

Changes in Hepatic Steatosis Before and After Direct-Acting Antiviral Treatment in People With HIV and Hepatitis C Coinfection

Esther Truscello,¹ Shouao Wang,² Jim Young,^{2,3,4} Giada Sebastiani,^{2,4} Sharon L. Walmsley,^{5,6} Mark Hull,⁷ Curtis Cooper,⁸ and Marina B. Klein^{2,3,6,9},
for the Canadian Coinfection Cohort Investigators

¹Faculty of Health, Medicine, and Life Sciences, Maastricht University, Maastricht, The Netherlands; ²Department of Medicine, Division of Infectious Diseases, Research Institute of the McGill University Health Centre, Montreal, Quebec, Canada; ³Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, Quebec, Canada; ⁴Division of Experimental Medicine, Department of Medicine, McGill University Health Centre, Montreal, Quebec, Canada; ⁵University Health Network, University of Toronto, Toronto, Ontario, Canada; ⁶Canadian Institutes of Health Research Canadian HIV Trials Network, Vancouver, British Columbia, Canada; ⁷Department of Medicine, British Columbia Centre for Excellence in HIV/AIDS, Vancouver, British Columbia, Canada; and ⁸Department of Medicine, Ottawa Hospital Research Institute, Ottawa, Ontario, Canada

Background. Both human immunodeficiency virus (HIV) and hepatitis C virus (HCV) infections increase the risk of hepatic steatosis (HS), which in turn contribute to the severity and progression of liver disease. Direct-acting antivirals (DAAs) can cure HCV but whether they reduce HS is unclear.

Methods. HS was assessed using the controlled attenuation parameter (CAP) and the Hepatic Steatosis Index (HSI) in participants coinfecting with HIV and HCV from the Canadian Coinfection Cohort. Changes in HS, before, during, and after successful DAA treatment were estimated using generalized additive mixed models, adjusted for covariates measured prior to treatment (age, sex, duration of HCV infection, body mass index, diabetes, prior exposure to dideoxynucleosides, and hazardous drinking).

Results. In total, 431 participants with at least 1 measure of CAP or HSI before treatment were included. CAP steadily increased over time: adjusted annual slope 3.3 dB/m (95% credible interval [CrI], 1.6–4.9) before, and 3.9 dB/m (95% CrI, 1.9–5.9) after DAA treatment, irrespective of pretreatment CAP. In contrast, HSI changed little over time: annual slope 0.2 (95% CrI, –0.1 to 0.5) before and 0.2 (95% CrI, –0.1 to 0.5) after, but demonstrated a marked reduction during treatment –4.5 (95% CrI, –5.9 to –3.1).

Conclusions. When assessed by CAP, HS was unaffected by DAA treatment and steadily increased over time. In contrast, HSI did not appear to reflect changes in HS, with the decrease during treatment likely related to resolution of hepatic inflammation. Ongoing HS may pose a risk for liver disease in coinfecting people cured of HCV.

Keywords. HIV-hepatitis C coinfection; hepatic steatosis; direct-acting antivirals; controlled attenuation parameter; Hepatic Steatosis Index.

Human immunodeficiency virus (HIV) affects the natural history of hepatitis C virus (HCV), and people coinfecting with HIV and HCV experience faster liver disease progression [1]. HIV and HCV infections are each independently associated with hepatic steatosis (HS), the accumulation of lipids in hepatocytes [2, 3]. HS prevalence ranges from

35% to 86% depending on population studied [4], although it is unclear if rates are affected by dual infection. HS can lead to hepatocellular injury through oxidative stress and a proinflammatory environment (steatohepatitis) [5]. Steatohepatitis, in turn, accelerates fibrosis progression leading to increased risks of cirrhosis, hepatocellular carcinoma, and all-cause mortality [6, 7].

