Screening HIV Patients at Risk for NAFLD Using MRI-PDFF and Transient Elastography: A European Multicenter Prospective Study

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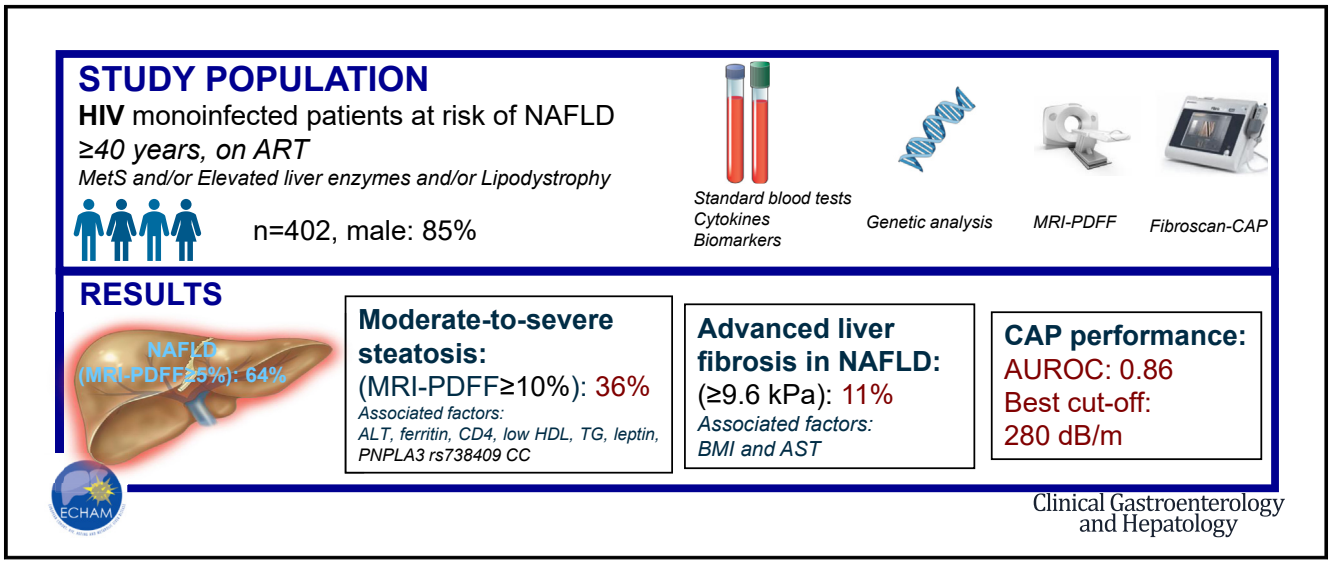

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Abbreviations used in this paper: AF, advanced fibrosis; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ART, antiretroviral treatment; AUROC, area under the receiver operating characteristic; BMI, body mass index; CAP, controlled attenuation parameter; CI, confidence interval; EACS, European AIDS Clinical Society; EASL, European Association for the Study of the Liver; FLI, fatty liver index; HIV, human immunodeficiency virus; HOMA, Homeostasis Model Assessment; IQR, interquartile range; IR, insulin resistance; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; LSM, liver stiffness measurement; MetS, metabolic syndrome; MRI-PDFF, magnetic resonance-imaging proton density fat fraction; PLWH, people living with HIV; ROC, receiver operating characteristic; ULN, upper limit of normal.

Most current article

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BACKGROUND & AIMS: **Nonalcoholic fatty liver disease (NAFLD) is a growing concern in the aging population with human immunodeficiency virus (HIV). Screening for NAFLD is recommended in patients with metabolic risk factors or unexplained transaminitis. This study aimed to prospectively assess the prevalence and associated factors of liver steatosis and advanced fibrosis (AF) in HIV-monoinfected patients at risk of NAFLD.**

METHODS: **We conducted a multicenter study in HIV-monoinfected patients, nonexcessive drinkers with metabolic syndrome, and/or persistently elevated liver enzymes, and/or clinical lipodystrophy. All participants had magnetic resonance imaging proton density fat fraction (MRI-PDFF), Fibroscan/controlled attenuation parameter (CAP), and cytokine and genetic analysis.**

RESULTS: **From March 2014 to November 2015, we enrolled 442 participants and analyzed 402: male (85%); median age, 55 years (interquartile range [IQR], 50-61 years); body mass index, 27.0 kg/m^2 (IQR, 23.6-28.7 kg/m^2); metabolic syndrome (67%); and CD4 cell count, 630/mm^3 (IQR, 510-832/mm^3). Overall 257 of 402 (64%) had NAFLD (MRI-PDFF ≥5%). Among them, 11.3% had a liver stiffness ≥9.6 kPa, suggestive of AF. Multivariable analysis identified 7 factors of steatosis: high CD4-cell count (odds ratio [OR], 4.04; 95% confidence interval [CI], 1.92–8.51), high leptin level (OR, 2.12; 95% CI, 1.14–3.93), non-CC PNPLA3*s738409* genetic polymorphism (OR, 1.92; 95% CI, 1.11–3.33), low high-density lipoprotein (OR, 1.83; 95% CI, 1.03–3.27), high triglycerides (OR, 1.48; 95% CI, 1.18–1.84), elevated alanine transaminase (OR, 1.23; 95% CI, 1.16–1.31), and hyper ferritinemia (OR, 1.05; 95% CI, 1.03–1.07). Two factors were associated with AF: high body mass index (OR, 1.23 ; 95% CI, 1.07–1.42 ; $P = .005$, and elevated aspartate aminotransferase (OR, 1.03; 95% CI, 1.01–1.05; $P = .001$). Using MRI-PDFF as a reference, CAP (best cutoff, 280 dB/m) had good accuracy (area under the receiver operating characteristic curve = 0.86; 95% CI, 0.82–0.90) for the diagnosis of moderate to severe steatosis.**

CONCLUSIONS: **In a large cohort of HIV-moninfected patients at risk of NAFLD, steatosis is present in two-thirds of cases, and around 10% have AF. The CAP technique is accurate for screening steatosis in this population.**

Keywords: Fibrosis; HIV; NAFLD; Risk Factors; Steatosis.

Nonalcoholic fatty liver disease (NAFLD) encompasses a spectrum of conditions ranging from simple fatty liver (nonalcoholic fatty liver), to nonalcoholic steatohepatitis (NASH), liver fibrosis, cirrhosis, and hepatocellular carcinoma.[1] Due to the global spread of obesity and type 2 diabetes, NAFLD is now the most common cause of chronic liver disease[2] and is expected to become the first indication for liver transplantation over the next decade in developed countries.[3] Advanced fibrosis (AF), including cirrhosis, is recognized as the most important predictor of clinical outcomes and mortality in patients with NASH.[4]

People living with human immunodeficiency virus (HIV) (PLWH) are considered at high risk of NAFLD due to an increased prevalence of traditional metabolic risk factors and aging.[5,6] Life expectancy of PLWH has, indeed, greatly improved and, at present, in Western countries more than one-half of PLWH are more than 50 years old with a high prevalence of age-related comorbidities.[6] Globally, the metabolic syndrome (MetS) affects 17% to 31% of PLWH[7] and, as a consequence, NAFLD in PLWH has now become a growing concern.[5] A systematic review and meta-analysis estimated the overall prevalence of NAFLD in monoinfected-PLWH as 35% (95% confidence interval [CI], 29%–42%) in the Western world[8] but underlined the limited number of studies, often based on heterogeneous diagnostic criteria. In contrast to the non-HIV population, data on NAFLD in PLWH is scarce and heterogeneous,[7,9–16] with liver histology being hardly performed in this population. This gap hampers the development of international strategies for the diagnosis and management of NAFLD in PLWH.[6]

In its 2019 guidelines, the European AIDS Clinical Society (EACS)[17] recommends to "assess and monitor disease severity in PLWH in case of suspected NAFLD and metabolic risk factors" and underlines the lack of data and the absence of optimal cutoff for the use of controlled attenuation parameter (CAP), a technology widely used now in outpatient clinical services.

