DOI: 10.1111/hiv.12799
HIV Medicine (2020), **21**, 96–108

ORIGINAL RESEARCH

Application of guidelines for the management of nonalcoholic fatty liver disease in three prospective cohorts of HIV-monoinfected patients*

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Objectives

Current guidelines recommend use of a diagnostic algorithm to assess disease severity in cases of suspected nonalcoholic fatty liver disease (NAFLD). We applied this algorithm to HIV-monoinfected patients.

Methods

We analysed three prospective screening programmes for NAFLD carried out in the following cohorts: the Liver Disease in HIV (LIVEHIV) cohort in Montreal, the Modena HIV Metabolic Clinic (MHMC) cohort and the Liver Pathologies in HIV in Palermo (LHivPa) cohort. In the LIVEHIV and LHivPa cohorts, NAFLD was diagnosed if the controlled attenuation parameter (CAP) was $\geq$ 248 dB/m; in the MHMC cohort, it was diagnosed if the liver/spleen Hounsfield unit (HU) ratio on abdominal computerized tomography scan was < 1.1. Medium/high-risk fibrosis category was defined as fibrosis-4 (FIB-4) $\geq$ 1.30. Patients requiring specialist referral to hepatology were defined as either having NAFLD and being in the medium/high-risk fibrosis category or having elevated alanine aminotransferase (ALT).

Results

A total of 1534 HIV-infected adults without significant alcohol intake or viral hepatitis coinfection were included in the study. Of these, 313 (20.4%) patients had the metabolic comorbidities (obesity and/or diabetes) required for entry in the diagnostic algorithm. Among these patients, 123 (39.3%) required specialist referral to hepatology, according to guidelines. A total of 1062 patients with extended metabolic comorbidities (any among obesity, diabetes, hypertension and dyslipidaemia) represented most of the cases of NAFLD (79%), elevated ALT (75.9%) and medium/high-risk fibrosis category (75.4%). When the algorithm was extended to these patients, it was found that 341 (32.1%) would require specialist referral to hepatology.

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Part of this work was presented at the Canadian Association for HIV Research, 26–29 April 2018, Vancouver, Canada, and the International Liver Congress, 10–14 April 2019, Vienna, Austria.

Conclusions

According to current guidelines, one in five HIV-monoinfected patients should undergo detailed assessment for NAFLD and disease severity. Moreover, one in ten should be referred to hepatology. Expansion of the algorithm to patients with any metabolic comorbidities may be considered.

Keywords: fibrosis-4, guidelines, HIV monoinfection, nonalcoholic fatty liver disease, specialist referral

Accepted 2 August 2019

Introduction

In Western countries, people infected with HIV now live longer thanks to the widespread use of antiretroviral treatment (ART) [1]. In this newly aging HIV-infected population, liver cirrhosis has become a leading cause of death [2]. In addition to coinfections with the hepatitis B (HBV) and C (HCV) viruses, nonalcoholic fatty liver disease (NAFLD) is an emerging concern for people aging with HIV infection [3]. NAFLD is characterized by excessive hepatic fat accumulation, defined as the presence of steatosis in > 5% of hepatocytes in the absence of other causes of liver disease. NAFLD is the most frequent hepatic disease in Western countries. Nonalcoholic steatohepatitis (NASH) is the progressive form of the disease characterized by liver fibrosis leading to cirrhosis and related complications [4]. NASH has become the second most common indication for liver transplantation in North America and is projected to become the leading indication in the next 10–20 years [5]. Furthermore, NASH is the fastest rising cause of hepatocellular carcinoma (HCC), the second leading cause of cancer-related death in the world [6]. HIV-infected patients are at higher risk of NAFLD than the general population as a result of multiple cofactors, including lifelong use of ART, HIV itself, host factors and highly prevalent metabolic comorbidities [7,8]. The reported prevalence of NAFLD ranges from to 13% to 65% in HIV-monoinfected patients [3,9–13]. Moreover, NASH and significant liver fibrosis may be at least twice as frequent in HIV-monoinfected patients as in the general population [14–18].

Recent guidelines from the European Association for the Study of the Liver (EASL) recommend use of a diagnostic algorithm to assess and monitor disease severity in the presence of suspected NAFLD and metabolic risk factors [19]. This stepwise algorithm is used to screen for NAFLD in order to define subsequent follow-up strategies and identify patients in need of specialist referral to hepatology, defined as those with elevated liver enzymes or the presence of NAFLD with medium/high risk of liver fibrosis as determined using serum biomarkers, such as fibrosis-4 (FIB-4) score. A similar pathway has been recommended by the European AIDS Clinical Society (EACS) [20]. Thus far, these guidelines have not been applied to HIV-monoinfected patients, a population potentially at higher risk for NAFLD.

The aim of this study was to apply the diagnostic algorithm recommended by EASL and EACS guidelines to assess and monitor disease severity in the presence of suspected NAFLD and metabolic comorbidities in three large cohorts of HIV-monoinfected patients.

Methods

Study design and population

We conducted a retrospective analysis of the Liver Disease in HIV (LIVEHIV), Modena HIV Metabolic Clinic (MHMC) and Liver Pathologies in HIV in Palermo (LHivPa) cohorts, which are three prospectively maintained cohorts of HIV-infected individuals [14,21,22]. Those enrolled in the LIVEHIV Cohort, which was established in September 2013 at McGill University Health Centre (MUHC) in Montreal, participate in a prospective routine screening programme for NAFLD and liver fibrosis. Consecutive patients undergo screening for NAFLD and liver fibrosis by transient elastography (TE) with the associated software controlled attenuation parameter (CAP) (Fibroscan®, Echosens, Paris, France). The MHMC cohort was initiated in January 2004 to assess longitudinal metabolic changes among people living with HIV. Patients undergo annual comprehensive assessments in multiple domains, including a computed tomography (CT) scan, measurement of metabolic and endocrinological variables, bone mineral density and organ function, and assessment of social factors. The LHivPa cohort was initiated in 2011 at the Infectious Diseases Outpatient Clinic of the 'Paolo Giaccone' University Hospital in Palermo. All the patients undergo a comprehensive evaluation including recording of demographic characteristics (age, race, gender, smoking, alcohol intake, comorbidities and medical treatment, including ART regimen), data on HIV infection (nadir CD4 count, date of HIV diagnosis and date of ART initiation) and laboratory data. Metabolic assessment with physical and biochemical parameters is conducted at least annually. Since January 2017, patients

have undergone screening for NAFLD and liver fibrosis by TE with CAP.

