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Prevalence and Predictors of Hepatic Steatosis in Patients with HIV/HCV Coinfection and the Impact of HCV Eradication

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Abstract

Human immunodeficiency virus (HIV)-induced metabolic abnormalities and antiretroviral therapy (ART), genetic factors, most importantly the rs738409 C > G p.I148M variant in the patatin-like phospholipase domain containing 3 (PNPLA3)-gene, as well as hepatitis C virus (HCV) coinfection may all cause hepatic steatosis (HS). However, recent studies suggest a protective effect of HCV infection on HS. Thus, we evaluated HS prior and after HCV eradication in an HIV/HCV-coinfected cohort at the Medical University of Vienna between January 2014 and June 2017. Two hundred forty-seven patients underwent liver stiffness measurement and controlled attenuation parameter (CAP)-based steatosis assessment. A subcohort of 138 patients also had follow-up CAP measurement after HCV eradication by direct-acting antivirals (DAAs). A CAP value ≥248 dB/m defined HS and all CAP values were adapted to compensate for body mass index (BMI) and diabetes mellitus. Among all 247 HIV/HCV-coinfected patients, HS was prevalent in 31%, mean age was 43.3 years, 75% were male, the main ethnicity was Caucasian (96%), and mean BMI was 23.33 kg/m^2. Independent risk factors for HS were BMI, years exposed to HIV, PNPLA3 G-alleles, and protease inhibitor (PI) intake. Notably, a significant increase in CAP (from 225 ± 52.9 to 235 ± 50.7 dB/m; $p = 0.047$) was observed after HCV eradication, whereas patients on PI-containing ART experienced a significant decrease in CAP. Overall, one-third of HIV/HCV-coinfected patients are affected by HS with PI-based ART and PNPLA3 impacting on HS prevalence. While HCV eradication by DAAs increased HS, as assessed by CAP, future studies should account for metabolic syndrome and evaluate whether changes in CAP-based steatosis assessments correspond to a clinically relevant outcome.

Keywords: HIV, hepatic steatosis, hepatitis C virus, controlled attenuation parameter

Introduction

Hepatitis C virus (HCV)-related liver disease is a major contributor to morbidity and mortality in individuals infected with human immunodeficiency virus (HIV).[1] Due to shared routes of transmission, HIV/HCV coinfection is common[2] and has been associated with a more rapid progression toward severe liver disease, compared with HCV monoinfection.[3] Several HIV-related factors such as drug-induced liver injury by antiretroviral therapy (ART) or immunological dysregulation might accelerate liver fibrosis progression and increase the risks for cirrhosis and hepatocellular carcinoma in HIV/HCV.[4,5] Thus, non-AIDS-related mortality remains significantly increased among individuals infected with HIV, even in the era of modern ART.[6]

Prior studies have suggested a link between hepatic steatosis (HS) and liver fibrosis progression in HCV-infected patients,[7] as well as an association with higher body mass index (BMI), diabetes mellitus (DM), older age, HCV genotype (GT) 3, hepatic inflammation,[8] and a G-allele [rs738409(G)] in patatin-like phospholipase domain containing 3 (PNPLA3)-gene.[9] Notably, HS seems to be more prevalent in HIV/HCV coinfected than in HCV monoinfected patients,[10] with concomitant ART playing a potential

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pathogenic role. Prior studies described a higher prevalence of HS among HIV patients exposed to ART for more than 4 years or if certain nucleoside analogs were used.[10,11] In addition, early ART regimens have been found to promote metabolic abnormalities (i.e., insulin resistance),[12] which are linked to HS in HIV/HCV.[13] However, recent studies surprisingly found a protective effect of non-GT-3-HCV infection for HS and a faster progression of HS and liver fibrosis in HIV+ individuals without HCV coinfection.[14,15]

These discrepant data on HS in HIV/HCV-coinfected patients may be explained by different methods and devices used for the assessment of HS. While liver biopsy is still regarded the diagnostic gold standard for diagnosis of HS, noninvasive magnetic resonance imaging- or ultrasound-based techniques are increasingly being used for HS evaluation. Controlled attenuation parameter (CAP), implemented in a transient elastography (TE) device, is now one of the most commonly used methods.[16] It is well-validated in HCV-infected patients, who undergo CAP and liver stiffness measurement (LSM) in a single examination.[16] A recent meta-analysis based on individual patient data presented optimized CAP cutoffs for HS quantification and provided important information on the influence of covariates (i.e., DM, BMI) on CAP results.[17]

The impact of HCV eradication on HS was assessed in studies using interferon (IFN)-based therapies.[18,19] Despite the use of individualized treatment strategies and the addition of first-generation direct-acting antivirals (DAAs),[20] sustained virological response (SVR) rates remained insufficient. Since IFN-free DAA regimens[21,22] and systematic screening strategies have been implemented,[23] HCV can now be effectively treated in HIV-coinfected patients. Current challenges in treating HCV in HIV-positive patients encompass insurance and pricing barriers, as well as the treating physician's education.[24]

In our study, we aimed to investigate the prevalence and predictors of HS, determined by CAP cutoffs according to Karlas et al.,[17] in HCV-viremic HIV-coinfected ''all-comers.'' Further, we aimed to assess the impact of HCV eradication with IFN-free DAA regimens on HS as well as on plasma lipids.

Methods

Study design and population

Patients undergoing TE for LSM and CAP for HS quantification were considered for this retrospective study. All patients with polymerase chain reaction-confirmed HIV/HCV coinfection attending the HIV and Liver Outpatient Clinic at the Medical University of Vienna between January 2014 and May 2018 were included in this study. Patients without HCV viremia (e.g., during or after antiviral therapy), or with spontaneous HCV clearance at the time of initial TE/CAP, were excluded.

