Published in final edited form as:
J Acquir Immune Defic Syndr. 2009 April 15; 50(5): 464–473. doi:10.1097/QAI.0b013e318198a88a.

Nonalcoholic Fatty Liver Disease (NAFLD) among HIV-Infected Persons

Nancy Crum-Cianflone, MD MPH[1,2,3], **Angelica Dilay, MPH**[3], **Gary Collins, MS**[4], **Dean Asher, MD**[5], **Richard Campin, MD**[5], **Sheila Medina**[1,2], **Zach Goodman, MD**[6], **Robin Parker, MD**[5], **Alan Lifson, PhD**[4], **Thomas Capozza, MD**[7], **Mary Bavaro, MD**[1], **Braden Hale, MD MPH**[1,2], and **Charles Hames, MD**[7]

[1]HIV Clinic, Naval Medical Center San Diego, San Diego, California [2]Infectious Disease Clinical Research Program (IDCRP), Bethesda Maryland [3]Public Health Department, San Diego State University, San Diego, California [4]Biostatistics Division, School of Public Health, University of Minnesota, Minneapolis, Minnesota [5]Radiology Department, Naval Medical Center San Diego, San Diego, California [6]Armed Forces Institute of Pathology, Washington DC [7]Gastroenterology Department, Naval Medical Center San Diego, San Diego, California

Abstract

Objective—To describe the prevalence and factors associated with nonalcoholic fatty liver disease (NAFLD) among HIV-infected persons not infected with hepatitis C virus (HCV).

Design—A cross-sectional study among HIV-infected patients in a large HIV clinic.

Methods—NAFLD was defined as steatosis among patients without viral hepatitis (B or C) co-infection or excessive alcohol use. The prevalence of NAFLD was identified by ultrasound examination evaluated by two radiologists blinded to the clinic information; liver biopsies were performed on a subset of the study population. Factors associated with NAFLD evaluated by proportional odds logistic regression models.

Results—Sixty-seven (31%) of 216 patients had NAFLD based on ultrasound evaluation. Among those with NAFLD, steatosis was graded as mild in 60%, moderate in 28%, and severe/ marked in 12%. Factors associated with the degree of steatosis on ultrasound examination in the multivariate model included increased waist circumference (odds ratio [OR] 2.1 per 10 cm, $p<0.001$), elevated triglycerides (OR= 1.2 per 100 mg/dl, $p=0.03$), and lower HDL levels (OR 0.7, $p=0.03$). African Americans were less likely to have NAFLD compared to Caucasians (14% vs. 35%), although this did not reach statistical significance (OR= 0.4, $p=0.08$). Similar associations were noted for the subset of patients diagnosed by liver biopsy. CD4 cell count, HIV viral load, duration of HIV infection, and antiretroviral medications were not independent risk factors associated with NAFLD after adjustment for dyslipidemia or waist circumference.

Correspondence: Dr. Nancy Crum-Cianflone, c/o Clinical Investigation Department (KCA), Naval Medical Center San Diego, 34800 Bob Wilson Drive, Ste. 5, San Diego, CA 92134-1005. Phone: 619/532-8134/40; FAX: 619/532-8137; E-mail: nancy.crum@med.navy.mil.

The opinions or ascertains contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Departments of the Army, Navy, or Air Force, or the Department of Defense. The authors have no commercial or other association that might pose a conflict of interest in this work.

This work is original and has not been published elsewhere. Some data contained in this manuscript were presented as abstract #822 at the 14th Conference on Retroviruses and Opportunistic Infections, February 25–28, 2007; Los Angeles, California.

Conclusion—NAFLD was common among this cohort of HIV-infected, HCV-seronegative patients. NAFLD was associated with a greater waist circumference, low HDL and high triglyceride levels. Antiretroviral medications were not associated with NAFLD; prospective studies are needed to confirm this finding.

Keywords

HIV; NAFLD; steatosis; liver disease; antiretroviral medication

BACKGROUND

As HIV-infected persons are experiencing longer life expectancies [1], other causes of morbidity and mortality among this group are increasingly being recognized. Recently, liver disease was identified as a leading cause of death among HIV-infected persons [2,3]. Patients with HIV infection frequently have elevated liver function tests (LFTs) [4], which are often attributed to viral hepatitis (B and C) co-infections or to antiretroviral medication effects. The epidemiology of nonalcoholic fatty liver disease (NAFLD) has not been studied among HIV patients without concurrent hepatitis C virus (HCV) infection, but may be an important cause of liver disease in this population.

NAFLD is now recognized as the most common liver disease among the general population since its description by Ludwig et al. in 1980 [5,6]. In the United States, 17–33% of the population has NAFLD [6–8], and its prevalence is likely rising due to increasing prevalence of obesity. NAFLD is defined as the accumulation of lipid droplets (mainly triglycerides) in hepatocytes occurring in the absence of excessive alcohol use or chronic active viral hepatitis [5,9]. The disease spectrum ranges from mild steatosis to nonalcoholic steatohepatitis (NASH), advanced stages of fibrosis, cirrhosis, and hepatocellular carcinoma [10,11]. Obesity, insulin resistance, diabetes mellitus, and dyslipidemia, which are components of the “metabolic syndrome” [12], are risk factors for NAFLD in the general population, and has been referred to as the hepatic component of the “metabolic syndrome” [13].

Data on the prevalence, predictors, and natural history of NAFLD among HIV-infected persons are limited. Before the advent of HAART, the literature reported steatosis but the etiology was unclear [14–17], and recent studies on steatosis among HIV patients have been conducted solely among those with hepatitis C virus (HCV) coinfection and HCV itself can result in fat deposition in the liver. In these studies, steatosis was noted in 40–72% of HIV-HCV coinfected patients, and proposed risk factors for fatty deposition included nucleoside agents (especially stavudine and didanosine), age, white race, components of the metabolic syndrome, HCV viral load, and HCV genotype 3 infection [18–25].

However, HIV patients without concurrent hepatitis C may be at particular risk for fatty liver disease due to increased prevalence for both risk factors proposed for the ‘two-hit’ pathogenesis of NAFLD: insulin resistance with release of free fatty acids from adipose tissue with subsequent hepatic triglyceride deposition as well as oxidative stress-cytokine mediated injury [26]. Regarding the first ‘hit’, HIV patients often have high rates of lipid and glucose abnormalities, an effect of the HIV infection itself or the antiretroviral medications. In addition to the potential metabolic side effects of antiretrovirals, nucleoside agents may cause direct hepatotoxicity and steatosis due to inhibition of mitochondrial DNA polymerase-γ. Protease inhibitors also may cause steatosis via the overexpression of the sterol regulatory protein, SREBP-1 [27,28]. The rising rates of diabetes and obesity among HIV-infected persons [29, 30], similar to the general U.S. population, may also contribute to NAFLD in this population. Regarding the second ‘hit’, HIV patients may be at risk due to a chronic inflammatory state

(e.g., increased TNF-α levels) induced by the virus. In addition, studies have suggested that gut-derived lipopolysaccharide may promote hepatic damage [31].

Given the lack of published reports regarding NAFLD among HIV patients uninfected with HCV, we performed a cross-sectional study among a well-characterized, ethnically diverse cohort of HIV-infected patients. Our aims were (1) to determine the prevalence of NAFLD, and (2) to identify factors associated with NAFLD among HIV-infected patients without HCV.

METHODS

Demographics of study population

We conducted a cross-sectional study to determine the prevalence and factors associated with NAFLD among HIV patients uninfected with HCV. Study subjects were HIV-infected patients receiving care at the Naval Medical Center San Diego (NMCSD), San Diego, California. HIV patients (n=450) attending the clinic are military active duty members, retirees, and dependents. Those on active duty service undergo periodic HIV screening (approximately every two years) and routine, mandatory drug testing; service members found positive for illicit drugs are discharged from active duty service and are not seen in our clinic. All study participants had confirmed HIV infection by enzyme-linked immunosorbent assay (ELISA) and Western Blot testing. Patients were excluded from participating in this study if they were under 18 years of age or were pregnant as determined by a positive urine beta-human chorionic gonadotropin (βhCG) test. All participants provided written informed consent, and the study was approved by the Institutional Review Board at NMCSD.