Several pathogenetic mechanisms might contribute to the development of HS in HIV-HCV coinfection. These are often differentiated as direct cytopathic effects of HCV (viral steatosis), seen predominantly in genotype 3 HCV infection, and indirect effects mediated through insulin resistance (metabolic steatosis), seen in HCV genotype 1, 2, or 4 infections [8]. HCV can directly disrupt lipid metabolism through upregulation of lipogenesis, accumulation of intrahepatic triglycerides, and by inducing mitochondrial dysfunction, which in turn decreases lipoprotein degradation [9]. HCV also induces insulin resistance, ultimately promoting lipogenesis and a hypocholesterolemic state [5, 9]. HIV has direct proapoptotic effect on hepatocytes, disrupts mitochondrial function, causes immune

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Correspondence: Marina B. Klein, MD, MSc, Division of Infectious Diseases and Chronic Viral Illness Service, McGill University Health Centre, 1001 Decarie Boulevard, D02.4110, Montreal H4A 3J1, Quebec, Canada (marina.klein@mcgill.ca).

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activation, and establishes a proinflammatory environment, contributing to insulin resistance [1, 7]. Certain early generation antiretrovirals such as dideoxynucleosides (d-drugs) and protease inhibitors, may directly contribute to HS by exacerbating metabolic disturbances and impairing lipid oxidation [10]. More recently, integrase inhibitors have been associated with weight gain, through mechanisms not yet known [11]. Increasing body mass index (BMI) has been associated with the risk of HS in a dose-dependent manner [12].

Direct-acting antivirals (DAAs) result in sustained virologic responses (SVR) in over 95% of those treated. Viral eradication may have effects beyond direct hepatic benefits. Changes in blood lipids seem to reverse in people with HCV mono-infection, possibly increasing cardiovascular risk [13, 14], but it is not clear whether HCV cure also leads to a reversal in hepatocyte lipid content. Both increases and decreases in HS have been reported after successful DAA treatment in people with HIV-HCV coinfection [15–17] and HCV mono-infection [18–20].

An accessible, noninvasive marker sensitive to changes over time is essential for long-term monitoring of HS and for evaluating effects of interventions, such as HCV treatment, on HS. Liver biopsy is too impractical and risky. Transient elastography, with a controlled attenuation parameter (CAP) to estimate hepatic fat content, has been validated to assess HS in people with HCV infection and is now recommended in guidelines [21, 22]. The Hepatic Steatosis Index (HSI), which uses commonly available laboratory and clinical parameters, was developed in patients with nonalcoholic fatty liver disease (NAFLD) [23] and is increasingly used to estimate presence of HS in both HIV and HCV mono-infected populations [24, 25].

We assessed whether successful treatment with DAAs reduces HS over time when measured by CAP or HSI in people with HIV-HCV coinfection who have many ongoing risk factors for HS. In addition, we assessed whether the presence of pretreatment HS and HCV genotype affect the course of HS in this patient population.

METHODS

Data Collection

The Canadian Coinfection Cohort (CCC) is a multicenter, open prospective study established in 2003, recruiting participants 16 years of age or older, with proven HIV-HCV coinfection from 18 centers in Canada. A total of 2115 participants had been recruited as of February 2023. Clinical and laboratory data were collected approximately every 6 months during follow-up visits. Starting in 2014, 15 sites (representing 97% of CCC participants) had access to transient elastography with CAP using Fibroscan (Echosense). Participants underwent assessments at least yearly after fasting for at least 4 hours as per manufacturer guidelines.

