HHS Public Access

Author manuscript

Hepatology. Author manuscript; available in PMC 2024 August 01.

Published in final edited form as:

Hepatology. 2023 August 01; 78(2): 578–591. doi:10.1097/HEP.0000000000000313.

Burden of Fatty Liver and Hepatic Fibrosis in Persons with HIV: A Diverse Cross-sectional US Multicenter Study

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Abstract

Background & Aims: The current prevalence of fatty liver disease (FLD) due to alcoholic (AFLD) and non-alcoholic (NAFLD) origins in US persons with HIV (PWH) is not well defined. We prospectively evaluated the burden of fatty liver disease and hepatic fibrosis in a diverse cohort of PWH.

Approach & Results: Consenting participants in outpatient HIV clinics in 3 centers in the US underwent detailed phenotyping including liver ultrasound and vibration-controlled transient elastography for controlled attenuation parameter (CAP) and liver stiffness measurement (LSM). The prevalence of AFLD, NAFLD, clinically significant and advanced fibrosis were determined. Uni- and multivariate logistic regression models were used to evaluate factors associated with the risk of NAFLD.

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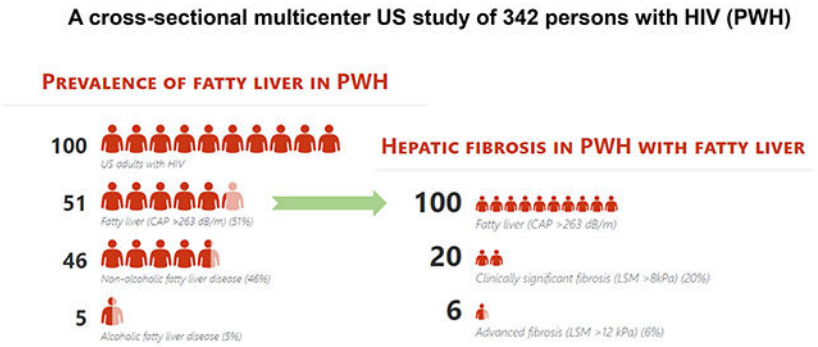
Author's contributions: Study concept, manuscript preparation (SG, JEL, KEC, NC); data (biosamples, meta-) acquisition (SG, JEL, PD, JAS, MR, MT, FA, KZ, GKR, SKG, KEC), statistical analysis (SSB, CKS), data interpretation and critical review of manuscript (SG, JEL, NS, PD, SSB, CKS, KZ, GKR, SKG, RTC, NC, KEC)

Results: Of 342 participants, 95.6% were on ART and 93.9% had adequate viral suppression, 48.7% (95% CI 43%-54%) had steatosis by ultrasound, and 50.6% (95% CI 45%-56%) had steatosis by CAP ≥263 dB/m. NAFLD accounted for 90% of FLD. In multivariable analysis, older age, higher BMI, diabetes, and higher ALT but not ART or $CD4^+$ cell count, were independently associated with increased NAFLD risk. In all PWH with fatty liver, the frequency of LSM 8-12 kPa was 13.9% (95% CI 9%-20%) and ≥12 kPa 6.4% (95% CI 3%-11%), with similar frequency of these LSM cutoffs in NAFLD.

Conclusions: Nearly half of virally-suppressed PWH have FLD, 90% of which is due to NAFLD. A fifth of PWH with FLD has clinically significant fibrosis and 6% have advanced fibrosis. These data lend support to systematic screening for high-risk NAFLD in PWH.

Graphical Abstract



Keywords

NAFLD; antiretroviral therapy; stiffness; CAP; prevalence

Introduction

Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease and a leading indication of liver transplantation in the US (1, 2). The burden and predictors of NAFLD in the US general population have been studied extensively, but limited data are available on the prevalence and factors associated with NAFLD and clinically significant fibrosis in US persons with HIV (PWH).

The increased longevity of PWH following wider use of antiretroviral therapy (ART) has come at the expense of increased weight and non-AIDS related morbidity and mortality from metabolic, hepatic and cardiovascular diseases (3–8). NAFLD is currently the leading liver disease in the aging HIV population (9–12). Using different imaging modalities or controlled attenuation parameter (CAP), NAFLD prevalence in persons with HIV mono-infection has been reported to be 15-54% (10, 13–16), and up to 73% in a study with histological evaluation of PWH and elevated liver enzymes (17). These prevalence estimates far exceed the reported prevalence of NAFLD in the general population (1, 18, 19). However, published reports of NAFLD prevalence in PWH were generated from single center studies with small numbers of participants, cohorts with concurrent hepatitis C virus. alcohol abuse, elevated transaminases, or metabolic syndrome; or from studies limiting

the population to single gender or military families (13, 14, 16, 17, 20–23). Therefore, systematic characterization of NAFLD burden in US PWH in large diverse, multi-ethnic, multi-gender, and multi-centric cohorts is needed.

The severity of underlying hepatic fibrosis in patients with NAFLD significantly impacts survival and increases the risk for poor clinical outcomes (24–26). Data on prevalence and severity of hepatic fibrosis in PWH are very limited (10). Factors influencing NAFLD severity in the general population, such as central obesity and insulin resistance, have been reported in some but not all studies to increase NAFLD risk in PWH (10, 13, 27). Indeed, studies of men with HIV report lower incidence of hepatic steatosis and lower body mass index (BMI) compared to controls (14, 28). The contributions of HIV viremia, its duration and control, and use of different classes of ART to NAFLD risk have been controversial (12). Some studies support a role for the duration of HIV and ART agents used (29–32), while others reported no such associations (13, 17, 33).

The goals of this study were to define the prevalence of and risk factors for fatty liver disease due to NAFLD and excessive alcohol in a contemporary, prospective, racially and ethnically diverse, multicentered US cohort. We determined the burden and predictive factors of clinically significant fibrosis in this population. As secondary aims, we described concordance between CAP and ultrasound diagnosis of hepatic steatosis and determined optimal cutoffs for CAP and ALT to detect ultrasound diagnosed hepatic steatosis in PWH.

Methods

Study participants

Consecutive adult PWH who provided written informed consent to participate in this study were prospectively enrolled from three outpatient HIV clinics at Indiana University School of Medicine, Massachusetts General Hospital, and University of Texas Health Science Center at Houston between 2018 and 2022. Inclusion criteria were age ≥ 18 years, documented HIV defined by a positive HIV antibody assay and/or detectable HIV-1 RNA, and stable ART regimen for three months prior to enrollment for those on ART at time of study entry. Exclusion criteria were evidence of or known history of hepatitis B or C co-infection, or other liver diseases (e.g., autoimmune hepatitis, cholestatic liver diseases, Wilson disease, hemochromatosis, etc.). The study protocol was approved by each site's Institutional Review Board (IRB). We enrolled all PWH who consented to participate in the study during the funding grant period, including those who were referred from their providers and those who reached out to the study team after seeing the study flyers.

Characterization of study participants

Trained study staff performed liver imaging with ultrasound, which was centrally read by two experienced radiologists to determine the presence of fatty liver (steatosis). Concordance between the two radiologists on the presence or absence of hepatic steatosis on ultrasound was assessed. To do this, the second radiologist, blind to the assessment of the first radiologist, determined the presence or absence of hepatic steatosis in a sub-sample of 59 participants.

Participants also underwent vibration-controlled transient elastography (VCTE) by Fibroscan® for CAP and liver stiffness measurement (LSM) by a trained study staff. Fibroscan® was performed by a maximum of two trained study staff at each study site. The use of M vs XL probe prompted by automated Fibroscan® notification. Each participant underwent history and physical examination by a study physician. Extensive data were collected including demographic (age, sex, race, ethnicity), anthropometrics (BMI, waist circumference), vital signs, medical and medicinal history, most recent laboratory and HIV data (HIV-1 RNA, $CD4^+$ T cell nadir and current count) data within 6 months of enrollment, and current and prior ART classes (protease inhibitors [PIs], non-nucleoside reverse transcriptase inhibitors [NNRTIs], integrase strand transfer inhibitors [INSTIs], nucleoside reverse transcriptase inhibitors [NRTIs], and entry inhibitors). Participants with HIV-1 RNA <200 copies/mL were considered to have achieved adequate viral suppression.

