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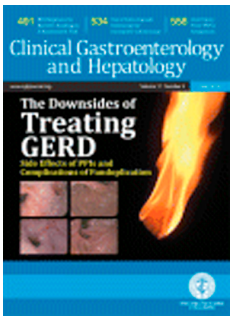

Screening HIV patients at risk for NAFLD using MRI-PDFF and transient elastography: a European multicenter prospective study

Maud Lemoine, Lambert Assoumou, Pierre-Marie Girard, Marc Antoine Valantin, Christine Katlama, Stephane De Wit, Pauline Campa, Hayette Rougier, Jean-Luc Meynard, Coca Necsoi, Anja D. Huefner, Jan Van Luzen, Julian Schulze zur Wiesch, Jean-Philippe Bastard, Soraya Fellahi, Stefan Mauss, Metodi V. Stankov, Axel Baumgarten, Gerrit Post, Lawrence Serfaty, Vlad Ratziu, Yves Menu, Jerome Schlue, Pierre Bedossa, Jacqueline Capeau, Dominique Costagliola, Georg Behrens, Patrick Ingiliz, on behalf of the ANRS-ECHAM group

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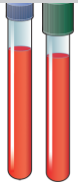
STUDY POPULATION

HIV monoinfected patients at risk of NAFLD

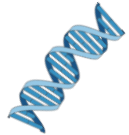
≥40 years, on ART

MetS and/or Elevated liver enzymes and/or Lipodystrophy

n=402, male: 85%



Standard blood tests
Cytokines
Biomarkers

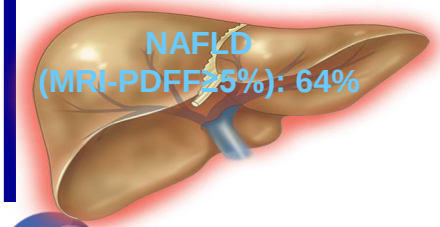


Genetic analysis

MRI-PDFF

Fibroscan-CAP

RESULTS



Moderate-to-severe steatosis:
(MRI-PDFF≥10%): 36%
Associated factors:
ALT, ferritin, CD4, low HDL, TG, leptin, PNPLA3 rs738409 CC

Advanced liver fibrosis in NAFLD:
(≥9.6 kPa): 11%
Associated factors:
BMI and AST

CAP performance:
AUROC: 0.86
Best cut-off:
280 dB/m

ECHAM

Clinical Gastroenterology and Hepatology

Screening HIV patients at risk for NAFLD using MRI-PDFF and transient elastography: a European multicenter prospective study

Maud Lemoine[1], Lambert Assoumou[2], Pierre-Marie Girard[3], Marc Antoine Valantin[4], Christine Katlama[4], Stephane De Wit[5], Pauline Campa[3], Hayette Rougier[3], Jean-Luc Meynard[3], Coca Necsoi[5] Anja D. Huefner[6], Jan Van Luzen[6], Julian Schulze zur Wiesch[6], Jean-Philippe Bastard[7,8,9,10], Soraya Fellahi [7,8,10], Stefan Mauss[11], Metodi V. Stankov[12], Axel Baumgarten[13], Gerrit Post[14], Lawrence Serfaty[15], Vlad Ratziu[16], Yves Menu[17], Jerome Schlue[18], Pierre Bedossa[19], Jacqueline Capeau[7,8], Dominique Costagliola[2], Georg Behrens*[12], Patrick Ingiliz*[13,14] on behalf of the ANRS-ECHAM group.