Until December 2018, we included all consecutive individual patients with HIV infection [as documented by positive enzyme-linked immunosorbent assay (ELISA) with western blot confirmation] aged ≥ 18 years with availability of clinical and biochemical parameters included in the EASL and EACS algorithm. Exclusion criteria were: (1) positivity for HCV antibody or HBV surface antigen, (2) evidence of other liver diseases (autoimmune hepatitis, primary sclerosing cholangitis, primary biliary cholangitis, haemochromatosis and Wilson's disease), (3) significant alcohol intake, defined as an Alcohol Use Disorders Identification Test (AUDIT-C) questionnaire score ≥ 4 for men and ≥ 3 for women [23], (4) a history of HCC, (5) liver transplantation and (6) only for the LIVEHIV and LHivPa cohorts, contraindications to TE examination (pregnancy or pacemaker insertion), failure of TE examination or unreliable measurement. All participants provided informed written consent. The Research Ethics Board of the Research Institute of MUHC (study code 14-182-BMD), University of Modena and Reggio Emilia (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.

Outcome measures

The purpose of this study was to apply EASL and EACS guidelines on NAFLD to the LIVEHIV, MHMC and LHivPa cohorts in order to estimate the need for specialist referral to hepatology. The decisional algorithm from those guidelines proposes that patients with obesity and/or diabetes (obesity/diabetes) first be categorized based on the presence/absence of NAFLD, then subsequently be categorized based on the presence or absence of elevated liver enzymes and fibrosis category (low versus medium/high), determined using serum fibrosis biomarkers [19,20].

The primary study outcome was estimation of the need for specialist referral to hepatology, defined as alanine aminotransferase (ALT) > upper limit of normal (ULN; 45 IU/L in the LIVEHIV cohort; 40 IU/L in the MHMC cohort; 41 IU/L in men and 31 IU/L in women in the LHivPa cohort) or NAFLD with medium/high-risk fibrosis category, as per the guidelines. NAFLD was defined as CAP ≥ 248 dB/m [11,24] in the LIVEHIV and LHivPa cohorts and as liver/spleen Hounsfield unit (HU) ratio < 1.1 on CT scan in the MHMC cohort [25,26]. In all cohorts, medium/high fibrosis category was defined as FIB-4 value ≥ 1.30 [27].

The secondary study outcome was optimization of the decisional algorithm in the specific setting of HIV infection. For this purpose, we analysed the proportion of patients with obesity/diabetes and with extended metabolic comorbidities (any among obesity, diabetes, hypertension and dyslipidaemia) among those with NAFLD, elevated ALT and FIB-4 ≥ 1.30.

Clinical and biological parameters

Clinical and biochemical data were collected within 3 months from the TE examination or the CT scan. ART drugs were classified as: nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs) and integrase inhibitors. HIV viral load was assessed using the Roche Cobas Amplicor assay (Roche Diagnostics, Hoffmann-La Roche Ltd., GE Medical Systems, Milwaukee, WI, USA; lower limit of detection 50 HIV-1 RNA copies/mL). The simple biomarker FIB-4 was also calculated as follows: [age (years) × AST]/[platelet count (× 10^9 cells/L) × $(ALT)^{1/2}$], where AST is aspartate aminotransferase [28]. Dyslipidaemia was defined as either elevated triglycerides (> 1.7 mmol/L) or low high-density lipoprotein (HDL) cholesterol (< 1.0 mmol/L).

Transient elastography examination with CAP in the LIVEHIV and LHivPa cohorts

TE examinations were performed by two experienced operators in patients who had been fasting for 4 h [29]. The standard M probe was used in all patients. The XL probe was used in cases of failure with the M probe. Examinations with no successful measurements after at least 10 attempts were deemed failures. The following criteria were applied to define the result of TE as reliable: at least 10 valid liver stiffness measurements (LSMs) and an interquartile range (IQR) < 30% of the median. Patients with known risk factors for false positive measurement were excluded [29]. Significant liver fibrosis (stage F2–4) and advanced liver disease, requiring hepatological surveillance for end-stage liver complications, were defined as LSM ≥ 7.1 and ≥ 10 kPa, respectively [30–32].

Computed tomography scan in the MHMC cohort

CT examinations were performed with a 64-multislice CT (LightSpeed VCT; General Electric Medical System). Hepatic and splenic attenuation values were measured by non-contrast CT using circular region-of-interest cursors in the two organs. Measurements were manually obtained in regions of uniform parenchyma attenuation, with care taken to avoid vessels and other areas that might give

spuriously increased or decreased measurements. Measurements from each point of the liver were averaged. The Liver:Spleen (L:S) ratio was calculated as follows: average attenuation value of liver (four points)/attenuation value of spleen [22,25,26].

Statistical analysis

We compared characteristics of participants by outcome status using Student's *t*-test or the Kruskal–Wallis test for continuous variables and Pearson's χ^2 or Fisher's exact test for categorical variables. Factors associated with the need for specialist referral to hepatology were determined using unadjusted and adjusted logistic regression models. We reported results as adjusted odds ratios (aORs) with 95% confidence interval (CIs). As a consequence of the cross-sectional nature of any such measured associations, we made no causal claims on the basis of these analyses. All adjusted regression models included covariates that were determined *a priori* to be clinically important. To establish which of the models had the best goodness-of-fit measure, the corrected Akaike information criteria (AICs) and the Bayesian information criteria (BICs) were compared among the models. A lower AIC and/or BIC indicated a better fit. All tests were two-tailed and with a significance level of $\alpha = 0.05$. Statistical analysis was performed using STATA 13.1 (STATA Corp. LP, College Station, TX).