Each participant completed an Alcohol Use Disorders Identification Test (AUDIT) questionnaire to assess alcohol consumption in the past year. AUDIT is a simple, ten-question test developed by the World Health Organization to determine if a person is a risky drinker or has alcohol use disorder. This instrument has been validated and allows quantification of daily drinks of alcohol consumed. A score of 8 or more indicates a strong likelihood of hazardous drinking (34, 35). Participants with fatty liver and AUDIT score < 8 were considered to have NAFLD, whereas those with fatty liver and AUDIT score ≥ 8 were considered to have alcoholic fatty liver disease (AFLD). Lean NAFLD was defined as NAFLD with BMI < 25 kg/m^2.

The prevalence of fatty liver was determined by both ultrasound and different CAP cutoffs (36–40). Further detailed fatty liver analyses were performed using a CAP cutoff of 263 dB/m (37). The prevalence of different LSM and fibrosis 4 (FIB-4) cutoffs were also determined (37, 41–43). Clinically significant fibrosis data and analyses were presented with the two recently proposed close LSM cutoffs (8 and 8.6 kPa) (37, 43).

Statistical Methods

To characterize the study participants, continuous variables were reported in mean (SD) and discrete variables were summarized in frequency and percent. The main study analysis was based on diagnosis of fatty liver by CAP ≥263 dB/m (37). Overall study participants were categorized into three groups, no fatty liver, NAFLD and AFLD based on CAP and AUDIT scores. Our primary goal was to report the prevalence of fatty liver. To estimate the accuracy of reporting prevalence of fatty liver, we calculated the confidence interval using the Simple Asymptotic Method. With a sample size of 342, a two-sided 95% confidence interval estimates will have a width of 10.6% while the true prevalence is around 50%.

Two-sample t-test for continuous variables and Chi-square or Fishers Exact test for discrete variables were used to compare two groups, no fatty liver vs. NAFLD as well as NAFLD vs. FLD. Similar tests were used for any other two groups comparisons. Statistical significance was defined as P value < 0.05.

Factors associated with the presence of NAFLD (CAP value ≥263 dB/m in patients with AUDIT <8) were identified. A multivariate logistic regression model was developed by

including all significant predictors at univariate analyses. Though factors associated with the presence of clinically significant fibrosis in patient with NAFLD (LSM ≥ 8.6 in patients with CAP ≥263 dB/m) were identified at univariate level, a multivariate model was not developed due the paucity of cases (n=27). The frequency of abnormal ALT was provided using two cutoffs [>40 U/L (44) and >30 U/L in men and >19 U/L in women (45)]. Logistic regression was used to calculate area under the curve (AUC) and to determine optimal cutoffs for CAP and ALT to identify ultrasound-diagnosed fatty liver for a fixed 90% sensitivity and specificity. Finally, Youden index was used to determine the cutoff for the best combination of sensitivity and specificity. Youden index is calculated by using equal weight on sensitivity and specificity and by measuring the maximum vertical distance between the receiver operating characteristics curve and the diagonal line which is also known as chance line. Kappa (k) statistics with 95% confidence interval were used to assess the strength of agreement on diagnosis of fatty liver disease based on ultrasound by two radiologists.

Results

Characteristics of study participants

In 342 participants, the mean age (SD) was 48.2 (12) years, 72.8% were males, 19.0% cisgender females, 8.2% transgender females, 49.1% White, 40.9% Black, 28.6% Hispanic, 17.5% with obesity, and 11.6% with diabetes (Table 1). There were significant demographic differences between study sites (Supplementary Table 1). The Texas site had fewer cisgender males but more transgender females, and Hispanic participants than the other sites whereas the Indiana site had the highest proportion of Black participants and Massachusetts the highest proportion of cisgender male and White participants.

The majority of participants (95.6%) were on ART. Exposure to PI was recorded in 26.9%, NNRTI in 13.5%, INSTI in 78.1%, entry inhibitors in 1.2%, and NRTI in 91.2% of participants. Adequate viral suppression was observed in 93.9%; mean current $CD4^+$ T cell count (SD) was 712.7 (337.8) cells/ul.

Prevalence of fatty liver by ultrasound and different CAP cutoffs

In the entire cohort, the prevalence of steatosis was 48.7% (95% CI 43%-54%) by ultrasound, 66.1% (95% CI 61%-71%) by CAP ≥ 238 dB/m, 50.6% (95% CI 45%-56%) by CAP ≥263 dB/m, and by CAP ≥290 dB/m 38.3% (33.1%-43.6%). The prevalence data for different CAP cutoffs in our cohort is shown in Supplementary Table 2. Nearly 90% of fatty liver was due to NAFLD (Figure 1. A).

The prevalence of fatty liver varied per site (Supplementary Table 1) and correlated with the racial and ethnic composition of the cohort at that site, with Indiana having the lowest prevalence of fatty liver (40.3%) and Texas having the highest (58.3%) ($P = 0.01$), corresponding to the Indiana site having the highest proportion of Black participants (63.7%) whereas the Texas site having the highest proportion of Hispanic participants (60.2%) ($P < 0.01$) (Supplementary Table 1).

Fatty liver prevalence in this cohort (50.6%) did not change after a sensitivity analysis excluding transgender women (51%) (Supplementary Table 3).

Notably, ALT >40 U/L was noted in only 18.9 % and AST >40 U/L in 10.8% of all participants, and the frequency of the lower cutoffs for abnormal ALT (>30 U/L in men and >19 U/L in women) was 39.2% in the entire cohort (Table 1).

In patients without excessive alcohol consumption, the prevalence of NAFLD was 48.5% (95% CI 43%-54%) by ultrasound, 66.1% (95% CI 61%-71%) by CAP ≥ 238 dB/m, and 51% (95% CI 45%-57%) by CAP ≥263 dB/m.

The prevalence of fatty liver in different study subgroups is shown in Figure 2. In the entire cohort, White (61% [95% CI 54%-69%]), Hispanic (59% [95% 36%-79%]), and cisgender women (60% [95% CI 47%-72%]) participants had the highest rates of fatty liver (Figure 2.A). Similarly, in participants without excessive alcohol use, White (57% [95% CI 49%-65%]), Hispanic (55% [95% CI 32%-76%) and cisgender women (58% [95% CI 45%-70%]) participants had the highest rates of NAFLD (Figure 2.B).

Prevalence of fibrosis in PWH and fatty liver (CAP ≥ 263 dB/m)

The prevalence of different cutoffs of LSM and FIB4 in all PWH and fatty liver, those with NAFLD and AFLD are shown in Table 2.

In all PWH with fatty liver, the frequency of LSM 8-12 kPa was 13.9% (95% CI 9%-20%) and ≥12 kPa 6.4% (95% CI 3%-11%), with similar frequency of these LSM cutoffs in participants with NAFLD (Figure 1. B and C). The frequencies of different LSM cutoffs in participants with fatty liver were slightly lower with ultrasound-diagnosed fatty liver compared to CAP ≥263 dB/m-defined fatty liver (Supplementary Table 4).

Lower estimates for frequencies of significant and advanced fibrosis were observed when using FIB4 (Table 2); the prevalence of significant fibrosis in PWH and fatty liver (FIB4 1.63-2.67) was 13.3% (95% CI 9%-19%) and advanced fibrosis (FIB4> 2.67) was 2.9% (95% CI 1%-7%) with similar frequency of these FIB4 cutoffs in participants with NAFLD.

Characteristics of participants with NAFLD

Compared to controls without fatty liver (Table 1), PWH with NAFLD were older, more frequently White, had higher frequency of overweight, obesity and diabetes, had larger waist circumference and higher ALT, AST, triglycerides, and insulin levels.

