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Return-to-health effect of modern combined antiretroviral therapy potentially predisposes HIV patients to hepatic steatosis

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Abstract

Prevalence and risk factors for hepatic steatosis (HS) in the human immunodeficiency virus (HIV)-positive population of western countries are controversially discussed and potentially confounded by coinfection with viral hepatitis. Significant HS (more than 10% of hepatocytes) can be accurately assessed using controlled attenuation parameter (CAP) determination. Aim of this study was to assess prevalence and factors associated with significant HS in HIV monoinfected patients.

A total of 364 HIV-infected patients (289 monoinfected) were included in this prospective, cross-sectional study. All patients underwent CAP determination. Steatosis was classified as S1 (significant steatosis) with CAP > 238 dB/m, S2 with CAP > 260 dB/m, and S3 with CAP > 292 dB/m. Multivariable logistic regression analyses were performed to assess the factors associated with HS in this cohort.

Significant HS was detected in 118 monoinfected patients (149 in the total cohort). In the total cohort as well as in the monoinfected patients alone, HS grade distribution showed a similar pattern (S1:29%, S2:34%, and S3:37%). Interestingly, patients with HS had a longer history of HIV infection and combined antiretroviral therapy (cART). Interalia, age, gender, ethnicity, and metabolic factors were strongly associated with HS, while body mass index (BMI), triglyceride, and glycated hemoglobin (HbA1c) levels were independently associated with significant HS.

HS is highly prevalent among HIV monoinfected patients. Although metabolic risk factors, such as obesity and poorly controlled diabetes, are independently associated with HS in HIV monoinfected patients, cART and control of HIV seem to play an indirect role in the development of HS, probably through the return-to-health effect.

Abbreviations: CAP = controlled attenuation parameter, cART = combined antiretroviral therapy, CD4 = cluster of differentiation 4, DM = diabetes mellitus, HbA1c = glycated hemoglobin, HCV = hepatitis C virus, HDL = high-density lipoprotein, HIV = human immunodeficiency virus, HS = hepatic steatosis, NAFLD = nonalcoholic fatty liver disease, NASH = nonalcoholic steatohepatitis.

Keywords: CAP, cART, HIV monoinfection, liver injury, NAFLD

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JKR and JT shared last coauthorship.

Ethics approval and consent to participate: Informed consent was obtained from each patient included in the study and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in the approval by the Ethics Committee of the University of Bonn (279/14).

Availability of data and materials: The datasets are available from the corresponding author on reasonable request.

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1. Introduction

Present day combined antiretroviral therapy (cART), leading to permanent suppression of human immunodeficiency virus (HIV) replication, has dramatically improved survival of HIV-infected patients. Chronic liver disease has emerged as an increasingly significant contributor to nonacquired immune deficiency syndrome related morbidity and mortality in the HIV-infected population.^[1] Independent of coinfection with hepatotropic viruses, increased rates of liver fibrosis and steatosis have been observed.^[5–7] On the one hand, HIV induces metabolic changes; on the other hand, long-term exposure to antiretroviral drugs may exert toxicities (in particular mitochondrial toxicity, dyslipidemia, and insulin resistance)^[2–4,33], which may further contribute to the development of clinically relevant liver disease.^[8–10] Hepatic steatosis (HS) may then progress to nonalcoholic steatohepatitis (NASH), an emerging cause of hepatocellular carcinoma.^[11] Furthermore, liver steatosis may predispose to acute liver failure, especially when those patients are exposed to additional hepatic risk factors.^[12]

Little information is available on the prevalence and potential risk factors for liver steatosis among HIV monoinfected patients. Indeed, most of the currently existing data on HS solely derives from HIV/hepatitis C virus (HCV) coinfecting patients. In these coinfecting patients, the prevalence rate for HS ranges between 20% and 80%.^[6,11,13,14] In a recently published, large Canadian study with more than 22% coinfecting patients, no difference in the grade of steatosis was observed between co- and mono-infected patients.^[15] Importantly, coinfection with HCV is a strong confounder for HS, not only due to changes in the measurement as a result of inflammation and fibrosis, but also because it is dependent on the HCV genotype.