All HIV patients meeting the inclusion/exclusion criteria were asked to join the study during their regular clinic visits; enrollment continued until 300 patients signed the informed consent. Study enrollment occurred during the period of January 2006 through June 2007. Of the study group, 257/300 (86%) had an ultrasound examination performed. Forty-three patients did not have the ultrasound done due to work issues, loss of military benefits, or relocation out of the area. Compared to the characteristics of patients attending this clinic, those who participated in this study were similar in age, race, and military status. Those who joined the study were slightly more likely to be male (93% vs. 88%, p=0.04) and had a slightly longer duration of HIV (10 vs. 9 years, p=0.01) than those who did not participate. We also compared those who joined the study who did and did not have an ultrasound examination performed, and found no significant differences except a lower percentage of females had an ultrasound than did not have the test (5% vs. 14% p=0.04).

Patients had a routine hepatitis panel (hepatitis B surface antigen, hepatitis B core antibody, and hepatitis C antibody tests) at HIV diagnosis; these tests were reviewed as part of this study. In addition, patients with elevated liver function tests and a positive hepatitis B core antibody with a negative surface antigen had a hepatitis B DNA drawn. In addition, those with abnormal LFTs and a CD4 cell count of <200 cells/mm^3 underwent both a hepatitis B DNA and hepatitis C RNA viral load testing. Chronic active hepatitis B infection was defined as having a positive surface antigen or having core antibody positive with a detectable hepatitis B DNA viral load. Likewise, a chronic hepatitis C infection was defined as having a positive antibody serology or RNA viral load. Patients found to have chronic hepatitis B (n=14), chronic hepatitis C (n=3), or chronic hepatitis B and C (n=4) were excluded from the analysis. Twenty one patients who self-reported excessive alcohol use, defined as >140g ethanol/week for men and >70g ethanol/week for women [7], were excluded; one of the 21 was also excluded for having chronic hepatitis B. This resulted in a total study population of 216 HIV patients in our study cohort.

Participants completed a questionnaire regarding current symptoms suggestive of liver disease, alcohol and drug use, and medical history. Study coordinators collected data from the patients'

medical records on medical diagnoses; past or present receipt of antiretroviral medications (type and duration in months of each medication); and the use of antidiabetic, antihypertensive, lipid-lowering medications, and medications which may cause fatty liver disease (e.g. corticosteroids, estrogens, amiodarone, valproate, methotrexate, and diltiazem). These data were entered onto study-specific case report forms. Duration of HIV was defined at the date of enrollment minus the midpoint between the date of last HIV seronegative and first seropositive (mean time of seroconversion of 16 months); for those without a documented HIV seronegative test (n=54, 25%), the first seropositive date was utilized in this calculation.

At study enrollment, body measurements of weight, height, waist, and hip were measured in a standardized fashion by clinical research coordinators. Body mass index (BMI) was categorized using NIH criteria for obesity (≥ 30 kg/m^2), overweight (25.0–29.9 kg/m^2), normal weight (18.5–24.9 kg/m^2), and underweight (<18.5 kg/m^2)[32].

We also determined the presence of the metabolic syndrome among the participants as defined by the ATP III guidelines by the presence of >3 of the following abnormalities: 1) abdominal obesity (abdominal circumference >102 cm for men and >88 cm for women), 2) elevated triglyceride level (>150 mg/dl), 3) decreased HDL level (<40 mg/dl for men and <50 mg/dl for women), 4) elevated blood pressure, and 5) elevated fasting glucose (>110 mg/dl) [12]. Because we did not collect data on the actual blood pressure, we defined elevated blood pressure as the use of an antihypertensive medication.

Laboratory data

Laboratory tests including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, fasting glucose, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, and hepatitis panel were recorded from the closest date to the ultrasound examination. In addition, the most recent CD4 cell count and HIV viral load was recorded at enrollment; an undetectable viral load was defined as <50 copies/ml. LFTs were repeated, among those with initially normal results, 6 months (range 3–10 months) later during a routine clinic visit. All blood tests were performed at NMCSD, with the exception of CD4 cell counts which were done at the Veterans Administration Hospital, La Jolla, California; both laboratories are certified by Clinical Laboratory Improvement Amendments (CLIA). Lactate levels are not routinely performed in our study population and were not done as part of this study. Data were analyzed using abnormal values of ALT >63 IU/L, AST >41 IU/L, alkaline phosphotase>126 mg/dl, and bilirubin >2.0 mg/dl which are the upper limits of normal at NMCSD. Bilirubin level was not considered to be elevated if that patient was currently prescribed either indinavir or atazanavir. LFT abnormalities were graded as follows: 1.25–2.5x the upper limit of normal (ULN) (grade 1), 2.6–5x ULN (grade 2), 5.1–10x ULN (grade 3), and > 10x ULN (grade 4).

Liver ultrasound examination

Each participant underwent a liver ultrasound which was completed by trained technicians and read by two radiologists (D.A., R.C., R.P.) who concurred on the reading and were blinded to the clinical data of the study. US examinations were performed a mean of 4.2 months (SD 3.5) from the time of enrollment/initial blood test; the US was followed by a second blood test as described above. Liver size was graded as normal ($\leq$ 15.5 cm), borderline (15.6– 16.0 cm), mild hepatomegaly (16.1–17.5 cm), moderate hepatomegaly (17.6– 20.0 cm), or marked hepatomegaly (> 20.0 cm). NAFLD was defined by an ultrasound showing steatosis described as diffusion in hepatic echogenicity according to Rumack et al [33]. The levels of diffusion for hepatic steatosis were classified accordingly in this study as mild, moderate, severe, and marked.

Liver histopathologic examination

Liver biopsies based on medical standards of care were offered to subjects with elevated liver enzymes and/or abnormal ultrasound results; 55/165 (33%) agreed to undergo a biopsy. The timing of the biopsy was a mean of 5.2 (SD 3.6) months from the time of the ultrasound examination. Participants who underwent a biopsy were similar to those who did not get a biopsy except the former group was more likely to have a higher BMI (28 vs. 26 kg/m^2, $p<0.001$), greater waist circumference (96 vs. 90 cm, $p=0.005$), and be on lipid lowering medications (47% vs. 28%, $p=0.04$). Each biopsy, stained with hematoxylin and eosin and with Masson's trichrome stain, was evaluated for features of fatty liver disease with an expanded version of the NAFLD activity score [34]. Specimens that did not contain 5 or more portal tracts were excluded. Biopsies were examined at 10x and 40x magnifications with microscopy. Grading of steatosis was categorized as absent (0%), minimal (<5%), mild (5–33%), moderate (34–66%), or severe (>66%). NASH was defined as steatosis and parenchymal inflammation with centrilobular pericellular fibrosis and/or hepatocellular ballooning, with or without Mallory-Denk bodies. Biopsies were assessed by a single pathologist (Z.G.) who was blinded to the clinical information of the participants.

Statistical analysis

The primary outcome of our study was the presence of steatosis (defined as mild, moderate, severe, and marked) on ultrasound examination. We also examined the prevalence of steatosis among the subset of patients with a liver biopsy.