CCC participants were included in this analysis if they achieved SVR following treatment with a second-generation DAA (eg, without interferon). SVR was defined as undetectable HCV RNA 12 weeks after treatment completion. Participants were excluded if reinfectd after successful interferon treatment, if previously unsuccessfully treated with DAAs, or if co-infected with hepatitis B virus (hepatitis B surface antigen positive). All participants meeting inclusion criteria and with at least 1 CAP or HSI measurement in the year prior to starting successful DAA treatment were included in our modelling. HSI was calculated as: $8 \times (\text{ALT/AST ratio}) + \text{BMI} + 2$ (if female) + 2 (if diabetes mellitus); where ALT is alanine aminotransferase (IU/L) and AST is aspartate aminotransferase (IU/L) [23]. Steatosis was defined as a CAP ≥ 248 dB/m [21] or an HSI ≥ 36 [23]. Diabetes mellitus was defined as having at least 1 of the following: (1) a recorded clinical diagnosis; (2) fasting glucose > 7.0 mmol/L or nonfasting glucose > 11.1 mmol/L; and (3) any use of insulin or antidiabetic medications. Alcohol use was assessed using the Alcohol Use Disorder Identification Test-C (AUDIT-C) [26]; hazardous drinking was defined as an AUDIT-C score of at least 4 for men and 3 for women.

The study was approved by the community advisory committee Canadian Institutes of Health Research-Canadian HIV Trials Network, by the Research Ethics Board of the McGill University Health Centre (2006-1875, BMB-06-006t), and by all institutional ethics boards of participating centers. All participants gave written informed consent in accordance with the ethical standards of the Helsinki Declaration.

Statistical Analysis

Generalized additive mixed models (GAMMs) were used to analyze the changes in CAP and HSI before, during, and after successful DAA treatment. This method allows for repeated measurements over time from the same individual, measurements at irregular intervals, and for the change in those measurements to be modelled using flexible spline functions rather than simple linear relationships. The *mgcv* package (version 1.8-41) with R (version 4.2) was used.

Changes in CAP over time were modelled as a γ distribution with identity link function; CAP is right-skewed and takes nonnegative continuous values. The GAMM included covariates measured prior to starting HCV treatment: age, sex, duration of HCV infection in years, diabetes, d-drug exposure, BMI, and hazardous drinking. Covariates were identified and selected a priori from literature on predictors of HS in people with either HIV-HCV coinfection or HCV mono-infection [10].

Changes in HSI over time were modelled as a γ distribution with a log link function. The log transformation implies that the influence of covariates on the mean response is multiplicative rather than additive. This GAMM included the same covariates

as before except sex, diabetes, and BMI were omitted because they are included in the HSI formula.

Both GAMMs included 2 smoothing terms. The first smoothing term was equivalent to a random intercept to accommodate repeated measurements from the same patient. The second smoothing term was an adaptive P-spline to account for the change in the outcome over time [27].

Time zero was the time at which DAA treatment started. All available measurements, before and after treatment, were used for those included. However, an individual's measurement sequences were left censored until 6 months after any earlier unsuccessful interferon-based treatment and right censored at any detectable HCV viremia (if reinfecting). Otherwise, measurement sequences were right censored at February 2023 (administrative censoring), loss to follow-up (no visit for 18 months), or death.

Each participant needed only a single CAP measurement (prior to treatment) to be included in the analysis. Including such participants avoids bias if participants with certain characteristics are more likely to be lost to follow-up [28]. Models for longitudinal data fit by maximum likelihood and with a random effect have the attractive property that inference from the model is not affected by drop-out, provided participant missingness depends only on the participant's random effect and covariate values and not on the value of the unobserved measurements [29].

A reference participant with the following characteristics was created by centering covariates: male, age 50 years, BMI 25, not diabetic, not hazardous drinking, infected with HCV for 20 years, and no d-drug exposure. Estimates were made for this patient of the rate of change in mean HS between 1.5 years and 0.5 years both before and after treatment. By sampling model parameters from their posterior distribution (using the predict function in mgcv), we repeatedly estimated slopes before and after treatment and then calculated the mean and approximate 95% credible interval (95% CrI) for the slope from the 2.5 and 97.5 percentiles of a distribution of 10 000 slope estimates [30]. We used a similar process to predict individual values from the model, such as whether a participant would have a CAP ≥ 248 dB/m at different points in time. When predicting individual values, we used the covariate values for each participant (including the participant's random intercept) rather than those of a reference participant (without a random intercept).