With regard to risk factors promoting steatosis in HIV infection, little is known and this issue is controversially discussed.^[16–22] Steatosis is mostly associated with metabolic risk factors (obesity, diabetes, and dyslipidemia) in the general population and might lead to severe liver disease. In HIV-positive population, the metabolic risk factors still play a role for the development of steatosis, the impact of long-term exposure to antiretroviral regimes for liver injury and specifically for steatosis has also been discussed. A recently published meta-analysis demonstrated that body mass index (BMI), waist circumference, diabetes mellitus (DM), hypertension, triglycerides, and cluster of differentiation 4 (CD4) cell count were associated with nonalcoholic fatty liver disease (NAFLD), whereas HIV specific parameters like HIV viral load, duration of HIV, duration of cART, and nadir CD4 count were not.^[23]

This study aimed to examine in more detail the prevalence and risk factors for severe HS in a large cohort of HIV monoinfected patients from the Infectious Diseases outpatient clinic at Bonn University.

2. Methods

2.1. Patients

This cross-sectional prospective study included 364 HIV-infected patients followed at the Infectious Diseases outpatient clinic at Bonn University. Patients with confirmed HIV infection and self-reported alcohol intake of no more than 30g/day (male participants) or 20g/day (female participants) were eligible for inclusion. The use of anabolics or hormones was not reported by patients but would have exclusion criteria. To assess the potential effect of concomitant HCV or hepatitis B virus coinfection, as well

as to minimize the potential effect of confounders, analyses were performed on the total study population and the group of 289 HIV monoinfected patients (Fig. 1A). Blood collection and controlled attenuation parameter (CAP) measurement were performed during a regular scheduled visit at our outpatient clinic. Informed consent was obtained from each patient included in the study and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in the approval by the institution's human research committee (279/14).

2.2. Data acquisition and follow-up

Laboratory work-up of metabolic (glycated hemoglobin [HbA1c], cholesterol, low-density lipoprotein, high-density lipoprotein [HDL], triglycerides, transaminases, bilirubin, creatinine, platelets, albumin, and thyroid-stimulating hormone), inflammatory/immunologic (c-reactive protein, CD4, and CD8), and HIV-relevant disease markers (viral load) was performed at the same time as transient elastography. Demographic and clinical characteristics as well as data on health trajectory of HIV infection and antiretroviral treatments were collected from the patient's health record and our department's database. Current comedication, alcohol consumption, and smoking status were recorded and the actual BMI was assessed.

2.3. Hepatic steatosis measurement

CAP measures the degree of ultrasound attenuation by hepatic fat at the central frequency of the FibroScan M probe, simultaneously with liver stiffness measurement. The technique can establish presence of HS affecting more than 10% of the hepatocytes in the liver biopsy^[24] and has been validated in different groups of patients.^[25–27]

CAP measurement was assessed using FibroScan 502 touch (ECHOSENS, France) performed by experienced and trained operators. According to standards, examinations with at least 10 valid measurements, a low variability defined as an interquartile range (IQR/M) smaller than 30% of the median value, and a successful acquisition rate of at least 60% were considered reliable and were approved for analysis.^[28]

The optimal threshold of CAP for the detection of HS is unknown in NAFLD. With values above 238 dB/m, we selected a conservative cut-off to define beginning significant HS (S1).^[24,25] As a solid criteria for the prevalence of clinically apparent, advanced steatosis, cut-off values of 260 dB/m (S2) and 292 dB/m (S3) were applied.

2.4. Statistical analysis

Demographic, clinical, and laboratory characteristics stratified by severity of HS were compared. Differences in continuous variables, expressed as medians, and 1st and 3rd quartiles were assessed using either nonparametric Mann–Whitney test or Kruskal–Wallis test. Categorical variables, expressed as absolute frequencies and percentages, were compared using Pearson chi squared test or Fisher exact tests. A correlation analysis estimated possible impacts on HS. Uni- and multivariable analyses were performed using logistic and Cox-regression models. SPSS version 22 (IBM Corporation, Armonk, NY) was used for statistical analysis.