All subjects screened before HCV treatment were included in the presented study as prevalence cohort. In addition, we analyzed the impact of HCV eradication on HS in a subgroup of HIV/HCV-coinfected patients receiving IFN-free DAA treatment, who underwent paired CAP measurements (follow-up cohort). Regimens of DAAs were used in accordance with the respective (reimbursement-dependent) HCV treatment recommendations.[25] The second LSM and CAP measurement were performed 12 weeks after cessation of treatment, that is, when SVR12 was assessed.

Assessed parameters

Demographic, clinical, and epidemiological characteristics were extracted from patients' medical records. The VERSANT® HCV Genotype 2.0 Assay Line Probe Assay (LiPA; Siemens Healthcare Diagnostics, Tarrytown, NY) was used to determine the HCV-GT, while HCV-RNA was quantified by the Abbott RealTime HCV assay (Abbott Molecular, Des Plaines, IL), providing a lower limit of quantification and detection at 12 IU/mL. As previously described, the Fibrosis-4 Score (Fib-4)[23] was calculated as age (years) × aspartate transaminase (AST; IU/L) × [platelet count (PLT); 10^9/L] × alanine transaminase [(ALT; IU/L)$^{1/2}$]$^{-1}$. The APRI score was calculated as AST × (upper limit of normal AST)$^{-1}$ × [PLT (10^9/L)]$^{-1}$ × 100.[26] The homeostasis model assessment for insulin resistance (HOMA-IR) was defined by fasting plasma insulin (mU/L) × fasting plasma glucose (mmol/L) × 22.5^{-1}.[27] Diagnoses of diabetes and/or arterial hypertension were documented.

Liver stiffness and CAP

LSM was performed by TE (FibroScan®; Echosens, Paris, France), as described elsewhere.[28] After an overnight fast, LSM and CAP were measured by the M-probe, or XL-probe as suggested by the TE device. The following liver stiffness cutoffs defined different liver fibrosis (F) stages: <7.1 kPa for F0/F1, ≥7.1 and <9.5 kPa for ≥F2, ≥9.5 and <12.5 kPa for ≥F3, and ≥12.5 kPa for ≥F4.[26] CAP measurements were obtained simultaneously to TE.[29] As previously suggested by Karlas et al.,[17] the CAP values were adjusted for BMI (4.4 dB/m was deducted for each BMI unit >25 and ≤30 kg/m^2, while 4.4 dB/m was added for each BMI unit <25 and ≥20 kg/m^2) and for the presence of DM (10 dB/m was deducted in diabetic subjects). CAP values ≥248 dB/m defined HS, however, additional severity stages of HS were not differentiated. Progression in HS after HCV eradication was defined empirically as a delta (Δ)CAP of >+10% of the individual baseline (BL) values.

Statistical analyses

We used GraphPad Prism 7.03 (GraphPad Software, Inc., La Jolla, CA) and IBM SPSS Statistics 24 (SPSS, Inc., Armonk, NY) for all statistical analyses. Categorical variables were reported as number (percentage) of patients with/without a certain characteristic, while continuous parameters were shown as mean ± standard deviation or median (interquartile range). Normal distribution was visually assessed by inspecting histograms of continuous variables. Student's *t*-test or Wilcoxon–Mann–Whitney U test was applied for group comparisons of parametric and nonparametric variables, respectively. Differences in categorical variables were assessed by chi-squared test or Fisher's exact test. For paired measurements, one-sample *t*-test of the respective delta or Wilcoxon signed-rank test was used for continuous variables, while the McNemar test was applied for categorical variables. Binary logistic regression models were computed for the prediction of dichotomous variables. A p value of ≤0.05 was defined to denote statistical significance.

Ethics

This study was approved by the Ethics Committee of the Medical University of Vienna (EK No. 1527/2017) and conducted in accordance with the revised Declaration of Helsinki.

Results

Patient characteristics

Three hundred three patients with HIV/HCV coinfection visited our outpatient ward since 2014. After exclusion of patients with negative HCV-RNA and patients without available CAP value measurements, 247 patients were included in the prevalence cohort (Fig. 1) with 31% (76/247) having HS as defined by CAP value ≥248 dB/m. A second TE, including CAP following HCV eradication with IFN-free treatment, was available in 138 patients who were included in the follow-up cohort.

Mean age was 43.3 years, the majority were Caucasian (96%; 238/247) and male (75%; 185/247), 55% (135/247) had a ''people who inject drugs'' (PWID) background, while 30% (73/247) were categorized as ''men who have sex with men'' (MSM). Mean BMI in the prevalence cohort was 23.3 kg/m^2. Only 3% (8/247) had diabetes and 9% (22/247) were diagnosed with arterial hypertension. Steatogenic PNPLA3 GTs were present in 4% (rs738409 G/G, 9/213) and 44% (rs738409 G/C, 94/213), respectively. The median time since HIV diagnosis was 11.3 years and the majority of patients were on ART (98%; 243/247). Eighty-two percent (199/243) showed suppressed HIV viremia (HIV-RNA <50 copies/mL). HCV-GT-1a was most frequent (49%; 120/245) followed by HCV-GT-3 (23%; 56/245). Liver fibrosis stage F0/1 and cirrhosis (F4) were observed in 49% (114/247) and 13% (33/247), respectively.