Results

After the exclusion criteria had been applied, 1534 HIV-monoinfected individuals were included in the study (Fig. 1). Table 1 reports the main demographic, clinical, biochemical and virological characteristics of the study population by cohort (LIVEHIV, MHMC and LHivPa). Patients in the LHivPa cohort were more likely to have NAFLD, while those in the MHMC cohort had higher FIB-4. Figure 2 depicts the proportion of patients with obesity/diabetes and with extended metabolic comorbidity (any among obesity, diabetes, hypertension and dyslipidaemia) among those with NAFLD, elevated ALT, FIB-4 $\geq$ 1.30 and, where available, LSM $\geq$ 10 kPa. Overall, patients with any metabolic comorbidities represented most of the cases of NAFLD (79%), elevated ALT (75.9%) and FIB-4 $\geq$ 1.30 (75.4%).

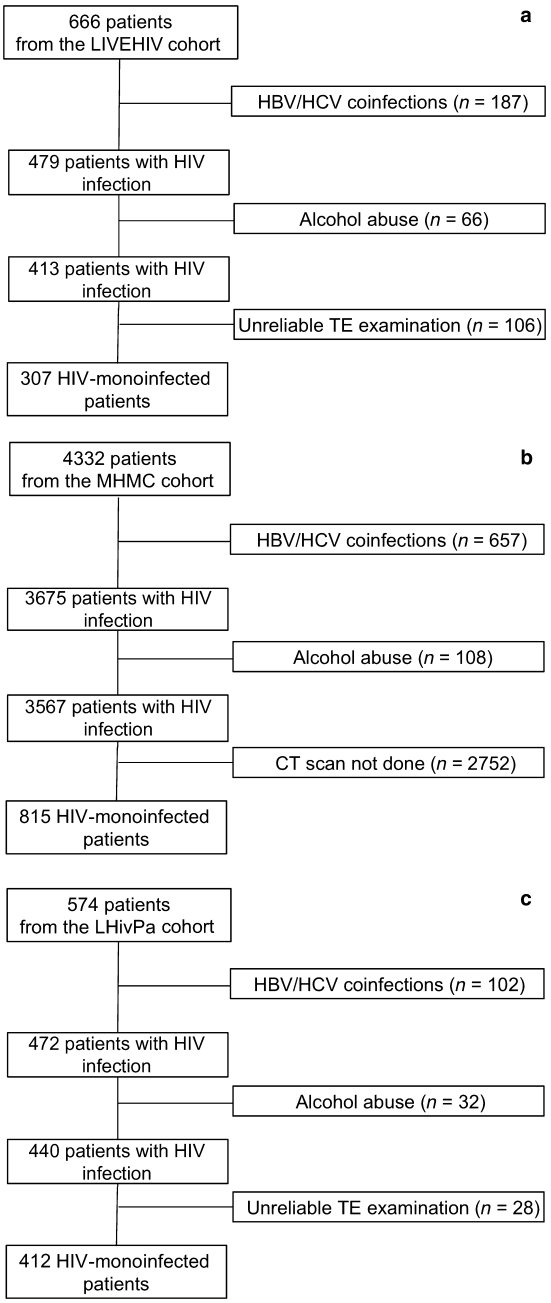

Fig. 1 Flow chart displaying the selection of study participants in (a) the Liver Disease in HIV (LIVEHIV) cohort, (b) the Modena HIV Metabolic Clinic (MHMC) cohort, and (c) the Liver Pathologies in HIV in Palermo (LHivPa) cohort. The transient elastography (TE) examination was considered reliable if the ratio of the interquartile range (IQR) to the median of the 10 measurements was no more than 30%. CT, computed tomography; HBV, hepatitis B virus; HCV, hepatitis C virus.

Application of the EASL and EACS algorithm for suspected NAFLD

Figure 3a depicts the diagnostic algorithm recommended by EASL and EACS to assess and monitor disease severity in the presence of suspected NAFLD applied to our pooled cohort of HIV-monoinfected patients. Obesity/diabetes was present in 313 (20.4%) patients, who

Table 1 Characteristics of the study population

	Whole study population (n = 1534)	LIVEHIV cohort (n = 307)	MHMC cohort (n = 815)	LHivPa cohort (n = 412)
Age (years)	49 (43–55)	49 (42–56)*	49 (45–54)*	48 (40–55)*
Male gender	1114 (72.7)	234 (76.5)	581 (71.3)	299 (72.6)
Ethnicity				
White/Caucasian	1291 (84.2)	127 (41.4)**	807 (99.0)**	357 (86.7)**
Black non-Hispanic	173 (11.3)	121 (39.4)**	1 (0.1)**	51 (12.4)**
BMI (kg/m^2)	24.1 (21.9–26.5)	25.1 (23.2–28.3)**	23.6 (21.3–25.8)**	24.2 (22.0–26.6)**
Obesity (BMI > 30)	130 (8.5)	47 (15.3)**	43 (5.3)**	40 (9.7)**
Diabetes	219 (14.3)	74 (24.1)*	122 (15.0)*	23 (5.6)**
Hypertension	534 (34.8)	56 (18.2)**	384 (47.1)**	94 (22.8)**
Active tobacco smoker	516 (33.6)	35 (11.4)**	300 (36.8)**	181 (43.9)**
MSM	560 (36.5)	115 (37.5)**	261 (32.0)**	184 (44.7)**
IDU[†]	254 (16.6)	11 (3.6)**	226 (27.7)**	17 (4.1)**
HIV infection duration (years)	16.0 (8.0–21.8)	12 (7–19)**	18.8 (13.7–23.3)**	10 (4–18)**
CD4 count (cells/μL)	633 (449–803)	695 (468–789)**	593 (437–774)**	666 (467–874)**
Undetectable HIV viral load (≤50 copies/mL)	1300 (84.7)	160 (52.1)**	758 (93.0)**	382 (92.7)**
Current ART regimen				
NRTIs	1313 (85.6)	281 (91.5)*	685 (84.0)*	347 (84.2)*
NNRTIs	678 (44.2)	188 (61.2)**	308 (37.8)**	182 (44.2)**
PIs	817 (53.3)	195 (63.5)**	463 (56.8)**	159 (38.6)**
Integrase inhibitors	543 (35.4)	94 (30.6)**	209 (25.6)**	240 (58.3)**
Dideoxynucleoside exposure[‡]	84 (7.5)	72 (23.5)	12 (1.5)	–
Platelets (10^9 cells/L)	215 (174–259)	203 (166–248)**	206 (162–247)**	240 (201–286)**
Total cholesterol (mmol/L)	4.8 (4.1–5.5)	4.6 (4.0–5.4)**	4.9 (4.2–5.7)**	4.6 (3.9–5.3)**
LDL cholesterol (mmol/L)	2.8 (2.3–3.5)	2.7 (2.2–3.4)**	3.0 (2.4–3.6)**	2.7 (2.1–3.2)**
HDL cholesterol (mmol/L)	1.2 (1.0–1.4)	1.1 (1.0–1.4)	1.2 (1.0–1.4)	1.2 (1.0–1.4)
Triglycerides (mmol/L)	1.4 (1.0–2.2)	1.3 (0.9–2.2)**	1.6 (1.1–2.4)**	1.2 (0.8–1.8)**
ALT (IU/L)	25 (18–38)	26 (20–35)**	28 (20–44)**	21 (15–29)**
AST (IU/L)	23 (19–30)	24 (20–30)**	25 (20–34)**	19 (16–23)**
NAFLD	514 (33.5)	106 (34.5)**	232 (28.5)**	176 (42.7)**
FIB-4	1.1 (0.8–1.5)	1.1 (0.8–1.5)**	1.2 (0.9–1.7)**	0.8 (0.6–1.2)**
LSM (kPa)[§]	4.9 (4.0–6.1)	4.9 (4.0–6.1)	–	4.8 (4.0–6.1)