3. Results

3.1. General characteristics of the cohort

In total, 364 patients were included in the study. The majority was male (78%), Caucasian (76%), with a mean age of 46 (range,

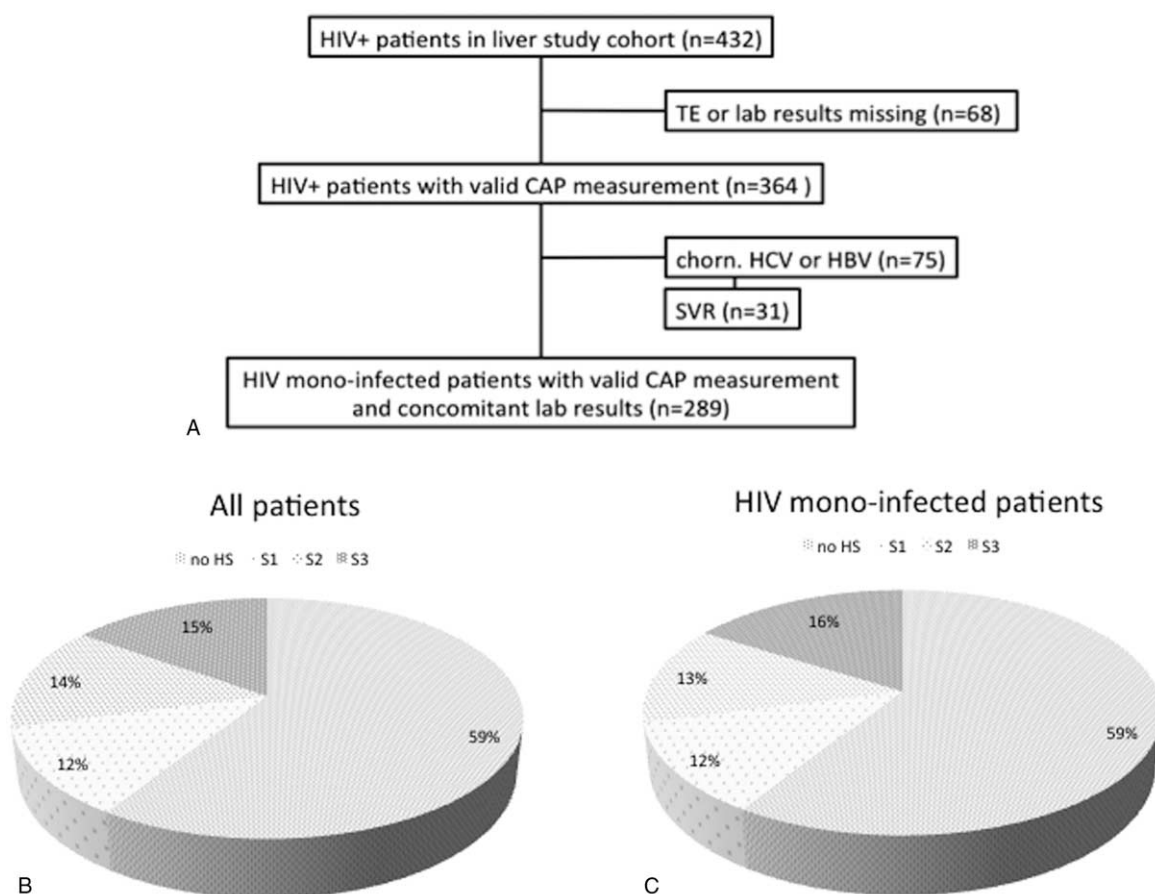


Figure 1. Flow chart displaying selection of study participants (A). Prevalence and distribution of hepatic steatosis in all patients (B) and in HIV monoinfected patients (C).

20–75) years. The baseline characteristics of the study subjects are shown in Table 1.

Two hundred and eighty seven patients (79%) were HIV monoinfected, 20 (6%) patients were hepatitis B surface antigen-positive, 57 (16%) were anti-HCV-positive, of which 31 (54%) had achieved sustained virologic response, 17 (31%) were HCV therapy naïve, and 9 (15%) either relapsed or were nonresponder to previously administered HCV treatments. Most of the patients (95%) were treated with cART and showed undetectable plasma HIV ribonucleic acid (83%). Ninety six (26%) patients were classified as Centers for Disease Control and Prevention category C. The mean CD4⁺ T cell count was 546 (range, 6–1478) cells/mm³.

