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Prevalence, Predictors, and Severity of Lean Nonalcoholic Fatty Liver Disease in Patients Living With Human Immunodeficiency Virus

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Background. The burden of nonalcoholic fatty liver disease (NAFLD) is growing in people living with human immunodeficiency virus (HIV). NAFLD is associated with obesity; however, it can occur in normoweight (lean) patients. We aimed to investigate lean NAFLD in patients living with HIV.

Methods. We included patients living with HIV mono-infection from 3 prospective cohorts. NAFLD was diagnosed by transient elastography (TE) and defined as controlled attenuation parameter ≥248 dB/m, in absence of alcohol abuse. Lean NAFLD was defined when a body mass index was <25 kg/m^2. Significant liver fibrosis was defined as TE ≥7.1 kPa. The presence of diabetes, hypertension, or hyperlipidemia defined metabolically abnormal patients.

Results. We included 1511 patients, of whom 57.4% were lean. The prevalence of lean NAFLD patients in the whole cohort was 13.9%. NAFLD affected 24.2% of lean patients. The proportions of lean NAFLD patients who were metabolically abnormal or had elevated alanine aminotransferase (ALT) were higher than among those who were lean patients without NAFLD (61.9% vs 48.9% and 36.7% vs 24.2%, respectively). Lean NAFLD patients had a higher prevalence of significant liver fibrosis than lean patients without NAFLD (15.7% vs 7.6%, respectively). After adjusting for sex, ethnicity, hypertension, CD4 cell count, nadir CD4 <200µ/L, and time since HIV diagnosis, predictors of NAFLD in lean patients were age (adjusted OR [aOR], 1.29; 95% confidence interval [CI], 1.04–1.59), high triglycerides (aOR, 1.34; 95% CI, 1.11–1.63), and high ALT (aOR, 1.15; 95% CI, 1.05–1.26), while a high level of high-density lipoprotein cholesterol was protective (aOR, 0.45; 95% CI, .26–.77).

Conclusions. NAFLD affects 1 in 4 lean patients living with HIV mono-infection. Investigations for NAFLD should be proposed in older patients with dyslipidemia and elevated ALT, even if normoweight.

Keywords. controlled attenuation parameter; transient elastography; liver fibrosis; dyslipidemia; alanine aminotransferase.

Nonalcoholic fatty liver disease (NAFLD) represents a worldwide epidemic, with a global prevalence estimated at 25.24% [1]. NAFLD is a liver fat accumulation exceeding 5% of hepatocytes in the absence of other causes of liver disease. NAFLD could lead to nonalcoholic steatohepatitis (NASH), liver fibrosis accumulation leading to cirrhosis and end-stage liver complications [2]. With the successful implementation of direct antiviral agents for the treatment of hepatitis C virus (HCV) and the drastic reduction of AIDS-related mortality in the post–antiretroviral therapy (ART) era [3], NAFLD is now emerging as the most frequent liver disease in patients living with HIV [4].

In people living with HIV, the prevalence of NAFLD ranges from 13 to 65% in the absence of viral hepatitis coinfection and alcohol abuse [5–9]. Patients living with HIV are at higher risk of NAFLD than the general population as a result of multiple cofactors, including lifelong use of ART, especially past exposure to hepatotoxic d-drugs (stavudine and didanosine); persistent immune activation and HIV-related inflammation; and extremely prevalent dysmetabolic conditions [10, 11]. Moreover, NASH and significant liver fibrosis are at least twice as frequent in patients living with HIV mono-infection than in the general population [12–16].

NAFLD is closely associated with the features of metabolic syndrome and obesity. A strong link between NAFLD and body mass index (BMI) has also been reported in patients living with HIV [6, 9, 17, 18]. However, patients who are not obese can also present with NAFLD. NAFLD is known as lean NAFLD in

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patients with a BMI <25 Kg/m^2. The prevalence of lean NAFLD ranges between 7% in the United States to 20% in Asia [19, 20]. As lean patients lack obvious excess visceral adipose tissue, differences in NAFLD mechanisms may exist, such as an impaired glucose metabolism, dysfunctional adipose tissue, and genetic factors [21]. Of note, a few studies reported a severe histological phenotype in lean patients with NAFLD, compared overweight/obese patients with NAFLD [20, 21].