We evaluated the following variables as potential predictors of NAFLD: demographics (age, gender, race); fasting glucose; fasting lipid levels (total cholesterol, LDL, HDL, triglycerides); liver function tests (ALT, AST, alkaline phosphotase, total bilirubin); BMI; waist circumference; use of antilipid, antihypertensive, and antidiabetic medications; estimated years of HIV infection; diagnosis of an opportunistic infection; CD4 cell count; HIV viral load; and antiretroviral medication use including duration. Univariate proportional odds logistic regression was used to determine the association of each variable with steatosis level (none, mild, moderate, or marked/severe). Each variable for which the regression coefficient was significant at a p-value<0.10 was included in a final multivariate proportional odds model. Correlations between variables were computed using Pearson's correlation coefficient. P-values of <0.05 and 95% confidence intervals that excluded 1.0 were considered to be statistically significant. Statistical analyses were performed using SAS version 9.1 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Baseline Demographic, Clinical, and Laboratory Characteristics

The mean age of the study population (n=216) was 40 years (SD 11); 204 (94%) were male; 103 (48%) reported being Caucasian, 59 (27%) African American, 30 (14%) Hispanic, and 24 (11%) other (Table 1). Fifty percent of the study population were on active duty military service, whereas 44% were retired and 6% were dependents. Four (2%) patients in the study reported the use of illicit substances. The mean duration of HIV infection was 10.0 years (SD 6.9); the mean CD4 cell count was 535 cells/mm^3; and 108 (50%) had an HIV viral load <50 copies/ml. At the time of the study, 141 (65%) of the patients were currently prescribed antiretroviral therapy; 156 (72%) had a history of receiving antiretroviral medications, with 121 (56%), 88 (41%), and 67 (31%) reporting current or prior protease inhibitor, stavudine, or didanosine use, respectively. Only six (3%) participants were on medications which may be associated with fatty liver deposition (2 on estrogens, 2 on prednisone, and two on diltiazem).

One hundred fifty-four patients (73%) had dyslipidemia, defined as abnormalities in any of the lipid levels; 33% had an elevated total cholesterol >200 mg/dl, 38% a LDL >130 mg/dl, 41% an elevated triglycerides >150 mg/dl, and 44% a low HDL <35 mg/dl. Twenty-nine percent of patients were receiving lipid-lowering medications, 23% were receiving antihypertensive medications, and 5% had diabetes mellitus. The mean BMI of the group was 26.0 kg/m^2 with 43% being overweight and 15% being obese. Abnormal ALT and AST levels were noted in 27 (13%) and 41 (19%) of the population, respectively. Of the elevated ALT and AST levels most were grade 1, with only two patients having grade 2 elevation and no patient with grade 3 or 4 elevation.

Prevalence of NAFLD

NAFLD was diagnosed in 67 (31%) of 216 HIV patients based on ultrasound results. Among those with NAFLD, the degree of hepatic steatosis ranged from mild (n=40, 60%) to moderate (n=19, 28%) to severe/ marked (n=8, 12%). In addition to steatosis, hepatomegaly was noted in 135 (63%) of all study patients on ultrasound examination: 73 (34%) had mild, 52 (24%) had moderate, and 10 (5%) had marked hepatomegaly. Of patients with NAFLD, 58 (87%) had hepatomegaly. Liver size was strongly associated with NAFLD, with a mean liver size of 16.3 cm (SD 1.8), 17.4 cm (SD 1.6), 18.7 cm (SD 2.2), and 19.3 cm (SD 4.3) among those with no, mild, moderate and severe steatosis, respectively (odds ratio (OR) 1.8 per 2 cm difference, p=0.002). Fifty-five HIV patients underwent a liver biopsy, of which 20 (36%) patients had biopsy-proven NAFLD. Steatosis on liver biopsy (graded as mild or above) was noted among 11%, 47%, 75%, and 100% of patients with the liver ultrasound showing no, mild, moderate, or severe steatosis, respectively (Table 2). NASH was present in 20% of the biopsy cases of NAFLD; possible early NASH (steatosis with minimal ballooning and no fibrosis) was documented in an additional 10% of patients with NAFLD.

Symptoms and Liver Function Tests among HIV Patients with NAFLD

The majority of participants in our study were asymptomatic; the most common complaint was fatigue (24%). Regarding abdominal symptoms, 12% reported diarrhea, 7% loss of appetite, 6% nausea, and 5% right upper quadrant pain. In comparing participants with and without NAFLD, the only symptom that was significantly different was a higher rate of fatigue among those with NAFLD (33% vs. 20%, p=0.04).

Liver function tests among patients with NAFLD were usually normal. ALT was elevated, at least once during the study period, among 10/67 (15%) patients with NAFLD. Elevated AST occurred in 15/67 (22%), total bilirubin in 1/67 (1.5%), and alkaline phosphotase in no patients with NAFLD. Any abnormality in one or more of the LFTs was present in 17/67 (25%) of NAFLD patients. Among patients without NAFLD, 38 (26%) had elevated LFTs. In this cohort, the sensitivity and specificity of abnormal LFTs for predicting NALFD was 25% and 74%, respectively. For each level of steatosis (none, mild, moderate, or severe/marked), the percent with elevated ALT was 11%, 8%, 21%, and 38%, respectively (OR 1.7, p=0.2).

Factors Associated with NAFLD

The presence of NAFLD was categorized into levels of severity: none, mild, moderate, and severe/marked (Table 1). In the univariate models, variables associated with the degree of NAFLD included higher body mass index (OR 2.0, p<0.001), greater waist circumference (OR 2.2 per 10 cm difference, p<0.001), lower HDL levels (OR 0.5 per 10 mg/dl difference, p<0.001), higher triglyceride levels (OR 1.4 per 100 mg/dl difference, p<0.001), the use of lipid-lowering medication (OR 2.2, p=0.008), and having the metabolic syndrome (OR 2.2, p=0.04). In addition, African American were less likely to have NAFLD as compared to Caucasians (OR 0.3, p=0.004). In addition, both overweight (OR=1.8, p=0.07) and obese patients (OR=3.8, p=0.001) were more likely to have NALFD as compared to patients who

were underweight or normal weight. The only HIV-related characteristics that showed a potential association with NAFLD were past or current stavudine use (OR 1.8, p=0.05) and duration of HIV infection (OR 1.2 for every 5 years, p=0.07). We also evaluated the total duration of stavudine among all patients ever receiving this medication (mean 44 +/− 29 months) and found no association (OR 1.1, p=0.35). Likewise the total duration of didanosine use among patients (24 +/− 27 months) showed no relationship with NAFLD (OR 1.0, p=0.90). Nadir or current CD4 cell count, HIV viral load, or protease inhibitor use also was not associated with NAFLD. Among those currently receiving HAART, we examined the current CD4 cell count, CD4 change from nadir to current value, and having a suppressed (<50 copies/ml) viral load, and found none to be associated with NAFLD (Table 1). Only six participants were receiving a non-HIV medication which may be associated with steatosis; 1/6 had steatosis among this group.

Variables included in the multivariate analyses included race, waist circumference, triglyceride level, HDL level, use of lipid-lowering medications, metabolic syndrome, duration of HIV infection, and prior stavudine use (Table 1). Because BMI was highly correlated with waist circumference (BMI: r=0.78, p<0.001), and waist size was more highly associated with NAFLD, BMI was excluded from the multivariate model. In the final multivariate model, higher waist circumference (OR= 2.1 for each 10 cm difference, p<0.001), lower HDL levels (OR 0.7 for each 10 mg/dl difference, p=0.03), and higher triglyceride levels (OR= 1.2 for each 100 mg/dl difference, p= 0.03) were associated with NAFLD (Table 1). African Americans compared to Caucasians were less likely to have NAFLD (14% vs. 35%), although this did not reach statistical significance in the multivariate model (OR= 0.4, p=0.08). The potential relationship between stavudine and NAFLD was not seen in the multivariate model when examined by receipt (yes/no) or by duration of use.

The univariate analyses were repeated using the liver biopsy to diagnose NAFLD (Table 3). African Americans compared to Caucasians had a lower prevalence of NAFLD (OR 0.1, p=0.03). Other predictors included greater waist circumference (OR 3.1 per 10 cm difference, p=0.001), lower HDL levels (OR 0.3 per 10 mg/dl difference, p=0.008) and higher triglyceride levels (OR 1.9 per 100 mg/dl difference, p=0.04). There were no associations between NAFLD and antiretroviral medication use.