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Abbreviations: AF: advanced fibrosis, APRI: aspartate-aminotransferase to platelet ratio, AST: aspartate-aminotransferase , ART: antiretroviral treatment, AUROC: area under the receiver operating characteristic, BMI: body mass index, CAP: controlled attenuation parameter, GGT: gammaglutamyltransferase, FF: fat fraction, FLI: fatty liver index, HOMA: Homeostasis Model Assessment, NAFLD: nonalcoholic fatty liver disease, NASH: nonalcoholic steatohepatitis, LE: liver enzymes, LSM: liver stiffness measurement, MetS: metabolic syndrome, MRI-PDFF: magnetic-resonance-imaging-proton-density fat fraction, NPV: negative predictive value, PPV: positive predictive value

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Abstract (254 words)

Background & aims: Non-alcoholic fatty liver disease (NAFLD) is a growing concern in the aging HIV population. 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, non-excessive drinkers with metabolic syndrome (MetS) and/or persistently elevated liver enzymes and/or clinical lipodystrophy. All participants had MRI-PDFF, Fibroscan®//CAP and cytokine and genetic analysis.

Results: From March 2014 to November 2015, we enrolled 442 participants and analysed 402: male (85%), median age 55 years (IQR 50-61), BMI 27.0 kg/m^2 (23.6-28.7), MetS (67%), CD4 cells count 630/mm^3 (510-832). Overall 257/402 (64%) had NAFLD (MRI-PDFF≥5%). Among them, 11.3% had a liver stiffness ≥9.6 kPa, suggestive of AF. Multivariable analysis identified seven factors of steatosis: high CD4-cell count (OR:4.04 (95%CI: 1.92-8.51)), high leptin level (OR:2.12 (1.14–3.93)), non-CC PNPLA3*s738409* genetic polymorphism (OR:1.92 (1.11-3.33)), low HDL (OR:1.83 (1.03-3.27)), high triglycerides (OR:1.48 (1.18-1.84)), elevated ALT (OR:1.23 (1.16-1.31)) and hyper ferritinemia (OR:1.05 (1.03-1.07). Two factors were associated with AF: high BMI (OR:1.23 (1.07-1.42), p=0.005, and elevated AST (OR:1.03 (1.01-1.05), p=0.001).Using MRI-PDFF as a reference, CAP (best cut-off 280 dB/m) had good accuracy (0.86 (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 third of cases and around 10% have AF. The CAP technique is accurate for screening steatosis in this population.

Key words: HIV, NAFLD, risk factors, steatosis, fibrosis

Introduction

Nonalcoholic fatty liver disease (NAFLD) encompasses a spectrum of conditions ranging from simple fatty liver (non-alcoholic fatty liver), to non-alcoholic steatohepatitis (NASH), liver fibrosis, cirrhosis and hepatocellular carcinoma.[1] Due to the global spread of obesity and type 2 diabetes, NAFLD is now the commonest 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 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 half of PLWH are more than 50 years with a high prevalence of age-related comorbidities[6]. Globally, the metabolic syndrome (MetS) affects 17% to 31% of PLWH[11] and, as a consequence, NAFLD in PLWH has now become a growing concern[7]. 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[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 cut-off for the use of 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 non-invasive method for the diagnosis of AF[18], we aimed to assess i. the prevalence, severity and risk

126 factors of liver steatosis and AF in moninfected PLWH at risk of NAFLD and ii. the performance of the
127 CAP technique and its best cut-off for the diagnosis of moderate-to-severe steatosis in this population.
128

129 **Patients and methods**

130 **Study population**

131 ECHAM (European Cohort on HIV, Aging and Metabolic liver disease) is a multicenter European study
132 (7 centers: Belgium (n=1), France (n=2) and Germany (n=4)). Between March 2014 and November
133 2015, HIV-1 infected individuals over 40 years, receiving ART for at least 5 years with HIV viral load
134 <400 copies/mL and CD4-T cell count >100/mm^3, were invited to participate to the study if they met at
135 least one following criteria: 1- MetS defined by the 2009 international criteria[19] (Group 1), 2- persistently
136 elevated liver enzymes defined by transaminases ≥1.5 upper limit of normal (ULN=35 IU/ml) and/or
137 gammaglutamyltransferase (GGT) level ≥2ULN (ULN=60 IU/L) on two blood samples within at least a
138 three-month interval (Group 2), or 3- clinical lipodystrophy as previously described[20] (Group 3).