The aim of this study was to determine the prevalence and predictors of NAFLD in lean patients living with HIV monoinfection who were enrolled in 3 large cohorts, by means of transient elastography (TE) with associated controlled attenuation parameter (CAP), a noninvasive test validated in HIV infection [9, 22, 23]. Secondary aims included determining the severity of NAFLD in lean patients, defined by liver fibrosis status.

METHODS

Study Design and Population

We conducted a retrospective, cross-sectional study from the liver disease in HIV (LIVEHIV), Modena HIV Metabolic Clinic (MHMC), and liver pathologies in HIV in Palermo (LHIVPA) cohorts [12, 17, 24]. The LIVEHIV cohort is a prospective, routine screening program for NAFLD and liver fibrosis established in September 2013 at McGill University Health Centre in Montreal, Canada. Patients living with HIV undergo screening for NAFLD and liver fibrosis by TE with CAP [12]. The MHMC cohort was initiated in 2004 in Modena, Italy, to assess longitudinal metabolic changes among people living with HIV through annual comprehensive assessments in multiple domains [17]. Patients have undergone TE with CAP since 2018 to assess liver disease. The LHIVPA cohort was initiated in 2011 at the Infectious Diseases Outpatient Clinic of the University Hospital in Palermo, Italy. Metabolic assessments through physical and biochemical parameters are conducted at least annually. Since 2017, patients living with HIV undergo TE with CAP [25]. Data regarding TE examinations were collected at cohort entry in the Canadian cohort, while data for patients included in the 2 Italian cohorts were collected as soon as TE examinations became available, as mentioned above. We included all consecutive patients living with HIV (as documented by positive enzyme-linked immunosorbent assay with Western blot confirmation) aged ≥18 years with the availability of TE with CAP and relevant clinical and biochemical parameters. The exclusion criteria were: (1) positivity for either an HCV antibody or hepatitis B surface antigen; (2) evidence of other liver disease; (3) significant alcohol intake, defined by Alcohol Use Disorders Identification Test (AUDIT-C) questionnaire scores ≥4 for men and ≥3 for women [26]; (4) a history of hepatocellular carcinoma or liver transplantation; and (5) contraindications to TE examination (pregnancy, pacemaker insertion) and a failure or unreliable measurement of a TE examination. All participants provided informed written consent. The Research Ethics Board of the Research Institute of McGill University Health Centre (study code 14-182-BMD), MHMC (study code 254/12), and the Ethics Committee of the Paolo Giaccone University Hospital (study code v.1.05.1.18) approved the study, which was conducted according to the Declaration of Helsinki.

Clinical and Biological Parameters

We included patients with available data within 3 months from the TE examination: namely, demographic information, HIV and medications history, BMI, liver biochemistries, lipid profile, and hematological and immuno-virological parameters. Type 2 diabetes mellitus was defined as a hemoglobin glycosylated of 6.5% or greater, or as previously diagnosed by an endocrinologist/treating physician. BMI categories were defined as follows: lean (BMI <25 Kg/m^2), overweight (BMI 25.0–29.9 Kg/m^2), and obese (BMI ≥30 Kg/m^2). A patient was defined as metabolically abnormal in the presence of diabetes, hypertension, or hyperlipidemia (triglycerides ≥1.7 mmol/L and/or high-density lipoprotein [HDL] cholesterol <1 mmol/L in men and <1.3 mmol/L in women), while the absence of all 3 conditions defined a metabolically normal patient.

Outcome Measures

The primary study outcome was the prevalence and predictors of lean NAFLD, defined as CAP ≥248 dB/m in patients with BMIs <25 Kg/m^2 [9, 27]. Since a few recent studies suggested higher cut-offs for CAP to define NAFLD, although these have not been validated yet in HIV, we conducted a sensitivity analysis with a CAP cut-off of 288 dB/m [28, 29].

Secondary outcomes include: (1) the prevalence of significant liver fibrosis (stages F2-F4, defined as a liver stiffness measurement [LSM] ≥7.1 kPa but <13 kPa) and cirrhosis (stage F4, defined as an LSM ≥13 kPa) by BMI category [22, 23, 30]; and (2) the incidence of liver fibrosis progression in a subgroup of patients with lean versus overweight/obese NAFLD and the availability of serial TE examinations, with follow-ups longer than 6 months. Liver fibrosis progression was defined as the development of significant liver fibrosis for those with an LSM <7.1 kPa at baseline, or the transition to cirrhosis for those with an LSM ≥7.1 but <13 kPa at baseline [23, 30].