PWH with NAFLD were more commonly on ART (98.1% vs 93.5%, P = 0.04) and had higher current (768.4 [352.5] vs 665.9 [318.7] cells/ul, P = 0.01), lower nadir CD4+ T cell counts (200.1 [206.8] vs 256.2 [189.4] cells/ul, P = 0.04), longer duration of HIV [15.7 (9.7) vs 12.4 (9.1) years, P < 0.01), and higher frequency of prior diagnosis of AIDS (34.2% vs 22.5%, P= 0.02), but there were no statistically significant differences between the two groups in the utilization of ART subclasses or the proportion with adequate virological suppression.

Notably, ALT >40 U/L was observed in only 30.1% and AST >40 U/L in 16.7% of participants with NAFLD. The frequency of the lower cutoffs for abnormal ALT (>30 U/Lin men and >19 U/L in women) was 53.1% in those with NAFLD (Table 1).

Characteristics of participants with Lean NAFLD

In the entire cohort, 14.9% (51/342) had lean NAFLD, which accounted for a third (51/155) of all NAFLD cases. Other than expected smaller waist circumference in those with lean versus overweight/obese NAFLD, there were no other significant differences between the two groups (Table 3). Of note, the mean waist circumference in PWH and lean NAFLD (97.1 cm) was still larger than expected for the general population (< 94cm for men and < 80 cm for women).

Factors associated with NAFLD

In univariate analysis (Table 4), older age, study site, larger waist circumference, higher BMI, diabetes, higher ALT, AST, triglycerides, insulin, and HOMA-IR, but not the $CD4^+$ cells counts or current ART use, were significantly associated with greater likelihood for NAFLD, whereas Black race was associated with lower risk. In multivariable analysis (Table 4), older age, study site, diabetes, and higher ALT were associated with greater likelihood for NAFLD, whereas Black race was associated with lower likelihood. Study site was the strongest independent factor associated with increased risk of NAFLD (OR 3.35 for the Texas site, 95% CI 1.31-8.60, P = 0.01), followed by diabetes (OR 3.20, 95% CI 1.02-10.07, P = 0.04).

Factors associated with clinically significant fibrosis in NAFLD

Of 158 participants with NAFLD, 27 (17%), had clinically significant fibrosis (LSM ≥ 8.6). In univariate analysis (Table 5), only larger waist circumference and higher BMI, but not current or nadir $CD4^+$ T cell counts, duration of HIV, or prior diagnosis of AIDS, were associated with higher risk for clinically significant fibrosis in NAFLD.

Concordance between study radiologists on detecting fatty liver by ultrasound

There was substantial agreement between the two study radiologists (k 0.63 [95% CI: 0.43-0.84]) on presence of hepatic steatosis on ultrasound (Supplementary table 5).

Concordance between ultrasound and different cut-offs of CAP

There was fair concordance between ultrasound- and CAP-diagnosed fatty liver with kappa of 0.28 (95% CI: 0.18-0.37) and 0.35 (95% CI: 0.25-0.45) for CAP cutoffs of ≥ 238 dB/m and CAP ≥ 263 dB/m, respectively (Supplementary Table 6).

Optimal cutoffs for ALT and CAP to identify ultrasound-diagnosed fatty liver

ALT and CAP showed modest AUC for detecting ultrasound-diagnosed steatosis (0.70 [95% CI (0.64-0.76)] and 0.72 [95% CI 0.66-0.77], respectively) (Supplementary Table 7). For ALT, the Youden's index cutoff balancing sensitivity and sensitivity was 32.8 U/L, which resulted in sensitivity of 0.59, specificity 0.74, positive predictive value 0.68, and negative predictive value 66%. For CAP, the Youden's index cutoff was 269.5 dB/m, which resulted

in sensitivity of 0.67, specificity 0.70, positive predictive value 0.69, and negative predictive value 0.69.

Discussion

In this diverse, prospective, US cohort of virally-suppressed PWH on ART, fatty liver was diagnosed in half of the participants and 90% of which was due to NAFLD. Lean NAFLD accounted for a third of the NAFLD cases, far exceeding estimates in the US general population. In patients with NAFLD, 21 % had clinically significant fibrosis (LSM ≥8 kPa) and 6% had advanced fibrosis (LSM >12 kPa). There were no differences between PWH with and without NAFLD in the utilization of ART subclasses or proportion with adequate virological suppression. Rather, metabolic and demographic factors were the independent factors influencing NAFLD risk in this population.

Emerging data indicate NAFLD is the leading cause of liver disease in PWH. As such, understanding the burden of NAFLD and clinically significant fibrosis in the US population of PWH is essential from a public health perspective. It is a first step toward identification of patients at high-risk for NAFLD with clinically significant fibrosis who could be offered therapeutic interventions, and towards identifying participants who could benefit from interventions targeting the cardiometabolic disturbances associated with NAFLD. Thus far, estimates of NAFLD and fibrosis prevalence in this population have stemmed from select populations, and when CAP measurement was used to define steatosis, varying cutoffs were utilized (13, 14, 17, 20, 22, 23, 46-49). Here, we screened for fatty liver using two imaging modalities: ultrasound, which is considered the traditional diagnostic modality for diagnosis of hepatic steatosis (50), and compared ultrasound-based prevalence estimates to prevalence estimates by different CAP cutoffs for diagnosis of steatosis. Expectedly, estimation of the prevalence of fatty liver by CAP depends on the chosen cutoff (38–40, 51). This prevalence ranges from 66.1% by CAP ≥ 238 dB/m to 38.3% by CAP ≥290 dB/m. Our data show the prevalence of fatty liver in PWH with a CAP ≥263 dB/m is the closest to that of ultrasound-based prevalence of nearly 50% in this population.

Previously studied populations of PWH have had high participant (single gender, limited racial/ethnic diversity, inclusion of alcoholic liver disease or viral hepatitis coinfection) and diagnostic (imaging modalities or CAP criteria) heterogeneity (12), making direct comparison with our findings challenging. However, in a systematic review and meta-analysis of NAFLD studies in PWH, the pooled prevalence of NAFLD diagnosed by imaging was 35% (10). While this estimate is lower than the approximately 50% prevalence in our cohort, studies in the meta-analysis included almost exclusively male participants, and most had lower rates of Black and Hispanic participants than our cohort. Greater gender and racial/ethnic diversity in our cohort could account for higher NAFLD prevalence. Additionally, in a German cohort of PWH on ART, baseline NAFLD prevalence was 46%, with 59% having prevalent steatosis by 24 months of follow-up (52). Thus, our prevalence rates are in alignment with published rates among PWH.

Our results show a geographic variance in the prevalence of fatty liver in PWH which corresponds to the racial and ethnic make-up of the population studied. Indeed, study site

was independently associated with the risk of NAFLD, with the Texas site, having the higher proportion of Hispanic participants, being associated with the highest risk for NAFLD.

In this diverse cohort of virally suppressed PWH on ART, we found a significant burden of clinically significant and advanced fibrosis; in all patients with fatty liver and those with NAFLD, clinically significant fibrosis (LSM >8 kPa) and advanced fibrosis (LSM >12 kPa) were observed in 20-21% and 6% of participants, respectively. Notably, estimates of significant and advanced fibrosis were lower with FIB4 compared to LSM.

Importantly, HIV viral load, $CD4^+$ T cell counts, ART or its subclasses were not independently associated with the risk of NAFLD. However, older age, higher BMI, study site, diabetes, higher ALT, and non-Black race were independent factors associated with greater NAFLD risk in this cohort. These findings are in line with other studies highlighting the larger impact of metabolic risk factors for NAFLD in PWH on current ART regimens (10, 17, 33, 53, 54).

Lean NAFLD was diagnosed in 15.8% of the participants and accounted for a third of the NAFLD cases in this cohort. This is higher than the estimated proportion of lean NAFLD in the general population, where it is estimated to account for 19% of the total NAFLD cases (55, 56). It is important to note that despite having a normal BMI of < 25 kg/m2, PWH had an abnormally increase waist circumference of 97.1 (9.2) cm compared to expected normal of < 80 cm in women and < 94 cm in men in the general population (57).