DISCUSSION

NAFLD defined by ultrasound examination is common among HIV patients occurring at a prevalence rate of 31%. Increased waist circumference, low HDL levels, and elevated triglyceride level were significantly associated with NAFLD, with trends towards a reduced rate of NAFLD among African Americans. HIV specific factors including antiretroviral medications were not associated with NAFLD in this study of HIV patients who were uninfected with HCV.

To our knowledge this is the first study in the HAART era to determine the prevalence of NAFLD among HIV patients without HCV coinfection. We found that 31% of our study population had NAFLD based on ultrasound imaging. The prevalence of NAFLD in the general population of the United States is similar, with an estimated rate of 17–33% [7,8]. The only other published reports of the prevalence of steatosis among HIV patients are among patients coinfected with HCV showing rates of 40–72% [25]; however, HCV itself can cause fatty deposition.

Our finding that nearly one-third of HIV patients have NAFLD may have important clinical implications. In the general population, NAFLD may progress to fibrosis, cirrhosis, and liver failure [6,7]. Although the natural history of NAFLD among HIV patients remains unknown,

NAFLD is likely an important cause of liver disease in this population. For example, NAFLD as the cause of idiopathic cirrhosis among HIV patients is increasingly being recognized [35]. Furthermore, NAFLD not only causes liver disease, but has been shown in the general population to predict cardiac disease and a decreased survival [6,36,37]. Given the high prevalence of NAFLD among HIV patients seen in this study, the impact of NAFLD as a marker for excess morbidity and mortality among HIV patients should be prospectively evaluated.

The strongest factor associated with NAFLD in our study was an increased waist circumference, an indicator of central adiposity. Studies of HIV-HCV coinfected patients also found that high BMI was significantly associated with steatosis, but they did not specifically evaluate waist circumference [25]. Waist circumference may be a better predictor of obesity-related health risks than BMI [38]; a study in the general population showed that visceral fat accumulation was predictive of NAFLD regardless of the BMI, including among non-overweight subjects [39]. These findings are likely related to the fact that visceral adipocytes are less mature and more likely to mobilize fat during insulin resistance, which is the first step in the pathogenesis of NAFLD. Furthermore, centrally located fat cells may act an endocrine organ secreting cytokines and adipokines (e.g., adiponectin and leptin) that are important in insulin resistance and fatty liver deposition [40,41]. Among HIV patients, an increased waist circumference may be an effect of both excessive caloric intake as well as lipohypertrophy.

Our study also suggests that relatively small changes in the BMI may lead to steatosis. The mean BMI measures among those with no, mild, moderate, and severe steatosis in our study were 25 kg/m^2, 26 kg/m^2, 28 kg/m^2, and 32 kg/m^2, respectively. In concurrence with our study, a recent investigation among HIV-negative persons showed that the development of steatosis was associated with an increase in BMI of as little as 1 kg/m^2 suggesting that small weight changes may produce significant metabolic changes [42]. This is particularly of concern in the HIV population in which the rates of elevated BMI appears to be rising. A recent study showed the rates of obesity and overweight were 14% and 31%, respectively [29], and in our population consisting of military beneficiaries, these rates were 15% and 43% respectively. Given the rising rates of obesity, NAFLD may become increasingly prevalent among HIV-infected persons.

High triglyceride levels and low HDL levels were also associated with NAFLD among our HIV-positive cohort. These findings have biologic plausibility since the pathogenesis of NAFLD involves deposition of triglycerides within the hepatocytes [26,40]. Studies among HIV-HCV coinfected patients and the general population have also found that elevated triglyceride and low HDL levels are independent factors for steatosis [21]. Of note, these lipid alterations are common among HIV-positive individuals, likely due to viral influences as well as antiretroviral medication effects [21,43]. Given these data, maintaining triglyceride and HDL levels within a normal range may be an important factor in the prevention of NAFLD among both HIV positive and negative persons.

We also noted that African Americans had a trend towards a lower prevalence of NAFLD than Caucasians. Our findings are concurrent with other investigations performed among HIV-HCV coinfected patients and the general population [19,24,44]. These findings are surprising given that obesity rates are higher among African Americans than Caucasians in the U.S. [45]. In our study cohort, 41% of African Americans were overweight, while 15% were obese. With these high rates of obesity, it would be expected that the prevalence of NAFLD in this population would be elevated; however, the contrary has been found in studies to date. Investigations of genetic factors and ethnic differences in lipid homeostasis are advocated to further explore the relationship between African American race and the lower prevalence of NAFLD.

Our study did not find a significant relationship between NAFLD and antiretroviral medications, specifically the nucleoside agents (e.g. stavudine and didanosine) and protease inhibitors. A study of NAFLD in HIV-infected children also found no association between ART use and NAFLD [46]. Studies to date have been conflicting regarding the impact of HAART on hepatosteatosis among HIV-HCV co-infected patients with most studies showing no relationship [18–20,23,47,48], while two studies have showed a relationship between didanosine, stavudine, and protease inhibitor use and steatosis [22,24]. Differences in study findings may be due to study population characteristics as well as the type and duration of antiretroviral use.

Although nearly 75% of our study patients had received antiretroviral medications, the number of patients and the mean duration of stavudine (41%, 44 months) or didanosine (31%, 24 months) use was somewhat limited. This level of usage may not have had a significant effect on the development of liver steatosis as detected by ultrasound evaluation. This is exemplified by a study of HIV-HCV patients where longer duration of antiretroviral therapy use (≥ 4 years) was found to be an independent predictor of steatosis [21]. In addition to the duration of antiretroviral exposure, host genetics (e.g., a novel host polymerase mutation) may play an important role in predicting which patients will develop steatosis after receipt of nucleoside agents [49]. In summary whether antiretroviral medications play a direct effect in the pathogenesis of hepatic steatosis and/or an indirect role through their effects on metabolic factors, such as fat accumulation and lipid levels, requires further study. Our study suggests that abdominal obesity and dyslipidemia are the most significant factors in the development of NAFLD among HIV patients. These metabolic abnormalities may be the result of lifestyle (e.g., diet, exercise) factors rather than antiretroviral medications; further studies are needed.

Similarly, we did not find that factors associated with HIV infection, such as duration of HIV infection, HIV viral load, or CD4 cell counts were associated with NAFLD. Similar results were found in other studies involving HIV-HCV coinfected patients [25]. Speculation exists on the relationship between HIV infection and NAFLD; however, HIV infection is still not a well-established risk factor for NAFLD.

The diagnosis of NAFLD among HIV patients remains challenging as it is typically a silent disease, with only fatigue being slightly more common among patients with NAFLD. Furthermore, liver enzyme abnormalities are commonly seen in HIV patients [4], and their sensitivity and specificity for detecting NAFLD were low. The lack of a strong association between ALT level and NAFLD was also noted in other studies [46], with one report showing 79% of patients with NAFLD had normal LFTs [44]. We repeated the analysis using lower cut-points for ALT (30 mg/dl for men and 19 mg/dl for women) [50] and found that the sensitivity for abnormal LFTs increased to 69%, but the specificity declined to 46%. Ultrasound examination is a more sensitive test for NAFLD. In addition to steatosis, ultrasound examination frequently detected hepatomegaly and there was an association between the degree hepatomegaly and the severity of steatosis in our study. Studies among HIV patients previously have noted that hepatomegaly may signify underlying steatosis [51]. Since NAFLD is usually asymptomatic and has variable LFT results, the diagnosis should be entertained among patients with the associated factors of visceral obesity and hyperlipidemia.

Limitations of our study included that causal relationships could not be assessed due to its cross-sectional design. Since the majority of our cohort was men (94%), our study findings may not be generalizable to women. Self-reporting of alcohol consumption may have been inaccurate, which may have led to incorrectly including or excluding patients within this study. Finally, ultrasonography was used to diagnose NAFLD in our study; the sensitivity and specificity of this test is estimated as 82–94% and 66–95%, respectively, compared to liver biopsy results [42,52]. Since ultrasound is more sensitive in detecting severe steatosis (>33%

fat on the liver) [53], we may have underestimated the prevalence of NAFLD in the study population. However, we did perform liver biopsies on a subset of our population and found similar prevalence and predictors of NAFLD.