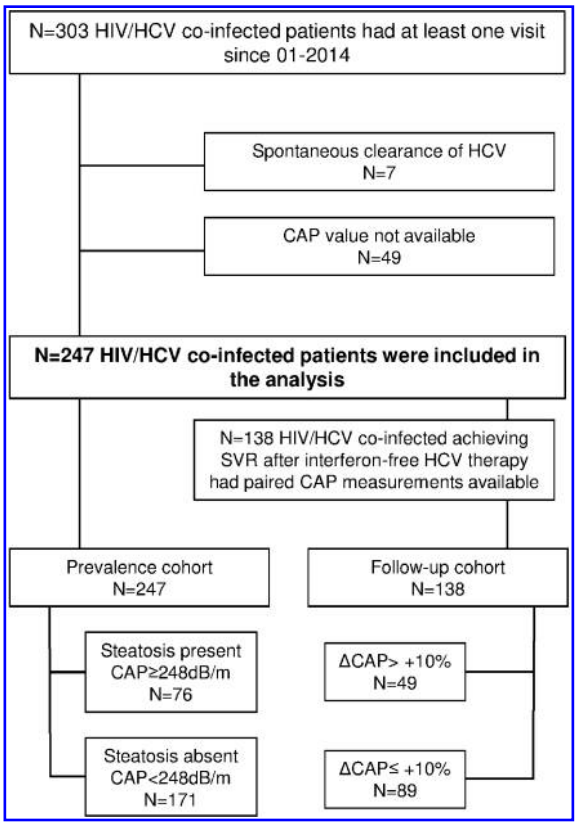

FIG. 1. Patient flowchart. CAP, controlled attenuation parameter; GT, genotype; HCV, hepatitis C virus; HIV, human immunodeficiency virus; SVR, sustained virological response.

Predictors for HS in HIV/HCV-coinfected patients

Higher BMI was associated with the presence of HS (22.6 ± 3.79 vs. 24.9 ± 4.3 kg/m^2; $p < 0.001$). Moreover, HOMA-IR was slightly increased [2.32 (3.69) vs. 3.32 (2.17); $p = 0.047$] in individuals with HS, while plasma lipids did not significantly differ (Fig. 2A). Most patients with PWID as the suspected route of HCV transmission had HS (71% vs. 47%; $p < 0.001$), whereas opioid substitution therapy, DM, arterial hypertension, and ethnicity were not associated with HS (Supplementary Table S1). While HS was absent in all three Asian patients, the number of subjects with non-Caucasian race (African American $N = 4$, Hispanic $N = 2$, Asian $N = 3$) seemed too small to accurately detect differences in HS prevalence and dynamics according to race in our prediction models. Further, protease inhibitor (PI) intake, as part of ART, was more frequent among patients with HS [39% (29/74) vs. 11% (18/167); $p < 0.001$] (Fig. 2B).

In logistic regression models (Table 1), the following parameters showed an association with HS: age, duration of HIV infection and HCV infection, exposure to ART, BMI, PNPLA3 G-alleles, and ART-PI intake.

Importantly, on multivariate analysis, longer duration of HIV infection [per year; adjusted odds ratio (aOR): 1.04 (1.01–1.07); $p = 0.006$], BMI {per unit; aOR: 1.18 [95% confidence intervals (95-CI) 1.09–1.28; $p < 0.001$], PNPLA3 [per ''G'' allele; aOR: 2.30 (95-CI 1.28–4.13); $p = 0.006$]}, and PI intake [aOR: 4.23 (95-CI 1.97–9.08); $p < 0.001$] remained independent risk factors for HS. Notably, HCV-GT-3 was not significantly associated with an increased risk for HS [OR: 1.39 (95-CI 0.74–2.61); $p = 0.309$].

Impact of HCV eradication

One hundred thirty-eight patients underwent paired CAP measurements and laboratory assessment. While the BMI did not significantly change (23.8 ± 4.36 vs. 24.1 ± 4.64 kg/m^2; $p = 0.113$), higher CAP values (225 ± 52.9 vs. 235 ± 50.7; $p = 0.047$) were observed after HCV eradication (Fig. 3). In contrast, SVR resulted in significant decreases of AST ($p < 0.001$), ALT ($p < 0.001$), gamma-glutamyl transpeptidase (GGT; $p < 0.001$) levels, as well as of liver stiffness ($p < 0.001$) (Table 2). Moreover, a low-density lipoprotein (LDL)-driven rise in total cholesterol (TCHOL; $p < 0.001$) was documented. Achieving SVR after HCV treatment was associated with an increase in the proportion of patients with HIV suppression [100% (128/128) vs. 85% (115/136) at BL; $p < 0.001$]. In addition, the CD4$^+$ T lymphocyte count increased ($p < 0.001$).

Predictors for changes of HS after HCV eradication

Patients with an increase in ΔCAP >10% of BL were more often MSM [51% (25/49) vs. 26% (23/89); $p = 0.013$] and had higher LDL values at BL (101 ± 32.1 vs. 82.1 ± 33.7 mg/dL;