Transient Elastography With Controlled Attenuation Parameter

TE examinations were performed on a patient who fasted for 4-hours by a maximum of 2 experienced operators at each site (>500 examinations before the study) [31]. The standard M probe was used in all patients. The XL probe was used in case of failure with the M probe and if the BMI was >30 Kg/m^2 [29]. The following criteria were applied to define the result of LSM as reliable: at least 10 validated measures and an interquartile range <30% of the median.

Statistical Analysis

The main outcome was lean NAFLD. The prevalence of lean NAFLD was computed by dividing the number of patients

with lean NAFLD by the whole study population. The reference group for the main comparison, as well as for the multivariable analysis, was lean patients without NAFLD. We also compared lean NAFLD patients with overweight and obese NAFLD patients by metabolic abnormality, elevated alanine aminotransferase (ALT), and significant liver fibrosis status. We compared the characteristics of participants by outcome status using the Student *t* test for continuous variables and Pearson's χ^2 for categorical variables. In case of more than 2 groups, subject characteristics were analyzed using an analysis of variance for normally distributed variables and by the Kruskal-Wallis test in case of a non-normal distribution. Predictors of lean NAFLD were determined using unadjusted and adjusted logistic regression models and were reported as adjusted odds ratios (aORs) with 95% confidence intervals (CIs). All adjusted regression models included covariates that were determined a priori to be clinically important, based on previous literature, or those with *P* values < .05 in a univariable analysis. To establish which of the models had the best goodness-of-fit measure, the corrected Akaike information criteria and the Bayesian information criteria were compared among the models, with lower values indicating a better fit. For the purpose of the incidence analysis in NAFLD patients with available follow-ups, the baseline (time 0) corresponded to the first visit after 1 January 2013. Patients included in the incidence analysis were observed until September 2018 or were censored either when they died or at their last clinic visit. We estimated incidence rates of liver fibrosis progression by dividing the number of participants developing the outcome by the number of person-years (PY) of follow-up. Poisson count models were used to calculate CIs for incidence rates. A complete case analysis was used for the multivariable models, and the percentage of missing data was less than 15%, unless specified. All tests were 2-tailed and with a significance level of $\alpha = .05$. Statistical analyses were performed using STATA 15 (STATA Corp. LP, College Station, TX).

RESULTS

After applying the inclusion and exclusion criteria, 1511 patients with HIV mono-infection were included (Figure 1). The distribution of BMI categories was as follows: 867 (57.4%) patients were lean, 473 (31.3%) were overweight, and 171 (11.3%) were obese. The prevalence of lean NAFLD in the whole study population was 13.9%. Table 1 reports the characteristics of the whole study population, as well as the univariable analysis of lean patients by NAFLD status. When compared to lean patients without NAFLD, lean patients with NAFLD were older and had higher BMIs. They had longer times since HIV diagnosis, higher CD4 cell counts, and were more likely to have an undetectable HIV viral load and nadir CD4 cell count <200/μL. Moreover, lean patients with NAFLD were more exposed to d-drugs and to integrase inhibitors. Lean patients with NAFLD were also more metabolically abnormal than lean patients without NAFLD (61.9% vs 48.9%, respectively; *P* < .001), while they showed similar degrees of metabolic abnormalities as overweight NAFLD patients (Figure 2A; Supplementary Table S1). Finally, although lean patients with NAFLD had a higher prevalence of elevated ALT than lean patients without NAFLD (36.7% vs 24.2%, respectively; *P* < .001), they exhibited a similar prevalence of elevated ALT as overweight patients (Figure 2B).

Predictors of Lean Nonalcoholic Fatty Liver Disease

After adjustments, independent predictors of NAFLD among lean patients were older age (aOR, 1.29; 95% CI, 1.04–1.59; *P* = .020), higher triglycerides (aOR, 1.34; 95% CI, 1.11–1.63;

