameter and liver stiffness measurements, with increasing prevalence of frailty seen in higher levels of steatosis in combination with fibrosis. In addition, our cohort is smaller, making it possible that our study might have been underpowered to detect differences in men living with HIV.

A major strength of our study is a comparison of men with and without HIV from the same cohort. To our knowledge, this is the first study to explore relationships between NAFLD, frailty, and physical function by HIV serostatus. Notably, the prevalence of hepatic steatosis in men with HIV from the MACS cohort has been lower than men without HIV.[26] The reason for this is not clear; however, it may pertain to the limitation of defining fatty liver

by noncontrast CT scan, which is not able to differentiate between degrees of steatosis or fibrosis. In addition, we used FIB-4 as a marker of fibrosis with a lower prevalence (1.4%) than the Italian cohort (10.2%) and may further limit our results.[21] Although no differences were seen in longitudinal analysis, we were limited in the analysis by the number of missing variables. Finally, our findings may not be applicable to the general population living with HIV as the MACS is a male cohort with few injection drug users and mostly comprises people with relatively high socioeconomic status.

In summary, we found that frailty was associated with NAFLD independent of traditional risk factors among men without HIV but not among men with HIV, despite the latter having greater prevalence of frailty. Further work is needed to identify the differences of the muscle–liver–adipose tissue axis in NAFLD without fibrosis in people living with HIV. These differences may play a role in determining targeted therapy for early NAFLD in PWH.

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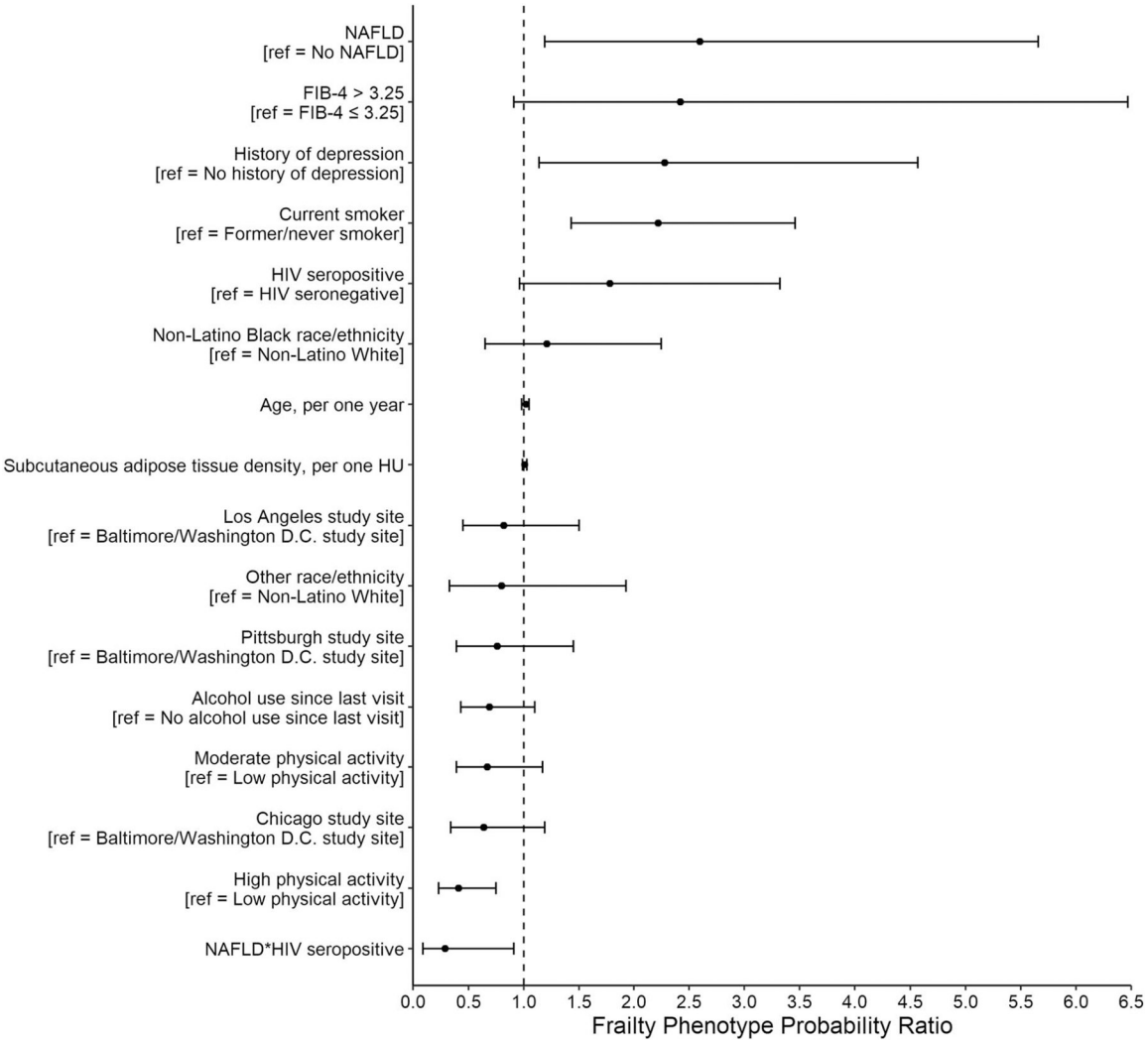

FIGURE 1.