In this prospective multicenter study, using magnetic resonance imaging proton density fat fraction (MRI-PDFF)[18] and liver stiffness measurement (LSM) (Fibroscan) as the best recommended noninvasive method for the diagnosis of AF,[18] we aimed to assess (1) the prevalence, severity, and risk factors of liver steatosis and AF in moninfected PLWH at risk of NAFLD; and (2) the performance of the CAP technique and its best cutoff for the diagnosis of moderate to severe steatosis in this population.

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Methods

Study population

ECHAM (European Cohort on HIV, Aging, and Metabolic liver disease) is a multicenter European study (7 centers: Belgium [n = 1], France [n = 2], and Germany [n = 4]). Between March 2014 and November 2015, HIV-1 infected individuals over 40 years, receiving antiretroviral treatment (ART) for at least 5 years with HIV viral load <400 copies/mL and CD4-T cell count >100/mm^3, were invited to participate to the study if they met at least 1 of the following criteria: (1) MetS defined by the 2009 international criteria[19] (Group 1); (2) persistently elevated liver enzymes defined by transaminases ≥1.5 upper limit of normal ([ULN] = 35 IU/mL) and/or gammaglutamyltransferase level ≥2 ULN (ULN = 60 IU/L) on 2 blood samples within at least a 3-month interval (Group 2); or (3) clinical lipodystrophy as previously described[20] (Group 3).

Participants were not eligible if they met one of the following criteria: positive hepatitis B or C virus serologies; coinfection with HIV-2; use of intravenous drugs within the last 6 months; current or past excessive alcohol intake (>30 g/day); genetic hemochromatosis; autoimmune hepatitis; primary or secondary biliary cirrhosis or cholangitis; alpha1 antitrypsin deficiency; Wilson's disease; secondary causes of NAFLD (ie, ongoing prolonged steroid therapy, current therapy with amiodarone, tamoxifen, methotrexate, nifedipine, or hycanthone, history of cancer chemotherapy; short bowel syndrome; polycystic ovarian syndrome; Weber-Christian disease); active opportunistic infection except for candida oesophagitis; ongoing cancer; pregnancy; or uncontrolled congestive heart failure. The study (ClinicalTrials.gov, Number: NCT02093754) was approved by the national ethic committees.

Demographic and Clinical Data

Demographic (ethnicity), epidemiological (smoking habit, alcohol consumption, HIV transmission, year of HIV diagnosis, duration of cumulative exposure to ART, year of ART initiation) and clinical (body mass index [BMI], waist and hip circumference, type of ART exposure, antidiabetic, antihypertensive, and hypolipidemic drugs): data were collected at enrollment in standardized electronic forms.

Biochemical Measurement

Blood samples were collected after a 12-hour overnight fast for determination of liver enzymes, glucose, cholesterol, triglycerides, and insulin. Measurements of circulating insulin were centralized (Architect; Abbott Laboratories, Rungis, France). Insulin resistance (IR) was assessed using the Homeostasis Model Assessment Method index (HOMA-IR) and defined as HOMA-IR index ≥2.5.[21]

What You Need to Know

Background

Aging human immunodeficiency virus (HIV)-monoinfected patients with metabolic syndrome, abnormal liver enzymes, or lipodystrophy are considered at risk of nonalcoholic fatty liver disease, but the severity and risk factors of liver steatosis and fibrosis remain debated in this population.

Findings

Moderate to severe steatosis (magnetic resonance imaging proton density fat fraction ≥10%) (36%) and advanced fibrosis (Fibroscan ≥9.6kPa) (11%) are frequent. High body mass index and aminotransferase are associated with advanced fibrosis.

Implications for patient care

Aging HIV-monoinfected patients with metabolic disorders or abnormal liver enzymes should be systematically screened for liver steatosis and fibrosis. The controlled attenuation parameter technique (best cutoff, 280 dB/m) can be used to identify patients with moderate to severe steatosis.

Serum Adipokines Measurement

Measurement of serum adipokines was centralized in the department of biochemistry and hormonology (Tenon Hospital, Paris, France): Leptin and high-sensitivity interleukin-6 were measured using an enzyme-linked immunosorbent assay (Quantikine R&D Systems, Oxford, UK). Serum adiponectin was measured by enzyme-linked immunosorbent assay (ALPCO, Salem, NH) and high-sensitivity C-reactive protein by immunonephelometry (IMMAGE, Beckman-Coulter).

Genetic Analysis

Genomic DNA was isolated from 200 μL of blood by QIAamp DNA Blood Mini Kit (QIAGEN, Hilden, Germany). Patatin-like phospholipase domain containing 3 (PNPLA3, rs738409 c.444C>G) and transmembrane6 superfamily 2 (TM6SF2, rs58542926 c.449C>T) polymorphisms were genotyped using TaqMan primers and probes for allelic discrimination (7500 Fast Real-Time PCR system, Applied Biosystems, Thermo Fisher Brand, Foster City, CA) per the manufacturer's recommendations.

Liver Steatosis Assessment

For the diagnosis of NAFLD, we used MRI-PDFF, the most accurate method for detecting and quantifying hepatic steatosis according to the 2021 European Association for the Study of the Liver (EASL) guidelines[18] and for which excellent performance was confirmed in our

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population using liver histology as a reference.[22] We used an MRI-PDFF cutoff of 5% for the definition of any degree of steatosis, and of 10% to identify moderate to severe liver steatosis (corresponding to ≥33% of hepatocytes on liver biopsy).[22,23]

All participants underwent a two-phase contrast hepatic MRI-PDFF with calculation of the hepatic fat fraction using a dedicated software. All machines included in-phase and out-of-phase T1 imaging (T1 Gradient Echo sequences with multiple echoes and T2* relaxometry). Fat fraction calculation in in-phase and out-of-phase were standardized within the study centers. For quality control, randomly selected MRI-PDFF reports were reviewed by a single highly experienced radiologist (Y.M.) blinded to clinical patient information.