We found substantial agreement between experienced body radiologists on diagnosis of hepatic steatosis in this study, which is better than reported interobserver agreement on diagnosis of steatosis on ultrasound in the general population (k 0.2-0.50) (58, 59). Our findings support the recent recommendation by the European AIDS Clinical Society Guidelines of ultrasound as the preferred imaging modality to diagnose NAFLD in PWH (50).

The diagnostic accuracy of CAP for detecting steatosis has been extensively studied in the general population using liver histology or magnetic resonance imaging proton density fat fraction (MRI-PDFF) as reference standard (60). In PWH, CAP has been evaluated against MRI-PDFF in two studies with different optimal cutoffs recommended for detecting steatosis (238 and 285 dB/m) (38, 39). However, to our knowledge, other than our data, there are no data assessing the concordance of CAP with ultrasound-diagnosed steatosis. Although using CAP ≥263 dB/m or ultrasound-based diagnosis yielded similar prevalence of steatosis of nearly 50% in this population, concordance between the two studies was only fair. The optimal CAP cutoff for ultrasound-diagnosed steatosis in this cohort was 269.5 dB/m, which had modest sensitivity 67.3% and specificity of 70.1%, versus a sensitivity 59% and specificity of 74% for the optimal cutoff of ALT of 32.8 U/L. Our data highlight the poor sensitivity of ALT as a marker for NAFLD in PWH. Nearly 70% of patients with NAFLD had an ALT < 40 U/L and 47% had lower levels than the Prati's proposed cutoffs of 30 U/L in men and 19 U/L in women (44, 45). These findings are similar to NAFLD in persons without HIV as 55% of patients with NAFLD in the Dionysis study and 79% of

patients with NAFLD in the Dallas Heart Cohort were noted to have normal ALT levels (< 40 U/L in males and < 31 U/L in women) (18, 61).

Limitations of this study include having a population of PWH predominantly on ART with viral suppression without history of hepatitis B or C co-infection, and who were willing to participate in research. As such, this study population may not reflect all PWH in the US. Data on duration of HIV viremia were not available thus we were unable to assess its effect on NAFLD risk in this cohort. There are limited data to assess the performance of non-invasive tests and correlation of different cutoffs for CAP and LSM with liver histology in patients with HIV-NAFLD (17). Other studies are ongoing to address this knowledge gap. To address potential questions about prevalence of different cut offs in our cohort, we have provided the frequency of different cutoffs for CAP and LSM in our cohort in this paper.

This study has several strengths, including the prospective, multicentric enrollment of a diverse population of PWH and use of two methods (ultrasound and CAP) to evaluate the prevalence of fatty liver in this population. Further, our study presented contemporaneous data on the topic including data on current ART regimens, characterized lean NAFLD in PWH, and provided unique data on concordance between CAP- and ultrasound-diagnosed hepatic steatosis in this population.

In conclusion, half of virally suppressed PWH have FLD, 90% of which is due to NAFLD. A fifth of PWH with FLD has clinically significant fibrosis and 6% have advanced fibrosis. These findings highlight a significant burden of NAFLD and hepatic fibrosis in this population. The data lend support to systematic screening for high risk NAFLD in PWH to allow early detection and intervention to prevent progression to advanced liver disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding Source:

NIDDK R01 DK112293 to SG, R01 DK126042 to JEL

Disclosures:

Samer Gawrieh consults for TransMedics and Pfizer. He received grants from Zydus, Viking and SonicIncytes.

Jordan E. Lake received grants from Gilead Sciences and Zydus. In the past 12 months she has received grants from Pfizer, CytoDyn, and Oncoimmune, and has served as a consultant to Merck and Theratechnologies

Gregory K. Robbins received grants paid to his institution from Gilead, Pfizer and Leonard Meron. He consults for SEED.

Samir K. Gupta advises and received grants from ViiV Healthcare. He advises Gilead.

Raymond T. Chung received grants from Boehringer, BMS, Abbvie, Gilead, Merck, Roche, Janssen, and GSK.

Naga Chalasani has received grants from Eli Lilly, Galectin Therapeutics, Intercept, and Exact Sciences. In the past 12 months, he has received consulting fees from Abbvie, Madrigal, Nusirt, Allergan, Siemens, Genentech, Zydus, La Jolla, Axcella, Foresite Labs, and Galectin Therapeutics.

Kathleen E. Corey advises and received grants from BMS. She advises Theratechnologies, and Novo Nordisk. She consults for AstraZeneca. She received grants from Boehringer-Ingelheim and Novartis.

Abbreviations used

ALT	Alanine aminotransferase
AFLD	Alcoholic fatty liver disease
APRI	AST to Platelet Ratio Index
ART	Antiretroviral therapy
AST	Aspartate aminotransferase
AUROC	Area under the receiver operating characteristic
BMI	Body mass index
CAP	Controlled attenuation parameter
CI	Confidence Intervals
FIB4	Fibrosis-4 score
FLD	Fatty liver disease
HIV	Human immunodeficiency virus
HOMA-IR	Homeostatic model assessment for insulin resistance
INSTI	Integrase strand transfer inhibitors
LSM	Liver stiffness measurement
NAFLD	Non-alcoholic fatty liver disease
NNRTI	Non-nucleoside reverse transcriptase inhibitors
NPV	Negative predictive value
NRTI	Nucleoside reverse transcriptase inhibitors
PI	Protease inhibitors
PPV	Positive predictive value
PWH	Persons with HIV
TAF	Tenofovir Alafenamide
TDF	Tenofovir disoproxil fumarate
VCTE	Vibration-controlled transient elastography