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

148 **Demographic and clinical data**

Demographic (ethnicity), epidemiological (smoking habit, alcohol consumption, HIV transmission, year of HIV diagnosis, duration of cumulative exposure to ARV, year of ARV initiation) and clinical (BMI, waist and hip circumference, type of ARV exposure, antidiabetic, antihypertensive and hypolipidemic drugs); data were collected at enrolment in standardized electronic forms.

Biochemical measurement

Blood samples were collected after a 12-hour overnight fast for determination of liver enzymes, glucose, cholesterol, triglycerides (TG) 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].

Serum adipokines measurement

Measurement of serum adipokines was centralized in the department of biochemistry and hormonology (Tenon hospital, Paris, France): Leptin, and high sensitivity (hs) IL-6 were measured using an enzyme-linked immunosorbent assay (ELISA) (Quantikine R&D Systems, Oxford, UK). Serum adiponectin was measured by ELISA (ALPCO Salem, NH, USA) and high-sensitivity C-reactive protein (hsCRP) 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, USA) 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 EASL guidelines[18] and which excellent performance

was confirmed in our population using liver histology as a reference[22]. We used an MRI-PDFF cut-off 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 (FF) using a dedicated software. All machines included In Phase (IP) and Out of Phase (OP) T1 imaging (T1 Gradient Echo sequences with multiple echoes and T2* relaxometry). FF calculation in IP and OP were standardised within the study centres. For quality control, randomly selected MRI-PDFF reports were reviewed by a single highly experienced radiologist (YM) 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 ~~trained~~ 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 ≥7.1kPa[25]. FIB-4 and aspartate-aminotransferase-to-platelet ratio index (APRI) were calculated as previously described[18]. Following the 2021 EASL recommendations on the use of non-invasive markers, we applied a cut-off 9.6kPa to detect advanced liver fibrosis[18].

Statistical analysis

The patients' characteristics were described, in the entire group and according to their inclusion criteria using median and interquartile range (25^{th}-75^{th} 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 Chi-square test or Fisher's exact test 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 <0.20 in the univariable analysis were retained for the multivariable analyses. Because of 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 multiple imputation approach. On each dataset, we generated 100 bootstrap samples. On each of the 500 samples, a backward selection technique (alpha=0.05) were applied and all factors that were selected in more than 75% of the models were retained.

Nonparametric 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 AUROC between 0.80-0.90 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 cut-off values for CAP and FLI were selected to maximize the sum of sensitivity and specificity.

Results

Study population

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 HBP (43% vs 65%, p=0.006) and ALT level (42.5 (32-65) versus 34 (24-50) IU/L, p=0.018)). Analysed participants were mainly male (n=340, 85%), median age 55 years (IQR: 50-61) and median BMI 27.0 kg/m^2 (23.6-28.7). All participants had controlled HIV-1 infection with a plasmatic HIV-1 RNA <50 copies/mL -except for 11 (3%) patients, a

median CD4-T cell count of 630/mm^3 (510-832) and a median duration of cART exposure of 16 years (11-19). Most of the participants were enrolled because of MetS (group1, 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 (76.3%) patients 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 three subgroups according to the underlying medical condition that qualified them for inclusion into the study. The participants' characteristics significantly differed between the three groups. As expected, patients with MetS had higher anthropometric parameters and metabolic disorders as compared to the two other groups.

All participants except 2 were assessed for PNPLA3 and TM66SF2 gene polymorphisms. PNPLA3 rs738409 C/C (230 (57.5%)) and TM66SF2 rs58542926 C/C (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 a MRI-PDFF ≥5% and 145 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<0.0001 (Table 1).