In summary, NAFLD was common in HIV-infected persons occurring in one-third of the population. This study demonstrated that increased waist circumference, low HDL and high triglyceride levels were predictors of NAFLD. These findings are relevant to both clinicians and patients as early recognition and management of these risk factors among HIV patients may prevent further progression of NAFLD and morbidity from liver disease among the HIV population.

Acknowledgments

Support for this work was provided by the Infectious Disease Clinical Research Program (IDCRP), Uniformed Services University of the Health Sciences (USUHS), Bethesda, MD, of which the TriService AIDS Clinical Consortium (TACC) is a component. The IDCRP is a DoD tri-service program executed through USUHS and the Henry M. Jackson Foundation for the Advancement of Military Medicine in collaboration with HHS/NIH/NIAID/DCR through Interagency Agreement HU0001-05-2-0011.

REFERENCES

1. Palella FJ Jr, Baker RK, Moorman AC, Chmiel JS, Wood KC, Brooks JT, Holmberg SD. HIV Outpatient Study Investigators. Mortality in the highly active antiretroviral therapy era: changing causes of death and disease in the HIV outpatient study. J Acquir Immune Defic Syndr 2006;43:27–34. [PubMed: 16878047]
2. Bica I, McGovern B, Dhar R, Stone D, McGowan K, Scheib R, Snydman DR. Increasing mortality due to end-stage liver disease in patients with human immunodeficiency virus infection. Clin Infect Dis 2001;32:492–497. [PubMed: 11170959]
3. Weber R, Sabin CA, Friis-Moller N, Reiss P, El-Sadr WM, Kirk O, et al. Liver-related deaths in persons infected with the human immunodeficieny virus: the D:A:D study. Arch Intern Med 2006;166:1632–1641. [PubMed: 16908797]
4. Pol S, Lebray P, Vallet-Pichard A. HIV infection and hepatic enzyme abnormalities: intricacies of the pathogenic mechanisms. Clin Infect Dis 2004;38:S65–S72. [PubMed: 14986277]
5. Ludwig J, Viggiano TR, McGill DB, Oh BJ. Nonalcoholic steatohepatitis: Mayo Clinic experiences with a hitherto unnamed disease. Mayo Clin Proc 1980;55:434–438. [PubMed: 7382552]
6. Adams LA, Lymp JF, St Sauver J, Sanderson SO, Lindor KD, Feldstein A, Angulo P. The natural history of nonalcoholic fatty liver disease: a population-based cohort study. Gastroenterology 2005;129:113–121. [PubMed: 16012941]
7. Farrell GC, Larter CZ. Nonalcoholic fatty liver disease: from steatosis to cirrhosis. Hepatology 2006;43:S99–S112. [PubMed: 16447287]
8. Neuschwander-Tetri, BA.; Caldwell, SH. Nonalcoholic steatohepatitis: summary of an AASLD Single Topic Conference; Hepatology; 2003. p. 1202-1219.
9. Sanyal AJ. AGA technical review on nonalcoholic fatty liver disease. Gastroenterology 2002;123:1705–1725. [PubMed: 12404245]
10. McCullough AJ. Pathophysiology of nonalcoholic steatohepatitis. J Clin Gastroenterol 2006;40:S17–S29. [PubMed: 16540762]
11. Matteoni CA, Younossi ZM, Gramlich T, Boparai N, Liu YC, McCullough AJ. Nonalcoholic fatty liver disease: a spectrum of clinical and pathological severity. Gastroenterology 1999;116:1413–1419. [PubMed: 10348825]
12. Expert Panel on Detection, Evaluation, and Treatment of High Cholesterol In Adults (Adult Treatment Panel III) Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP). JAMA 2001;285:2486–2497. [PubMed: 11368702]
13. Pagano G, Pacini G, Musso G, Gambino R, Mecca F, Depetris N, et al. Nonalcoholic steatohepatitis, insulin resistance, and metabolic syndrome: further evidence for an etiologic association. Hepatology 2002;35:367–372. [PubMed: 11826410]

14. Poles MA, Dieterich DT, Schwarz ED, Weinshel EH, Lew EA, Lew R, Scholes JV. Liver biopsy findings in 501 patients infected with human immunodeficiency virus (HIV). J Acquir Immune Defic Syndr Hum Retrovirol 1996;11:170–177. [PubMed: 8556399]
15. Grumbach K, Coleman BG, Gal AA, Arger PH, Mintz MC, Arenson RL, Aquino L. Hepatic and biliary tract abnormalities in patients with AIDS. Sonographic-pathologic correlation. J Ultrasound Med 1989;8:247–254. [PubMed: 2654415]
16. Beale TJ, Wetton CW, Crofton ME. A sonographic-pathological correlation of liver biopsies in patients with the acquired immunodeficiency syndrome (AIDS). Clin Radiol 1995;50:761–764. [PubMed: 7489625]
17. Trojan A, Kreuzer KA, Flury R, Schmid M, Schneider J, Schröder S. Liver changes in AIDS. Retrospective analysis of 227 autopsies of HIV-positive patients. Pathologe 1998;19:194–200. [PubMed: 9648144]
18. Neau D, Winnock M, Castéra L, Bail BL, Loko MA, Géraut L, et al. Groupe d'Epidémiologie Clinique du SIDA en Aquitaine. Prevalence of and factors associated with hepatic steatosis in patients coinfected with hepatitis C virus and HIV: Agence Nationale pour la Recherche contre le SIDA et les hépatites virales CO3 Aquitaine Cohort. J Acquir Immune Defic Syndr 2007;45:168–173. [PubMed: 17527092]
19. Marks KM, Petrovic LM, Talal AH, Murray MP, Gulick RM, Glesby MJ. Histological findings and clinical characteristics associated with hepatic steatosis in patients coinfected with HIV and hepatitis C. J Infect Dis 2005;192:1943–1949. [PubMed: 16267765]
20. Bani-Sadr F, Carrat F, Bedossa P, Piroth L, Cacoub P, Perronne C, Degott C, Pol S. ANRS HC02 - Ribavic Study team. Hepatic steatosis in HIV-HCV coinfected patients: analysis of risk factors. AIDS 2006;20:525–531. [PubMed: 16470116]
21. Gaslightwala I, Bini EJ. Impact of human immunodeficiency virus infection on the prevalence and severity of steatosis in patients with chronic hepatitis C virus infection. J Hepatol 2006;44:1026–1032. [PubMed: 16618518]
22. McGovern BH, Ditelberg JS, Taylor LE, Gandhi RT, Christopoulos KA, Chapman S, et al. Hepatic steatosis is associated with fibrosis, nucleoside analogue use, and hepatitis C virus genotype 3 infection in HIV-seropositive patients. Clin Infect Dis 2006;43:365–372. [PubMed: 16804853]
23. Monto A, Dove LM, Bostrom A, Kakar S, Tien PC, Wright TL. Hepatic steatosis in HIV/hepatitis C coinfection: prevalence and significance compared with hepatitis C monoinfection. Hepatology 2005;42:310–316. [PubMed: 16025515]
24. Sulkowski MS, Mehta SH, Torbenson M, Afdhal NH, Mirel L, Moore RD, Thomas DL. Hepatic steatosis and antiretroviral drug use among adults coinfected with HIV and hepatitis C virus. AIDS 2005;19:585–592. [PubMed: 15802977]
25. Zeremiski M, Talal AH. Dideoxynucleoside analogues should be used cautiously in patients with hepatic steatosis. Clin Infect Dis 2006;43:373–376. [PubMed: 16804854]
26. Day CP, James OF. Steatohepatitis: a tale of two "hits"? Gastroenterology 1998;114:842–884. [PubMed: 9547102]
27. Riddle TM, Kuhel DG, Woollett LA, Fichtenbaum CJ, Hui DY. HIV protease inhibitor induces fatty acid and sterol biosynthesis in liver and adipose tissues due to the accumulation of activated sterol regulatory element binding proteins in the nucleus. J Biol Chem 2001;275:37514–37519. [PubMed: 11546771]
28. Lemoine M, Barbu V, Girard PM, Kim M, Bastard JP, Wendum D, et al. Altered hepatic expression of SREBP-1 and PPARgamma is associated with liver injury in insulin-resistant lipodystrophic HIV-infected patients. AIDS 2006:387–395. [PubMed: 16439872]
29. Amorosa V, Synnestvedt M, Gross R, Friedman H, MacGregor RR, Gudonis D, et al. A tale of 2 epidemics: the intersection between obesity and HIV infection in Philadelphia. J Acquir Immune Defic Syndr 2005;39:557–561. [PubMed: 16044007]
30. Brown TT, Li X, Cole SR, Kingsley LA, Palella FJ, Riddler SA, et al. Antiretroviral therapy and the prevalence and incidence of diabetes mellitus in the multicenter AIDS cohort study. Arch Intern Med 2005;165:1179–1184. [PubMed: 15911733]
31. Wigg AJ, Roberts-Thomson IC, Dymock RB, McCarthy PJ, Grose RH, Cummins AG. The role of small intestinal bacterial overgrowth, intestinal permeability, endotoxaemia, and tumour necrosis