ALT, alanine aminotransferase; ART, antiretroviral therapy; AST, aspartate aminotransferase; BMI, body mass index; FIB-4, fibrosis-4 score; HDL, high-density lipoprotein; IDU, injecting drug use; IU, international units; LDL, low-density lipoprotein; LHivPa, Liver Pathologies in HIV in Palermo; LIVEHIV, Liver Disease in HIV; LSM, liver stiffness measurement; MHMC, Modena HIV Metabolic Clinic; MSM, men who have sex with men; NAFLD, nonalcoholic fatty liver disease; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.
Continuous variables are expressed as median (interquartile range) and categorical variables as number (%).
The P-values refer to comparisons among the three centres using the Kruskal–Wallis test or χ^2 test.
*$P < 0.05$.
**$P < 0.001$.
[†]Patients in the MHMC cohort were more likely to be injecting drug users. They represent the first wave of the HIV infection epidemic in this risk group. The majority of them (90%) were former heroin addicts. Only a few were on methadone replacement therapy.
[‡]Available for LIVEHIV and MHMC cohorts only.
[§]Available in the LIVEHIV and LivHIVPa cohorts only.

entered the algorithm. Of these, 152 had NAFLD, giving a prevalence of 48.6%. Among patients with NAFLD, 86 (56.6%) were in need of specialist referral to hepatology. Among patients without NAFLD, 37 (23%) had elevated ALT and were in need of specialist referral to hepatology. Overall, 123 patients with obesity/diabetes required specialist referral to hepatology as per the EASL and EACS diagnostic algorithm, representing 8% of the whole patient population and 39.3% of those who entered the diagnostic algorithm. Among the other patients who entered the algorithm, 66 (21.1%) and 124 (39.6%) required follow-up every 2 years and every 3–5 years, respectively.

Figure 3b depicts the diagnostic algorithm when the entry criteria were expanded to patients with any metabolic comorbidities, which were present in 1062 (69.2%) cases. Of these, 406 had NAFLD, giving a prevalence of 38.2%. Among patients with NAFLD, 201 (49.5%) were in need of specialist referral to hepatology. Among patients without NAFLD, 140 (21.3%) had elevated ALT and were in need of specialist referral to hepatology. Overall, 341 patients with any metabolic comorbidities required specialist referral to hepatology as per the EASL and EACS diagnostic algorithm, representing 22.2% of the whole patient population and 32.1% of those who entered the diagnostic algorithm. Among the other patients who

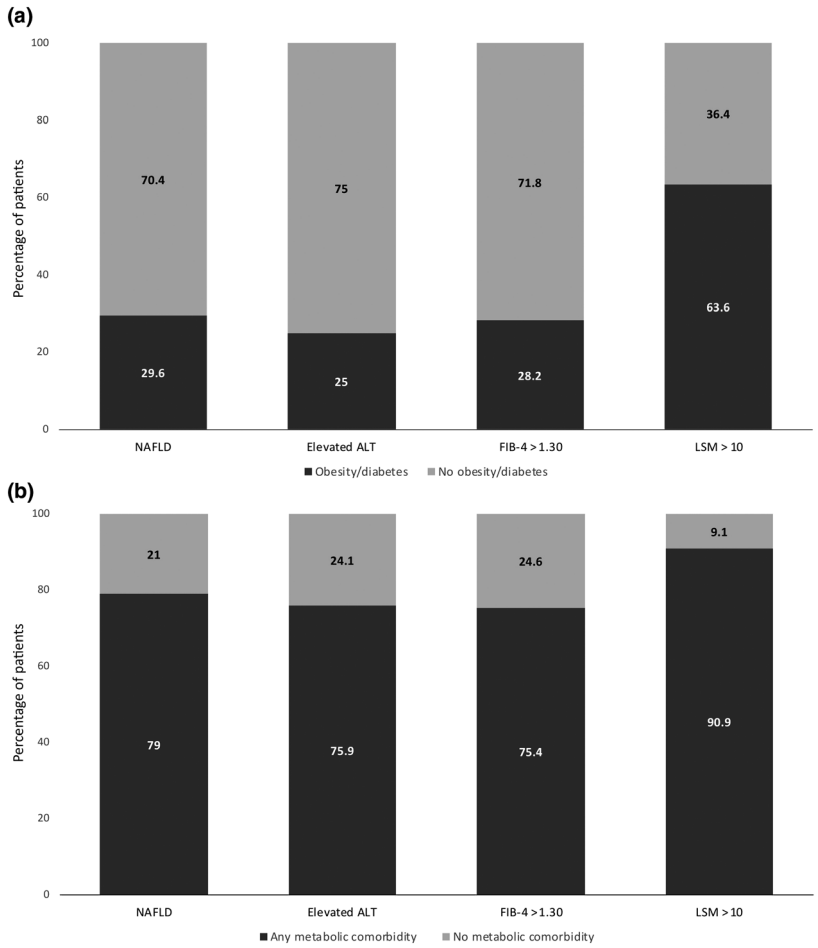

Fig. 2 (a) Proportion of patients with and without obesity/diabetes in those with nonalcoholic fatty liver disease (NAFLD), elevated alanine aminotransferase (ALT), fibrosis-4 (FIB-4) > 1.30 and liver stiffness measurement (LSM) > 10 kPa; (b) proportion of patients with and without any metabolic comorbidities in those with NAFLD, elevated ALT, FIB-4 > 1.30 and LSM > 10 kPa. LSM was available in the Liver Disease in HIV (LIVEHIV) and Liver Pathologies in HIV in Palermo (LivHIVPa) cohorts only.

entered the algorithm, 205 (19.3%) and 516 (48.6%) required follow-up every 2 years and every 3–5 years, respectively.