As compared to patients with MRI-PDFF<10%, patients with MRI-PDFF ≥10% had a higher proportion of metabolic disorders (MetS: 79.3% *versus* 59.9%, p<0.001), higher CD4-T cell (720/mm^3 (555-903) *vs* 597 (488-772) /mm^3, p<0.0001), higher liver transaminases (ALT (49 IU/L (34-96) *vs* 29 IU/L n7.80) *vs* 5.10 (4.30-6.30), p<0.001) and a higher proportion of AF (16/109 (14.7%) *vs* 9/194 (4.6%) p=0.002).

Patients with MRI-PDFF ≥10% carried more frequently a single nucleotide polymorphism of PNLAP3 genes compared to patients with MRI-PDFF<10% (75/144 *vs* 95/256, p=0.0005) (Suppl.Table 1).

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

Prevalence and risk factors of advanced liver fibrosis (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 to patients with valid LSM (data not shown).

Amongst 194 patients with valid LSM, 22 (11.3%) had a LSM ≥9.6 kPa suggesting AF including 11 (5.7%) patients with LSM ≥12.5 kPa suggestive of cirrhosis. As compared to 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 genetic profile (PNPLA3 and TM6SF2) was similar (Suppl.Table 2).

Multivariable analysis identified two factors associated with AF: high BMI (OR: 1.23 (1.07-1.42), p=0.005) and high AST level (OR: 1.02 (1.01-1.05), p=0.001) (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 at 0.862 (0.823-0.901) and a best cut-off 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 at 0.692 (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 (i.e aged over 40 years, exposed to cART for more than

5 years with a MetS or persistently elevated liver enzymes or clinical lipodystrophy). We selected this population, as now recommended by the EACS guidelines[17], in order 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 liver stiffness measurement, 11% had advanced fibrosis including 6% with cirrhosis.

Not surprisingly, patients with MetS had the highest prevalence of NAFLD (71%) whilst 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 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 (e.g., 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 of moderate-to-severe liver steatosis measured by CT-scan in consecutive PLWH.[15] Other studies, however, did not report association between exposure to NRTI or protease inhibitors (PIs) and liver steatosis.[11]

As described in non-HIV patients[26], we found an association between PNLPL3A variants and the presence of moderate-to-severe liver steatosis. In monoinfected PLWH, only one 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 HIV-NAFLD patients, has been assessed in only one study conducted in 70 HIV-monoinfected subjects at risk of NAFLD[27]. As recently mentioned[6,17] the best cut-off 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 cut-off of 280 dB/m, close to the 285 cut-off proposed by Ajmera et al. and the 275 cut-off recently proposed by the EASL in non-HIV subjects with NAFLD[18].

The high rate of liver steatosis found in our study may be alarming. Indeed, the results of a longitudinal study conducted in Canada in monoinfected-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 advanced liver fibrosis 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 analysed mainly males and well-controlled HIV on long-term ART, whose profile is not representative of the general HIV-monoinfected 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-monoinfected 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 (cut-off 248 dB/m)[14] while a recent Danish analysis using CT-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 since its diagnosis requires liver biopsy, an invasive procedure, not widely accepted by the patients[22].

In conclusion, when applying the EACS recommendations on the largest multicentre European cohort of 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 advanced fibrosis (11%) is high. One third had moderate-to-severe liver steatosis (MRI-PDFF≥10%), which could be easily identified using CAP (best cut-off 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-monoinfected, 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 NALD as observed in non-HIV subjects.

Legends

Figure 1: study flow diagram

Figure 2: Performance of CAP and FLI for the diagnosis of moderate to severe liver steatosis using MRI -PDFF as reference

Table 1. Characteristics of the study population

Table 2: Factors associated with moderate to severe liver steatosis (MRI-PDFF >10%)

Table 3: Factors associated with advanced liver fibrosis as defined by LSM≥ 9.6kPa

Table 4: Performance of CAP method and Fatty Liver Index (FLI) for the diagnosis of liver steatosis using MRI- PDFF as a gold standard.