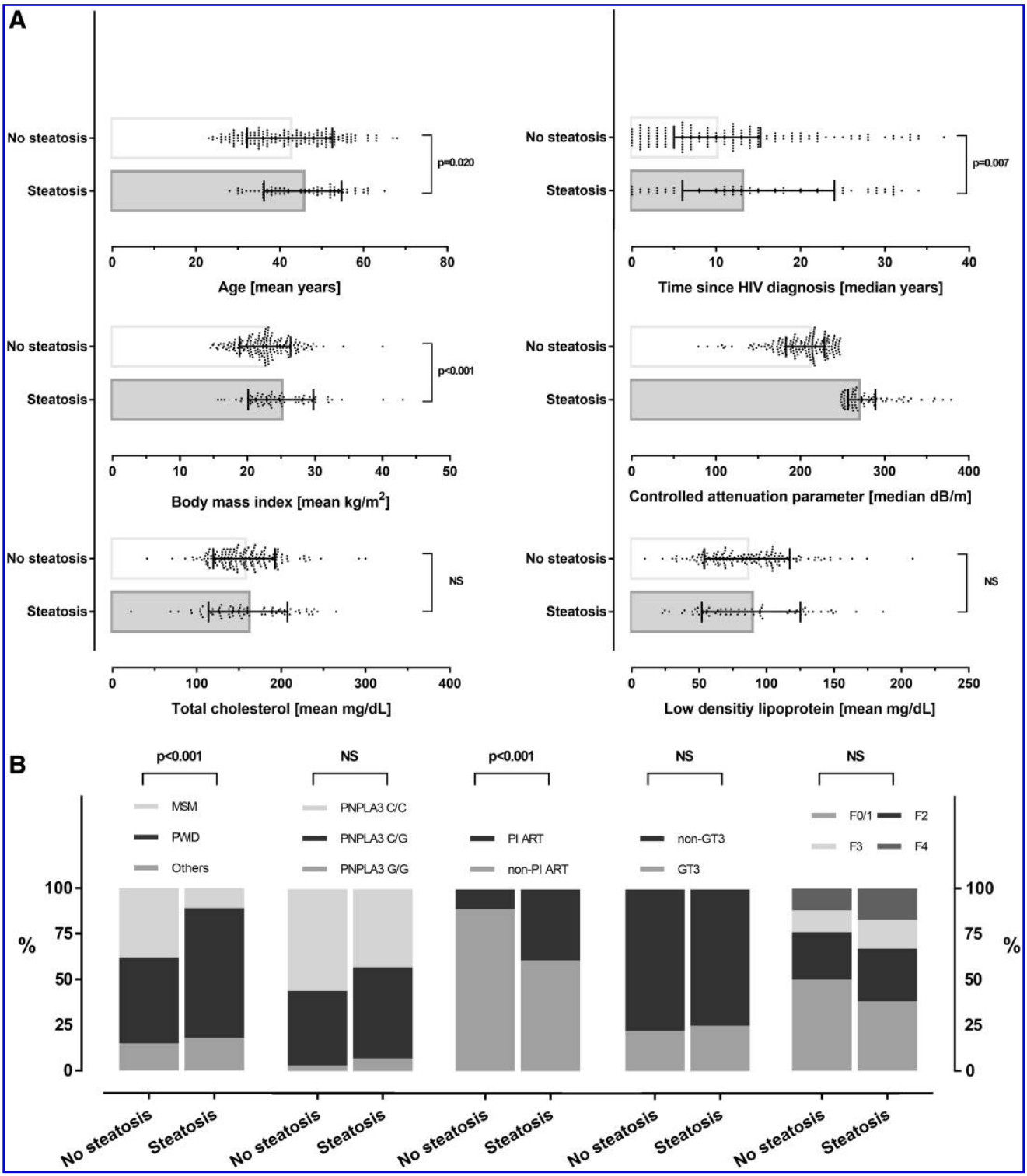

FIG. 2. Patient characteristics of continuous **(A)** and categorical **(B)** variables of the prevalence cohort in regard to hepatic steatosis status. Statistics: **(A)** Symbols indicate the values of individual patients, and the bold error bars represent the SD or IQR, as appropriate. Independent sample *t*-test was used for comparison of means, while Wilcoxon–Mann–Whitney U test was used for comparison of medians. **(B)** Chi-squared test or Fisher's exact test was used for statistical analysis. ART, antiretroviral therapy; BMI, body mass index; CAP, controlled attenuation parameter; GT, genotype; HIV, human immunodeficiency virus; IQR, interquartile range; MSM, men who have sex with men; NS, not significant; PI, protease inhibitor; PWID, people who inject drugs; SD, standard deviation.