Subgroup Analyses

Analyses were repeated stratified by CAP when starting treatment (above or below 248 dB/m) and by genotype (genotype 3 vs genotypes 1, 2, 4). These other genotypes have been associated with promoting "metabolic" steatosis rather than driving "viral steatosis" hypothesized to occur with genotype 3.

Sensitivity Analyses

For CAP, several sensitivity analyses were used to assess the influence of covariates. First, analyses were rerun without

adjusting for covariates. Second, analyses were repeated restricting the data to those with all covariates measured at least within 1 year prior to starting treatment. Third, analyses were rerun with time-dependent use of integrase inhibitors as an additional covariate, because of the association between integrase inhibitors and weight gain.

For HSI, 2 additional analyses were used to assess change over time in the main components of the index. Separate models were fit to both BMI and the ALT/AST ratio using the same model as used in the main analysis of HSI.

RESULTS

Patient Characteristics

In total, 687 participants achieved SVR with second-generation DAAs, and 627 met inclusion criteria (Figure 1). After excluding those with missing outcome or covariate data, 399 and 98 participants were included in the HSI and CAP analyses, respectively. Pretreatment characteristics were similar among participants meeting inclusion criteria and those included in the CAP and HSI analyses (Table 1).

Prior to treatment, participants were middle aged and around 30% were female (Table 1). Most did not have steatosis (74% CAP < 248 dB/m) when starting DAA treatment. Only 67 (17%) were infected with HCV genotype 3. Most participants were virally suppressed (around 90% with HIV RNA < 50 copies/mL). Around 80% reported ever using injection drugs, with 30% still actively using, and 35% reported hazardous drinking.

Measurement sequences for HSI and CAP started a median 3.8 and 1.1 years before treatment, respectively, and extended a median 2.8 and 2.4 years after treatment (Supplementary Table 1). Sequences for HSI and CAP contained a median of 5 and 2 measures before treatment, respectively, and a median of 4 and 2 measures after treatment. Many sequences ended when the participant was lost to follow-up (52% and 58% for HSI and CAP, respectively; Supplementary Table 2); a relatively high percentage ended when the participant died (13% and 7%, respectively).

Changes in CAP and HSI Before, During, and After Treatment Overall

The mean response curve showed a gradual increase in CAP over time, which remained unaffected by SVR (Figure 2). The adjusted slope estimates before and after treatment were 3.3 dB/m/year (95% CrI, 1.6–4.9) and 3.9 dB/m/year (95% CrI, 1.9–5.9), respectively (Table 2); both estimates were not materially different from the estimate during treatment (4.3 dB/m/year; 95% CrI, 2.1–6.4). These findings were supported by sensitivity analyses. Excluding covariates, using pretreatment values no more than 1 year before starting treatment and adding time updated integrase inhibitor exposure as a covariate resulted in similar response curves and slope estimates as in the main analysis (Table 2).