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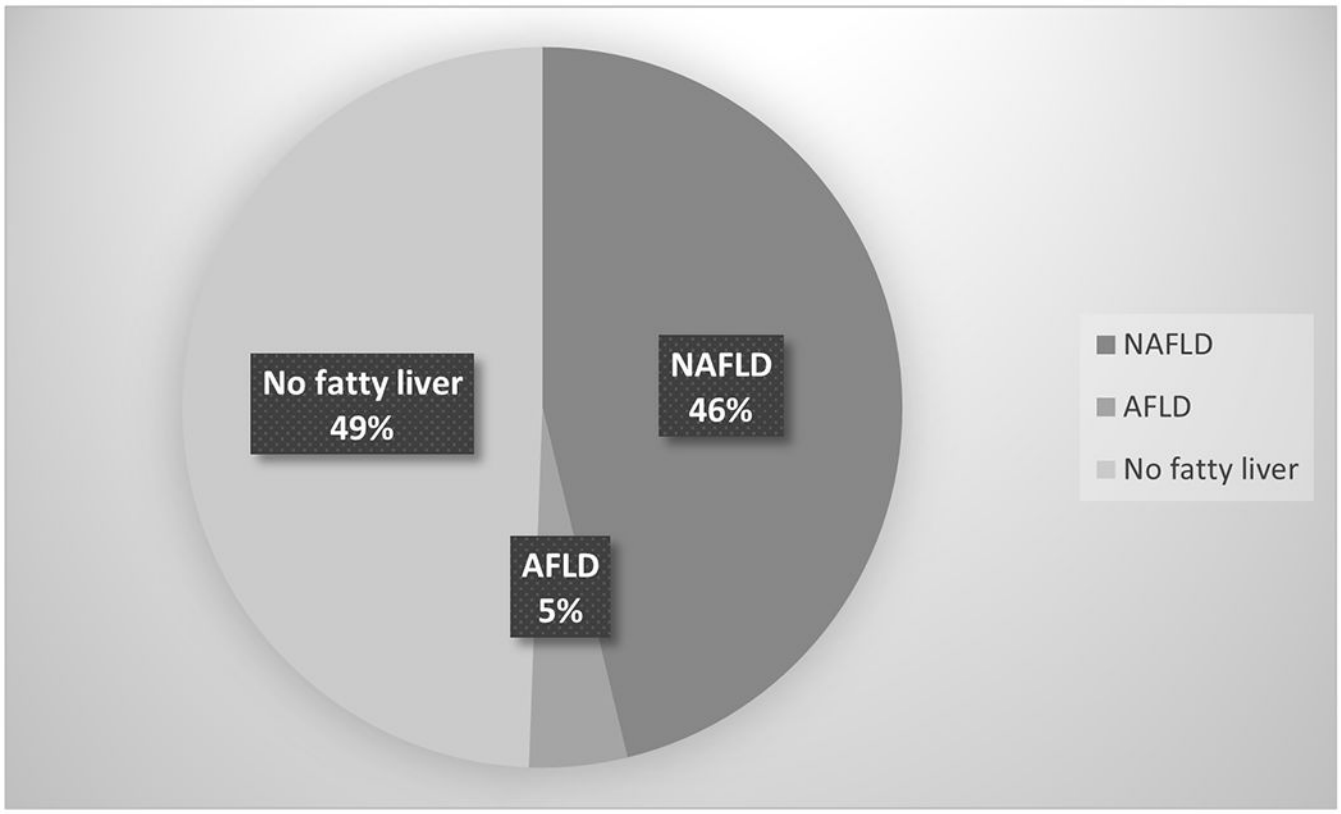
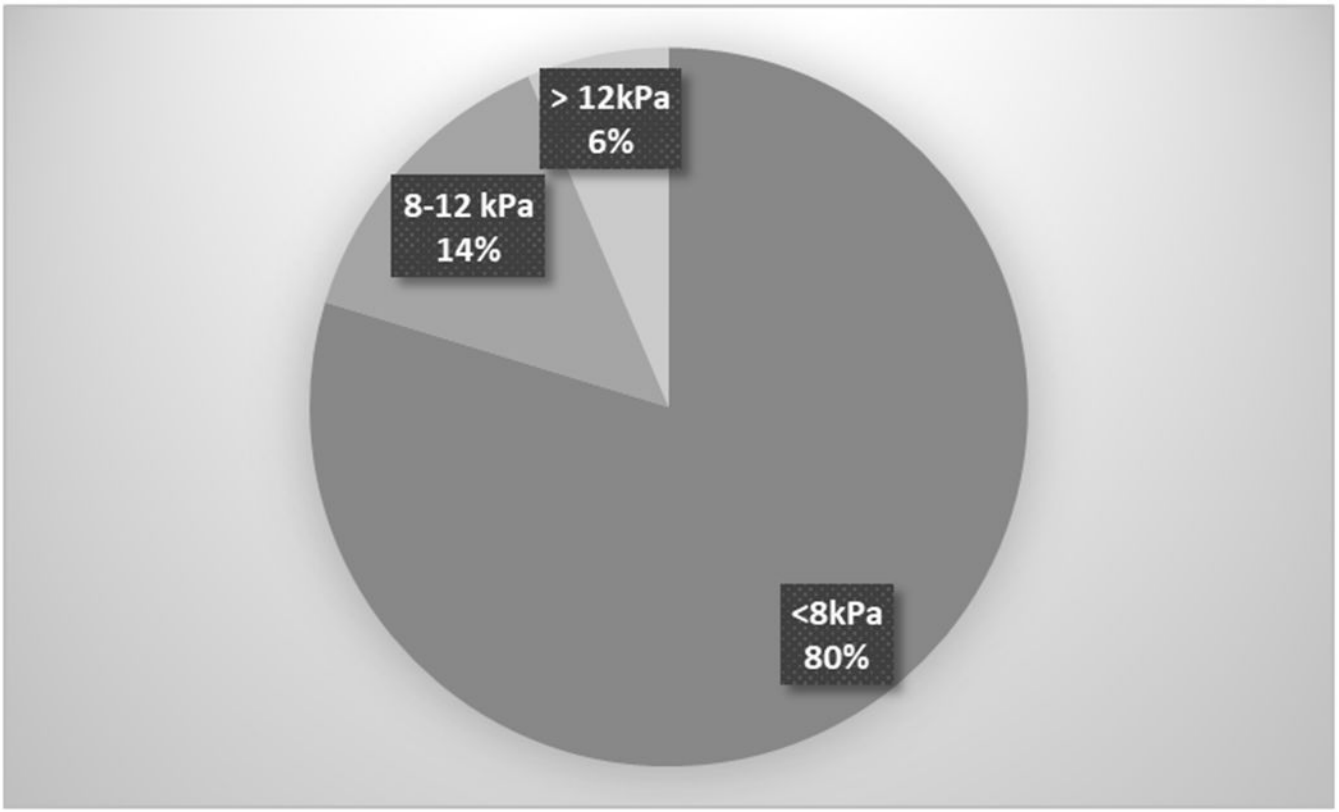