We also collected CAP values (dB/m) co-localized to LSM and calculated the fatty liver index (FLI), an algorithm often used in non-HIV subjects.[24]

Liver Fibrosis Measurement

All patients had LSM, obtained in an overnight fasting state using transient elastography (Fibroscan 502, M probe, Echosens, France) and performed by experienced operators. Results were expressed in kilopascal (kPa) as the median value of 10 successful acquisitions. Failure was defined as no single successful measurement (valid shot = 0) and unreliable measurement as IQR/LSM of >0.30 when LSM is ≥7.1 kPa.[25] Fibrosis-4 score and aspartate aminotransferase to platelet ratio index were calculated as previously described.[18] Following the 2021 EASL recommendations on the use of noninvasive markers, we applied a cutoff 9.6 kPa to detect advanced liver fibrosis (AF).[18]

Statistical Analysis

The patients' characteristics were described, in the entire group and according to their inclusion criteria, using median and interquartile range (IQR) (25th–75th percentiles) for continuous variables and number and percentage for categorical variables. We also compared chracteritics of excluded and included participants. Non-parametric Kruskal-Wallis test was used to compare continuous variables between the 3 groups, and for categorical variables, the χ^2 test or the Fisher exact test were used when sample size was too small in any of the categories. The percentage and the associated 95% CI for steatosis and fibrosis were calculated. Univariable and multivariable logistic regression models were used to assess factors associated with moderate to severe steatosis defined by MRI-PDFF ≥10%, and AF defined by LSM ≥9.6 kPa.[18] Variables with *P*-value < .20 in the univariable analysis were retained for the multivariable analyses. Because of the very high number of variables and to select the most pertinent associated variables, we used a multiple imputation and boostrap approach: we created 5 datasets in which missing data were imputed using a multiple imputation approach. On each dataset, we generated 100 bootstrap samples. On each of the 500 samples, a backward selection technique (alpha = 0.05) was applied, and all factors that were selected in more than 75% of the models were retained.

Nonparametric receiver operating characteristic (ROC) analysis was conducted to assess the performance of CAP and FLI for the diagnosis of steatosis using MRI-PDFF as a reference. The performance was considered good for the area under the ROC (AUROC) between 0.80 and 0.90 and excellent if >0.90. The performances were also assessed in terms of sensitivity, specificity, positive and negative predictive values, and the likelihood ratio for a positive test result (LR+) and the likelihood ratio for a negative test result (LR−). Optimal cutoff values for CAP and FLI were selected to maximize the sum of sensitivity and specificity.

Results

Study Population

A total of 461 HIV mono-infected individuals were screened, 442 met the inclusion criteria, and 402 with complete metabolic and liver assessment were further analyzed (Figure 1). No statistical differences were found between excluded and analyzed participants except for high blood pressure (43% vs 65%; *P* = .006) and alanine aminotransferase (ALT) level (42.5 [IQR, 32–65] vs 34 [IQR, 24–50] IU/L; *P* = .018). Analyzed participants were mainly male (n = 340; 85%), median age was 55 years (IQR, 50–61 years), and median BMI was 27.0 kg/m^2 (IQR, 23.6–28.7 kg/m^2). All participants had controlled HIV-1 infection with a plasmatic HIV-1 RNA <50 copies/mL except for 11 patients (3%), a median CD4-T cell count of 630/mm^3 (IQR, 510–832/mm^3) and a median duration of cART exposure of 16 years (IQR, 11–19 years). Most of the participants were

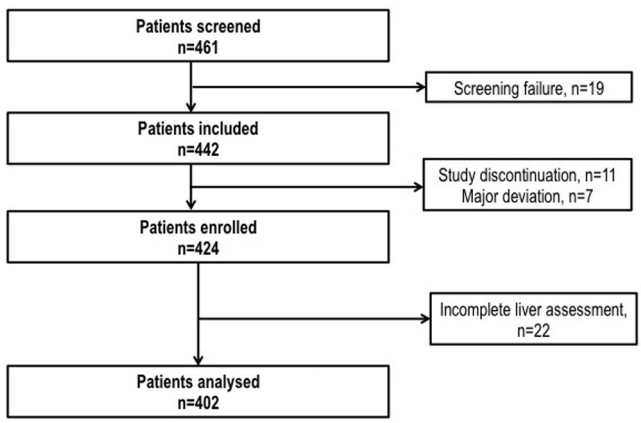

Figure 1. Study flow diagram.

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enrolled because of MetS (group 1, n = 269; 67%); a minority, (group 2, 36; 8.9%) because of persistently elevated liver enzymes without MetS, and 97 (24.1%) because of clinical lipodystrophy (group 3): 74 patients (76.3%) had both lipohypertrophy and lipoatrophy, 13 (13.4%) had isolated lipoatrophy, and 10 (10.4%) isolated lipohypertrophy.

Table 1 summarizes the characteristics of the study population and the 3 subgroups according to the underlying medical condition that qualified them for inclusion into the study. The participants' characteristics significantly differed between the 3 groups. As expected, patients with MetS had higher anthropometric parameters and metabolic disorders as compared with the 2 other groups.

All participants except 2 were assessed for PNPLA3 and TM66SF2 gene polymorphisms. PNPLA3 rs738409 C/C (n = 230; 57.5%) and TM66SF2 rs58542926 C/C (n = 341; 85.3%) were the most frequent polymorphisms observed. No difference in gene polymorphism frequency was observed between the 3 subgroups of patients.

Prevalence and Risk Factors of Liver Steatosis

Among the 402 study patients, 257 had an MRI-PDFF ≥5%, and 145 had an MRI-PDFF ≥10%, giving a prevalence of steatosis at any degree of 64% (95% CI, 59%–69%) and of moderate to severe steatosis of 36% (95% CI, 31%–41%). The proportion of steatosis (MRI PDFF ≥10%) was the highest in patients with MetS (43%) and abnormal liver enzymes (44%) and the lowest in patients with isolated lipodystrophy (14%; $P < .0001$) (Table 1).

As compared with patients with MRI-PDFF <10%, patients with MRI-PDFF ≥10% had a higher proportion of metabolic disorders (MetS: 79.3% vs 59.9%; $P < .001$), higher CD4-T cell (720/mm^3 [IQR, 555–903/mm^3] vs 597/mm^3 [IQR, 488–772/mm^3]; $P < .0001$), higher liver transaminases (ALT, 49 IU/L [IQR, 34–96 IU/L] vs 29 IU/L n7.80); $P < .001$), and a higher proportion of AF (16/109; 14.7% vs 9/194; 4.6%; $P = .002$; Supplementary Table 2).

Patients with MRI-PDFF ≥10% more frequently carried a single nucleotide polymorphism of PNLAP3 genes compared with patients with MRI-PDFF <10% (75/144 vs 95/256; $P = .0005$) (Supplementary Table 1).

In multivariable analysis, 7 factors were independently associated with moderate to severe steatosis: CD4 cell count (OR, 4.04; 95% CI, 1.92–8.51), leptin level (≥3.2 μg/L; OR, 2.12; 95% CI, 1.14–3.93), non-CC PNPLA3*s738409* genetic polymorphism (OR, 1.92; 95% CI, 1.11–3.33), low HDL (<1 mmol/L for men and <1.3 mmol/L for women; OR, 1.83; 95% CI, 1.03–3.27), triglyceride level (OR, 1.48; 95% CI, 1.18–1.84), ALT level (OR, 1.23; 95% CI, 1.16–1.31), and ferritin level (OR, 1.05; 95% CI, 1.03–1.07) (Table 2).

Prevalence and Risk Factors of AF in Patients With NAFLD

Among the 257 patients with NAFLD, 63 (24.5%) had invalid LSM and 194 had valid results; as expected, patients with invalid LSM had higher BMI and higher metabolic disorders compared with patients with valid LSM (data not shown).

Among 194 patients with valid LSM, 22 (11.3%) had a LSM ≥9.6 kPa, suggesting AF, including 11 patients (5.7%) with LSM ≥12.5 kPa, suggestive of cirrhosis. As compared with patients with LSM <9.6 kPa, patients with AF had more metabolic disorders and higher degree of liver steatosis with higher leptin levels and leptin-to-adiponectin ratio, but the genetic profile (PNPLA3 and TM6SF2) was similar (Supplementary Table 2).