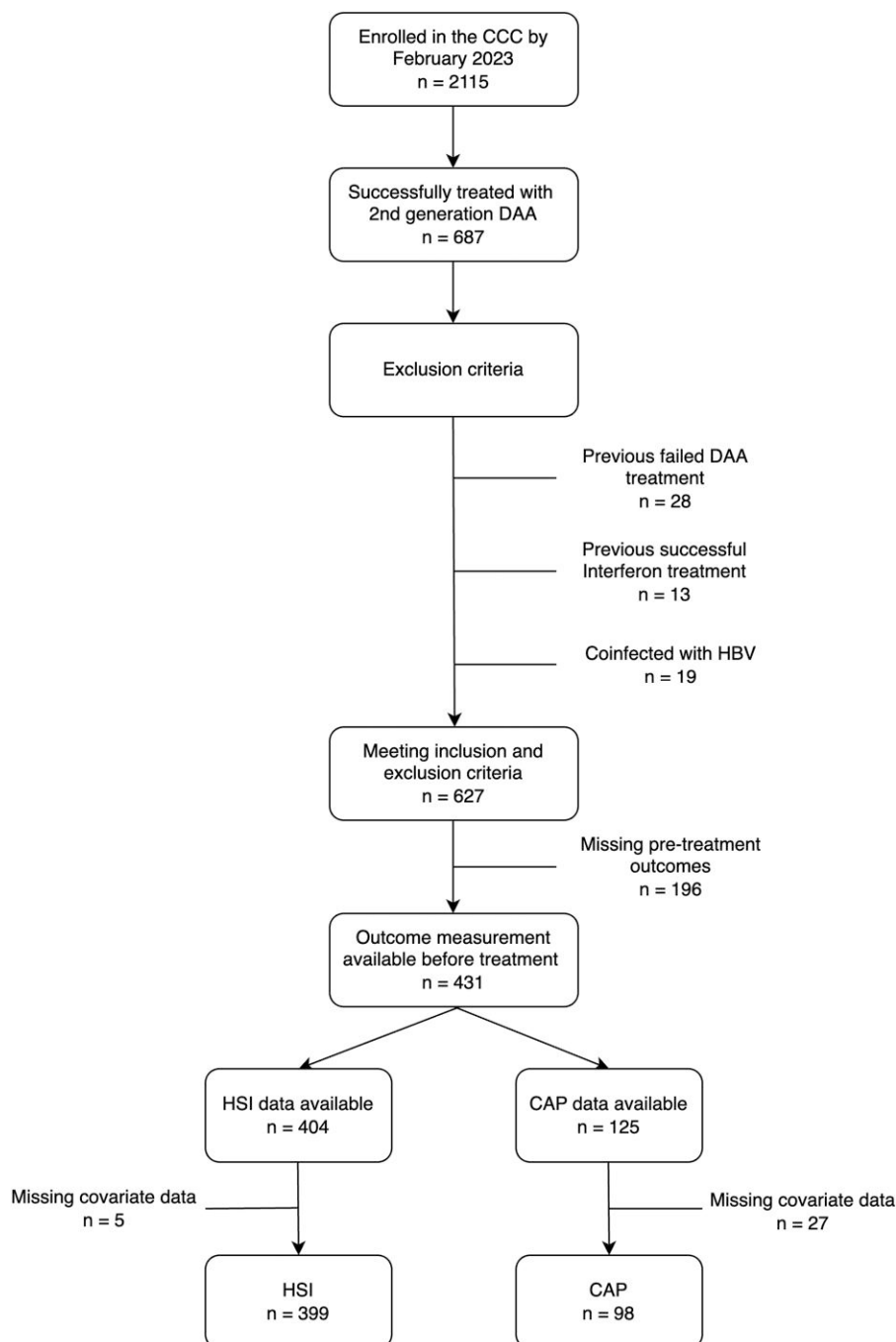


Figure 1. Participant selection flow diagram. Abbreviations: CAP, controlled attenuation parameter; CCC, Canadian Coinfection Cohort; DAA, direct-acting antiviral; HBV, hepatitis B virus; HSI, Hepatic Steatosis Index.

In contrast, the rate of change for HSI over time remained relatively flat and constant, with slope estimates 0.2 (95% CrI, −0.1 to 0.5) and 0.2 (95% CrI, −0.1 to 0.4) before and after treatment, respectively. During treatment, however, a steep decline in the response was seen, showing the effect of DAA treatment on HSI (Figure 2), with a slope estimate of −4.5 (95% CrI, −5.9 to −3.1). Sensitivity analyses of HSI

components showed a steady increase in BMI over time, like CAP, unaffected by DAA treatment (Figure 3). Conversely, ALT/AST ratio decreased during treatment but was otherwise constant (Figure 3), the same as response as seen in the index itself.