factor alpha in the pathogenesis of non-alcoholic steatohepatitis. Gut 2001;48:206–211. [PubMed: 11156641]

32. National Institutes of Health. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults--The Evidence Report. Obes Res 1998;6:51S–209S. [PubMed: 9813653]
33. Rumack, CM.; Wilson, S.; Charboneau, WJ.; Johnson, J. Diagnostic Ultrasound. Vol. 3rd ed. Vol. Vol 1. St. Louis, Mo: Elsevier Mosby; 2005.
34. Ishak K, Baptista A, Bianchi L, Callea F, De Groote J, Gudat F, et al. Histological grading and staging of chronic hepatitis. J Hepatol 1995;22:696–699. [PubMed: 7560864]
35. Loulergue P, Callard P, Bonnard P, Pialoux G. Hepatic steatosis as an emerging cause of cirrhosis in HIV-infected patients. J Acquir Immune Defic Syndr 2007;45:365. [PubMed: 17592341]
36. Arslan U, Türkoğlu S, Balcioğlu S, Tavil Y, Karakan T, Cengel A. Association between nonalcoholic fatty liver disease and coronary artery disease. Coron Artery Dis 2007;18:433–436. [PubMed: 17700213]
37. Ekstedt M, Franzén LE, Mathiesen UL, Thorelius L, Holmqvist M, Bodemar G, Kechagias S. Long-term follow-up of patients with NAFLD and elevated liver enzymes. Hepatology 2006;44:865–873. [PubMed: 17006923]
38. Janssen I, Katzmarzyk PT, Ross R. Waist circumference and not body mass index explains obesity-related health risk. Am J Clin Nutr 2004;79:379–384. [PubMed: 14985210]
39. Eguchi Y, Eguchi T, Mizuta T, Ide Y, Yasutake T, Iwakiri R, et al. Visceral fat accumulation and insulin resistance are important factors in nonalcoholic fatty liver disease. J Gastroenterol 2006;41:462–469. [PubMed: 16799888]
40. Machado M, Cortez-Pinto H. Non-alcoholic steatohepatitis and metabolic syndrome. Curr Opin Clin Nutr Metab Care 2006;9:637–642. [PubMed: 16912563]
41. Diehl AM, Li ZP, Lin HZ, Yang SQ. Cytokines and the pathogenesis of nonalchoholic steatohepatitis. Gut 2005;54:303–306. [PubMed: 15647199]
42. Hamaguchi M, Kojima T, Takeda N, Nakagawa T, Taniguchi H, Fujii K, et al. The metabolic syndrome as a predictor of nonalcoholic fatty liver disease. Ann Intern Med 2005;143:722–728. [PubMed: 16287793]
43. Jacobson DL, Tang AM, Spiegelman D, Thomas AM, Skinner S, Gorbach SL, Wanke C. Incidence of metabolic syndrome in a cohort of HIV-infected adults and prevalence relative to the US population (National Health and Nutrition Examination Survey). J Acquir Immune Defic Syndr 2006;43:458–466. [PubMed: 16980905]
44. Browning JD, Szczepaniak LS, Dobbins R, Nuremberg P, Horton JD, Cohen JC, et al. Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. Hepatology 2004;40:1387–1395. [PubMed: 15565570]
45. Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM. Prevalence of overweight and obesity in the United States, 1999–2004. JAMA 2006;295:1549–1555. [PubMed: 16595758]
46. Albisetti M, Braegger CP, Stallmach T, Willi UV, Nadal D. Hepatic steatosis: a frequent non-specific finding in HIV-infected children. Eur J Pediatr 1999;158:971–974. [PubMed: 10592072]
47. Bäuerle J, Miquel R, Laguno M, Mallolas J, Murillas J, Gatell JM, Walker UA. Hepatic steatosis with stavudine in HIV/hepatitis C co-infection (letter). AIDS 2005;19:1441–1442. [PubMed: 16103783]
48. Castéra L, Loko MA, Le Bail B, Coffie P, De Ledinghen V, Trimoulet P, et al. Groupe D'epidémiologie Clinique du Sida en Aquitaine (GECSA). Hepatic steatosis in HIV-HCV coinfected patients in France: comparison with HCV monoinfected patients matched for body mass index and HCV genotype. Aliment Pharmacol Ther 2007;26:1489–1498. [PubMed: 17903235]
49. Yamanaka H, Gatanaga H, Kosalaraksa P, Matsuoka-Aizawa S, Takahashi T, Kimura S, Oka S. Novel mutation of human DNA polymerase gamma associated with mitochondrial toxicity induced by anti-HIV treatment. J Infect Dis 2007;195:1419–1425. [PubMed: 17436221]
50. Prati D, Taioli E, Zanella A, Della Torre E, Butelli S, et al. Updated definitions of healthy ranges for serum alanine aminotransferase levels. Ann Intern Med 2002;137:1–9. [PubMed: 12093239]
51. Frieman JP, Helfert KE, Hamrell MR, Stein DS. Hepatomegaly with severe steatosis in HIV-seropositive patients. AIDS 1993;7:379–385. [PubMed: 8471200]

52. Joseph AE, Savery muttu SH, al-Sam S, Cook MG, Maxwell JD. Comperiosn of liver histology with ultrasonography in assessing diffuse parenchymal liver disease. Clin Radiol 1991;43:26–31. [PubMed: 1999069]

53. Saadeh S, Younossi ZM, Remer EM, Gramlich T, Ong JP, Hurley M, et al. The utility of radiological imaging in nonalcoholic fatty liver disease. Gastroenterology 2002;123:745–750. [PubMed: 12198701]

Table 1

Demographic, Clinical, and Laboratory Characteristics by Steatosis Level Diagnosed by Liver Ultrasound with Univariate and Multivariate Analyses