Specialist referral to hepatology

Table 2 reports the characteristics of patients with and without the need for specialist referral to hepatology and the related univariable analysis. When the entry criterion of the algorithm was obesity/diabetes, the need for specialist referral to hepatology was independently predicted by injecting drug use (IDU) (aOR 3.14; 95% CI 1.33–7.39; $P = 0.009$), while black ethnicity was protective (aOR 0.24; 95% CI 0.08–0.71; $P = 0.01$; Table 3). When the entry criterion of the algorithm was any metabolic comorbidities, the need for specialist referral to hepatology was independently predicted by male sex (aOR 2.34; 95% CI 1.51–3.62; $P < 0.001$), diabetes (aOR 1.78; 95% CI 1.21–2.61; $P = 0.003$), hypertension (aOR 1.44; 95% CI 1.02–2.04; $P = 0.038$) and IDU (aOR 2.57; 95% CI 1.75–3.79; $P < 0.001$), while black ethnicity was protective (aOR 0.24; 95% CI 0.11–0.56; $P = 0.001$; Table 3). These multivariable models had lower AIC and BIC values than the others, hence providing support for their choice. In the LIVEHIV and LHivPa cohorts, LSM in obese/diabetic patients with a need for specialist referral indicated significant liver fibrosis and advanced liver disease in 14 (32.6%) and eight (18.6%) cases, respectively (Fig. 3a). Sixteen patients (37.2%) had been enrolled in clinical trials, including trials of vitamin E treatment or ART switch. Eight patients (37.2%) had also undergone a liver biopsy. The mean liver biopsy length was