The predicted changes in CAP translate into an increase in the proportion of people with HS (CAP $\geq$ 248 dB/m) from

Table 1. Participant Characteristics When Starting a Successful Direct-Acting Antiviral Treatment for Hepatitis C

Characteristic	Study Population (n = 627)	With Pretreatment Outcome Measurement and Covariates	
		HSI (n = 399) ^a	CAP (n = 98)
Age, median, y	51	51	52
Female, %	28	31	27
MSM, %	29	37	36
IDU ever, % (% missing)	83 (17)	83	82
IDU past 6 mo, % (% missing)	32 (22)	29	31
Hazardous drinking, % (% missing)	37 (30)	36	36
Diabetes, % (% missing)	17 (35)	17	18
HCV duration, y	23	24	25
HCV genotype, %			
1	61	70	67
2	3	4	4
3	17	16	19
4	3	4	3
Missing	17	7	6
Antiretroviral therapy naive, %	2	0	0
Exposure to d-drugs, % ^b	27	28	39
Exposure to integrase inhibitors, % ^c	48	49	49
HIV RNA < 50 copies/mL, % (% missing)	90 (25)	90	93
CD4 cell count, median, cells/μL (% missing)	530 (21)	520	480
LDL, median, mmol/L (% missing)	2.0 (42)	2.1 (25)	2.2 (18)
Triglycerides, median, mmol/L (% missing)	1.2 (43)	1.2 (27)	1.4 (18)
BMI, median, kg/m ² (% missing)	24 (31)	24	24
Waist circumference, median, cm (% missing)			
Men	93 (45)	93 (22)	91 (7)
Women	92 (39)	92 (24)	91 (12)
CAP, median, dB/m	NA	NA	210
HSI, median	NA	34	34
Hepatic steatosis, HSI≥36 or CAP≥248 dB/m, %	NA	39	26

Statistics reported are either a median or a percentage for the data available, and where relevant the percentage missing is shown in parentheses.

Abbreviations: BMI, body mass index; CAP, controlled attenuation parameter; d-drug, dideoxynucleoside drug; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HSI, Hepatic Steatosis Index; IDU, injection drug use; LDL, low-density lipoprotein; MSM, men reporting sex with men; NA, not available.

^aAmong 627 participants in the study population, 81 had no measurement of liver enzymes (alanine transaminase and aspartate transaminase) in the year before starting HCV treatment; among those with a liver enzyme measurement, 142 had no weight measurement and a further 5 had no AUDIT-C score.

^bExposed to early generation antiretroviral therapies containing dideoxynucleosides.

^cPast or current exposure to antiretroviral therapies containing an integrase inhibitor.

19% (95% CrI, 14%–26%) prior to treatment to 27% (95% CrI, 20%–34%) 2 years after treatment (Table 3). In contrast, the predicted changes in HSI translate into a higher proportion with HS (HSI ≥ 36) before treatment (34%; 95% CrI, 31%–37%), which then decreased over time (28%; 95% CrI, 26%–30%).

Change in CAP in Pretreatment Subgroups

As seen in the main model for CAP, a gradual increase in CAP was seen in both those with and without HS when starting treatment, with no effect of DAA treatment (Figure 4). The estimated increase over time was somewhat higher in participants without pretreatment steatosis (Table 2).

CAP appeared to behave somewhat differently with genotype 3 infection, showing no real increase over time, either before or after treatment, in contrast to other genotypes (Table 2). However, these slope estimates were less precise than other

slope estimates due to the small number of participants with genotype 3 infection (approximately 20%; Table 1).

DISCUSSION

Among people with HIV and HCV, we found that HS, when measured by CAP, steadily increased over time without signs of abating. Successful HCV treatment had no effect on this increase regardless of the presence of HS when starting treatment. This continuous increase in HS appears clinically important—those with HS are estimated to increase by 30% (from mean of 19% before treatment to 27% 2 years after treatment)—potentially negating some of the benefits of curing HCV on liver health. Given HS can increase risks of fibrosis and cirrhosis, it will be important to monitor patients with HIV-HCV co-infection for HS after SVR and, if necessary, intervene to ensure the benefits of curing HCV are realized.