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Authors' contribution: ML, GB, PI, DC, JC and LA have designed the study. ML is the recipient of the funding and the chief investigator of the study; with the support of HR, project manager of the study, she was responsible of the study procedure and its compliance to ethic regulations.

PMG,PC,MAV,VK,CN,SDW,GB,JVL,JSW,AH,SM,LS,VR,AB,PI were in charge of patient recruitment. YM was in charge of the MRI-PDFF calibration and analysis. PB and JS were responsible for the histopathological analysis. JPB, SF, JC were in charge of the measurement of adipokine levels and GB and MVS of the genetic analysis. LA and DC are responsible of the data management and statistical analysis. ML,PI,LA,DC and JC drafted the manuscript. All authors read it and approved it.

Data availability: the datasets generated during the ECHAM study and analysed for the current study are available from the corresponding author and the data management team (LA and DC) on reasonable request.

	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 (years), median (IQR)	55 (50-61)	57 (52-63)	52 (46-57)	52 (49-56)	<0.001
Male, n (%)	340 (85)	227 (84)	34 (94)	79 (81)	0.180
Non African ethnicity, n (%)	316 (79)	211 (78)	32 (89)	73 (75)	0.322
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, years, years	19 (14-24)	19 (13-23)	18 (10-21)	20 (16-26)	0.137
~~**Year of HIV diagnosis (IQR)**~~	~~1995 (1991-2001)~~	~~1995 (1991-2001)~~	~~1997 (1994-2005)~~	~~1995 (1989-1999)~~	~~0.025~~
~~**Year of ART initiation (IQR)**~~	~~1998 (1995-2002)~~	~~1998 (1995-2002)~~	~~2001 (1997-2007)~~	~~1997 (1995-1999)~~	~~0.011~~
Time since ART initiation,					

years					
Duration of the cumulative exposure to ART, years (IQR)	16 (11-19)	16 (12-19)	13 (7-17)	16 (13-19)	0.008
HIV RNA >50 cp/mL, n (%)	11 (3)	8 (3)	0 (0)	3 (3)	0.572
Nadir CD4, median (IQR)	184 (84-266)	179 (78-259)	213 (119-277)	194 (93-280)	0.129
CD4 /mm³, median, (IQR)	630 (510-832)	616 (498-814)	612 (503-844)	643 (536-882)	0.801
CD4/CD8 ratio, median (IQR)	0.86 (0.60-1.18)	0.82 (0.55-1.09)	0.92 (0.67-1.26)	0.98 (0.70-1.29)	0.002
Metabolic parameters					
BMI, kg/m², median (IQR)	27.0 (23.6-28.7)	26.8 (24.6-29.2)	24.7 (23.4-26.5)	23.7 (21.6-27.0)	<0.001
Obesity (BMI≥30 kg/m²), n (%)	71 (18)	58 (22)	3 (8)	10 (10)	<0.001
Waist circumference, cm, median (IQR)	98 (92-105)	101 (95-106)	94 (92-99)	91 (86-99)	<0.001
Male	98 (92-104)	100 (96-107)	94 (91-98)	90 (85-97)	<0.001
Female	101 (93-105)	101 (94-105)	103 (94-111)	99 (92-103)	0.774
Elevated BP (Systolic > 140 and/or diastolic >90) and/or treated HBP, n (%)	262 (65)	203 (75)	14 (39)	45 (46)	<0.001
Impaired fasting glycemia (≥ 5.6 mmol/L) and/or anti-diabetic treatment, n (%)	151 (38)	136 (51)	6 (17)	9 (9)	<0.001