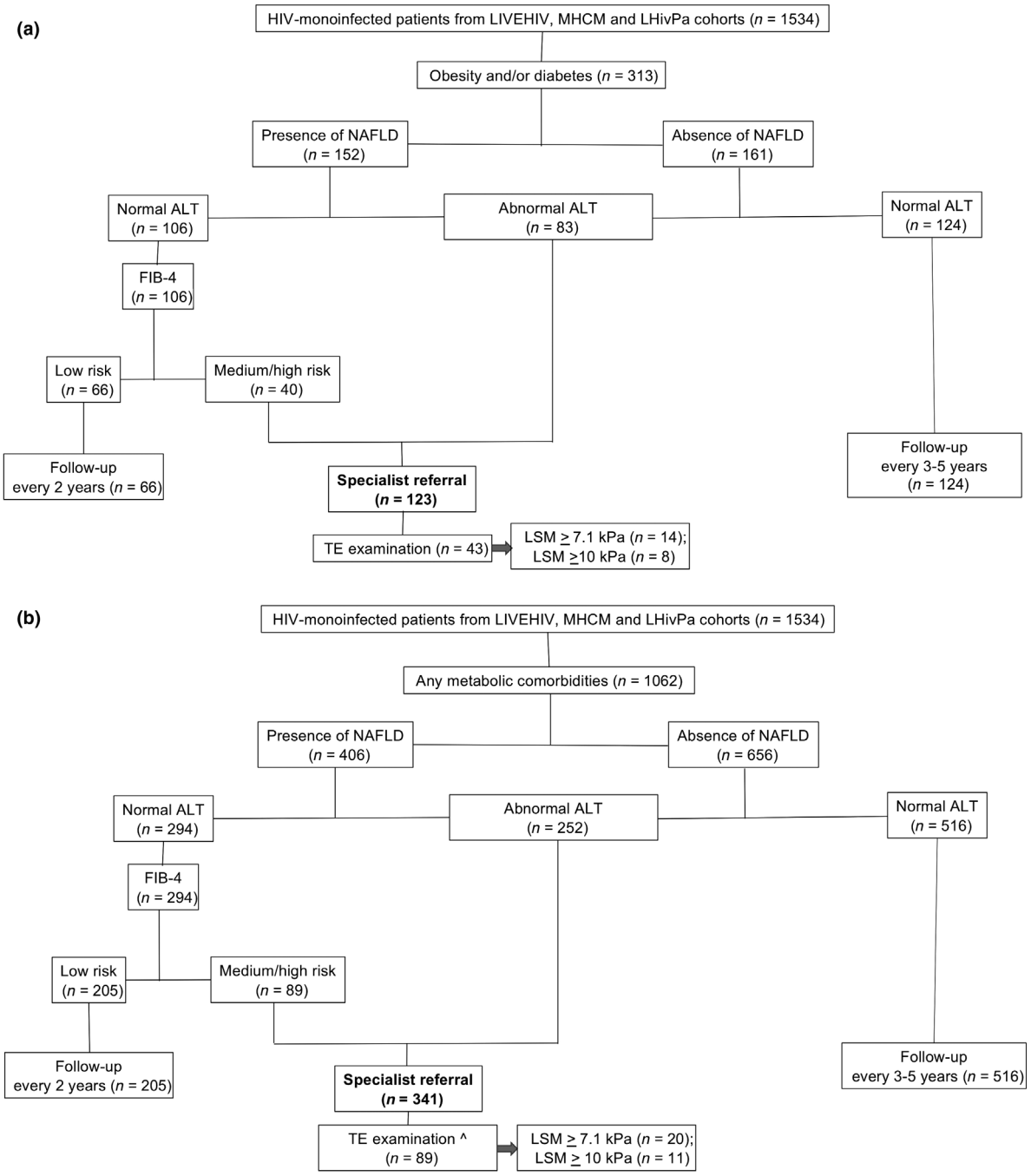

Fig. 3 European Association for the Study of the Liver (EASL)/European AIDS Clinical Society (EACS) diagnostic algorithm applied to 1534 HIV-monoinfected patients from the Liver Disease in HIV (LIVEHIV), Modena HIV Metabolic Clinic (MHMC) and Liver Pathologies in HIV in Palermo (LHivPa) cohorts and relative decisional tree. (a) The entry criterion was the presence of obesity and/or diabetes (n = 313). (b) The entry criterion was the presence of any metabolic comorbidities among obesity, diabetes, hypertension and dyslipidaemia (n = 1062). Transient elastography (TE) examination was available in the LIVEHIV and LivHIVPa cohorts only. ALT, alanine aminotransferase; FIB-4, fibrosis-4 score; LSM, liver stiffness measurement; NAFLD, nonalcoholic fatty liver disease.

18 ± 5 mm. NASH was present in all patients who underwent the biopsy. Significant liver fibrosis (stages F2–4) and cirrhosis (F4) were present in four (50%) and one (12.5%) cases, respectively [33]. Among patients who underwent a liver biopsy, one patient was listed for liver transplantation and was awaiting a graft. When the entry

criteria were expanded to patients with any metabolic comorbidities, LSM obtained by TE performed in patients with a need for specialist referral indicated significant liver fibrosis and advanced liver disease in 20 (22.5%) and 11 (12.4%) cases, respectively (Fig. 3b).

Characteristics of patients without metabolic comorbidities

Overall, patients without metabolic comorbidities represented 21, 24.1 and 24.6% of those with NAFLD, those with elevated ALT and those in the medium/high fibrosis risk category, respectively (Fig. 2b). Table S1 depicts the characteristics of 472 patients without metabolic comorbidities with NAFLD (22.9%), with elevated ALT (16.9%) and in the FIB-4 category (27.3%). Among patients with available TE, LSM suggested advanced liver disease in only 0.9% of cases with FIB-4 < 1.30.

Discussion

The aim of this study, based on a large and well-characterized population without significant alcohol intake recruited from three prospective cohorts, was to apply recent NAFLD guidelines to HIV-monoinfected patients. We found that 20.4% of HIV-monoinfected patients had obesity and/or diabetes and should enter the recommended diagnostic algorithm for assessment of NAFLD and liver disease severity. When the criteria for entry to the diagnostic algorithm were extended to patients with any metabolic comorbidities, which encompassed most of the patients with NAFLD, with elevated ALT or in the medium/high-risk fibrosis category, this figure increased to 69.2%. Our findings suggested that 8% and 22.2% of the general HIV-monoinfected population should undergo specialist referral to hepatology when the entry criterion for the algorithm was obesity/diabetes or any metabolic comorbidities, respectively.

Table 2 Univariable analyses by outcome status, that is, the need for specialist referral to hepatology in patients with obesity and/or diabetes and in patients with any metabolic comorbidities

	Patients with obesity and/or diabetes (n = 313)		Patients with any metabolic comorbidities (n = 1062)	
	Need for specialist referral (n = 123)	No need for specialist referral (n = 190)	Need for specialist referral (n = 341)	No need for specialist referral (n = 721)
Age (years)	55 (48–60)*	51 (44–57)	51 (46–56)**	49 (44–55)
Male	102 (82.9)**	122 (64.2)	294 (86.2)**	522 (72.5)
Ethnicity				
Caucasian	108 (87.8)*	122 (64.2)	313 (91.8)**	604 (83.8)
Black non-Hispanic	7 (5.7)*	56 (29.5)	11 (3.2)**	92 (12.8)
BMI (kg/m^2)	26.6 (23.5–31.2)	28.8 (24.8–32.2)	24.9 (22.7–27.7)	24.6 (22.2–27.1)
Hypertension	75 (61.0)*	88 (46.3)	208 (61)**	326 (45.2)
Diabetes	93 (75.6)	126 (66.3)	93 (27.3)**	126 (17.5)
Active tobacco smoker	35 (28.5)	42 (22.1)	119 (34.9)	232 (32.2)
MSM	35 (28.5)	48 (25.3)	113 (33.1)	275 (38.1)
IDU	26 (21.1)*	17 (9.0)	99 (29)**	93 (12.9)
HIV infection duration (years)	17.7 (10.8–23.7)*	15.1 (8.0–20.0)	18.8 (12.8–23.8)**	16.1 (8.0–21.6)
CD4 count (cells/μL)	577 (437–802)	636 (443–791)	591 (415–798)	636.5 (444–816)
Undetectable HIV viral load (≤ 50 copies/mL)	98 (79.7)	141 (74.2)	287 (84.2)	597 (82.8)
Current ART regimen				
NRTIs	102 (82.9)*	173 (91.1)	288 (84.5)	609 (84.5)
NNRTIs	48 (39.0)*	98 (51.6)	138 (40.5)	315 (43.7)
PIs	74 (60.2)	107 (56.3)	200 (58.7)	403 (55.9)
Integrase inhibitors	48 (39.0)	66 (34.7)	115 (33.7)	270 (37.4)
Total cholesterol (mmol/L)	4.4 (3.8–5.4)*	4.8 (4.1–5.4)	4.7 (3.9–5.4)**	4.9 (4.2–5.7)
LDL cholesterol (mmol/L)	2.5 (2.0–3.3)*	2.8 (2.3–3.6)	2.7 (2.1–3.4)**	3.0 (2.4–3.6)
HDL cholesterol (mmol/L)	1.1 (0.9–1.3)	1.2 (1.0–1.4)	1.0 (0.9–1.2)*	1.1 (0.9–1.3)
Triglycerides (mmol/L)	1.6 (1.1–2.5)*	1.5 (1.0–2.1)	1.9 (1.2–2.5)*	1.8 (1.2–2.5)
LSM (kPa)†	6.5 (5.1–8.9)*	5.1 (4.2–6.7)	5.8 (4.6–6.9)**	4.8 (3.9–5.9)

ART, antiretroviral therapy; BMI, body mass index; HDL, high-density lipoprotein; IDU, injecting drug use; LDL, low-density lipoprotein; LSM, liver stiffness measurement; MSM, men who have sex with men; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.
The need for specialist referral to hepatology was defined as either having elevated alanine aminotransferase or having nonalcoholic fatty liver disease and being in the medium/high-risk category determined using FIB-4. Continuous variables are expressed as median (interquartile range) and categorical variables as number (%).
The P-values refer to the comparison between patients with and without the need for specialist referral to hepatology using the t-test or χ^2 test.
*$P < 0.05$.
**$P < 0.001$.
†Available in the LIVEHIV and LivHIVPa cohorts only.