Overweight, defined by a BMI of at least 25 and less than 30 kg/m², was observed in 93 (32%) and obesity, defined by a BMI of at least 30 kg/m², in 16 (6%) HIV monoinfected individuals (Supplemental Table 2, <http://links.lww.com/MD/C220>). Twelve (4%) HIV monoinfected patients had the diagnosis of DM, with 9 (75%) receiving antidiabetic treatment and 10 (4%) presenting HbA1c levels greater than 6.5%. Blood triglycerides of at least 150 mg/dL were detected in 125 (43%), and blood HDL cholesterol levels less than 40 mg/dL were observed in 63 (22%) HIV monoinfected patients.

3.2. Prevalence of hepatic steatosis

Median CAP was 230 (range, 100–367) dB/m and 229 dB/m when including coinfecting patients. Significant HS, that is, CAP

≥238 dB/m, was observed in 118 (41%) patients, of whom 34 (29%) had S1, 38 (32%) S2, and 46 (39%) S3. No significant difference in prevalence and distribution (41%, and 29%, 34%, 37%, respectively) of HS was observed in the coinfecting patients (Table 2, Supplementary Table 1, <http://links.lww.com/MD/C220>).

Age, metabolic conditions (BMI, cholesterol, HDL, LDL, levels of triglyceride, glucose, and HbA1c), and markers of liver injury (alanine aminotransferase, gamma-glutamyltransferase) correlated with altered CAP measurement, whereas HIV viral load showed an inverse trend. Interestingly, the total duration of HIV infection and the duration of cART showed positive correlations with HS (Table 3). Similar findings were obtained when considering the whole cohort (Supplemental Table 3, <http://links.lww.com/MD/C220>).

As expected, patients with significant steatosis showed higher mean HbA1c levels (5.4 [3.6–11.4] vs 5.2 [2.7–8.1] %; *P* = .007), higher mean BMI (26 [19–36] vs 23 [16–41] kg/m²; *P* < .001), higher triglyceride levels (183 [53–1193] vs 116 [28–753] mg/dL; *P* < .001), and lower HDL cholesterol (43 [18–100] vs 49 [8–127] mg/dL; *P* = .004) compared to patients without steatosis. DM, gender, and ethnicity revealed a significant impact on HS (Table 1). Interestingly, apart from gender, ethnicity also revealed a significant difference in median CAP values (Fig. 2A–D), with higher levels in males and in Caucasians.

More severe steatosis was observed in patients with longer duration of known HIV infection (9 [0–26] vs 7 [0–29] years;

Table 1
Baseline characteristics.

Variables	Total study population				HIV monoinfected patients			
	All patients (n=364)	CAP < 238 (n=215)	CAP ≥ 238 (n=149)	P	All patients (n=289)	CAP < 238 (n=171)	CAP ≥ 238 (n=118)	P
Age (range), y	46 (20–75)	43 (20–75)	49 (25–74)	.0001	45 (20–75)	42 (20–75)	49 (25–74)	.0001
Male gender (no, %)	285 (78)	159 (74)	126 (85)	.010	225 (78)	126 (74)	99 (84)	.027
Caucasian/African/other (no)	278/55/31	150/41/24	128/14/7	.0001	215/49/25	115/37/19	100/12/6	.001
CDC-C (no, %)	96 (26)	48 (22)	48 (32)	.024	76 (26)	39 (23)	37 (31)	.069
CD4 cells (range), cells/mm ³	518 (6–1478)	496 (6–1478)	561 (29–1268)	.036	502 (29–1478)	493 (37–1478)	545 (29–1268)	.097
HIV viremia >40c/mL (no, %)	61 (17)	45 (21)	16 (11)	.012	50 (17)	35 (21)	15 (13)	.062
Time since HIV diagnosis (range), y	9 (0–29)	7 (0–29)	10 (0–29)	.004	8 (0–29)	7 (0–29)	9 (0–26)	.019
Time under cART (range), y	7 (0–27)	6 (0–27)	8 (0–24)	.009	6 (0–23)	6 (0–23)	8 (0–23)	.045
BMI (range), kg/m ²	24 (15–41)	23 (15–41)	26 (19–36)	.0001	24 (16–41)	23 (16–41)	26 (19–36)	.0001
Cholesterol (range), mg/dL	192 (72–342)	185 (72–342)	205 (88–304)	.003	198 (72–342)	188 (72–342)	209 (115–304)	.0001
HDL (range), mg/dL	45 (8–127)	48 (8–127)	43 (18–100)	.005	46 (8–127)	49 (8–127)	43 (18–100)	.004
LDL (range), mg/dL	116 (41–210)	113 (42–210)	119 (41–203)	ns	119 (42–210)	113 (42–210)	127 (57–203)	.002
Triglycerides (range), mg/dL	139 (28–1549)	120 (28–1549)	176 (43–1193)	.0001	139 (28–1193)	116 (28–753)	183 (53–1193)	.0001
HbA1c (range), %	5.3 (2.7–11.4)	5.3 (2.7–8.1)	5.4 (3.6–11.4)	.013	5.3 (2.7–11.4)	5.2 (2.7–8.1)	5.4 (3.6–11.4)	.007
AST/GOT (range), U/L	22 (9–183)	21 (9–183)	23 (12–147)	.055	21 (9–147)	20 (9–65)	22 (12–147)	.035
ALT/GPT (range), U/L	31 (8–161)	29 (8–161)	33 (15–16)	.007	30 (8–151)	29 (8–99)	32 (17–151)	.004
GGT (range), U/L	44 (12–568)	40 (12–340)	49 (20–568)	.001	43 (12–568)	39 (12–340)	50 (20–568)	.0001
Chronic HCV/HBsAg-positive/SVR (no)	57/20/31	34/11/17	23/9	n.s.				
LPVr history (no, %)	111 (31)	56 (26)	55 (37)	.013	79 (28)	39 (23)	40 (34)	.017