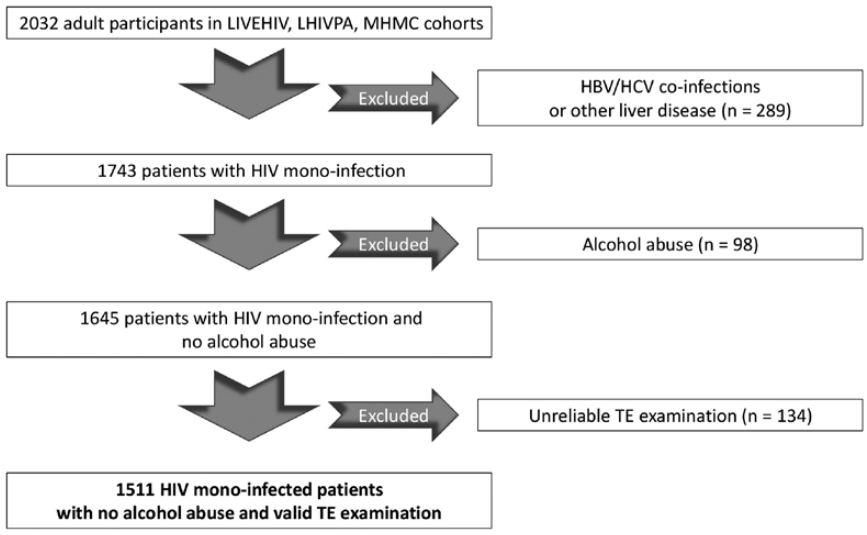

Figure 1. Flow chart displaying the selection of study participants in the cohort. Liver stiffness measures by Fibroscan were considered reliable if the ratio of the interquartile range over the median of the 10 measures was no more than 30%. Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; LHIVPA, liver pathologies and HIV in Palermo; LIVEHIV, liver disease in HIV; MHMC, Modena HIV Metabolic Clinic; TE, transient elastography.

Table 1. Participant Characteristics

	Whole Study Population, n = 1511	Lean Without NAFLD, n = 657	Lean NAFLD, n = 210	*P* Value
Age, years	50.4 (10.5)	49.1 (11.1)	52.3 (9.3)	<.001
Male sex (%)	1133 (75.0)	481 (73.2)	165 (78.6)	.123
Ethnicity (%)				
White/Caucasian	1265 (83.7)	567 (86.3)	189 (90.0)	.428
Black non-Hispanic	176 (11.6)	57 (8.7)	11 (5.2)	
Hypertension (%)	380 (25.2)	122 (18.6)	57 (27.1)	.011
Active tobacco smoker (%)	460 (30.4)	234 (35.6)	71 (33.8)	.678
Diabetes (%)	222 (14.7)	77 (11.7)	26 (12.4)	.294
History of cardiovascular event (%)	85 (5.6)	34 (5.2)	12 (5.7)	.726
BMI, kg/m^2	25.0 (4.4)	22.0 (2.0)	23.1 (1.6)	<.001
Time since HIV diagnosis, years	16.0 (9.9)	16.2 (10.4)	18.1 (9.5)	.012
Undetectable HIV viral load, < 40 copies/mL (%)	1088 (72.0)	462 (70.3)	171 (81.4)	.002
CD4 cell count (cells/μL)	698.4 (311.9)	685.8 (316.9)	736.9 (283.0)	.019
Nadir CD4 cell count < 200/μL (%)	669 (45.7)	268 (40.8)	106 (50.4)	.024
Current ART regimen (%)[a]				
NRTIs	699 (82.7)	277 (81.4)	104 (85.2)	.484
NNRTIs	244 (28.9)	100 (29.4)	43 (35.2)	.252
PIs	317 (37.5)	115 (33.8)	42 (34.4)	.912
Integrase inhibitors	434 (51.4)	165 (48.5)	72 (59.0)	.049
Past exposure to d-drugs (%)[a]	516 (58.2)	124 (36.6)	97 (51.0)	<.001
ALT (IU/L)	25.9 (18.1)	23.6 (18.1)	28.7 (21.4)	<.001
AST (IU/L)	23.6 (11.2)	23.4 (10.8)	23.8 (16.7)	.755
Triglycerides (mmol/L)	1.6 (1.2)	1.3 (.8)	1.9 (1.9)	<.001
Total cholesterol (mmol/L)	4.7 (1.0)	4.6 (1.0)	4.8 (1.1)	.030
HDL cholesterol (mmol/L)	1.3 (.4)	1.4 (.4)	1.2 (.4)	<.001
Fasting glucose (mmol/L)	5.2 (1.1)	5.0 (1.1)	5.2 (1.0)	.074
LSM (kPa)	5.7 (4.0)	5.0 (2.3)	6.1 (5.6)	<.001
CAP (dB/m)	237.2 (56.3)	199.5 (33.9)	280.9 (30.5)	<.001

Data are of the whole study population (n = 1511) and a univariable analysis of lean patients by NAFLD status (n = 867). Continuous variables are expressed as means (standard deviations) and categorical variables as numbers (%). The *P* values refer to the Student *t* test or χ^2 test between lean patients with and without NAFLD.