Regression Results		Steatosis Level by Ultrasound				Logistic			
						Univariate		Multivariate	
Demographics	**All Patients**	**None**	**Mild**	**Moderate**	**Severe/ Marked**	**OR[1]**	**p-value**	**OR[1] (95% CI)**	**p-value**
No. of Patients	216	149	40	19	8				
Age (years)[2,3]	39.6 ± 11.1	39.3 ± 11.5	38.7 ± 9.3	42.9 ± 10.6	40.8 ± 12.8	1.1	0.46		
Female	12 (5.6%)	10 (6.7%)	1 (2.5%)	1 (5.3%)	0 (0.0%)	0.4	0.29		
Race/Ethnicity									
White	103 (47.7%)	67 (45.0%)	22 (55.0%)	10 (52.6%)	4 (50.0%)				
African American	59 (27.3%)	51 (34.2%)	6 (15.0%)	2 (10.5%)	0 (0.0%)	0.3	0.004	0.4 (0.2, 1.1)	0.08
Hispanics	30 (13.9%)	19 (12.8%)	4 (10%)	4 (21.1%)	3 (37.5%)	1.3	0.57	1.4 (0.6, 3.3)	0.48
Other[4]	24 (11.1%)	12 (8.1%)	8 (20.0%)	3 (15.8%)	1 (12.5%)	1.7	0.24	1.7 (0.4, 6.8)	0.48
Military status									
Active Duty	107 (49.5%)	75 (50.3%)	21 (52.5%)	8 (42.1%)	3 (37.5%)				
Retired	96 (44.4%)	63 (42.3%)	18 (45.0%)	10 (52.6%)	5 (62.5%)	1.3	0.39		
Dependent	13 (6.0%)	11 (7.4%)	1 (2.5%)	1 (5.3%)	0 (0.0%)	0.4	0.30		
Body Composition									
Body mass index (kg/m)^2	26.0 ± 4.1	25.5 ± 3.9	26.1 ± 3.6	27.8 ± 4.3	32.1 ± 5.2	2.0	< 0.001		
< 25.0 kg/m	92 (42.6%)	71 (47.7%)	17 (42.5%)	4 (21.1%)	0 (0.0%)				
25.0 – 29.9 kg/m	92 (42.6%)	62 (41.6%)	15 (37.5%)	11 (57.9%)	4 (50.0%)	1.8	0.07		
≥ 30.0 kg/m	32 (14.8%)	16 (10.7%)	8 (20.0%)	4 (21.1%)	4 (50.0%)	3.8	0.001		
Waist (cm)[2,5]	90.4 ± 11.9	87.9 ± 10.1	91.0 ± 10.3	100.8 ± 12.2	111.3 ± 17.1	2.2	<0.001	2.1 (1.6, 2.8)	<0.001
Lipid panel									
Fasting glucose (mg/dl)[2,6]	91.5 ± 21.0	90.3 ± 20.8	92.8 ± 22.1	98.5 ± 22.4	90.6 ± 14.5	1.2	0.20		
Total cholesterol (mg/dl)[2,7]	185.9 ± 41.9	183.7 ± 39.2	188.2 ± 42.7	199.1 ± 56.0	183.5 ± 50.0	1.2	0.22		
HDL (mg/dl)[2,8]	40.3 ± 12.3	42.5 ± 12.7	37.6 ± 11.5	33.9 ± 7.8	30.8 ± 6.5	0.5	<0.001	0.7 (0.5, 1.0)	0.03
LDL (mg/dl)[2,9]	113.8 ± 34.2	114.2 ± 33.0	108.9 ± 28.7	118.9 ± 53.0	119.9 ± 43.9	1.0	0.91		
Triglycerides (mg/dl)[3,10]	172.1 ± 158.3	136.7 ± 99.9	230.6 ± 251.5	308.8 ± 189.6	201.0 ± 109.1	1.4	<0.001	1.2 (1.0, 1.5)	0.03
Metabolic syndrome[11]	162 (75.0%)	106 (71.1%)	31 (77.5%)	18 (94.7%)	7 (87.5%)	2.2	0.04		
Concurrent Medications									
On diabetes mellitus drugs	11 (5.1%)	7 (4.7%)	2 (5.0%)	2 (10.5%)	0 (0.0%)	1.3	0.68		
On lipid-lowering drugs	63 (29.2%)	35 (23.5%)	16 (40.0%)	10 (52.6%)	2 (25.0%)	2.2	0.008	1.3 (0.7, 2.7)	0.39
On hypertension drugs	49 (22.7%)	32 (21.5%)	9 (22.5%)	5 (26.3%)	3 (37.5%)	1.3	0.43		
Liver Function Tests[12]									
ALT > 63 IU/L[13,14]	27 (12.6%)	17 (11.5%)	3 (7.5%)	4 (21.1%)	3 (37.5%)	1.7	0.21		
AST > 41 IU/L[13,14]	41 (19.1%)	27 (18.2%)	4 (10.0%)	7 (36.8%)	3 (37.5%)	1.4	0.30		
Alkaline phosphatase > 126 IU/L[14,15]	6 (2.8%)	6 (4.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	----	0.30		
Total bilirubin > 2[13,14,16]	6 (2.8%)	5 (3.4%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	0.4	0.42		
Any liver test abnormality[14]	55 (25.6%)	38 (25.7%)	7 (17.5%)	7 (36.8%)	3 (37.5%)	1.1	0.77		
HIV Characteristics									
Years HIV+[2,17]	10.0 ± 6.9	9.5 ± 6.8	11.2 ± 6.6	11.5 ± 7.3	11.1 ± 8.2	1.2	0.07	1.1 (0.8, 1.6)	0.52
Prior OI	18 (8.3%)	13 (8.7%)	2 (5.0%)	2 (10.5%)	1 (12.5%)	0.9	0.88		
Nadir CD4 count (cells/mm^2)[2,18]	295.1 ± 203.0	304.9 ± 214.9	289.7 ± 175.5	215.4 ± 124.1	329.4 ± 239.8	1.0	0.25		
Current CD4 count (cells/mm^3)[2,19]	535.2 ± 247.5	538.9 ± 242.7	527.4 ± 271.3	524.1 ± 244.0	529.8 ± 268.2	1.0	0.74		
HIV RNA <50 copies/mL	108 (50.0%)	75 (50.3%)	21 (52.5%)	7 (36.8%)	5 (62.5%)	0.9	0.83		
Among those on HAART, current CD4 count (cells/mm^3)[2,19]	533.5 ± 264.2	533.2 ± 251.8	522.7 ± 313.9	578.9 ± 257.8	480.4 ± 293.8	1.0	0.89		
Among those on HAART, HIV RNA <50 copies/mL	104 (73.8%)	73 (76.0%)	20 (74.1%)	7 (53.8%)	4 (80.0%)	0.8	0.67		

J Acquir Immune Defic Syndr. Author manuscript; available in PMC 2009 November 25.

Regression Results		Steatosis Level by Ultrasound				Logistic Univariate		Multivariate	
Demographics	**All Patients**	**None**	**Mild**	**Moderate**	**Severe/ Marked**	**OR[1]**	**p-value**	**OR[1] (95% CI)**	**p-value**
Among those on HAART, CD4 change from nadir to current (cells/mm^3)[2,18]	321.8 ± 224.1	317.6 ± 218.7	301.5 ± 255.8	411.2 ± 214.2	279.0 ± 166.1	1.0	0.65		
Antiretroviral History[20]									
Any Antiretrovirals	156 (72.2%)	104 (69.8%)	33 (82.5%)	14 (73.7%)	5 (62.5%)	1.4	0.33		
Didanosine	68 (31.5%)	43 (28.9%)	13 (32.5%)	8 (42.1%)	4 (50.0%)	1.5	0.15		
Stavudine	88 (40.7%)	54 (36.2%)	20 (50.0%)	11 (57.9%)	3 (37.5%)	1.8	0.05	0.9 (0.3, 2.2)	0.76
Protease inhibitor	122 (56.5%)	80 (53.7%)	25 (62.5%)	13 (68.4%)	4 (50.0%)	1.4	0.24		

ALT, Alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; HDL, high density lipoprotein; LDL, low density lipoprotein; OI, opportunistic infection; OR, odds ratio; ULN, upper limit of normal.

[1] Odds ratios from proportional odds models.

[2] Mean ± S.D.

[3] Odds ratio associated with a 10 year difference.

[4] Other races included Filipino (n=12), Pacific Islander (n=1), other Asian (n=1), or other/mixed (n=10).

[5] Odds ratio associated with a 10 cm. difference.

[6] Odds ratio associated with a 20 mg/dl difference.

[7] Odds ratio associated with a 40 mg/dl difference.