Baseline subject characteristics. Data are shown as median (IQR) or n (%). ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, CDC = Centers for Disease Control and Prevention, GOT = glutamate-oxalacetate-transaminase, GPT = glutamate-pyruvate-transaminase, HBsAg = hepatitis B surface antigen, IQR = interquartile range, LPVr = ritonavir-boosted lopinavir, ns = not statistical significant, SVR = sustained virologic response.

P = .019], although uncontrolled HIV infection (viral load ≥40 copies/mL) did not have a statistically significant influence on CAP values (Table 2). However, patients in Centers for Disease Control and Prevention class C had higher HS levels than patients without acquired immune deficiency syndrome-defining events (*P* = .039) (Fig. 1E, F).

In contrast to liver fibrosis development, no significant differences in HS were observed regarding anti-HCV positivity

(222 dB/m), sustained virologic response (238 dB/m), hepatitis B surface antigen positivity (239 dB/m), and HIV monoinfected patients (229 dB/m).

3.3. Factors associated with hepatic steatosis

Logistic regression analysis revealed that many demographic (age, gender, and ethnicity), metabolic (BMI, triglyceride, DM

Table 2
HIV monoinfected population.

Variables	All patients (n=289)	S0 (n=171)	S1 (n=34)	S2 (n=38)	S3 (n=46)	P
Age (range), y	45 (20–75)	43 (20–75)	47 (30–73)	47 (25–74)	53 (33–74)	.000
Male gender (no, %)	225 (78)	126 (74)	27 (79)	28 (74)	44 (96)	.009
Caucasian (no, %)	215 (74)	115 (67)	28 (82)	31 (82)	41 (89)	.007
African (no, %)	49 (17)	37 (22)	3 (9)	4 (11)	5 (11)	.086
BMI (range), kg/m ²	24 (16–41)	23 (16–41)	25 (19–29)	26 (20–36)	28 (20–36)	.000
Cholesterol (range), mg/dL	197 (72–342)	189 (72–342)	199 (115–304)	206 (132–284)	218 (121–290)	.000
HDL (range), mg/dL	49 (8–127)	51 (8–127)	50 (25–94)	48 (27–100)	40 (18–74)	.001
LDL (range), mg/dL	120 (42–210)	115 (42–210)	125 (69–185)	129 (81–199)	133 (57–203)	.013
Triglycerides (range), mg/dL	184 (28–1193)	146 (28–753)	164 (53–508)	231 (55–1048)	293 (76–1193)	.000
AST/GOT (range), U/L	24 (9–147)	22 (9–65)	28 (14–147)	23 (12–41)	26 (16–61)	.045
ALT/GPT (range), U/L	35 (8–151)	33 (8–99)	34 (17–78)	34 (17–50)	45 (20–151)	.003
GGT (range), U/L	56 (12–568)	48 (12–340)	61 (22–295)	61 (20–157)	79 (22–568)	.000
HbA1c (range), %	5.4 (2.7–11.4)	5.2 (2.7–8.1)	5.2 (3.6–7.2)	5.5 (4.9–7.9)	6.0 (3.8–11.4)	.014
DM 2 (no, %)	12 (4)	3 (2)	0 (0)	2 (5)	7 (15)	.000
On antidiabetics (no, %)	9 (75)	3 (100)	0 (0)	1 (50)	5 (71)	.010
LPVr history (no, %)	79 (28)	39 (23)	9 (29)	9 (24)	22 (49)	.024
Time since HIV diagnosis (range), y	9 (0–29)	9 (0–29)	11 (0–26)	9 (0–23)	10 (0–26)	.104
Time cART naive (range), y	2 (0–17)	2 (0–17)	3 (0–12)	1 (0–7)	1 (0–12)	.107
Time under cART (range), y	8 (0–23)	7 (0–23)	9 (0–19)	8 (0–23)	9 (0–22)	.227