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)	<0.001
Hypertriglyceridemia (triglycerides >1.7 mmol/L or treatment) n (%)	192 (48)	157 (58)	7 (19)	28 (29)	<0.001
HDL cholesterol levels, (mmol/L), median (IQR)	1.17 (0.91-1.40)	1.10 (0.90-1.30)	1.30 (1.20-1.77)	1.29 (1-1.58)	<0.001
Low HDL (<1 mmol/L for men and <1.3 mmol/L for women), n (%)	255 (63)	210 (78)	8 (22)	37 (38)	<0.001
HOMA, median (IQR)	2.69 (1.73-4.61)	3.21 (2.07-5.64)	2.44 (1.46-4.22)	1.94 (1.32-2.56)	<0.001
HOMA ≥ 2.5, n (%)	218 (54)	175 (65)	17 (47)	26 (27)	<0.001
Glucose (mmol/L), median (IQR)	5.3 (4.8-6.0)	5.5 (4.9-6.3)	5.1 (4.8-5.4)	4.9 (4.5-5.4)	<0.001
Leptin (microg/L), media (IQR)	5.2 (2.7-10.6)	6.1 (3.3-12.3)	4.3 (1.9-7.4)	3.5 (1.7-7.4)	<0.001
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)	<0.001
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)	0.554
Adiponectin (mg/L), median (IQR)	2.8 (1.9–4.0)	2.7 (1.8-3.8)	3.3 (1.7-4.7)	3.0 (2.2-4.6)	0.078
Leptin/adiponectin ratio, median (IQR)	2.1 (1.0-4.1)	2.5 (1.2-4.3)	1.4 (0.6-2.9)	1.2 (0.6-2.9)	<0.001

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)	<0.001
hsIL6 (pg/ml), median (IQR)	1.7 (1.1–3.0)	1.9 (1.3-3.1)	1.5 (0.9-2.3)	1.4 (1.0-2.7)	0.0001
Genetic polymorphisms (n=400)					
PNPLA3 rs738409					0.096
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					0.246
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), median (IQR)	34 (24-50)	35 (24-53)	62 (43-91)	28 (19-35)	<0.001
AST (IU/L), median (IQR)	29 (23-37)	30 (23-40)	38 (31-54)	27 (21-32)	<0.001
GGT (IU/L), median (IQR)	48 (29-81)	51 (31-83)	85 (54-159)	34 (24-55)	<0.001
Platelet count (/mm3), median (IQR)	213 (178-253)	210 (175-253)	203 (177-235)	220 (184-258)	0.289
Median MRI-PDFF, % (IQR)	7.0 (2.40-12.0)	7.73 (3.90-13.90)	8.05 (2.98-15.00)	3.33 (0-7.15)	<0.001
FF ≥5% on MRI-PDFF	257 (64)	191 (71)	24 (67)	42 (43)	<0.001
FF ≥10% n (%)	145 (36)	115 (43)	16 (44)	14 (14)	<0.001
CAP dB/m. median (IQR) (n=356)	260 (222 – 307)	267 (234-316)	261 (227-303)	228 (200-266)	<0.001

FLI, median (IQR)	67.2 (43.9-84.2)	74.2 (55.5-87.9)	58.5 (46.4-71.8)	42.4 (25.6-58.3)	<0.001
APRI, median (IQR)	0.36 (0.26-0.53)	0.38 (0.26-0.57)	0.45 (0.35-0.69)	0.30 (0.23-0.44)	<0.001
Fibroscan, median (IQR) 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)	<0.001
LSM <8 kPa, n (%) n=303 ***(193/32/78)***	251/303 (82.8%)	146/193 (75.7)	30/32 (93.8)	75/78 (96.2)	<0.001
LSM **≥12.5 kPa, n (%) n=303** ***(193/32/78)***	13/303 (4.3)	13/193 (6.7)	0 (0)	0 (0)	0.021

Table 1. Characteristics of the ECHAM study population (n=402)