Multivariate cross-sectional analysis for a frailty phenotype*. Points represent adjusted probability ratios and whiskers 95% confidence intervals. *Poisson regression with robust variance estimates, adjusting for HIV status, age (years), race/ethnicity, SAT density, current smoking, alcohol use, FIB-4 below or above 3.25, history of depression, physical activity level, and study site.

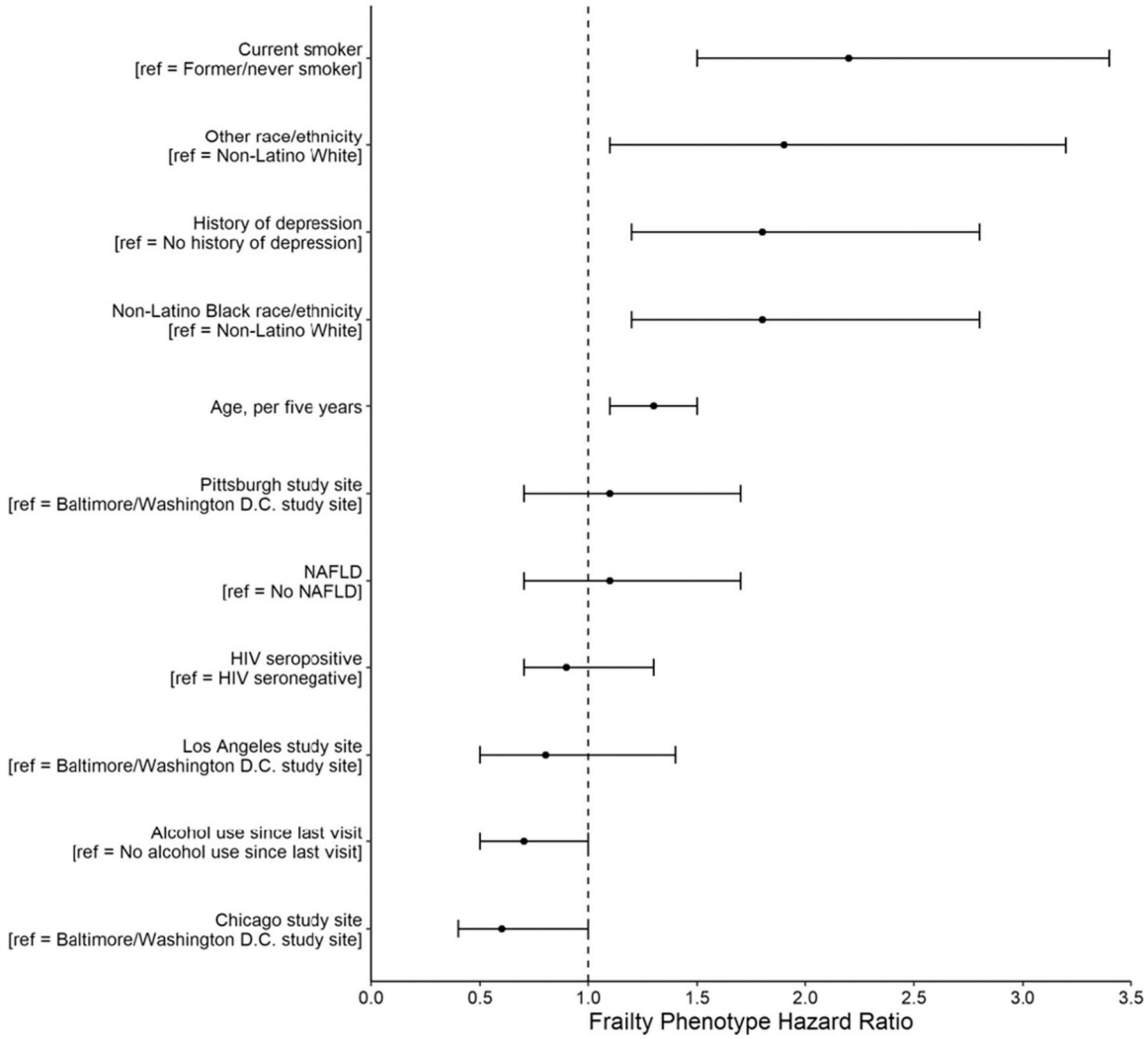

FIGURE 2.