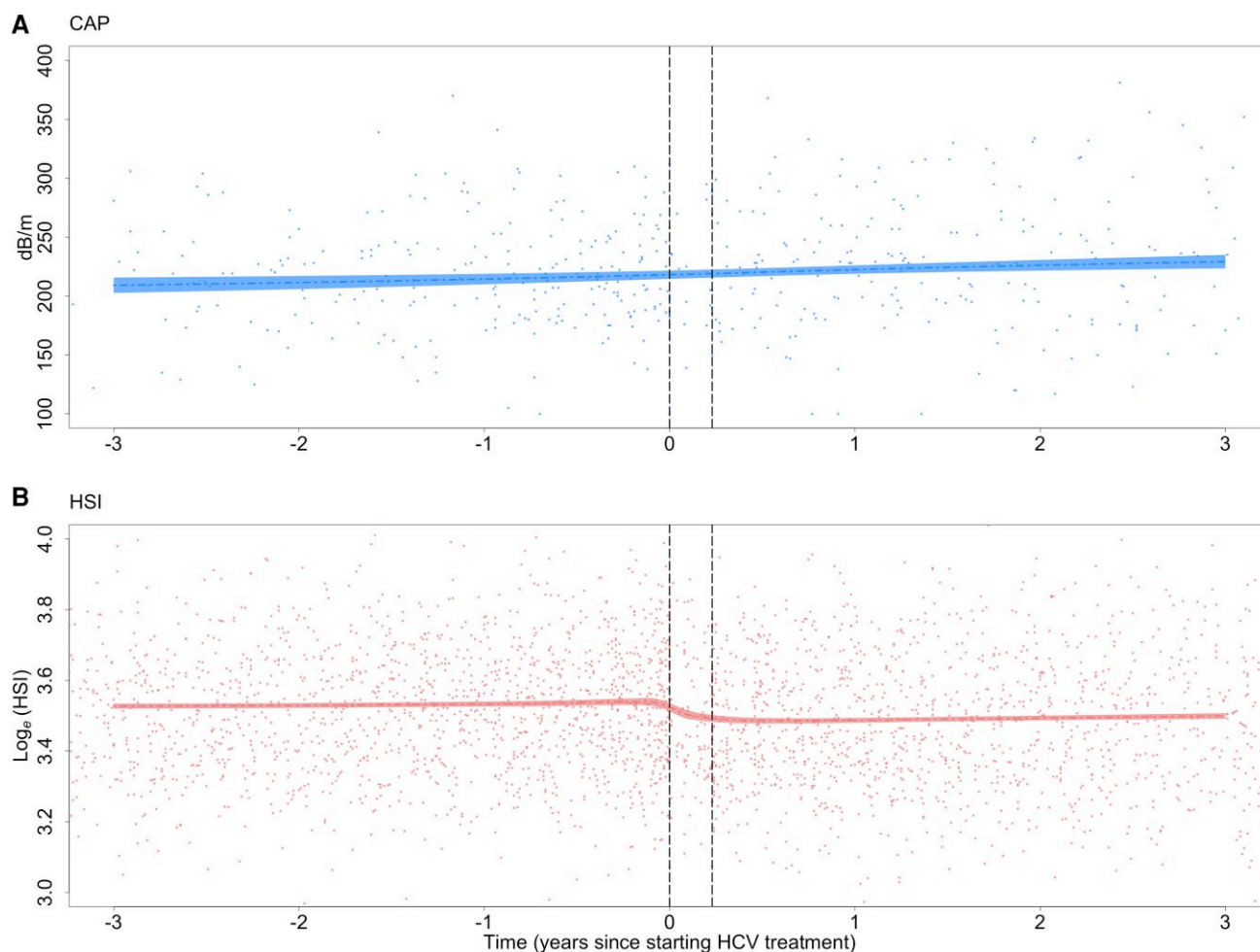


Figure 2. Mean response curves from the main models for (A) the CAP and (B) the HSI. Vertical reference lines represent the usual 12-week treatment period. Abbreviations: CAP, controlled attenuation parameter; HCV, hepatitis C virus; HSI, Hepatic Steatosis Index.