Abbreviations: ALT, alanine aminotransferase; ART, antiretroviral therapy; AST, aspartate aminotransferase; BMI, body mass index; CAP, controlled attenuation parameter; d-drugs, stavudine/didanosine; HDL, high-density lipoprotein; HIV, human immunodeficiency virus; IU, international units; LSM, liver stiffness measurement; NAFLD, nonalcoholic fatty liver disease; NNRTIs, nonnucleoside reverse transcriptase inhibitors; NRTIs, nucleoside/nucleotide reverse transcriptase inhibitors; PIs, protease inhibitors.

[a]Data on current ART regimens were available for a total of 845 patients (55.9%), including 122 lean patients with NAFLD and 340 lean patients without NAFLD patients. Data on past exposure to d-drugs were available for 887 (58.7%) of patients, including 189 lean patients with NAFLD and 339 lean patients without NAFLD.

P = .002), and higher ALT (aOR, 1.15; 95% CI, 1.05–1.26; *P* = .002), while higher HDL cholesterol was protective (aOR, 0.45; 95% CI, .26–.77; *P* = .004; Table 2). We also conducted a sensitivity analysis by building a multivariable model including integrase inhibitors, with similar results as the previously mentioned model (Supplementary Table S2). When using the 288 dB/m CAP cut-off to diagnose NAFLD, the prevalence of lean NAFLD was 4.4%. Supplementary Table S3 depicts the multivariable model for predictors of lean NAFLD when using the 288 dB/m CAP cut-off.

Liver Fibrosis in Lean Nonalcoholic Fatty Liver Disease

Figure 3A reports the distribution of NAFLD and significant liver fibrosis status by BMI category. The distribution of liver fibrosis stages in lean patients with and without NAFLD, as well as in obese and overweight NAFLD patients, is depicted in Figure 3B. Lean NAFLD patients had a higher prevalence of significant liver fibrosis/cirrhosis (15.7% vs 7.6%, respectively; *P* < .001), compared to lean patients without NAFLD. On the other side, the prevalence of significant liver fibrosis and cirrhosis was similar between lean and overweight NAFLD patients. Out of 157 NAFLD patients with available follow-ups, 15 (9.6%) patients were excluded from the analysis for having the outcome (cirrhosis) at baseline. Of the remaining 142 cases (see Supplementary Table S4 for main characteristics), 38 (26.8%) had fibrosis progression during a median follow-up of 26 months (interquartile range, 6–54), accounting for an incidence rate of 18.5 per 100 PY (95% CI, 13.4–25.4). There was no significant difference in fibrosis progression between lean versus overweight/obese patients (24.5 per 100 PY [95% CI, 11.0–54.5] vs 17.6 per 100 PY [95% CI, 12.5–24.9], respectively). The overall median absolute change in LSM at the end of follow-up was 0.8 kPa (interquartile range, .6–2.2). In 1 overweight case (0.7%) LSM improved during the follow-up from the F2 to F0-F1 fibrosis category, while in 4 cases (2.8%), of which 2 patients were lean and 2 were overweight, LSM improved from F4