Table 1. Prevalence Cohort

Patient characteristics (n = *247*)	*OR for steatosis (CAP ≥248 dB/m)*	p	*aOR*	p
Epidemiological characteristics				
Sex				
Male	0.62 (0.34–1.13)	0.119		
Age (per 5 years)	1.18 (1.03–1.35)	**0.021**	1.04 (0.85–1.26)	0.732
Ethnicity				
Caucasian	0.90 (0.22–3.71)	0.887		
African American ($N=4$), Hispanic ($N=2$), or Asian ($N=3$)	1.11 (0.27–4.55)	0.887		
Transmission				
MSM	0.19 (0.09–0.42)	**<0.001**		
PWID	2.73 (1.53–4.87)	**0.001**		
Others	1.32 (0.64–2.71)	0.450		
Weight (per 5 kg)	1.17 (1.07–1.29)	**0.001**		
BMI (per kg/m^2)	1.14 (1.07–1.22)	**<0.001**	1.18 (1.09–1.28)	**<0.001**
DM	1.36 (0.32–5.83)	0.682		
Hypertension	1.31 (0.53–3.27)	0.562		
PNPLA3 (rs738409)				
G-risk allele	1.62 (0.99–2.64)	0.054	2.30 (1.28–4.13)	**0.006**
Laboratory parameters				
Platelet count (per 10 G/L)	0.97 (0.93–1.00)	0.057		
Prothrombin time (per 10%)	1.10 (0.96–1.27)	0.168		
Bilirubin (per mg/dL)	0.96 (0.82–1.13)	0.634		
Albumin (per 5 g/dL)	1.22 (0.87–1.70)	0.246		
AST (per 10 U/L)	0.95 (0.89–1.01)	0.074		
ALT (per 10 U/L)	0.96 (0.93–0.99)	**0.023**		
GGT (per 10 U/L)	1.00 (0.99–1.02)	0.686		
TG (per 10 mg/dL)	1.00 (0.96–1.04)	0.990		
TCHOL (per 10 mg/dL)	1.03 (0.96–1.10)	0.427		
HDL (per 10 mg/dL)	1.04 (0.89–1.21)	0.630		
LDL (per 10 mg/dL)	1.03 (0.94–1.12)	0.530		
HOMA-IR	1.01 (0.97–1.04)	0.664		
HIV infection parameters				
Time since diagnosis of HIV (per year)	1.04 (1.01–1.07)	**0.003**	1.04 (1.01–1.07)	**0.006**
CD4$^+$ T lymphocyte count (per 50 cells/μL)	0.98 (0.93–1.02)	0.329		
HIV-RNA <50 copies/mL	1.24 (0.60–2.56)	0.569		
HIV-RNA <400 copies/mL	1.87 (0.60–5.79)	0.279		
ART				
PI	5.33 (2.71–1.49)	**<0.001**	4.23 (1.97–9.08)	**<0.001**
N(t)RTI	0.35 (0.10–1.18)	0.092		
NNRTI	0.78 (0.40–1.52)	0.469		
INSTI	0.47 (0.27–0.81)	**0.007**	1.13 (0.50–2.56)	0.768
Time on ART (per year)	1.05 (1.01–1.09)	**0.013**	1.00 (0.95–1.06)	0.930
HCV infection parameters				
Time since diagnosis of HCV (per year)	1.04 (1.01–1.06)	**0.011**	1.01 (0.97–1.06)	0.606
HCV-RNA (per log IU/mL)	1.06 (0.84–1.35)	0.615		
HCV-GT				
1a	0.60 (0.35–1.04)	0.069		
1b	1.85 (0.92–3.72)	0.082		
2	1.13 (0.20–6.30)	0.890		
3	1.39 (0.74–2.61)	0.309		
4	0.83 (0.31–2.21)	0.710		
Liver stiffness				
F0/F1 (<7.1 kPa)	0.62 (0.36–1.08)	0.094		
F2 (≥7.1 and <9.5 kPa)	1.14 (0.63–2.08)	0.668		
F3 (≥9.5 and <12.5 kPa)	1.34 (0.62–2.88)	0.456		
F4 (≥12.5 kPa)	1.56 (0.73–3.32)	0.251		

Bold *p* values denote statistical significance.

ALT, alanine transaminase; aOR, adjusted odds ratio; ART, antiretroviral therapy; AST, aspartate transaminase; BMI, body mass index; CAP, controlled attenuation parameter; DM, diabetes mellitus; GGT, gamma-glutamyl transpeptidase; GT, genotype; HCV, hepatitis C virus; HDL, high-density lipoprotein; HIV, human immunodeficiency virus; HOMA-IR, homeostasis model assessment for insulin resistance; INSTI, integrase inhibitors; LDL, low-density lipoprotein; MSM, men who have sex with men; NNRTI, non-nucleoside reverse-transcriptase inhibitor; N(t)RTI, nucleos(t)idic reverse transcriptase inhibitor; OR, odds ratio; PI, protease inhibitor; PNPLA3, patatin-like phospholipase domain containing 3; PWID, people who inject drugs; TCHOL, total cholesterol; TG, triglyceride.

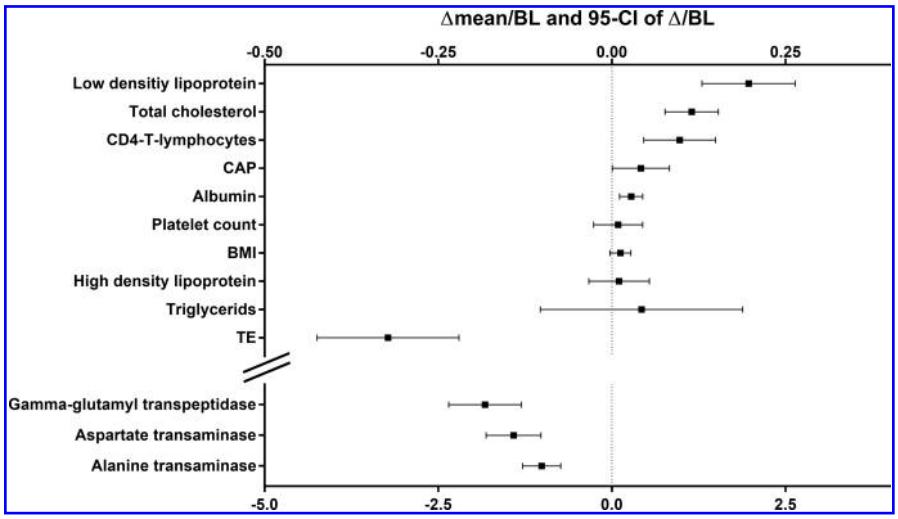

FIG. 3. Relative changes 95-CI after hepatitis C virus eradication of laboratory parameters, BMI, CAP, and TE, compared with BL. Statistics: The Δ was calculated for each variable and normal distribution of the corresponding Δ was verified. The one-sample *t*-test was used to calculate 95-CI. Symbols indicate the mean relative Δ and the error bars represent its 95-CI of the respective parameter. 95-CI, 95% confidence interval; BL, baseline; BMI, body mass index; CAP, controlled attenuation parameter; TE, transient elastography.

$p = 0.005$). Notably, higher BL HCV-RNA was associated with increasing ΔCAP >10% (7.17 ± 9.56 vs. 6.13 ± 0.79 log IU/mL; $p < 0.001$), while HCV-GT or DAA regimen had no impact on HS (Table 2). Individuals on PI-containing ART more frequently had no change in HS [34% (30/87) vs. 8% in non-PI-ART users (4/49); $p = 0.001$]. Interestingly, while the mean CAP increased in the overall follow-up cohort, it decreased significantly from BL to follow-up among patients receiving a PI-containing ART (253 ± 56.5 vs. 231 ± 60.8 dB/m; $p = 0.040$). Importantly, the discontinuation of PI-ART regimens due to potential drug/drug interactions (DDI) with HCV regimens prior/during DAA treatment was not associated with a change in ΔCAP >10% of BL ($p = 0.926$).