[8] Odds ratio associated with a 10 mg/dl difference.

[9] Odds ratio associated with a 30 mg/dl difference.

[10] Odds ratio associated with a 100 mg/dl difference.

[11] Three or more of the following: Waist > 102 cm. (men) or > 88 cm. (women), triglycerides ≥ 150, HDL < 40 (men) or < 50 (women), fasting glucose ≥ 110, or receipt of a antihypertensive medication.

[12] If none of the liver function test results were elevated at the initial visit, tests were repeated 3–6 months later.

[13] Elevated is defined as > ULN.

[14] Initial or follow-up visit.

[15] P-value is from Fisher's exact test.

[16] Unless patient was on atazanavir or indinavir.

[17] Odds ratio associated with a 5 year difference.

[18] Odds ratio associated with a 50 cell difference.

[19] Odds ratio associated with a 100 cell difference.

[20] Past and/or current receipt of medication.

Table 2

Steatosis Level by Ultrasound and Liver Biopsy

	Steatosis Level by Liver Biopsy				
Steatosis Level by Ultrasound	**None**	**Minimal**	**Mild**	**Moderate**	**Total**
None	14 (87.5%)	11 (57.9%)	3 (15.8%)	0 (0%)	28 (50.9%)
Mild	2 (12.5%)	6 (31.6%)	7 (36.8%)	0 (0%)	15 (27.3%)
Moderate	0 (0%)	2 (10.5%)	6 (31.6%)	0 (0%)	8 (14.5%)
Severe/Marked	0 (0%)	0 (0%)	3 (15.8%)	1 (100%)	4 (7.3%)
Total	16 (100%)	19 (100%)	19 (100%)	1 (100%)	55 (100%)

Table 3

Demographic, Clinical, and Laboratory Characteristics by Steatosis Level Diagnosed by Liver Bopsy with Univariate Analyses

Demographics	All Patients	Steatosis Score on Biopsy		Logistic Regression Univariate Model	
		None/minimal	Mild/moderate	OR[1] (95% CI)	p-value
No. of Patients	55	35	20		
Age (years)[2,3]	40.9 ± 10.8	41.7 ± 11.4	39.6 ± 9.9	0.8 (0.5, 1.4)	0.49
Female	2 (3.6%)	2 (5.7%)	0 (0.0%)	---	0.53
Race/Ethnicity					
White	29 (52.7%)	15 (42.9%)	14 (70.0%)		
African American	13 (23.6%)	12 (34.3%)	1 (5.0%)	0.1 (0.0, 0.8)	0.03
Hispanics	6 (10.9%)	2 (5.7%)	4 (20.0%)	2.1 (0.3, 14)	0.42
Other[4]	7 (12.7%)	6 (17.1%)	1 (5.0%)	0.2 (0.0, 1.7)	0.13
Military status					0.62
Active	21 (38.2%)	12 (34.3%)	9 (45.0%)		
Retired	32 (58.2%)	21 (60.0%)	11 (55.0%)		
Dependent	2 (3.6%)	2 (5.7%)	0 (0%)		
Body Composition					
Body mass index (kg/m)^2	27.9 ± 4.3	27.0 ± 3.6	29.4 ± 5.0	2.0 (1.0, 4.0)	0.06
< 25.0 kg/m	14 (25.5%)	11 (31.4%)	3 (15.0%)		
25.0 – 29.9 kg/m	26 (47.3%)	16 (45.7%)	10 (50.0%)	2.3 (0.5, 10)	0.28
≥ 30.0 kg/m	15 (27.3%)	8 (22.9%)	7 (35.0%)	3.2 (0.6, 16)	0.16
Waist (cm)[2,5]	95.8 ± 13.5	90.6 ± 10.1	104.8 ± 14.1	3.1 (1.6, 6.1)	0.001
Lipid panel					
Fasting glucose (mg/dl)[2,6]	95.9 ± 23.7	95.0 ± 24.2	97.3 ± 23.5	1.1 (0.7, 1.7)	0.73
Total cholesterol (mg/dl)[2,7]	189.1 ± 47.9	187.8 ± 49.1	191.2 ± 47.0	1.1 (0.7, 1.7)	0.80
HDL (mg/dl)[2,8]	36.8 ± 9.5	39.8 ± 9.5	32.0 ± 7.2	0.3 (0.1, 0.7)	0.008
LDL (mg/dl)[2,9]	116.0 ± 39.8	117.2 ± 40.0	113.8 ± 40.4	0.9 (0.6, 1.5)	0.77
Triglycerides (mg/dl)[2,10]	184.3 ± 104.9	159.5 ± 88.8	225.3 ± 118.3	1.9 (1.0, 3.6)	0.04
Metabolic syndrome[11]	46 (83.6%)	27 (77.1%)	19 (95.0%)	5.6 (0.6, 49)	0.12
Concurrent Medications					
On diabetes mellitus drugs	4 (7.3%)	3 (8.6%)	1 (5.0%)	0.6 (0.1, 5.8)	0.63
On lipid-lowering drugs	25 (45.5%)	15 (42.9%)	10 (50.0%)	1.3 (0.4, 4.0)	0.61
On hypertension drugs	16 (29.1%)	12 (34.3%)	4 (20.0%)	0.5 (0.1, 1.8)	0.27
HIV Characteristics					
Years HIV+[2,12]	11.0 ± 7.0	11.4 ± 7.3	10.4 ± 6.7	0.9 (0.6, 1.3)	0.59
Prior OI	5 (9.1%)	4 (11.4%)	1 (5.0%)	0.4 (0.0, 3.9)	0.44
Nadir CD4 count (cells/mm^2)[2,13]	294.0 ± 209.5	285.9 ± 234.2	308.2 ± 162.0	1.0 (0.9, 1.2)	0.70
Current CD4 count (cells/mm^3)[2,14]	566.5 ± 275.3	537.1 ± 239.2	617.9 ± 329.6	1.1 (0.9, 1.4)	0.30
HIV RNA <50 copies/mL	28 (50.9%)	18 (51.4%)	10 (50.0%)	0.9 (0.3, 2.8)	0.92
Antiretroviral History[15]					
Any antiretroviral	43 (78.2%)	28 (80%)	15 (75.0%)	0.7 (0.2, 2.8)	0.67
Didanosine	19 (34.5%)	13 (37.1%)	6 (30.0%)	0.7 (0.2, 2.4)	0.59
Stavudine	28 (50.9%)	20 (57.1%)	8 (40.0%)	0.5 (0.2, 1.5)	0.22
Protease inhibitor	32 (58.2%)	20 (57.1%)	12 (60.0%)	1.1 (0.4, 3.4)	0.84

ALT, Alanine aminotransferase; AST, aspartate aminotransferase; HDL, high density lipoprotein; LDL, low density lipoprotein; OI, opportunistic infection; OR, odds ratio; ULN, upper limit of normal.

[1]Odds ratios from proportional odds models.

J Acquir Immune Defic Syndr. Author manuscript; available in PMC 2009 November 25.

[2] Mean ± S.D.

[3] Odds ratio associated with a 10 year difference.

[4] Other races included Filipino, Pacific Islander, other Asian, or other/mixed.

[5] Odds ratio associated with a 10 cm. difference.

[6] Odds ratio associated with a 20 mg/dl difference.

[7] Odds ratio associated with a 40 mg/dl difference.

[8] Odds ratio associated with a 10 mg/dl difference.

[9] Odds ratio associated with a 30 mg/dl difference.

[10] Odds ratio associated with a 100 mg/dl difference.

[11] Three or more of the following: Waist > 102 cm. (men) or > 88 cm. (women), triglycerides ≥ 150, HDL < 40 (men) or < 50 (women), fasting glucose ≥ 110, or receipt of a antihypertensive medication.

[12] Odds ratio associated with a 5 year difference.

[13] Odds ratio associated with a 50 cell difference.

[14] Odds ratio associated with a 100 cell difference.

[15] Past and/or current receipt of medication.