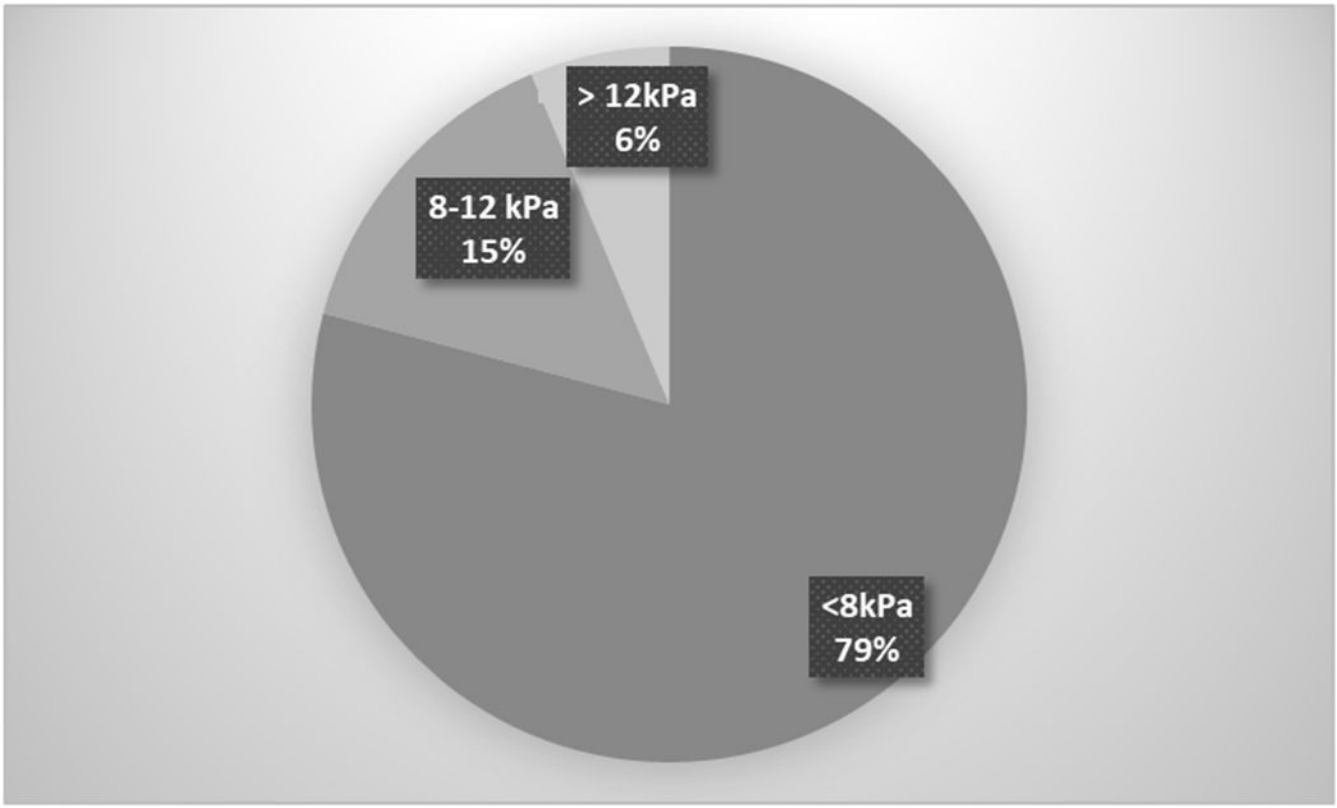


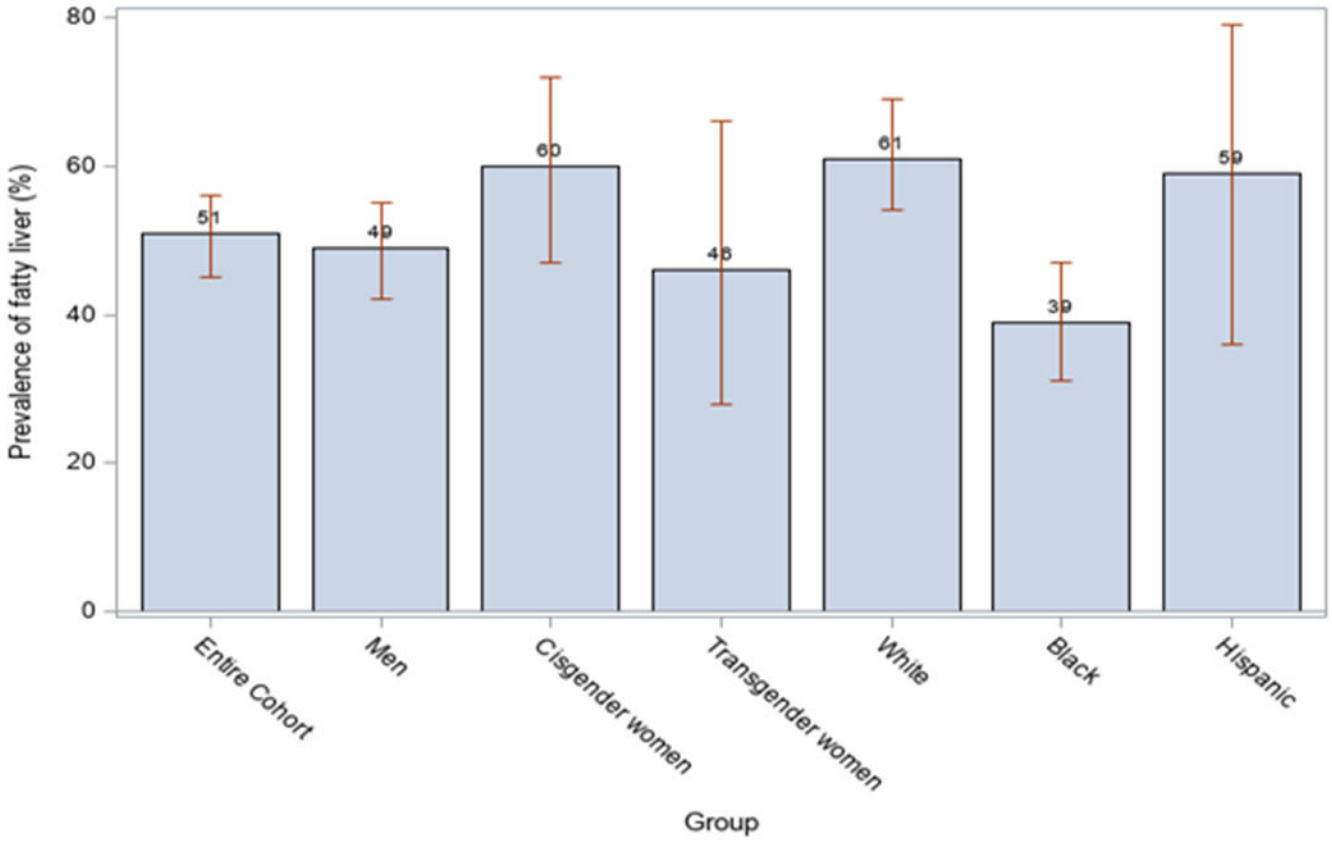
Figure 1.

Prevalence of fatty liver disease (CAP ≥ 263 dB/m), clinically significant and advanced fibrosis in person with HIV

A. The entire cohort

B. Clinically significant and advanced fibrosis in participants with fatty liver

C. Clinically significant and advanced fibrosis in participants with NAFLD



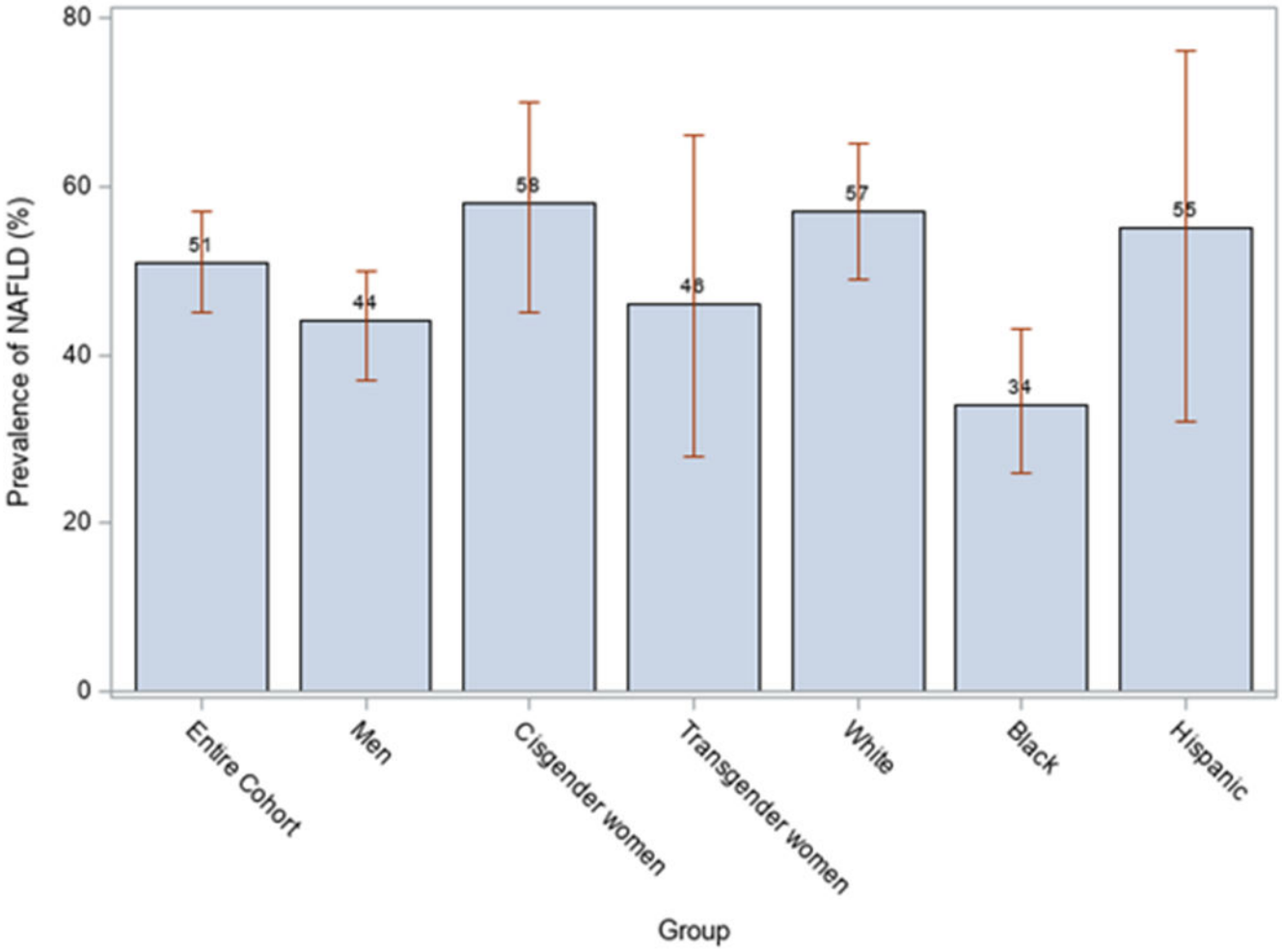


Figure 2. Prevalence of fatty liver (CAP ≥ 263 dB/m) and NAFLD in different study subgroups

A. Entire cohort

B. Participants without excessive alcohol use

Table 1.