Baseline subject characteristics. overall and by significant hepatic steatosis as determined by CAP ≥238 kPa. Data are shown as median (IQR) or n (%). ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, CAP = controlled attenuation parameter, cART = combined antiretroviral therapy, DM = diabetes mellitus, GGT = gamma-glutamyltransferase, GOT = glutamate-oxalacetate-transaminase, GPT = glutamate-pyruvate-transaminase, HbA1c = glycated hemoglobin, HDL = high-density lipoprotein, HIV = human immunodeficiency virus, IQR = interquartile range, LDL = low-density lipoprotein, LPVr = ritonavir-boosted lopinavir.

Table 3
Associations of CAP with different variables in HIV monoinfected patients.

	CAP		N
	R	P	
Body weight	0.502	.0001	283
BMI	0.49	.0001	274
Triglycerides	0.307	.0001	274
Age	0.322	.0001	289
Cholesterol	0.251	.0001	275
LDL	0.263	.0001	216
HbA1c	0.252	.0001	216
Glucose	0.223	.0001	276
HDL	-0.209	.002	217
GGT	0.166	.006	274
GPT	0.16	.007	279
FIB4	0.177	.009	220
Creatinine	0.152	.011	278
Transient elastography	0.114	.054	289
APRI	0.086	.203	220
Cumulative cART duration	0.102	.093	271
Duration of HIV	0.09	.014	289

Correlations of patient characteristics and clinical parameters with HS assessed by CAP measurement. APRI=aspartate aminotransferase to platelet ratio index, BMI=body mass index, CAP=controlled attenuation parameter, cART=combined antiretroviral therapy, GGT=gamma-glutamyltransferase, GPT=glutamate-pyruvate-transaminase, HbA1c=glycated hemoglobin, HDL=high-density lipoprotein, HIV=human immunodeficiency virus, HS=hepatic steatosis, LDL=low-density lipoprotein.

type 2, HbA1c, cholesterol, HDL, and LDL), and hepatic parameters (aminotransferase and gamma-glutamyltransferase levels), but not time since HIV diagnosis, were significantly associated with significant HS. More parameters were found when considering the whole cohort, suggesting that coinfection

might bias the analysis of risk factors for the development of significant steatosis in HIV infection (Supplemental Table 4, <http://links.lww.com/MD/C220>). Subsequent multivariable analysis identified only BMI, HbA1c, and triglyceride levels as independently associated with significant HS (Table 4).

Regarding antiretroviral therapy only ritonavir-boosted lopinavir (LPV/r) was associated with the development of liver steatosis. In the current study, no other PIs nor other antiretroviral drug classes could be identified to have an impact on the severity of steatosis. The effect of the duration of HIV infection and cART duration mainly seems to depend on metabolic changes (BMI, HbA1c, and triglycerides), which in HIV monoinfected patients, are strongly and independently associated with HS, while in the whole population, age also seems to play an important role (Supplemental Table 4, <http://links.lww.com/MD/C220>).

4. Discussion

Our findings outline that significant HS is highly prevalent in HIV-infected patients. Using CAP-derived data from a large and unselected real-life cohort, this cross-sectional study is likely to be more accurate than previous estimations.