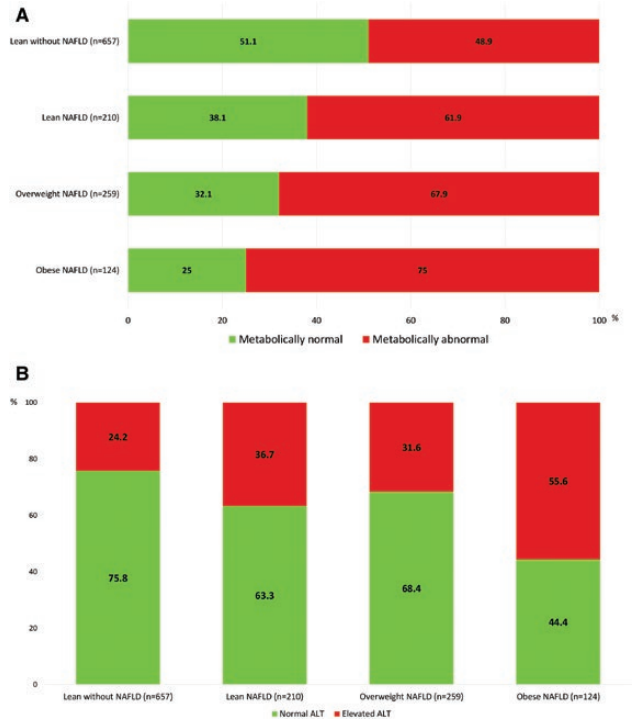

Figure 2. *A*, Distribution of metabolically abnormal or normal lean patients with and without NAFLD and overweight and obese NAFLD patients. *B*, Prevalence of elevated ALT in lean patients with and without NAFLD and in overweight and obese NAFLD patients. Abbreviations: ALT, alanine aminotransferase; NAFLD, nonalcoholic fatty liver disease.

to F2. A reduction in BMI and/or CAP was observed in 80% of patients with improved liver fibrosis (data not shown).

DISCUSSION

In a large population of patients living with HIV mono-infection recruited from 3 cohorts and undergoing a routine screening program for liver disease, we found an overall prevalence of lean NAFLD of 13.9%. Importantly, lean NAFLD patients were more metabolically abnormal and had higher proportions of elevated ALT and significant liver fibrosis than lean patients without NAFLD. Finally, our findings indicate that investigations for NAFLD should be considered in older patients living with HIV mono-infection with dyslipidemia and elevated ALT, even if they have a normal BMI.

NAFLD is emerging as the leading cause of chronic liver disease in people living with HIV, with higher rates than in the general population [5–9]. A recent meta-analysis of 5 studies reported an overall prevalence of NAFLD at 35.3% [6]. Besides commonly presenting with other metabolic conditions, such as insulin resistance and dyslipidemia, patients living with HIV have unique risk factors for NAFLD, including HIV-related inflammation, even in the presence of a suppressed viral load, ART, persistent immunoactivation, and lipodystrophy [5, 10, 32].

The NAFLD epidemic has paralleled the increase in overweight and obesity rates, which affect 39% and 13% of the global population, respectively [33]. However, a subset of patients develops NAFLD with a BMI below 25 Kg/m^2, denoted as lean NAFLD. NAFLD in lean individuals has been initially considered a less severe form of liver disease than NAFLD in overweight/obese patients [34]. This concept has been recently challenged. A cross-sectional study of 466 NAFLD patients with biopsy data showed that the rate of liver cirrhosis was at 8.1% in lean patients [21]. The only longitudinal study conducted in 646 Caucasian patients with biopsy-proven NAFLD reported an increased risk for developing severe liver disease in lean patients (hazard ratio, 2.69), compared to overweight patients, during a mean follow-up of 19.9 years [20]. The pathogenesis of lean NAFLD is not completely understood. Lean NAFLD patients may have a distinct metabolism and an obesity-resistant profile, and may adapt better to an excess intake of calories [35]. Compared to nonlean NAFLD patients, lean ones have lower levels of adiponectin and higher levels of leptin. Moreover, they present with higher levels of bile acids, which play a role in the digestion of fats, and of fibroblast growth factor 19, which increases energy expenditure and may partly explain why these patients remain lean [34, 35]. Changes in gut microbiota, as well as genetics, could also influence the development of NAFLD in lean patients. Finally, lifestyle, diet, and underreported alcohol use may contribute to this clinical phenotype [35].

To the best of our knowledge, there has been no study investigating lean NAFLD in patients living with HIV. This is particularly important considering that patients living with HIV mono-infection with NAFLD tend to have lower BMIs when compared to uninfected NAFLD patients [36]. Moreover, changes in anthropometric characteristics in patients living with HIV, such as a shift of body fat deposits from the subcutaneous to the visceral compartment, have been described [10]. Most of the studies conducted thus far reported BMI as the