Characteristics of study participants

Variables	Overall (N = 342)	A) No fatty liver (CAP <263 dB/m) (N = 169)	B) NAFLD (CAP ≥263 dB/m and AUDIT <8) (N = 158)	C) AFLD (CAP ≥263 dB/m and AUDIT≥8) (N = 15)	P-value A Vs B	P-value B Vs C
Age (Year)	48.2 (12.0)	45.3 (13.2)	51.4 (10.2)	48.5 (6.5)	<0.01	0.29
Gender					0.18	0.39
Male	249 (72.8%)	128 (75.7%)	108 (68.4%)	13 (86.7%)		
Cisgender Female	65 (19%)	26 (15.4%)	37 (23.4%)	2 (13.3%)		
Transgender female	28 (8.2%)	15 (8.9%)	13 (8.2%)	0		
Race					<0.01	0.38
White	168 (49.1%)	65 (38.5%)	96 (60.8%)	7 (46.7%)		
Black	140 (40.9%)	86 (50.9%)	47 (29.7%)	7 (46.7%)		
Other	34 (9.9%)	18 (10.6%)	15 (9.5%)	1 (6.7%)		
Ethnicity					0.18	0.62
Hispanic or Latino	98 (28.6%)	40 (23.7%)	52 (32.9%)	6 (40%)		
Non-Hispanic	242 (70.8%)	128 (75.7%)	105 (66.5%)	9 (60%)		
Unknown	2 (0.6%)	1 (0.6%)	1 (0.6%)	0		
BMI (kg/m^2)		22.8 (5.6)	27.7 (5.4)	29.4 (4.6)	<0.01	0.49
<18.5	25 (7.4%)	22 (13.2%)	3 (1.9%)	0		
18.5-24.9	156 (46.3%)	106 (63.5%)	48 (31%)	2 (13.3%)		
25-29.9	97 (28.8%)	31 (18.6%)	58 (37.4%)	8 (53.3%)		
≥30	59 (17.5%)	8 (4.8%)	46 (29.7%)	5 (33.3%)		
Missing	5	5				
Waist circumference, cm	100.9 (16.1)	92.2 (13.3)	109.5 (13.9)	110.5 (11.5)	<0.01	0.78
Diabetes Mellitus	39 (11.6%)	9 (5.4%)	27 (17.3%)	3 (21.4%)	<0.01	0.72
ALT (U/L)	31.7 (27.6)	22.8 (10.7)	39.2 (34.6)	50.5 (40.2)	<0.01	0.24
ALT >40 (U/L)	63 (18.9%)	10 (6.1%)	47 (30.1%)	6 (40%)	<0.01	0.56
Abnormal ALT (>30 U/Lin men and >19 U/L in women)	123 (39.2%)	36 (23.4%)	77 (53.1%)	10 (66.7%)	<0.01	0.42

Variables	Overall (N = 342)	A) No fatty liver (CAP <263 dB/m) (N = 169)	B) NAFLD (CAP ≥263 dB/m and AUDIT <8) (N = 158)	C) AFLD (CAP ≥263 dB/m and AUDIT≥8) (N = 15)	P-value A Vs B	P-value B Vs C
AST (U/L)	26.3 (15.9)	22.5 (9.2)	29.4 (19.1)	36.3 (24.6)	<0.01	0.19
AST >40 (U/L)	36 (10.8%)	6 (3.7%)	26 (16.7%)	4 (26.7%)	<0.01	0.30
Platelets (10^9/L)	239.0 (67.0)	237.2 (69.5)	243.5 (65.4)	212.5 (48.5)	0.41	0.08
Triglycerides (mg/dL)	152.3 (109.3)	124.2 (67.3)	174.9 (129.1)	215.3 (162.2)	<0.01	0.26
Fasting glucose (mg/dL)	96.0 (42.9)	85.2 (16.3)	109.6 (61.0)	-	0.11	-
Insulin, median (IQR) (μU/mL)	12.7 (7-26.6)	7.4 (5.1-12.3)	23.4 (11.9-33.4)	46.8 (12.4-109.0)	<0.01	0.27
HOMA-IR	5.1 (13.5)	1.9 (3.3)	10.0 (20.7)	-	0.14	-
APRI	0.4 (0.3)	0.4 (0.3)	0.4 (0.4)	0.5 (0.4)	0.02	0.39
FIB4	1.1 (0.7)	1.1 (0.7)	1.1 (0.6)	1.2 (0.6)	0.36	0.48
Current ART	327 (95.6%)	158 (93.5%)	155 (98.1%)	14 (93.3%)	0.04	0.31
Exposure to ART classes (current/prior use)						
% PI	92 (26.9%)	50 (29.6%)	38 (24.1%)	4 (26.7%)	0.26	0.76
% NNRTI	46 (13.5%)	21 (12.4%)	23 (14.6%)	2 (13.3%)	0.57	1.00
% INSTI	267 (78.1%)	130 (76.9%)	128 (81%)	9 (60%)	0.37	0.09
% Entry Inhibitors	4 (1.2%)	1 (0.6%)	3 (1.9%)	0	0.36	1.00
% NRTI	312 (91.2%)	151 (89.3%)	148 (93.7%)	13 (86.7%)	0.16	0.28
For NRTI:						
% Abacavir	25 (7.6%)	8 (5.1%)	16 (10.3%)	1 (7.1%)	0.09	1.00
% Didanosine	0	0	0	0	-	-
% Emtricitabine	278 (85%)	137 (86.7%)	128 (82.6%)	13 (92.9%)	0.31	0.47
% Lamivudine	33 (10.1%)	13 (8.2%)	20 (12.9%)	0	0.18	0.38
% Stavudine	0	0	0	0	-	-
% TDF	76 (23.2%)	43 (27.2%)	30 (19.3%)	3 (21.4%)	0.10	0.74
% TAF	205 (62.7%)	94 (59.5%)	101 (65.2%)	10 (71.4%)	0.30	0.77
% Zidovudine	2 (0.6%)	2 (1.3%)	0	0	0.50	-
% Zalcitabine	0	0	0	0	-	-
% HIV RNA <200 copies/mL	321 (93.9%)	157 (92.9%)	151 (95.6%)	13 (86.7%)	0.30	0.18

Variables	Overall (N = 342)	A) No fatty liver (CAP <263 dB/m) (N = 169)	B) NAFLD (CAP ≥263 dB/m and AUDIT <8) (N = 158)	C) AFLD (CAP ≥263 dB/m and AUDIT≥8) (N = 15)	P-value A Vs B	P-value B Vs C
% HIV RNA <50 copies/mL	303 (88.6%)	149 (88.2%)	141 (89.2%)	13 (86.7%)	0.76	0.67
% HIV RNA <20 copies/mL	44 (12.9%)	17 (10.1%)	25 (15.8%)	2 (13.3%)	0.12	1.00
Current $CD4^+$ cells/ul	712.7 (337.8)	665.9 (318.7)	768.4 (352.5)	646.6 (316.5)	0.01	0.21
Nadir $CD4^+$ cells/ul	227.6 (204.5)	256.2 (189.4)	200.1 (206.8)	207.1 (283.9)	0.04	0.91
Duration of HIV (Years)	14.1 (9.5)	12.4 (9.1)	15.7 (9.7)	16.3 (8.3)	<0.01	0.82
Prior AIDS diagnosis	100 (29.2%)	38 (22.5%)	54 (34.2%)	8 (53.3%)	0.02	0.14

Table 2.