Most published data on the prevalence of HS in HIV-infected patients were obtained from liver biopsy studies in HIV/HCV coinfecting patients.^[11,13,14] Even recently published data from a prospective cohort holds a bias by including HCV coinfecting patients, as depending on the genotype, HCV might or might not predispose to HS.^[29] Usually, these patients have severe fibrosis, which impairs the CAP measurement.^[30] Our study clearly focused on HIV monoinfected patients to make the cohort less heterogeneous than previous studies. Although this study is not primarily designed to compare mono- and coinfecting patients, we found

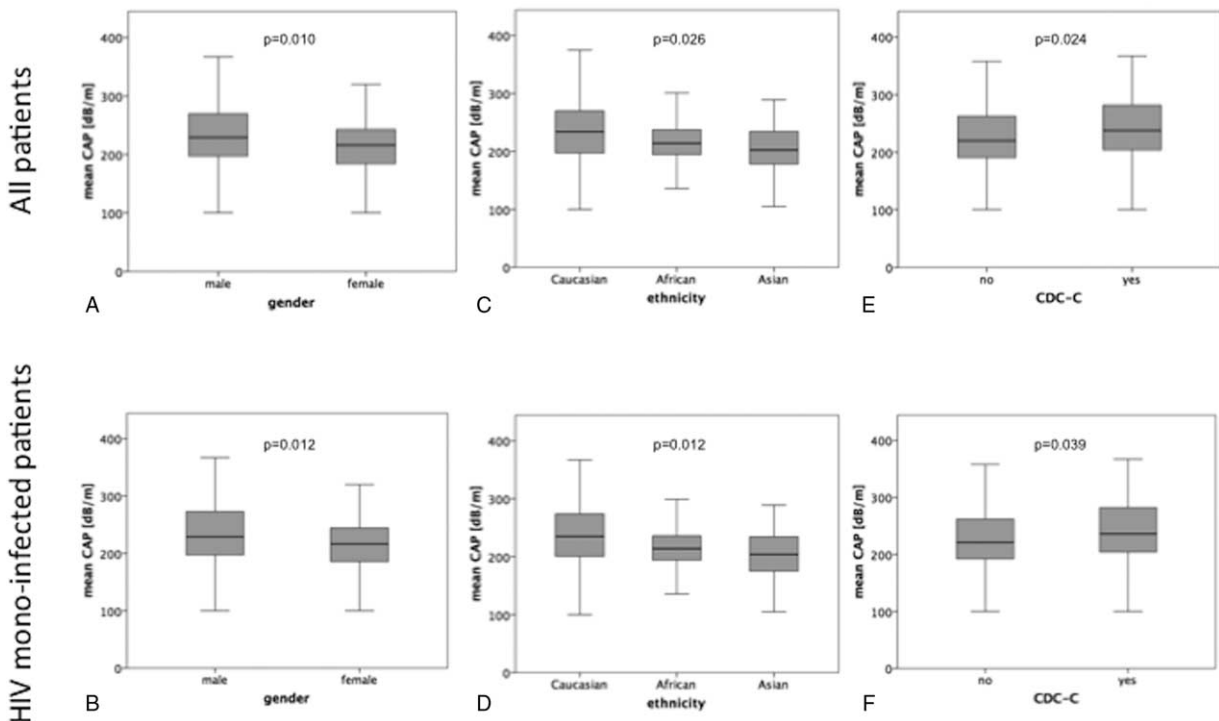


Figure 2. Association between hepatic steatosis and gender, ethnicity, and CDC-C in all patients (A, C, E, respectively) and in HIV-monoinfected patients (B, D, F, respectively). Data are presented as box plots. CDC=centers for disease control and prevention.