Table 2. Multivariable Analysis

Variable	OR, 95% CI	aOR, 95% CI	*P* Value
Age, per 10 years	1.34 (1.15–1.57)	1.29 (1.04–1.59)	.020
Male sex, yes vs no	1.34 (.92–1.95)	0.99 (.64–1.54)	.970
Black ethnicity, yes vs no	0.58 (.30–1.13)	1.18 (.55–2.55)	.670
Hypertension, yes vs no	1.63 (1.14–2.35)	1.10 (.72–1.68)	.654
Triglycerides, per mmol/L	1.56 (1.32–1.85)	1.34 (1.11–1.63)	.002
HDL cholesterol, per mmol/L	0.32 (.20–.51)	0.45 (.26–.77)	.004
Time since HIV diagnosis, per 10 years	1.20 (1.03–1.40)	0.99 (.80–1.22)	.913
CD4 cell count, per 100 cell/µL	1.05 (1.00–1.10)	1.05 (1.00–1.11)	.056
Nadir CD4 cell count <200/µL, yes vs no	1.44 (1.04–2.00)	1.40 (.98–2.00)	.068
ALT, per 10 IU/L	1.13 (1.04–1.22)	1.15 (1.05–1.26)	.002

Data are of predictors of NAFLD in lean patients living with HIV mono-infection (n = 867). ORs and 95% CIs are presented for each variable in the unadjusted and adjusted analysis.

Abbreviations: aOR, adjusted odds ratio; ALT, alanine aminotransferase; CI, confidence interval; HDL, high-density lipoprotein; HIV, human immunodeficiency virus; OR, odds ratio.

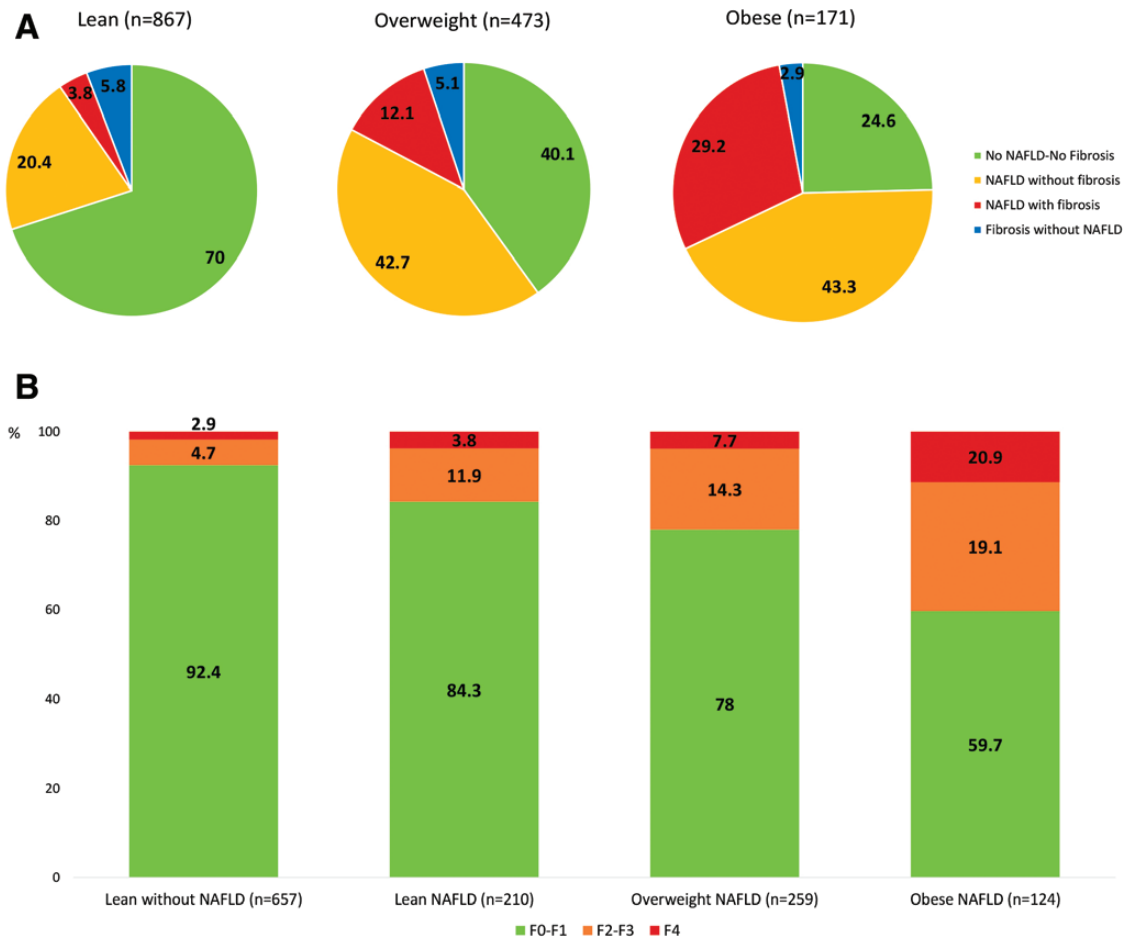

Figure 3. *A*, Distribution of NAFLD and significant liver fibrosis status by BMI category. *B*, Distribution of liver fibrosis stages in lean patients with and without NAFLD, as well as in obese and overweight NAFLD patients. Abbreviations: BMI, body mass index; NAFLD, nonalcoholic fatty liver disease.