In logistic regression models (Supplementary Table S2), independent factors not associated with change in CAP were PI-containing ART before DAA initiation [aOR: 4.75 (95-CI 1.32–17.14); $p = 0.017$] and high HCV-RNA [per log IU; aOR: 1.77 (95-CI 1.14–2.74); $p = 0.011$], while elevated BL LDL levels were indicative for HS progression [per 10 IU; aOR: 1.18 (95-CI 1.02–1.35); $p = 0.022$].

Discussion

By using the CAP as a noninvasive tool for HS assessment, we found that nearly one-third of HIV/HCV presenting at our center are affected by HS—with similar prevalence being reported in previous reports.[14] The use of PI-containing ART and the duration of HIV infection were found to increase the risk of HS in HIV/HCV patients. Further, we observed an increase of CAP after DAA-induced HCV eradication and an increase in TCHOL levels—indicating an expressed impact of HCV on hepatic lipid metabolism.

The capabilities of CAP for detecting increased fat content have been shown earlier[29] and while the limited reliability of the assessment in patients with high BMI has been discussed previously,[30] sufficient corrective algorithms and the XL-probe have been introduced to overcome this potential limitation.[17,31] Both methods were applied in our study to compensate for high BMI. Moreover, since alcohol intake could be another confounder, we have rigorously interviewed patients about any alcohol use during the study period and thus are confident that our patients did not have harmful alcohol intake during the treatment period.

Previous data have shown a significant impact of SVR to IFN-based therapy on HS improvement in patients with HCV-GT3 monoinfection, strongly suggesting a direct steatogenic effect of HCV-GT3.[18,19] However, since treatment response to IFN-based regimens was low and dependent on multiple other host factors,[32] IFN-associated SVR might introduce a potential bias. As IFN-free DAA-based regimens result in SVR rates >95%,[22,33,34] these patient cohorts are not preselected by treatment response and changes in HS can be assessed with a low risk of bias. Further, histological HS assessment involves a considerable risk of severe complications[35] and thus is often limited to patients with evidence of ongoing liver disease. Accordingly, liver biopsy-based studies are prone to selection bias in addition to the commonly observed sample variability due to irregularities in liver parenchyma.[36] However, variability is also a concern in CAP measurements. While there are insufficient data on the intra- and interobserver agreement of individual CAP measurements, our personal experience is that CAP measurements well correlate with steatosis and are accurate if quality criteria for LSM are fulfilled (as in our study). Still, we cannot completely exclude that CAP variability impacted on the results.

Several independent risk factors for HS could be identified in our prevalence cohort. As previously reported,[37] HS was linked to increased BMI, HOMA-IR index, and the presence of a PNPLA3-G allele. Only 3% of our cohort was diagnosed with DM, which is in line with the previously reported prevalence of DM among HIV/HCV.[38] Due to type 2 error, the low prevalence of DM may have contributed to the lack of a significant association between DM and HS. Moreover, the low prevalence of DM indicates a low frequency of metabolic syndrome, which could explain why hypertension, high TCHOL levels, and low high-density lipoprotein levels as metabolic syndrome determinants[39] were not predictive for HS. Since waist circumference as a critical diagnostic component for metabolic syndrome was not available, a diagnosis of metabolic syndrome could not be accurately established and thus was not included in the prediction models. However, PI-based ART was associated with the highest aOR for the