Table 3 Multivariable analysis of factors associated with the need for specialist referral to hepatology in patients with obesity and/or diabetes (n = 313) and in patients with any metabolic comorbidities (n = 1062)

Variable	OR (95% CI)	aOR (95% CI)
Obesity and/or diabetes		
Age (per 10 years)	1.35 (1.06–1.72)	0.97 (0.68–1.40)
Male sex (yes versus no)	2.71 (1.55–4.72)	1.92 (0.91–4.04)
Black ethnicity (yes versus no)	0.15 (0.06–0.34)	0.24 (0.08–0.71)
Hypertension (yes versus no)	1.81 (1.14–2.87)	1.32 (0.68–2.55)
IDU (yes versus no)	2.73 (1.41–5.28)	3.14 (1.33–7.39)
Undetectable HIV viral load (yes versus no)	1.36 (0.74–2.49)	0.49 (0.21–1.15)
NNRTI exposure (yes versus no)	0.60 (0.36–0.99)	0.79 (0.43–1.47)
Triglycerides (per mmol/L)	1.22 (1.01–1.48)	1.14 (0.89–1.46)
Any metabolic comorbidities		
Age (per 10 years)	1.27 (1.10–1.47)	0.97 (0.78–1.21)
Male sex (yes versus no)	2.37 (1.67–3.36)	2.34 (1.51–3.62)
Black ethnicity (yes versus no)	0.23 (0.12–0.45)	0.24 (0.11–0.56)
Diabetes (yes versus no)	1.77 (1.30–2.41)	1.78 (1.21–2.61)
Hypertension (yes versus no)	1.89 (1.46–2.46)	1.44 (1.02–2.04)
IDU (yes versus no)	2.76 (2.01–3.80)	2.57 (1.75–3.79)
Undetectable HIV viral load (yes versus no)	1.12 (0.75–1.66)	0.63 (0.38–1.04)
NNRTI exposure (yes versus no)	0.88 (0.66–1.18)	1.09 (0.78–1.52)

aOR, adjusted odds ratio; BMI, body mass index; CI, confidence interval; IDU, injecting drug use; MSM, men who have sex with men; NNRTI, nonnucleoside reverse transcriptase inhibitor; OR, odds ratio; PI, protease inhibitor.
Odds ratios and 95% confidence interval are presented for each variable in the unadjusted and adjusted analysis.

NAFLD is increasingly contributing to the burden of liver disease in people living with HIV. NAFLD is not only more frequent in the setting of HIV infection, with a prevalence of up to 65%, but also more severe [9]. Patients with HIV-associated NAFLD have more advanced liver disease and higher rates of NASH compared to age/sex-matched HIV-negative controls [15]. NASH has been reported in up to 57.1% of HIV-monoinfected patients with chronically elevated ALT and in 10% of those attending a routine screening programme [17,34,35]. Furthermore, NAFLD is associated with high rates of progression to liver fibrosis and cirrhosis in HIV-monoinfected patients [14]. However, NAFLD lacks specific signs or symptoms, and cannot be readily diagnosed using routine blood tests, such as liver transaminases. In the general population, up to 79% of patients with NAFLD have normal ALT levels [36]. Similarly, 67 to 83% of HIV-monoinfected patients with NAFLD have normal ALT [11,37]. Nevertheless, persistently elevated ALT may suggest the presence of NASH or significant liver fibrosis [34,35,38,39]. Overall, there is a need for a diagnostic algorithm for the assessment of HIV-infected patients who have or are at risk of developing NAFLD and significant liver disease requiring specialist referral to hepatology.

The EASL and EACS guidelines recommend use of a stepwise diagnostic algorithm to screen for NAFLD and liver fibrosis in patients with obesity and/or diabetes by noninvasive diagnostic methods. NAFLD is strongly associated with central obesity and insulin resistance states [4,40]. In our pooled cohort, one in five HIV-monoinfected patients had obesity and/or type 2 diabetes. Insulin resistance is particularly frequent in aging HIV-monoinfected patients and those on specific ART regimens [7,41]. The Multicenter AIDS Cohort Study showed that the relative risk of incident diabetes in HIV-infected patients with chronic ART use was four times higher than in HIV-negative controls (10% versus 3%, respectively, over 4 years) [42]. Similarly, the 14.9% prevalence of diabetes found in our pooled cohort of patients undergoing routine screening programmes is higher than that reported in the Canadian and Italian general populations [43,44]. However, restricting the application of the EASL and EACS guidelines to patients with obesity/diabetes would miss 362/1534 (23.6%), 249/1534 (16.2%) and 377/1534 (25%) patients with NAFLD, with elevated ALT and in the medium/high-risk fibrosis category, respectively. Conversely, extending the entry criteria of the diagnostic algorithm to include patients with hypertension and/or dyslipidaemia would miss only 108/1534 (7%), 80/1534 (5.2%) and 129/1534 (8.4%) patients with NAFLD, with elevated ALT and in the medium/high-risk fibrosis category, respectively. Indeed, both hypertension and dyslipidaemia are risk factors for NAFLD [4,19]. Moreover, hypertension has been associated with NASH and a doubled rate of liver fibrosis progression [19,45]. Hypertension and dyslipidaemia are more frequent in HIV-infected individuals than in the general population, and this is possibly explained by a higher prevalence of smoking and HIV-specific factors such as immune activation, inflammation and long-term effects of ART in the HIV-infected patients [7,8,46]. Considering the link between NAFLD and cardiovascular mortality, as well as the higher cardiovascular risk in HIV-infected individuals, expanding the entry criteria of the algorithm could improve not only liver-related but also cardiovascular risk stratification [1].