Prevalence of different cut offs of LSM in patients with fatty liver (CAP ≥263 dB/m)

Fibrosis severity by LSM cut-offs (kPa)	FLD (Total) N = 173	NAFLD (AUDIT <8) N = 158	AFLD (AUDIT≥8) N = 15
≥5.6 kPa (95% CI)	94 (54.3%) (46%-62%)	85 (53.8%) (46%-62%)	9 (60%) (32%-84%)
≥6.5 kPa (95% CI)	60 (34.7%) (28%-42%)	56 (35.4%) (28%-43%)	4 (26.7%) (8%-55%)
≥7.1 kPa (95% CI)	49 (28.3%) (22%-36%)	46 (29.1%) (22%-37%)	3 (20%) (4%-48%)
≥8.6 kPa (95% CI)	29 (16.8%) (12%-23%)	27 (17.1%) (12%-24%)	2 (13.3%) (2%-41%)
≥12.1 kPa (95% CI)	11 (6.4%) (3%-11%)	10 (6.3%) (3%-11%)	1 (6.7%) (1%-32%)
≥13.1 kPa (95% CI)	9 (5.2%) (2%-10%)	9 (5.7%) (3%-11%)	0
<8kPa (95% CI)	138 (79.8%) (73%-86%)	125 (79.1%) (72%-85%)	13 (86.7%) (60%-98%)
8-12 kPa (95% CI)	24 (13.9%) (9%-20%)	23 (14.6%) (10%-21%)	1 (6.7%) (1%-32%)
> 12kPa (95% CI)	11 (6.4%) (3%-11%)	10 (6.3%) (3%-11%)	1 (6.7%) (1%-32%)
FIB4 cutoffs			
<1.63 (95% CI)	145 (83.8%) (78%-89%)	133 (84.2%) (78%-90%)	12 (80%) (52%-96%)
1.63-2.67 (95% CI)	23 (13.3%) (9%-19%)	20 (12.7%) (8%-19%)	3 (20%) (4%-48%)
>2.67 (95% CI)	5 (2.9%) (1%-7%)	5 (3.2%) (1%-7%)	0

Table 3.

Characteristics of study participants with NAFLD (based on CAP ≥263) stratified by BMI

Variables N = 155	BMI<25 kg/m^2 N = 51	BMI≥25 kg/m^2 N = 104	P-value
Age (Year)	52.8 (9.5)	50.8 (10.4)	0.25
Gender			0.09
Male	39 (76.5%)	66 (63.5%)	
Cisgender Female	11 (21.6%)	26 (25%)	
Transgender female	1 (1.9%)	12 (11.5%)	
Race			0.22
White	34 (66.7%)	60 (57.7%)	
Black	11 (21.6%)	36 (34.6%)	
Other	6 (11.8%)	8 (7.7%)	
Ethnicity			0.19
Hispanic or Latino	21 (41.9%)	29 (27.9%)	
Non-Hispanic	30 (58.0%)	74 (71.1%)	
Unknown	0	1 (1%)	
Waist circumference (cm)	96.6 (8.8)	115.9 (11.4)	<0.01
Diabetes Mellitus	13 (25.5%)	14 (13.7%)	0.07
ALT (U/L)	43.0 (35.0)	37.7 (34.8)	0.38
ALT >40 (U/L)	19 (38%)	28 (27.2%)	0.17
Abnormal ALT (>30 U/L in men and >19 U/L in women)	28 (56%)	48 (52.2%)	0.66
AST (U/L)	32.4 (19.8)	28.2 (18.9)	0.21
AST >40 (U/L)	12 (24%)	14 (13.6%)	0.11
Platelets 10^9/L)	239.1 (71.6)	245.0 (62.0)	0.60
Triglycerides (mg/dL)	178.6 (184.6)	172.4 (94.4)	0.83
Fasting glucose (mg/dL)	97.6 (12.3)	118.8 (79.8)	0.41
Insulin, median (IQR) (μU/mL)	16.1 (10.6-33.6)	24.4 (15.4-34.0)	0.69
HOMA-IR, median (IQR)	8.2 (7.9-12.7)	4.6 (1.4-6.9)	0.30
APRI	0.5 (0.4)	0.4 (0.4)	0.41
FIB4	1.3 (0.7)	1.1 (0.6)	0.07
CAP (dB/m)	310.1 (32.5)	321.3 (37.4)	0.07
LSM			
≥7.1 kPa	13 (25.5%)	32 (30.8%)	0.50
≥8.6 kPa	6 (11.8%)	20 (19.2%)	0.24
≥13.1 kPa	1 (2%)	8 (7.7%)	0.27
% HIV RNA <200 copies/mL	48 (94.1%)	100 (96.1%)	0.69
% HIV RNA <50 copies/mL	45 (88.2%)	93 (89.4%)	0.82
% HIV RNA <20 copies/mL	9 (17.7%)	15 (14.4%)	0.60
Current ART	51 (100%)	101 (97.1%)	0.55

Variables N = 155	BMI<25 kg/m^2 N = 51	BMI≥25 kg/m^2 N = 104	P-value
Exposure to ART classes (current/prior use)			
% PI	8 (15.7%)	29 (27.9%)	0.09
% NNRTI	7 (13.7%)	16 (15.4%)	0.79
% INSTI	46 (90.2%)	80 (76.9%)	0.05
% NRTI	48 (94.1%)	97 (93.3%)	1.00
% Entry inhibitors	0	3 (2.9%)	0.55

Table 4.

Factors associated with NAFLD (CAP ≥263 dB/m) in univariate and multivariable analyses

	Univariate analysis			Multivariable analysis		
Variables	**OR**	**CI**	**P-Value**	**OR**	**CI**	**P-Value**
Age	1.04	1.02-1.06	<0.01	1.04	1.01-1.08	0.02
Gender						
Male	Reference					
Cisgender Female	1.71	0.96-3.07	0.97			
Transgender female	0.91	0.40-2.06	0.96			
Race						
White	Reference					
Black	0.36	0.22-0.59	0.01	0.42	0.19-0.92	0.03
Other	0.60	0.28-1.33	0.98	0.52	0.14-1.87	0.31
Ethnicity						
Hispanic or Latino	1.66	0.99-2.74	0.97			
Non-Hispanic	Reference					
Study site						
Indiana	Reference					
Massachusetts	1.91	1.10-3.31	0.02	2.42	0.92-6.39	0.08
Texas	1.93	1.12-3.33	0.02	3.35	1.31-8.60	0.01
Waist circumference, cm	1.10	1.08-1.13	<0.01	1.05	0.99-1.10	0.04
BMI	1.25	1.18-1.33	<0.01			
Diabetes Mellitus						
No	Reference					
Yes	3.30	1.50-7.29	<0.01	3.20	1.02-10.07	0.04
ALT	1.05	1.03-1.07	<0.01	1.05	1.01-1.08	0.01
AST	1.04	1.02-1.06	<0.01			
Platelets	1.00	0.99-1.01	0.48			
Triglycerides	1.01	1.00-1.01	<0.01			
Fasting glucose	1.03	0.99-1.06	0.14			
Insulin	1.05	1.02-1.08	<0.01			
HOMA-IR	2.05	1.20-3.53	0.01			
Current CD4	1.00	1.00-1.002	0.02			
Nadir CD4	0.99	0.99-1.00	0.06			
Current ART	3.25	0.86-12.25	0.08			

Table 5.

Factors associated with clinically significant fibrosis in NAFLD (CAP ≥263 dB/m, and LSM ≥ 8.6) in univariate analysis

	Univariate analysis		
Variables	**OR**	**CI**	**P-value**
Age	0.99	0.96-1.04	0.82
Gender			
Male	Reference		
Cisgender Female	1.48	0.58-3.78	0.96
Transgender female	1.07	0.22-5.32	0.97
Race			
White	Reference		
Black	0.95	0.38-2.40	0.83
Other	0.72	0.15-3.47	0.70
Ethnicity			
Hispanic or Latino	0.88	0.35-2.18	0.96
Non-Hispanic	Reference		
Waist circumference, cm	1.05	1.02-1.09	<0.01
BMI	1.10	1.03-1.17	<0.01
Diabetes Mellitus			
No	Reference		
Yes	2.44	0.93-6.36	0.07
ALT	1.01	0.99-1.02	0.30
AST	1.02	0.99-1.04	0.08
Platelets	0.99	0.99-1.00	0.51
Triglycerides	1.00	0.99-1.00	0.74
Fasting glucose	1.00	0.99-1.02	0.81
Insulin	1.00	0.99-1.01	0.98
HOMA-IR	0.98	0.89-1.08	0.66
Current CD4	1.00	0.99-1.00	0.91
Nadir CD4	0.99	0.99-1.00	0.33
Duration of HIV	0.99	0.96-1.04	0.98
Prior diagnosis of AIDS (ref = No)	1.11	0.49-2.54	0.80