Multivariate longitudinal analysis for a frailty phenotype.* Points represent adjusted hazard ratios and whiskers 95% confidence intervals. *Multivariate complementary log–log regression model after adjusting for HIV serostatus, study site, age (per 5 years), race/ethnicity, alcohol use, current smoking, and history of depression.

TABLE 1.

Clinical and Demographic Characteristics

Characteristics	Men Without HIV		Men With HIV		*P*
	No NAFLD (N = 158)	NAFLD (N = 42)	No NAFLD (N = 246)	NAFLD (N = 46)	
Age (yr)	55 (51, 61)	58 (50, 64)	52 (48, 58)	52 (47, 57)	<0.001
Black race	26%	10%	32%	13%	0.009
Body mass index (kg/m^3)	26 (24, 29)	30 (27, 33)	25 (23, 28)	27 (26, 31)	
Metabolic syndrome	58%	81%	70%	89%	<0.001
Insulin resistance (HOMA-IR ≥ 2.5)	57%	85%	65%	84%	<0.001
Liver fibrosis (FIB-4 > 3.25)	0%	0%	3%	0%	0.112
Alcohol use since last visit					0.033
None	18%	10%	25%	30%	
At least some	82%	90%	75%	70%	
Never/former smoker	83%	85%	76%	85%	0.260
Frailty	9%	21%	18%	11%	0.094
SAT area (mm^2)	220.3 (163.0–292.0)	285.4 (235.1–391.1)	176.7 (110.3–269.2)	185.6 (134.1–238.1)	<0.001
SAT density (HU)	−97.8 (−102.7 to 93.5)	−98.2 (−102.9 to 92.5)	−95.0 (−100.1 to 87.7)	−96.2 (−102.1 to 87.4)	<0.001
VAT area (mm^2)	135.7 (83.1 to 190.9)	222.2 (133.0 to 302.8)	137.8 (80.8 to 199.6)	218.1 (144.2 to 306.6)	<0.001
VAT density (HU)	−90.8 (−95.0 to 85.3)	−94.3 (−98.0 to 90.8)	−89.8 (−95.9 to 84.5)	−95.8 (−100.1 to 92.6)	<0.001
CD4$^+$ T lymphocyte count (cells/μL)			604 (424, 748)	638 (521, 833)	0.192
CD4$^+$ T lymphocyte count <200 (cells/μL)			4%	0%	0.602
Detectable HIV-1 RNA			12%	7%	0.440
Years on ART			9 (6, 13)	10 (8, 14)	0.021
Years on PI			5.5 (0.5, 10.5)	9.8 (3.2,13.3)	0.012

Frequency or median (interquartile range) presented.

HOMA-IR, homeostatic model assessment of insulin resistance; HU, hounsfield units; PI, protease inhibitor.

TABLE 2.

Probability of Frailty by Presence of HIV and Hepatic Steatosis

	Probability Ratio (95% CI)
Men without HIV with steatosis	0.2713 (0.01 to 9.24)
Men without HIV without steatosis	0.1055 (0.003 to 3.60)
Men with HIV with steatosis	0.1377 (0.005 to 3.67)
Men with HIV without steatosis	0.1926 (0.01 to 5.31)

Probability ratios, adjusting for NAFLD, HIV status, age, race/ethnicity, SAT density, smoking status, alcohol use, FIB-4 index, history of depression, physical activity level, and study site.

TABLE 3.

Linear Regression Between Hepatic Steatosis and Physical Function Parameters

	Gait Speed (m/s)		Grip Strength (kg)	
	Estimate (SE)	***P***	**Estimate (SE)**	***P***
Hepatic steatosis	−0.003 (0.023)	0.90	0.461 (1.110)	0.68
HIV serostatus	−0.022 (0.018)	0.22	0.413 (0.885)	0.64
Age	−0.003 (0.001)	0.06	−0.250 (0.067)	<0.01
Black race	−0.062 (0.023)	<0.01	−1.801 (1.071)	0.09
VAT density	0.002 (0.001)	0.07		
Metabolic syndrome	−0.020 (0.021)	0.33		
HOMA-IR ≥2.5	−0.013 (0.020)	0.50		
Tobacco use	−0.034 (0.022)	0.13		
Current use of alcohol	0.046 (0.021)	0.03	2.354 (1.042)	0.02
Moderate physical activity	0.078 (0.028)	0.01	3.542 (1.212)	<0.01
High physical activity	0.064 (0.023)	<0.01	4.205 (1.204)	<0.01

Linear regression, adjusting for HIV status, age, race/ethnicity, VAT density, presence of metabolic syndrome, HOMA-IR below or above 2.5, smoking status, alcohol use, and physical activity level. HOMA-IR, homeostatic model assessment of insulin resistance.