Multivariable analysis identified 2 factors associated with AF: high BMI (OR, 1.23; 95% CI, 1.07–1.42; $P = .005$) and high AST level (OR, 1.02; 95% CI, 1.01–1.05; $P = .001$) (Table 3).

Performance of CAP and Fatty Liver Index (FLI) Using MRI-PDFF as a Reference

Valid CAP values were obtained in 356 patients (89%). Using MRI-PDFF as a reference, CAP had good performance for the diagnosis of moderate to severe liver steatosis (MRI-PDF ≥10%) with an AUROC of 0.862 (IQR, 0.823–0.901) and a best cutoff of 280 dB/m with a sensitivity of 75%, a specificity of 83%, and 80% of patients correctly classified. In contrast to CAP, FLI had a poor performance with an AUROC of 0.692 (IQR, 0.636–0.749) (Table 4, Figure 2).

Discussion

In this multicenter European study, we conducted a comprehensive hepatic and metabolic assessment of HIV-monoinfected patients at risk of NAFLD (ie, aged over 40 years, exposed to cART for more than 5 years, and with a MetS or persistently elevated liver enzymes or clinical lipodystrophy). We selected this population, as now recommended by the EACS guidelines,[17] to describe the burden of NAFLD in the potentially most affected PLWH who are most likely to be referred for liver assessment in clinical practice.

We found a high proportion of NAFLD (64%), including 36% presenting moderate to severe steatosis, and, using LSM, 11% had advanced fibrosis, including 6% with cirrhosis.

Not surprisingly, patients with MetS had the highest prevalence of NAFLD (71%), whereas patients with isolated lipodystrophy had a lower prevalence (43%) and a markedly better metabolic profile and insulin sensitivity, suggesting that the dysmetabolic profile with insulin resistance observed in subjects with MetS plays a key

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Table 1. Characteristics of the ECHAM Study Population (n = 402)

	Whole population N = 402	Patients with MetS (group 1) n = 269	Abnormal LE without MetS (group 2) n = 36	Patients with isolated LipoD (group 3) n = 97	*P* value
Age, y	55 (50–61)	57 (52–63)	52 (46–57)	52 (49–56)	< .001
Male	340 (85)	227 (84)	34 (94)	79 (81)	.180
Non African ethnicity	316 (79)	211 (78)	32 (89)	73 (75)	.322
Clinical lipodystrophy at inclusion	301 (75)	191 (71)	13 (36)	97 (100)	
MetS at inclusion	269 (67)	269 (100)	0 (0)	0 (0)	
Persistent abnormal LFT at inclusion	98 (24)	62 (23)	36 (100)	0 (0)	
HIV parameters					
Time since HIV diagnosis, y	19 (14–24)	19 (13–23)	18 (10–21)	20 (16–26)	.137
Time since ART initiation, y					
Duration of the cumulative exposure to ART, y	16 (11–19)	16 (12–19)	13 (7–17)	16 (13–19)	.008
HIV RNA >50 cp/mL	11 (3)	8 (3)	0 (0)	3 (3)	.572
Nadir CD4, /mm^3	184 (84–266)	179 (78–259)	213 (119–277)	194 (93–280)	.129
CD4, /mm^3	630 (510–832)	616 (498–814)	612 (503–844)	643 (536–882)	.801
CD4/CD8 ratio	0.86 (0.60–1.18)	0.82 (0.55–1.09)	0.92 (0.67–1.26)	0.98 (0.70–1.29)	.002
Metabolic parameters					
BMI, kg/m^2	27.0 (23.6–28.7)	26.8 (24.6–29.2)	24.7 (23.4–26.5)	23.7 (21.6–27.0)	< .001
Obesity (BMI ≥30 kg/m^2)	71 (18)	58 (22)	3 (8)	10 (10)	< .001
Waist circumference, cm	98 (92–105)	101 (95–106)	94 (92–99)	91 (86–99)	< .001
Male	98 (92–104)	100 (96–107)	94 (91–98)	90 (85–97)	< .001
Female	101 (93–105)	101 (94–105)	103 (94–111)	99 (92–103)	.774
Elevated BP (systolic > 140 and/or diastolic >90) and/or treated HBP	262 (65)	203 (75)	14 (39)	45 (46)	< .001
Impaired fasting glycemia (≥5.6 mmol/L) and/or anti-diabetic treatment	151 (38)	136 (51)	6 (17)	9 (9)	< .001
Triglycerides, mmol/L	1.60 (1.10–2.50)	1.82 (1.29–2.90)	1.15 (0.80–1.70)	1.30 (0.90–1.87)	< .001
Hypertriglyceridemia (triglycerides >1.7 mmol/L or treatment)	192 (48)	157 (58)	7 (19)	28 (29)	< .001
HDL cholesterol levels, mmol/L	1.17 (0.91–1.40)	1.10 (0.90–1.30)	1.30 (1.20–1.77)	1.29 (1–1.58)	< .001
Low HDL (<1 mmol/L for men and <1.3 mmol/L for women)	255 (63)	210 (78)	8 (22)	37 (38)	< .001
HOMA	2.69 (1.73–4.61)	3.21 (2.07–5.64)	2.44 (1.46–4.22)	1.94 (1.32–2.56)	< .001
HOMA ≥2.5	218 (54)	175 (65)	17 (47)	26 (27)	< .001
Glucose, mmol/L	5.3 (4.8–6.0)	5.5 (4.9–6.3)	5.1 (4.8–5.4)	4.9 (4.5–5.4)	< .001
Leptin, microg/L	5.2 (2.7–10.6)	6.1 (3.3–12.3)	4.3 (1.9–7.4)	3.5 (1.7–7.4)	< .001
Male	4.4 (2.4–7.9)	5.3 (3.2–9.6)	3.7 (1.9–6.2)	2.6 (1.4–4.9)	< .001
Female	23.3 (14.2–39.1)	21.5 (13.4–39.1)	27.4 (22.9–31.8)	28.2 (16.5–40.4)	.554
Adiponectin, mg/L	2.8 (1.9–4.0)	2.7 (1.8–3.8)	3.3 (1.7–4.7)	3.0 (2.2–4.6)	.078
Leptin/adiponectin ratio	2.1 (1.0–4.1)	2.5 (1.2–4.3)	1.4 (0.6–2.9)	1.2 (0.6–2.9)	< .001
hsCRP, mg/L	1.6 (0.7–3.3)	1.7 (0.8–3.3)	1.4 (0.6–2.9)	1.2 (0.6–2.9)	< .001
hsIL6, pg/mL	1.7 (1.1–3.0)	1.9 (1.3–3.1)	1.5 (0.9–2.3)	1.4 (1.0–2.7)	.0001
Genetic polymorphisms (n = 400)					
PNPLA3 rs738409					.096
CC	230 (57%)	155 (58%)	17(47%)	58 (61%)	
CG/GG	143 (35%)/28 (7%)	97 (36%)/16 (6%)	17 (47%)/2 (6%)	28 (29%)/10 (10%)	
TM6SF2 rs58542926					.246
CC	341 (85%)	233 (87%)	29 (81%)	79(82%)	
CT/TT	48 (12%)/11 (3%)	25 (9%)/10 (4%)	7 (19%)/0 (0%)	16 (17%)/1 (1%)	
Hepatic parameters					
ALT, IU/L	34 (24–50)	35 (24–53)	62 (43–91)	28 (19–35)	< .001
AST, IU/L	29 (23–37)	30 (23–40)	38 (31–54)	27 (21–32)	< .001
GGT, IU/L	48 (29–81)	51 (31–83)	85 (54–159)	34 (24–55)	< .001
Platelet count, /mm^3	213 (178–253)	210 (175–253)	203 (177–235)	220 (184–258)	.289
MRI-PDFF, %	7.0 (2.40–12.0)	7.73 (3.90–13.90)	8.05 (2.98–15.00)	3.33 (0–7.15)	< .001
FF ≥5% on MRI-PDFF	257 (64)	191 (71)	24 (67)	42 (43)	< .001
FF ≥10%	145 (36)	115 (43)	16 (44)	14 (14)	< .001