main predictor of NAFLD in HIV mono-infection, such that in clinical practice a high level of suspicion for NAFLD has been recommended in overweight patients [9, 17, 18, 25]. In the present study, we found that lean NAFLD is a frequent entity in patients living with HIV, affecting 24.2% of lean patients and representing 35.4% of all NAFLD patients. Our population was consecutively screened for NAFLD using TE with associated CAP, thus reducing the selection bias. This noninvasive tool has been widely used in patients living with HIV and has been validated against liver biopsy, with reported areas under the curve of 0.88 for NAFLD and up to 0.93 for liver fibrosis [9, 22, 23, 37]. Importantly, we found that lean NAFLD patients are metabolically abnormal in 61.9% of cases and have elevated ALT in 36.7% of cases. Moreover, lean NAFLD had significant liver fibrosis in 11.9% of cases and cirrhosis in 3.8% of cases. This result highlights that, also in the setting of HIV infection, lean NAFLD should not be considered a benign condition, as 1 in 6 patients actually have significant liver disease and 3.8% will require surveillance for hepatocellular carcinoma and esophageal varices. In a multivariable analysis, independent predictors of NAFLD among lean patients living with HIV mono-infection, besides older age, were higher triglycerides and lower HDL cholesterol, thus also underlying the relevance of metabolic factors for this clinical phenotype. High ALT also was as an independent predictor of NAFLD. A recent study using liver biopsy as a reference in patients living with HIV mono-infection found that elevated ALT had good performance to diagnose NASH, with an area under the curve of 0.83 [22]. As such, we could speculate that a significant proportion of patients living with HIV mono-infection with lean NAFLD may have underlying NASH. None of the studied HIV variables were associated with lean NAFLD, despite being previously associated with overall NAFLD in patients living with HIV mono-infection [6, 13, 38]. However, the lack of data on biomarkers of immune activation and chronic inflammation prevents us from making conclusions.

Our study has several strengths, including the large patient population recruited from 3 diverse routine screening programs for liver disease and the use of an easily accessible and validated noninvasive tool to diagnose NAFLD. Several limitations of our

study must be acknowledged. First, we used BMI to categorize lean and overweight/obese groups. As BMI may underestimate obesity in patients with low muscle mass and/or high visceral adiposity, the use of waist circumference could have been more suitable for the characterization of a lean NAFLD phenotype. Second, detailed data on ART drugs were not available in the whole study population; as such, we were not able to study the effect of specific regimens on lean NAFLD. However, a sensitivity analysis conducted in patients with available ART data showed no difference in predictors of lean NAFLD. Third, we did not have availability of polymorphisms in the patatin-like phospholipase domain-containing 3 gene, previously associated with NAFLD in both the general population and patients living with HIV [39, 40]. Fourth, we lack data on parameters of insulin sensitivity other than fasting glucose.

In conclusion, our results suggest that lean NAFLD is a frequent occurrence in patients living with HIV mono-infection. Lean NAFLD patients are more metabolically abnormal than lean patients without NAFLD. Although lean NAFLD has been previously considered benign, our study shows that those patients can present with significant liver fibrosis and cirrhosis. Clinicians practicing HIV medicine should maintain a high degree of suspicion for NAFLD in lean patients living with HIV mono-infection, especially in the presence of dyslipidemia or elevated ALT. Further studies are needed, with longitudinal designs and data on genetic variants, insulin markers, single ART regimens, and body fat distribution.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. G. G. and G. S. are both senior authors on this work. A. Cervo and G. S. contributed to the conception, study design, collection and interpretation of the data, statistical analysis, and first draft of the manuscript. J. M., G. M., F. S., S. P., T. K., B. L., M. D., and A. Cascio contributed to the collection and interpretation of the data. G. G. contributed to the conception, study design, and collection and interpretation of the data. All authors approved the final version of the article.

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