Table 4**Logistic regression.**

	P	Multivariable	
		Adjusted odds ratio	95% Confidence interval for odds ratio
BMI	<.001	1.331	1.185–1.495
Triglycerides	.008	1.003	1.001–1.006
HbA1c	.019	1.735	1.096–2.744

Multivariable analysis for CAP ≥ 238 dB/m in HIV monoinfected patients. BMI = body mass index, CAP = controlled attenuation parameter, HbA1c = glycated hemoglobin, HIV = human immunodeficiency virus.

evidence that many HIV-specific factors, which significantly correlate with CAP, are found only in the coinfecting patients, such as transient elastography, aspartate aminotransferase to platelet ratio index score, HIV viral load, and duration of cART. These factors are strongly associated with liver fibrosis and inflammation, which is another bias present in our previous studies.^[7,31]

Other studies using liver biopsy, which is an invasive diagnostic tool and not applicable for screening purpose, hold a significant selection bias. Steatosis involving at least 10% of hepatocytes can be accurately detected applying a CAP cut-off of 238 dB/m.^[24,25] Significant steatosis was found in 41% of our study population, with an emphasis on S2 and S3 steatosis. This is in line with 2 previously published CAP-based studies rendering the prevalence of significant HS in HIV-infected patients to about 30% to 40%.^[15,17,18] Nevertheless, these data were either derived from a much smaller cohort or included 20% to 50% patients with concomitant chronic HCV infection. The 60% prevalence rate of HS determined in a liver biopsy study, including 14 HIV monoinfected patients with persistent liver enzyme elevations, seems overestimated. Nevertheless, it showed that 26% of HIV-infected patients without viral hepatitis, DM, or alcohol use fulfilled the histological criteria for NASH.^[22]

In the general population, increased BMI, insulin resistance, and dyslipidemia are the main risk factors for NAFLD and NASH.^[32] NAFLD is characterized by greater hepatic uptake rates of plasma fatty acids as a consequence of an increased release from an expanded mass of adipose tissue with diminished insulin responsiveness. Furthermore, hyperinsulinemia promotes the upregulation of de novo lipogenesis in the liver.^[32] In our study, metabolic factors were strongly related to steatosis development. Nevertheless, we observed higher rates of significant HS compared to the general population, where prevalence amounts up to 25%.^[32] HIV itself induces metabolic changes, while long-term exposure to antiretroviral drugs may also exert toxicities, which could further contribute to the development of clinically relevant liver disease.^[8–10] Nucleoside analogue reverse transcriptase inhibitors were in particular associated with mitochondrial toxicity.^[34] Impaired beta-oxidation of fatty acids leads to increased hepatic lipid accumulation. Existing studies have found no relationship between HS and individual antiretroviral drugs.^[6,13–16] However, our data show that LPV/r has a significant impact on the severity of steatosis. Whether this is due to a direct drug effect or a secondary effect by the metabolic changes induced by PIs cannot be determined with certainty.

Importantly, HIV-infected patients show an increase in BMI shortly after starting cART. Especially those with a lower nadir CD4 T-cell count, gained more lean mass and fat during the first 96 weeks of cART.^[35] This is consistent with our findings, namely that a longer time since HIV diagnosis and longer periods of cART are associated with presence of HS. However, these were

not independent associations but could predispose the patients to metabolic changes, which finally were independent and strongly associated with presence of HS. Possibly, the return-to-health effect of cART is one of the reasons for the presence of HS in HIV monoinfected patients. This is also supported by our previous data, showing that cART and control of HIV replication is protective for liver fibrosis and liver injury in HIV monoinfected patients. However, in these patients, HS might be induced by other mechanisms and not be the result of direct hepatic effects of HIV or cART. This may be supported by the finding of a gender and ethnicity influence on CAP-value, despite the fact that these patient groups were randomly distributed among the population.

The main limitations of this study are its cross-sectional design, which limits the ability to evaluate change in variables of interest over time, and the presence of a nonrandomized study population. Homeostasis model assessment index to quantify insulin resistance and dual-energy X-ray absorptiometry or magnetic resonance tomography imaging to quantify body composition changes were not available. Alcohol consumption as well as anabolic use was self-reported by the patients, for example, binge drinking behavior may have been underestimated. No drug and anabolic screening tests were performed. Finally, while liver biopsy remains the gold standard for the assessment of HS, the acceptability and potential risks of biopsy make its application difficult for a large study population.

5. Conclusions

In conclusion, we found that prevalence of HS in HIV-infected patients is higher than in the general population. Overweight, dyslipidemia, and poorly controlled diabetes were independent factors for HS in HIV monoinfected patients. Suppression of viral replication might contribute to the development of steatosis. Controlling HIV replication might not condition liver disease by causing metabolic disorders, instead, this may be due to the return-to-health effect.

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