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Table 1. Continued

	Whole population N = 402	Patients with MetS (group 1) n = 269	Abnormal LE without MetS (group 2) n = 36	Patients with isolated LipoD (group 3) n = 97	*P* value
CAP, dB/m (n = 356)	260 (222 – 307)	267 (234–316)	261 (227–303)	228 (200–266)	< .001
FLI	67.2 (43.9–84.2)	74.2 (55.5–87.9)	58.5 (46.4–71.8)	42.4 (25.6–58.3)	< .001
APRI	0.36 (0.26–0.53)	0.38 (0.26–0.57)	0.45 (0.35–0.69)	0.30 (0.23–0.44)	< .001
Fibroscan (n = 303)	5.4 (4.4–6.8)	5.7 (4.8–7.8)	5.6 (4.4–6.2)	4.9 (4.1–5.7)	< .001
LSM <8 kPa (n = 303; 193/32/78)	251/303 (82.8%)	146/193 (75.7)	30/32 (93.8)	75/78 (96.2)	< .001
LSM ≥12.5 kPa (n = 303;193/32/78)	13/303 (4.3)	13/193 (6.7)	0 (0)	0 (0)	.021

Note: Categorical variables are expressed as raw numbers and percentages (%), continuous variables are reported as median and 25th-75th percentiles (interquartile range).

ALT, Alanine aminotransferase; APRI, AST to platelet ratio index; ART, antiretroviral therapy; AST, aspartate aminotransferase; BMI, body mass index; BP, blood pressure; CAP, controlled attenuation parameter; CD, cluster of differentiation; FF, fat fraction; FLI, fatty liver index; HBP, high blood pressure; HDL, high-density lipoprotein; HIV, human immunodeficiency virus; HOMA, Homeostasis Model Assessment Method; hs-CRP, high-sensitivity C-reactive protein; hs-IL, high-sensitivity interleukin; IQR, interquartile range; LDL, low-density lipoprotein; LE, liver enzymes; LFT, liver function test; LipoD, lipodystrophy; LSM, liver stiffness measurement; MetS, metabolic syndrome; PNPLA, Patatin-like phospholipase.

HOMA index was defined as follows: fasting insulin (mU/L) × fasting plasma glucose (mmol/L)/22.5 Insulin resistance was defined by a HOMA index ≥2.5.

role in the development of NAFLD, as observed in the general population.[1]

In addition to the classic metabolic parameters associated with liver steatosis (triglycerides, low HDL, ferritin, and leptin levels), we identified ALT level and CD4-T cell count as associated factors of liver steatosis. The role of an improved immune system in this population as a risk factor of liver steatosis has been previously suggested.[8,14] This finding could reflect an immunological phenomenon or could mark a "healthier" general condition or the contribution of modern HIV drugs (eg, integrase inhibitors) but remains to be further evaluated. We did not find any association between ART class and CD4-T cell levels.

We did not find association between a specific HIV drug class and liver steatosis in our study, and we were unable to collect the duration of cumulative drug exposure to each specific ARV agent. Indeed, our study enrolled PLWH treated for more than 10 years with different combinations and dosages. However, discrepant results have been previously reported.[14] In a Danish study, exposure to an integrase inhibitor has been also identified as a risk factor for moderate to severe liver steatosis measured by computed tomography scan in consecutive PLWH.[15] Other studies, however, did not report association between exposure to nucleoside reverse transcriptase inhibitors or protease inhibitors and liver steatosis.[7]

Table 2. Factors Associated With Moderate to Severe Liver Steatosis (MRI-PDFF ≥10%)

	Univariable analysis		Multivariable analysis	
Variable	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
ALT level, UI/L, per 5 units	1.23 (1.17–1.30)	< .001	1.23 (1.16–1.31)	< .001
CD4 T cell count per log2 unit	3.22 (1.83–5.65)	< .001	4.04 (1.92–8.51)	< .001
Ferritin, ng/mL, per 10 units	1.06 (1.04–1.08)	< .001	1.05 (1.03–1.07)	< .001
Triglycerides, mmol/L, per unit	1.54 (1.30–1.84)	< .001	1.48 (1.18–1.84)	.001
Leptin, μg/L				
<3.2	1		1	
≥3.2	2.68 (1.66–4.31)	< .001	2.12 (1.14–3.93)	.017
Low HDL level (<1 mmol/L for men and <1.3 mmol/L for women)				
no	1		1	
yes	2.39 (1.56–3.66)	< .001	1.83 (1.03–3.27)	.041
PNPLA3 rs738409				
C/C	1		1	
Not C/C	1.84 (1.22–2.79)	.004	1.92 (1.11–3.33)	.020

ALT, Alanine aminotransferase; CI, confidence interval; HDL, high-density lipoprotein; OR, odds ratio; PNPLA3, patatin-like phospholipase domain containing.

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Table 3. Factors Associated With Advanced Liver Fibrosis as Defined by LSM ≥ 9.6kPa in Patients With MRI-PDFF ≥ 5%

	Univariable analysis		Multivariable analysis	
Variable	OR (95% CI)	*P*-value	OR (95% CI)	*P* value
BMI, kg/m^2	1.180 (1.08-1.29)	< .001	1.23 (1.07-1.42)	.005
AST, IU/L	1.03 (1.01-1.05)	< .001	1.02 (1.01-1.05)	.001

AST, Aspartate aminotransferase; BMI, body mass index; CI, confidence interval; LSM, liver stiffness measurement; MRI-PDFF, magnetic resonance imaging proton density fat fraction; OR, odds ratio.

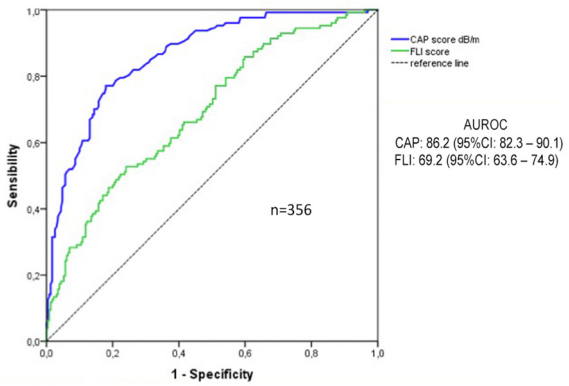
As described in patients without HIV,[26] we found an association between PNLPL3A variants and the presence of moderate to severe liver steatosis. In monoinfected PLWH, only 1 study analyzed the association between PNLPLA3 variants and liver steatosis in 62 patients and observed that a single nucleotide polymorphism (rs738409;C>G) was associated with the degree of liver steatosis and ALT level.[16]