TABLE 2. FOLLOW-UP COHORT

Patient characteristics (N = *138*)	*At baseline* (N = *138*)	*At follow-up* (N = *138*)	p	Δ*CAP* ≤ *+10%* (n = *89*)	Δ*CAP* > *+10%* (n = *49*)	p
Epidemiological characteristics						
Sex						
Male, % (*n*/all)	78 (107/138)			74 (66/89)	84 (41/49)	0.286
Age (years)	44.8 ± 10.1			46.0 ± 9.45	42.4 ± 10.9	**0.045**
Transmission, % (*n*/all)						
MSM	35 (48/138)			26 (23/89)	51 (25/49)	**0.013**
PWID	49 (67/138)			55 (49/89)	37 (18/49)	
Others	17 (23/138)			19 (17/89)	12 (6/49)	
Weight (kg)	72.1 ± 15.4	72.6 ± 16.2	0.136	72.2 ± 16.6	71.7 ± 13.2	0.847
BMI (kg/m^2)	23.8 ± 4.36	24.1 ± 4.64	0.113	23.9 ± 4.30	23.5 ± 4.19	0.591
DM, % (*n*/all)	5 (7/138)			4 (4/89)	6 (3/49)	0.699
Hypertension, % (*n*/all)	9 (13/138)			8 (7/89)	12 (6/49)	0.544
PNPLA3, % (*n*/all)						
CC	50 (65/131)			51 (45/88)	47 (20/43)	0.711
GG	3 (4/131)			3 (3/88)	2 (1/43)	1
Laboratory parameters						
Platelet count (G/L)	199 ± 73.0	201 ± 67.4	0.616	190 ± 74.3	217 ± 68.0	**0.036**
Prothrombin time (%)	90.3 ± 20.8	88.9 ± 17.9	0.506	89.3 ± 21.0	92.0 ± 20.6	0.476
Bilirubin (mg/dL)	0.56 (0.38)	0.42 (0.27)	0.149	0.59 (0.39)	0.51 (0.36)	0.296
Albumin (g/dL)	44.0 ± 4.17	45.3 ± 4.32	**0.001**	43.4 ± 4.08	45.0 ± 4.18	0.029
AST (U/L)	52.0 (52.3)	24.0 (9.00)	**<0.001**	51.0 (47.0)	53.0 (61.5)	0.966
ALT (U/L)	53.0 (81.0)	18.0 (9.25)	**<0.001**	51.0 (73.5)	53.0 (117)	0.441
GGT (U/L)	70.5 (116)	22.0 (14.0)	**<0.001**	81.0 (108)	57.0 (123)	0.474
TG (mg/dL)	103 (70.0)	97.0 (76.5)	0.564	104 (76.8)	97.0 (66.0)	0.631
TCHOL (mg/dL)	159 ± 41.0	179 ± 43.1	**<0.001**	156 ± 42.5	166 ± 37.5	0.151
HDL (mg/dL)	46.3 ± 19.0	47.5 ± 15.5	0.639	47.2 ± 21.1	44.6 ± 13.8	0.501
LDL (mg/dL)	88.3 ± 34.2	105 ± 36.3	**<0.001**	82.1 ± 33.7	101 ± 32.1	**0.005**
HOMA-IR	3.44 (2.79)	1.85 (2.64)	0.106	3.36 (2.52)	3.93 (8.54)	0.316
FIB-4	1.55 (1.52)	1.22 (1.04)	**<0.001**	1.68 (1.83)	1.32 (0.87)	**0.018**
APRI	0.59 (0.86)	0.24 (0.17)	**<0.001**	0.60 (0.86)	0.59 (0.79)	0.227
HIV infection parameters						
Time since diagnosis of HIV (years)	12.7 (16.6)			14.9 (16.6)	9.41 (14.5)	**0.018**
CD4$^+$ T lymphocyte count (cells/μL)	569 ± 276	648 ± 328	**<0.001**	544 (378)	591 (504)	0.403
HIV-RNA <50 copies/mL	85% (115/136)	100% (128/128)	**<0.001**	85% (75/88)	83% (40/48)	0.807
HIV-RNA <400 copies/mL	93% (127/136)	100% (128/128)	**0.008**	93% (82/88)	94% (45/48)	1
ART before HCV treatment, % (*n*/all)						
PI	25 (34/136)			34 (30/87)	8 (4/49)	**0.001**
N(t)RTI	94 (128/136)			92 (80/87)	98 (48/49)	0.258
NNRTI	30 (42/136)			24 (21/87)	41 (21/49)	**0.042**
INSTI	48 (65/136)			46 (40/87)	51 (25/49)	0.596
Time on ART (years)	6.80 (11.2)			8.69 (13.0)	4.22 (8.41)	**0.006**
HCV infection parameters						
Time since diagnosis of HCV (years)	7.55 (17.7)			10.4 (19.0)	1.75 (10.6)	**0.002**
HCV-RNA (log IU/mL)	6.14 (1.24)			6.13 ± 0.79	7.17 ± 9.56	**<0.001**
HCV-GT, % (*n*/all)						
1a	53 (73/138)			45 (40/89)	67 (33/49)	0.068
1b	12 (16/138)			16 (14/89)	4 (2/49)	
2	2 (3/138)			3 (3/89)	0 (0/49)	
3	22 (30/138)			24 (21/89)	18 (9/49)	
4	12 (16/138)			12 (11/89)	10 (5/49)	
Liver stiffness, % (*n*/all)						
F0/F1 (<7.1 kPa)	36 (50/138)	70 (97/138)	**<0.001**	30 (27/89)	47 (23/49)	0.052
F2 (≥7.1 and <9.5 kPa)	33 (45/138)	14 (20/138)	**0.001**	33 (29/89)	33 (16/49)	0.993
F3 (≥9.5 and <12.5 kPa)	15 (21/138)	5 (7/138)	**0.011**	17 (15/89)	12 (6/49)	0.471
F4 (≥12.5 kPa)	16 (22/138)	10 (14/138)	**0.021**	20 (18/89)	8 (4/49)	0.064
TE (kPa)	7.85 (4.20)	5.95 (3.33)	**<0.001**	8.50 (5.40)	7.30 (3.70)	**0.013**
Steatosis, % (*n*/all)						
S0	70 (96/138)	61 (84/138)	0.082	60 (53/89)	88 (43/49)	**0.001**
≥S1	30 (42/138)	39 (54/138)	0.082	40 (36/89)	12 (6/49)	**0.001**
CAP values (dB/m)	225 ± 52.9	235 ± 50.7	**0.047**	242 ± 48.0	194 ± 47.3	**<0.001**

Bold *p* values denote statistical significance.

ALT, alanine transaminase; ART, antiretroviral therapy; AST, aspartate transaminase; BMI, body mass index; CAP, controlled attenuation parameter; DM, diabetes mellitus; GGT, gamma-glutamyl transpeptidase; GT, genotype; HCV, hepatitis C virus; HDL, high-density lipoprotein; HIV, human immunodeficiency virus; HOMA-IR, homeostasis model assessment for insulin resistance; INSTI, integrase inhibitor; LDL, low-density lipoprotein; MSM, men who have sex with men; NNRTI, non-nucleoside reverse-transcriptase inhibitor; N(t)RTI, nucleos(t)idic reverse transcriptase inhibitor; PI, protease inhibitor; PNPLA3, patatin-like phospholipase domain containing 3; PWID, people who inject drugs; TCHOL, total cholesterol; TE, transient elastography; TG, triglyceride.