Our population was screened for NAFLD using CAP in the LIVEHIV and LHivPa cohorts and CT scans in the MHMC cohort. CAP is TE software able to quantify fat in the liver, with a reported sensitivity of 89–91% [40,47]. CAP has been validated and applied in HIV-monoinfected patients [10,11,13,48]. Unenhanced CT scan is increasingly used in HIV-infected patients to detect moderate to severe hepatic steatosis based on attenuation difference between the liver and spleen, with sensitivity and specificity of 82% and 100%, respectively [25,26]. In our pooled cohort of 1534 patients, we found a prevalence of

NAFLD of 33.5%, a figure that is consistent with the literature [9].

When applying the EASL and EACS diagnostic algorithm, we found that 123 patients would require specialist referral to hepatology, representing 39.3% and 8% of patients with obesity/diabetes and of the whole cohort, respectively. When the criteria of entry into the diagnostic algorithm were expanded to any metabolic comorbidities, these figures were 32.1% and 22.2%, respectively. Our findings suggest that application of the diagnostic algorithm to HIV-monoinfected patients with any metabolic comorbidities should be considered. When available, LSM performed in patients with a need for specialist referral indicated significant liver fibrosis and advanced liver disease in 32.6% and 18.6% of patients with obesity/diabetes and in 22.5% and 12.4% of those with any metabolic comorbidities, respectively. These patients may need specialized interventions, including diagnostic liver biopsy, surveillance for HCC and referral for liver transplant. Interestingly, IDU was an independent factor associated with the need for specialist referral to hepatology. This finding could be related to poorer control of HIV in injecting drug users as a consequence of lower adherence to ART [49]. Indeed, IDU patients had lower CD4 cell counts and longer durations of HIV infection (data not shown). Black ethnicity was a protective factor for the need for specialist referral. Previous reports showed that black ethnicity is associated with milder liver disease severity in both the general population and in HIV-infected patients [50,51].

Only 0.9% of patients without any metabolic comorbidities and FIB-4 < 1.30 had an LSM suggesting advanced liver disease. Our findings suggest that FIB-4 could safely be used to exclude the presence of advanced liver disease in HIV-monoinfected patients without any metabolic comorbidities. Considering the 22.9% prevalence of NAFLD we found in this subgroup, a TE examination could still be considered when available, particularly in patients with FIB-4 ≥ 1.30. Indeed, there may be a subgroup of HIV-monoinfected patients at risk of NAFLD and liver fibrosis for reasons beyond the metabolic risk factors for NAFLD, probably as a consequence of immunological components intrinsic to HIV infection and to the chronic use of ART. HIV also functions to decrease the number of Kupffer cells in the liver, and in doing so significantly impairs the ability of the liver to clear products of microbial translocation from the portal blood [52].

Our study has several strengths. First, we applied the diagnostic algorithm recommended by the EASL and EACS guidelines in a large population of HIV-monoinfected patients recruited from three prospective and diverse routine screening programmes for liver disease. Despite the clinical differences among these cohorts and the different diagnostic tools employed for NAFLD, we obtained similar results in terms of the prevalence of liver disease. Secondly, we adopted two easily accessible and validated noninvasive diagnostic tools for NAFLD. Thirdly, in the LIVEHIV and the LivHIVPa cohorts we correlated our findings with TE examination.

We acknowledge several limitations of this study. First, it was conducted at tertiary-care referral centres, and so the prevalence of the outcome could be higher than in other settings. Secondly, liver biopsy, the gold standard for NAFLD and liver fibrosis diagnosis, was unavailable for most of our patients. However, screening studies employing liver biopsy are unfeasible and ethically questionable, and liver biopsy is not recommended for routine clinical use. This is further supported by the fact that the EASL and EACS guidelines recommend noninvasive tests as initial screening tools. Thirdly, the cross-sectional study design limits our ability to speculate on the dynamics of the disease over time and does not allow us to infer any causal association.

In conclusion, according to current EASL and EACS guidelines, one in five HIV-monoinfected patients with obesity/diabetes would require specialist referral to hepatology. Expansion of the algorithm to patients with any metabolic comorbidities may be considered. The recommended diagnostic algorithm could help target screening and interventions studies in the busy setting of HIV clinics, as well as help select patients who would benefit the most from hepatological referral.

Acknowledgements

Funding: ViiV and Merck provided a grant to establish the diagnostic centre for hepatic fibrosis and steatosis at McGill University Health Centre. GS is supported by a Junior 1 and 2 Salary Award from Fonds de Recherche Québec en Sante (FRQS) (#27127 and #267806) and a research salary from the Department of Medicine of McGill University. SC holds an Italian Liver Foundation Fellowship. TP holds a Ser Cymru II Precision Medicine Fellowship.

Conflicts of interest: GS has acted as a speaker for Merck, Gilead and Abbvie, has served as an advisory board member for Merck, Novartis and Gilead and has received research funding from Merck and Echosens. GM has acted as a speaker for Merck, Gilead, ViiV and Janssen, and has served as an advisory board member for ViiV, Gilead and Janssen. PG has acted as a consultant for Merck and Gilead. JF has received consulting fees from Theratechnologies, Inc., and has received payment for lectures from

ViiV Canada, Gilead Canada, and Abbott Canada. GG has acted as a speaker for Merck, Gilead and ViiV, served as an advisory board member for Merck and ViiV, and received research funding from Merck Gilead and ViiV. SC, AM, GM, AdC, AnC, TP, IF, GB and JM have nothing to disclose.

Authors' contributions

GS contributed to the conception of the study, the study design, data collection and interpretation of the data, statistical analysis and the writing of the first draft of the manuscript. SC contributed to data collection, interpretation of the data and the writing of the first draft of the manuscript. GM, AM, JF, AdC, AnC, SP, TP, PG, GB, IF and JM contributed to data collection and interpretation of the data. GG contributed to the conception of the study, the study design, data collection and interpretation of the data. All authors approved the final version of the manuscript.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 Characteristics of patients with no metabolic comorbidity and with nonalcoholic fatty liver disease (NAFLD), or with elevated alanine aminotransferase (ALT) or in the fibrosis-4 (FIB-4) $\geq$ 1.30 category (n = 472).