As MRI-PDFF is unlikely to be broadly used in routine HIV care, we validated the accuracy of CAP against MRI-PDFF for the detection of liver steatosis. The diagnostic performance of CAP in patients with HIV-NAFLD has been assessed in only 1 study conducted in 70 HIV-monoinfected subjects at risk of NAFLD.[27] As recently mentioned,[6,17] the best cutoff of CAP needs to be confirmed. In our study, we found a very good performance of CAP for the diagnosis of moderate to severe steatosis and a best cutoff of 280 dB/m, close to the 285 cutoff proposed by Ajmera et al and the 275 dB/m cutoff recently proposed by the EASL in non-HIV subjects with NAFLD.[18]

Table 4. Performance of CAP Method and FLI for the Diagnosis of Liver Steatosis Using MRI-PDFF as a Gold Standard

	Moderate to severe liver steatosis (≥10% MRI-PDFF)	
	CAP	FLI
AUROC (95% CI)	0.862 (0.823-0.901)	0.692 (0.636-0.749)
Cutoff	280 dB/m	75
Correctly classified, %	80	68
Sensitivity, %	75	57
Specificity, %	83	74
PPV, %	71	55
NPV, %	86	75
PLR	4.4	2.2
NLR	0.3	0.6

AUROC, Area under the receiver operating characteristic; CAP, controlled attenuation parameter; CI, confidence interval; FLI, fatty liver index; MRI-PDFF, magnetic resonance imaging proton density fat fraction; NLR, neutrophil-lymphocyte ratio; NPV, negative predictive value; PLR, platelet-lymphocyte ratio; PPV, positive predictive value.



AUROC: area under the receiver operating characteritic
CAP: Controlled Attenuation Parameter
CI: confidence interval
FLI: Fatty Liver Index
MRI-PDFF: Magnetic resonance imaging proton density fat fraction

Figure 2. Performance of CAP and FLI for the diagnosis of moderate to severe liver steatosis using MRI-PDFF as reference. ALT, alanine aminotransferase; PNPLA3, Patatin-like phospholipase domain containing 3.

The high rate of liver steatosis found in our study may be alarming. Indeed, the results of a longitudinal study conducted in Canada in mono-infected PLWH found that hepatic steatosis at any degree was an independent factor of liver fibrosis progression using Fibroscan.[12] The long-term follow-up of our participants will be important to identify additional risk factors of liver disease progression in this population.

In our study, we observed AF in 11% of study subjects, and BMI and AST level were identified as independent factors. This finding suggests that, as observed in non-HIV patients, obesity plays a key role in liver fibrogenesis in this population and clinical management of HIV-monoinfected patients should focus on life style changes and weight loss, as suggested in non-HIV individuals with NAFLD.[1] However, lean NAFLD is also frequently observed in HIV patients (24% according to a recent study[28]) with a risk of AF, suggesting that BMI might not be the cornerstone of NAFLD in this population.

Our study has strengths and limitations. To the best of our knowledge, it is the largest European multicenter study on NAFLD in monoinfected PLWH at risk for metabolic disorders. The long-term follow-up of these patients will fill knowledge gaps on liver disease progression in this population.[6] We collected a large amount of data and were able to analyze the contribution of metabolic, inflammatory, and genetic markers in NAFLD in this population. We analyzed mainly males and well-controlled HIV on long-term ART, whose profile is not representative of the general HIV-mono-infected population. Therefore, our rate of liver steatosis might be higher than that reported in unselected PLWH. In a large Canadian routine screening study of HIV-mono-infected

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patients (n = 541), Pembroke et al also reported 35% of liver steatosis using the CAP technique (≥248 dB/m) and 19% rate of liver fibrosis (LSM ≥7.2 kPa).[12] Similar results were reported in a Brazilian study using the CAP technique (cutoff, 248 dB/m),[14] whereas a recent Danish analysis using computed tomography scan found a prevalence of moderate to severe steatosis of only 8.6%.[15] Finally, we were unable to assess the proportion of patients with NASH because its diagnosis requires liver biopsy, an invasive procedure, not widely accepted by the patients.[22]

Conclusion

In conclusion, when applying the EACS recommendations on the largest multicenter European cohort of patients with HIV-NAFLD, our study confirms that in aging PLWH with metabolic disorders (MetS and/or lipodystrophy) and/or abnormal liver enzymes, the proportion of NAFLD (64%) and AF (11%) is high. One-third had moderate to severe liver steatosis (MRI-PDFF ≥10%), which could be easily identified using CAP (best cutoff, 280 dB/m). PLWH with high BMI and AST level should be of particular attention for liver fibrosis screening and monitoring. In the absence of validated drugs for the treatment of NAFLD in HIV-mono-infected patients, our data confirms that the control of metabolic disorders in this population is critical, although genetic factors also play a role in the development of NAFLD as observed in non-HIV subjects.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2022.03.048.

References

1. European Association for the Study of the Liver, European Association for the Study of Diabetes, European Association for the Study of Obesity. EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol 2016;64:1388–1402.
2. Younossi Z, Anstee QM, Marietti M, et al. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. Nat Rev Gastroenterol Hepatol 2017;15:11–20.
3. Paik JM, Golabi P, Younossi Y, Mishra A, Younossi ZM. Changes in the global burden of chronic liver diseases from 2012 to 2017: the growing impact of NAFLD. Hepatology 2020; 72:1605–1616.
4. Singh S, Allen AM, Wang Z, et al. Fibrosis progression in nonalcoholic fatty liver vs nonalcoholic steatohepatitis: a systematic review and meta-analysis of paired-biopsy studies. Clin Gastroenterol Hepatol 2015;13:643–654.e1-9; quiz: e39-40.
5. Verna EC. Non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in patients with HIV. Lancet Gastroenterol Hepatol 2017;2:211–223.
6. Lake JE, Overton T, Naggie S, et al. Expert panel review on nonalcoholic fatty liver disease in persons with human immunodeficiency virus. Clin Gastroenterol Hepatol 2022; 20:256–268.
7. Vuille-Lessard E, Lebouche B, Lennox L, et al. nonalcoholic fatty liver disease diagnosed by transient elastography with controlled attenuation parameter in unselected HIV mono-infected patients. AIDS 2016;30:2635–2643.
8. Maurice JB, Patel A, Scott AJ, Patel K, Thursz M, Lemoine M. Prevalence and risk factors of non-alcoholic fatty liver disease in HIV-monoinfection: a systematic review and meta-analysis. AIDS 2017;31:1621–1632.
9. Nguyen KA, Peer N, Mills EJ, et al. A meta-analysis of the metabolic syndrome prevalence in the global HIV-infected population. PLoS One 2016;11:e0150970.
10. Lombardi R, Sambatakou H, Mariolis I, et al. Prevalence and predictors of liver steatosis and fibrosis in unselected patients with HIV mono-infection. Dig Liver Dis 2016;1471–1477.
11. Guaraldi G, Squillace N, Stentarelli C, et al. Nonalcoholic fatty liver disease in HIV-infected patients referred to a metabolic clinic: prevalence, characteristics, and predictors. Clin Infect Dis 2008;47:250–257.
12. Pembroke T, Deschenes M, Lebouche B, et al. Hepatic steatosis progresses faster in HIV mono-infected than HIV/HCV co-infected patients and is associated with liver fibrosis. J Hepatol 2017;67:801–808.
13. Price JC, Seaberg EC, Latanich R, et al. Risk factors for fatty liver in the Multicenter AIDS Cohort Study. Am J Gastroenterol 2014;109:695–704.
14. Perazzo H, Cardoso SW, Yanavich C, et al. Predictive factors associated with liver fibrosis and steatosis by transient elastography in patients with HIV mono-infection under long-term combined antiretroviral therapy. J Int AIDS Soc 2018;21:e25201.
15. Kirkegaard-Klitbo DM, Fuchs A, Stender S, et al. Prevalence and risk factors of moderate-to-severe hepatic steatosis in human immunodeficiency virus infection: the Copenhagen Comorbidity Liver Study. J Infect Dis 2020;222:1353–1362.
16. Morse CG, McLaughlin M, Matthews L, et al. Nonalcoholic steatohepatitis and hepatic fibrosis in HIV-1-monoinfected adults with elevated aminotransferase levels on antiretroviral therapy. Clin Infect Dis 2015;60:1569–1578.
17. European AIDS Clinical Society. Guidelines. Version 10.0, 2019. Available at: https://www.eacsociety.org/files/2019_guidelines-10.0_final.pdf.
18. European Association for the Study of the Liver, Clinical Practice Guidelines Panel, Panel Member. EASL Clinical Practice Guidelines (CPGS) on non-invasive tests for evaluation of liver disease severity and prognosis- 2021 update. J Hepatol 2021; 75:659–689.
19. Alberti KG, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 2009;120:1640–1645.
20. Duvivier C, Ghosn J, Assoumou L, et al. ANRS 121 study group. Initial therapy with nucleoside reverse transcriptase inhibitor-containing regimens is more effective than with regimens that spare them with no difference in short-term fat distribution: Hippocampe-ANRS 121 Trial. J Antimicrob Chemother 2008; 62:797–808.