Categorical variables are expressed as raw numbers and percentages (%), continuous variables are reported as median and 25th-75th percentiles. Abbreviations: BMI: body mass index; FF: fat fraction MetS: metabolic syndrome; LFT: liver function test, HIV: humqn immunodeficiency virus; ART: antiretroviral therapy; CD: cluster of differentiation; BP: blood pressure; HDL: high-density lipoprotein; LDL: low-density lipoprotein; hsCRP: high-sensity C-reactive protein; hsIL: high-sensity interleukin; PNPLA: Patatin-like phospholipase; ALT: alanine aminotransferase, AST: aspartate aminotransferase;LE: liver enzymes, LipoD: lipodystrophy, IQR: interquartile range; FLI: Fatty Liver Index; HOMA: Homeostasis Model Assessment Method index was defined as follows: fasting insulin (mU/L) x fasting plasma glucose (mmol/L)/22.5 24. Insulin resistance was defined by a HOMA index ≥2.5.

Variable		Univariable analysis		Multivariable analysis	
		OR (CI 95%)	p-value	OR (CI 95%)	p-value
ALT level, UI/L, per 5 units		1.23 (1.17-1.30)	<0.001	1.23 (1.16-1.31)	<0.001
CD4 T cell count per log2 unit		3.22 (1.83-5.65)	<0.001	4.04 (1.92-8.51)	<0.001
Ferritin (ng/mL), per 10 units		1.06 (1.04-1.08)	<0.001	1.05 (1.03-1.07)	<0.001
Triglycerides, mmol/L, per unit		1.54 (1.30-1.84)	<0.001	1.48 (1.18-1.84)	0.001
Leptin (µg/L)	<3.2	1		1	
	≥3.2	2.68 (1.66-4.31)	<0.001	2.12 (1.14-3.93)	0.017
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)	<0.001	1.83 (1.03-3.27)	0.041
PNPLA3 rs738409	C/C	1		1	
	Not C/C	1.84 (1.22-2.79)	0.004	1.92 (1.11-3.33)	0.020

Table 2: Factors associated with moderate to severe liver steatosis (MRI-PDFF ≥10%)

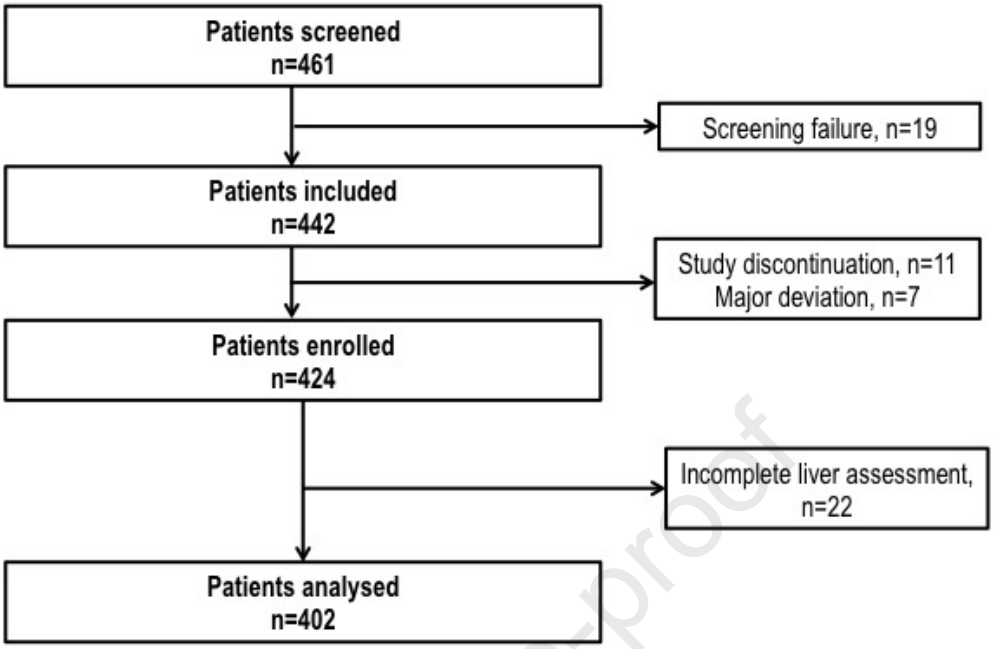
Variable	Univariable analysis	Multivariable analysis	