presence of HS. Two studies, one conducted by Macias et al. in 2014[40] including 505 HIV+ (including a subgroup of 159 HCV-coinfected patients) individuals and the other by Vuille-Lessard et al. in 2016[41] including 300 HIV+ individuals, found no significant association between PI-containing ART and HS measured by CAP. Interestingly, while we observed an overall increase in CAP after HCV eradication, patients receiving a PI-containing ART had a significant decrease in CAP after HCV eradication. Moreover, the observed effect was independent of PI discontinuation, which was required in some of the patients to circumvent DDI with HCV-DAAs. Thus, our data suggest a steatogenic effect of PI-containing ART only in the presence of HCV. However, since CAP values were the highest among patients with PI intake at BL, our observation might be affected by the statistical phenomenon referred to as ''regression to the mean.''[42] It occurs frequently when the mean of a specific parameter of a cohort diverges extremely from the expected value. At a subsequent measurement, it will tend to be closer to the average. Taken together, this effect may augment the high statistical significance observed for CAP regression after HCV eradication in patients on a PI.

Further, switching from a PI-containing ART to an non-nucleoside reverse-transcriptase inhibitor (NNRTI) or integrase inhibitor (INSTI) plus nucleos(t)idic reverse-transcriptase inhibitor [N(t)RTI] backbone leads to decreases in triglycerides, TCHOL, and LDL in HIV-monoinfected patients.[43,44] In addition, PI intake modulates the impact of alcohol consumption on hepatic fibrogenesis.[45] HCV itself, however, also impacts hepatic lipid metabolism and transport: HCV circulates as highly lipidated particles and takes advantage of the LDL receptor and the Niemann Pick C1-Like 1 protein as entry factors.[46] Once it has entered the hepatocytes, it induces the sterol response element binding protein (SREBP).[46] Consecutively, HCV promotes the expression of fatty acid synthase along with HMG-co-A reductase while simultaneously inhibiting cholesterol secretion.[47] Hence, decreased levels of LDL and further TCHOL have been described in HCV patients.[48] Moreover, causality is confirmed by the increase of serum LDL after HCV eradication[49]—which was also observed in our follow-up cohort. In addition, we found significant increases in CAP after HCV eradication, a subsequent effect of HCV eradication that was previously reported for HIV-negative patients.[50] This may be also due to a ''return-to-health effect,''[51] which might be associated with increased appetite and a psychogenic ''de-depression'' after HCV eradication.[52,53] However, BMI did not significantly change between BL and follow-up—which suggests that a ''return-to-health effect'' may not be a major determinant of increasing CAP after HCV eradication in our cohort. Still, a cutoff for a ''clinically meaningful'' change in CAP that corresponds to clinical outcomes has not yet been established. A recently published study suggested that a change of more than 38 dB/m in CAP would indicate a >1% change in magnetic resonance imaging-estimated proton density fat fraction (PDFF).[54] However, in general, CAP had a poor performance for predicting changes in PDFF and the study was not designed to assess the clinical impact of this absolute change in CAP. Thus, our results derived from the follow-up cohort are limited by the unknown clinical significance of the measured dynamics in CAP.

In conclusion, HS can be found in about one-third of HIV/HCV-coinfected patients. Next to host factors such as BMI and PNPLA3 risk alleles, the duration of HIV infection and exposure to PI-containing ART are independent risk factors for HS in HIV/HCV patients. Importantly, HCV eradication by DAA-based therapy seems to increase CAP values—in parallel to increases in cholesterol, that is, in LDL plasma levels. Interestingly, elevated BL LDL and the use of non-PI-ART regimens were associated with increases in CAP values after HCV eradication. Ultimately, it remains to be established if HIV patients with elevated CAP values and LDL levels after HCV eradication are at higher risk of HS and its associated metabolic and cardiovascular events.

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Authors' Contributions

Study concept and design (D.C and T.R.), acquisition of data (D.C., M.M., T.B., P.S., D.B., C.S., G.F.L., T.S., and T.R.), analysis and interpretation of data (D.C., M.M., P.S., and T.R.), drafting of the article (D.C., M.M., and T.R.), and critical revision of the article for important intellectual content (D.C., M.M., T.B., P.S., D.B., B.S., C.S., G.F.L., T.S., P.F., M.T., and T.R.).

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D.C. received payments for consulting from MSD and Gilead, as well as travel support from AbbVie and Gilead. M.M. received honoraria for consulting and payments for lectures from AbbVie, Bristol-Myers Squibb, Gilead, and Janssen, as well as travel support from AbbVie and Gilead. T.B. received speaker fees from MSD and received travel support from AbbVie, Gilead, MSD, and Medis. P.S. received speaker fees from Boehringer Ingelheim and Bristol-Myers Squibb. D.B. has nothing to disclose. B.S. received travel support from AbbVie and Gilead. C.S. received travel support from Gilead. G.F.L. received payments for lectures from Gilead; received travel support from Gilead and GSK; received honoraria for consulting from Gilead and GSK. T.S. has nothing to disclose. P.F. received unrestricted research grants from Gilead, as well as honoraria for board membership and consulting from AbbVie and MSD. M.T. received grants from Albireo, CymaBay, Falk, Gilead, Intercept, MSD, and Takeda; advisory board fees from Albireo, Gilead, Falk, Novartis, Intercept, MSD, Phenex, and Regulus; and speaker and/or travel fees from Intercept, Gilead, Falk, and MSD. He is also listed as coinventor on patents on medical use of nor-UDCA (filed by the Medical University of Graz). T.R. received payments for lectures from Roche and MSD; received travel support from Gilead, MSD, and Roche; received grant support from AbbVie, Gilead, and MSD; and consulted for AbbVie, Gilead, and MSD.

Supplementary Material

Supplementary Table S1
Supplementary Table S2

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