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21. Wallace TM, Matthews DR. The assessment of insulin resistance in man. Diabet Med 2002;19:527–534.
22. Lemoine M, Assoumou L, De Wit S, et al. , ANRS-ECHAM Group. Diagnostic accuracy of noninvasive markers of steatosis, NASH, and liver fibrosis in HIV-monoinfected individuals at risk of nonalcoholic fatty liver disease (NAFLD): results from the ECHAM Study. J Acquir Immune Defic Syndr 2019; 80:e86–e94.
23. Tang A, Tan J, Sun M, et al. Nonalcoholic fatty liver disease: MR imaging of liver proton density fat fraction to assess hepatic steatosis. Radiology 2013;267:422–431.
24. Bedogni G, Bellentani S, Miglioli L, et al. The fatty liver index: a simple and accurate predictor of hepatic steatosis in the general population. BMC Gastroenterol 2006;6:33.
25. Boursier J, Zarski JP, de Ledinghen V, et al. Multicentric Group from ANRS/HC/EP23 FIBROSTAR Studies. Determination of reliability criteria for liver stiffness evaluation by transient elastography. Hepatology 2013;57:1182–1191.
26. Rotman Y, Koh C, Zmuda JM, et al. , NASH CRN. The association of genetic variability in patatin-like phospholipase domain-containing protein 3 (PNPLA3) with histological severity of nonalcoholic fatty liver disease. Hepatology 2010;52:894–903.
27. Ajmera VH, Cachay ER, Ramers CB, et al. Optimal threshold of controlled attenuation parameter for detection of HIV-associated NAFLD with magnetic resonance imaging as the reference standard. Clin Infect Dis 2021;72:2124–2131.
28. Cervo A, Milic J, Mazzola G, et al. Prevalence, predictors, and severity of lean nonalcoholic fatty liver disease in patients living with HIV. Clin Infect Dis 2020;71:e694–e701.

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Conflicts of interest
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Supplementary Table 1. Characteristics of the Study Population According to the Degree of Liver Steatosis as Measured By MRI-PDFF

	Patients with MRI-PDFF $< 10\%$ (n = 257)	Patients with MRI-PDFF $\geq 10\%$ (n = 145)	*P* value
Age (years), median (IQR)	55 (50-61)	52 (50-60)	.991
Male, n (%)	207 (81)	133 (92)	.004
Non African ethnicity, n (%)	204 (79.4)	138 (95.3)	<.001
Clinical lipodystrophy only, at inclusion, n (%)	83 (32.3)	14 (9.7)	.043
MetS only, at inclusion, n (%)	154 (59.9)	115 (79.3)	.002
Persistent abnormal LFT without MetS at inclusion, n (%)	20 (7.8)	16 (11.0)	.124
HIV parameters			
Year of HIV diagnosis	1995 (1991-2001)	1995 (1991-2000)	.656
Year of ART initiation	1998 (1995-2002)	1998 (1996-2002)	.549
Duration of the cumulative exposure to ART, years median (IQR)	16 (11-19)	15 (12-18)	.353
HIV RNA >50 cp/mL, n (%)	5 (1.9)	6 (4.1)	.206
Nadir CD4/mm^3, median (IQR)	179.5 (83-264.5)	192 (91-280)	.266
CD4 /mm^3, median, (IQR)	597 (488-772)	720 (555-903)	<.001
CD4/CD8 ratio, median (IQR)	0.86 (0.61-1.19)	0.87 (0.55-1.14)	.691
Metabolic parameters			
BMI, kg/m^2, median (IQR)	25.6 (23.0-28.0)	27.0 (24.3-29.9)	.0001
Obesity (BMI$\geq$30 kg/m^2), n (%)	36 (14.0)	35 (24.1)	.004
Waist circumference, cm, median (IQR)	97 (90-103)	102 (95-107)	<.001
Elevated BP (Systolic > 140 and/or diastolic >90) and/or treated HBP, n (%)	163 (63.4)	99 (68.3)	.327
Glucose (mmol/L), median (IQR)	5.10 (4.70-5.60)	5.60 (5.00-6.50)	.0005
Impaired fasting glycemia ($\geq$ 5.6 mmol/L) and/or anti-diabetic treatment, n (%)	81 (31.5)	70 (48.3)	<.001
Triglycerides (mmol/L), median (IQR)	1.50 (1.00-2.03)	1.93 (1.40-3.47)	<.001
Hypertriglyceridemia (triglycerides >1.7 mmol/L or treatment), n (%)	101 (39.3)	91 (62.8)	.001
HDL cholesterol (mmol/L), median (IQR)	1.20 (1.0-1.50)	1.03 (0.84-1.30)	<.001
Low HDL (<1 mmol/L for men and <1.3 mmol/L for women), n (%)	68 (26.5)	67 (46.2)	<.001
HOMA, median (IQR)	2.3 (1.6-3.9)	3.7 (2.4-5.9)	.109
HOMA $\geq$2.5, n (%)	111 (43.2)	107 (73.8)	<.001
Leptin (microg/L), median (IQR)	4.3 (2.4-10.7)	6.0 (3.8-10.3)	.428
Adiponectin (mg/L), median (IQR)	3.14 (2.13-4.56)	2.37 (1.59-3.43)	.0004
Leptin/adiponectin ratio, median (IQR)	1.73 (0.80-3.85)	2.59 (1.49-4.80)	.059
hsCRP (mg/L), median (IQR)	1.5 (0.7-3.1)	1.7 (0.9-3.6)	.410
hsIL-6 (pg/ml), median (IQR)	1.7 (1.1-2.7)	2.0 (1.3-3.2)	.787
Genetic polymorphisms (n=400)			
PNPLA3 rs738409			.0005
CC	161 (62.9)	69 (47.9)	
Not CC	95 (37.1)	75 (52.1)	
TM6SF2 rs58542926			.804
CC	219 (85.5)	122 (84.7)	
Not CC	37 (14.5)	22 (15.3)	
Hepatic parameters			
ALT (IU/L), median (IQR)	29 (21-40)	49 (34-96)	<.001
AST (IU/L), median (IQR)	27 (22-33)	36 (29-56)	<.001
GGT (IU/L), median (IQR)	43 (25-69)	59 (38-91)	.050
Platelet count (/mm^3), median (IQR)	214 (178-252)	211 (169-256)	.480
CAP dB/m. median (IQR) (n = 356)	238 (206-264)	313 (278-337)	<.001
APRI, median (IQR)	0.34 (0.24-0.44)	0.47 (0.31-0.74)	<.001