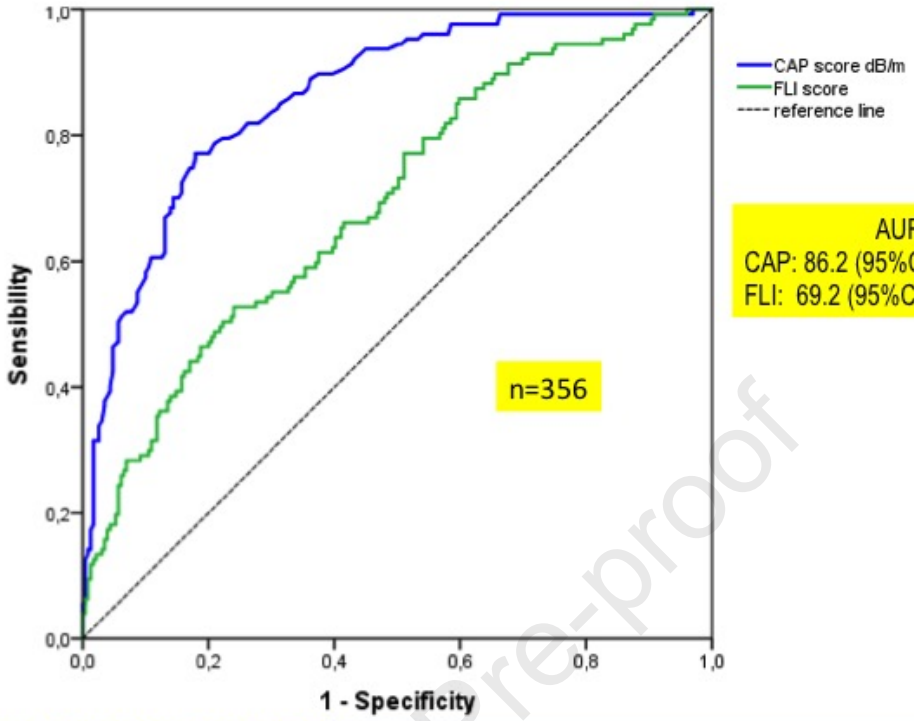
	OR (95% CI)	p-value	OR (95% CI)	P value
BMI (kg/m2)	1.180 (1.08-1.29)	<0.001	1.23 (1.07-1.42)	0.005
AST (IU/L)	1.03 (1.01-1.05)	<0.001	1.02 (1.01-1.05)	0.001

Table 3: Factors associated with advanced liver fibrosis as defined by LSM ≥ 9.6kPa in patients with MRI-PDFF ≥ 5%.

	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)
Cut-off	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

Table 4: Performance of CAP method and Fatty Liver Index (FLI) for the diagnosis of liver steatosis using MRI- PDFF as a gold standard.





AUROC
CAP: 86.2 (95%CI: 82.3 – 90.1)
FLI: 69.2 (95%CI: 63.6 – 74.9)

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

What You Need to Know:

Background: Aging HIV-monoinfected patients with metabolic syndrome, abnormal liver enzymes, or lipodystrophy are considered at risk of NAFLD but the severity and risk factors of liver steatosis and fibrosis remain debated in this population.

Findings: moderate-to-severe steatosis (MRI-PDFF≥10%) (36%) and advanced fibrosis (Fibroscan≥9.6kPa) (11%), are frequent. High BMI and AST are associated with advanced fibrosis.

Implications for the patients: Aging HIV-monoinfected patients metabolic disorders or abnormal liver enzymes should be systematically screened for liver steatosis and fibrosis.

The CAP technique (best cut-off 280 dB/m) can be used to identify patients with moderate-to-severe steatosis.