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Supplementary Table 1. Continued

	Patients with MRI-PDFF < 10% (n = 257)	Patients with MRI-PDFF ≥ 10% (n = 145)	*P* value
FIB-4 (IQR)	1.29 (1.01-1.62)	1.45 (1.01-2.04)	.002
Fibroscan kPa, median (IQR)	5.10 (4.30-6.30)	5.90 (4.90-7.80)	.022
Fibroscan ≥9.6 kPa (n=303, (194/109) n (%)	9 (4.6)	16 (14.7)	.002
Fibroscan ≥12.5 kPa n (%)	7 (3.6)	6 (5.5)	.434

NOTE. Categorical variables are expressed as raw numbers and percentages (%), continuous variables are reported as median and 25th-75th percentiles. HOMA was defined as follows: fasting insulin (mU/L) × fasting plasma glucose (mmol/L)/22.5. Insulin resistance was defined by a HOMA index ≥2.5.
BMI, body mass index; FF, fat fraction; HOMA, Homeostasis Model Assessment Method index; IQR, interquartile range; LFT, liver function tests; MetS, metabolic syndrome.

Supplementary Table 2. Characteristics of the Participants With NAFLD (MRI-PDFF ≥5%) According to the Presence of Advanced Liver Fibrosis as Measured by LSM

	Patients with LSM < 9.6 kPa (n = 172)	Patients with LSM ≥ 9.6 kPa (n = 22)	*P* value*
Age (years), median (IQR)	55 (50-62)	55 (51-59)	.892
Male, n (%)	158 (91.9)	20 (90.9)	.700 +
Non African ethnicity, n (%)	152 (88.4)	20 (90.9)	1.00 +
MetS at inclusion, n (%)	120 (69.8)	20 (90.9)	.043 +
Persistent abnormal LFT without MetS at inclusion n (%)	21 (12.2)	1 (4.5)	.478 +
Clinical lipodystrophy only, at inclusion, n (%)	31 (18)	1 (4.5)	.135 +
HIV parameters			
Year of HIV diagnosis, median (IQR)	1995 (1991-2001)	1995 (1992-1999)	.623
Duration of cumulative exposure to ART, years, median (IQR)	16.7 (12.7-19.1)	15.8 (9.9-17.1)	.123
HIV RNA >50 cp/mL, n (%)	5 (2.9)	1 (4.5)	.519 +
Nadir CD4/mm^3, median (IQR)	193 (88-287)	195 (131-219)	.872
CD4 /mm^3, median, (IQR)	669 (522-878)	597 (524-879)	.864
CD4/CD8 ratio, median (IQR)	0.87 (0.61-1.17)	0.75 (0.46-1.06)	.165
Metabolic parameters			
BMI, kg/m^2, median (IQR)	25.45 (23.90-28.26)	28.47 (25.36-30.86)	<.006
Obesity (BMI≥30 kg/m^2), n (%)	22 (12.8)	6 (27.3)	.069
Waist circumference, cm, median (IQR)	98 (92-105)	105.5 (97-110)	.006
Treated HBP, n (%)	111 (64.5)	18 (81.8)	.149 +
Glucose (mmol/L), median (IQR)	5.4 (4.9-6)	6.3 (5.1-7.7)	.009
Impaired fasting glycemia (≥ 5.6 mmol/L) and/or anti-diabetic treatment, n (%)	76 (44.2)	15 (68.2)	.034
Triglycerides (mmol/L), median (IQR)	1.80 (1.30-2.90)	1.78 (1.30-3.20)	.842
Hypertriglyceridemia (triglycerides >1.7 mmol/L or treatment) n (%)	96 (55.8)	12 (54.5)	.910
HDL cholesterol (mmol/L), median (IQR)	1.10 (0.90-1.30)	0.95 (0.80-1.10)	.005
Low HDL (<1 mmol/L for men and <1.3 mmol/L for women), n (%)*	68 (39.5%)	13 (59.1)	.080
HOMA, median (IQR)	2.96 (2.00-4.51)	5.84 (2.91-11.15)	.002
HOMA ≥ 2.5, n (%)	106 (61.6)	17 (77.3)	.151
Leptin (microg/L), median (IQR)	4.65 (2.70-7.80)	7.90 (5.50-12.30)	.008
Adiponectin (mg/L), median (IQR)	2.40 (1.62-3.31)	2.23 (1.83-3.69)	.570
Leptin/adiponectin ratio, median (IQR)	2.13 (1.09-3.83)	3.35 (2.28-5.69)	.033
hsCRP (mg/L), median (IQR)	1.4 (0.7-3.0)	2.6 (1.2-6.8)	.023
hsIL-6 (pg/ml), median (IQR)	1.74 (1.15-3.0)	2.36 (1.35-3.25)	.259

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Supplementary Table 2. Continued

	Patients with LSM $<$ 9.6 kPa (n = 172)	Patients with LSM $\geq$ 9.6 kPa (n = 22)	*P* value*
Genetic polymorphisms			
PNPLA3 rs738409			.719
CC	93 (54.1)	11 (50.0)	
Non CC	79 (45.9)	11 (50.0)	
TM6SF2 rs58542926			.750
CC	144 (83.7)	19 (86.4)	
Non CC	28 (16.3)	3 (13.6)	
Hepatic parameters			
ALT (IU/L), median (IQR)	39 (28-59)	75 (37-112)	.006
AST (IU/L), median (IQR)	31 (25-41)	55 (31-73)	.001
GGT (IU/L), median (IQR)	52 (32-84)	96 (62-138)	.002
Platelet count (/mm3), median (IQR)	211 (178-247)	169 (154-195)	.003
CAP dB/m, median (IQR)	278 (245-320)	319 (278-354)	.002
MRI-PDFF, median (IQR)	10.0 (7.0-15.6)	15.20 (8.13-21.0)	.019
MRI-PDFF $\geq$10% n (%)	93 (54.1)	16 (72.7)	.097
APRI, median (IQR)	0.40 (0.28-0.50)	0.63 (0.54-0.16)	$<$.001
FIB-4, median (IQR)	1.38 (1.01-1.77)	1.84 (1.45-2.85)	.001
Fibroscan $\geq$12.5 kPa n (%)	NA	11 (50)	NA

NOTE. Categorical variables are expressed as raw numbers and percentages (%), continuous variables are reported as median and 25th-75th percentiles. HOMA was defined as follows: fasting insulin (mU/L) $\times$ fasting plasma glucose (mmol/L)/22.5. Insulin resistance was defined by a HOMA index $\geq$2.5.

BMI, body mass index; FF, fat fraction; HOMA, Homeostasis Model Assessment Method index; IQR, interquartile range; LFT, liver function tests; MetS, metabolic syndrome; NA, not applicable.

*Calculated with Mann-Whitney-U test for continuous variables and for categorical variables by Pearson Chi-square test or Fisher's exact test if any the sample size in any of the categories was below 5 (marked with +).

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