If chronic HCV were the principal driver of HS, either directly (viral steatosis) or indirectly (metabolic steatosis), we would have expected to see improvement in CAP following treatment. The lack of any appreciable reduction in CAP, even years after HCV cure, suggests that HS is not readily reversible by DAAs or is being driven principally by factors other than chronic HCV in a coinfecting population. Metabolic dysfunction-associated steatotic liver disease (MASLD, formerly NAFLD) in the setting of HIV infection is multifactorial [10]. Contributing factors include HIV and antiretroviral-induced metabolic changes, genetic factors, and other exposures such as alcohol. In our analysis, prior HIV treatment with d-drugs was associated with higher CAP at treatment initiation while integrase inhibitor exposure was not. Accounting for d-drugs and for time updated integrase inhibitor use did not change our results. Nor did accounting for age, sex, hazardous drinking, BMI, and diabetes—the main factors known to increase risk of HS (Supplementary Tables 2 and 3). Without a clear

specific cause, lifestyle modification and weight reduction remain the mainstays of HS management. Vitamin E [31] and glucagon-like peptide-1 receptor agonists [32, 33] represent additional promising avenues for intervention in HIV infection. Recently, a large number of new molecules have been shown to slow HS progression and reverse steatohepatitis and fibrosis in trials of people without viral infection and should be evaluated in people with HIV, including those cured of HCV [34, 35].

While other studies have described an increase in CAP following successful DAA treatment in HIV-HCV coinfection [16, 36] and HCV mono-infection [37, 38], in some cases attributing it to curing HCV, these studies compared CAP at the start of treatment to measurements at 1 or a few time points after SVR. Our analyses shows that CAP starts increasing well before treatment. Thus, the posttreatment increase in HS is most likely not a consequence of SVR, but rather a continuous, uninterrupted increase in steatosis over time. In our

Table 2. Slope Estimates for Transient Elastography With CAP and HSI Before, During, and After a Successful Treatment for HCV With a Second-Generation Direct-Acting Antiviral Therapy

Marker and Model	Slope Estimate (95% Credible Interval)					
	1.5–0.5 y Before Treatment		During Treatment, 12-wk Treatment Period Assumed		0.5–1.5 y After Treatment	
HSI						
Adjusted, main model ^a	0.2	(−0.1 to 0.5)	−4.5	(−5.9 to −3.1)	0.2	(−0.1 to 0.4)
Adjusted, within 1 y ^b	0.2	(−0.1 to 0.5)	−4.5	(−6.0 to −3.0)	0.2	(−0.1 to 0.5)
No covariates	0.2	(−0.1 to 0.5)	−4.5	(−5.9 to −3.1)	0.2	(−0.1 to 0.5)
CAP						
Adjusted, main model ^c	3.3	(1.6 to 4.9)	4.3	(2.1 to 6.4)	3.9	(1.9 to 5.9)
Adjusted, within 1 y ^b	4.5	(2.5 to 6.3)	5.8	(3.3 to 8.2)	5.3	(3.0 to 7.6)
Adjusted, INSTI exposure ^d	3.4	(1.7 to 5.1)	4.5	(2.2 to 6.6)	4.1	(2.1 to 6.1)
No covariates	3.2	(1.7 to 4.8)	4.2	(2.2 to 6.3)	3.9	(2.0 to 5.8)
CAP subgroups						
Pretreatment CAP < 248 dB/m ^c	3.7	(1.9 to 5.6)	4.9	(2.5 to 7.3)	4.5	(2.3 to 6.7)
Pretreatment CAP ≥ 248 dB/m ^c	2.1	(−1.3 to 5.3)	2.7	(−1.7 to 6.9)	2.4	(−1.5 to 6.3)
HCV genotype 1, 2, or 4 ^c	3.8	(1.1 to 6.5)	5.5	(2.5 to 8.4)	5.4	(2.9 to 7.8)
HCV genotype 3 ^c	−0.5	(−4.7 to 3.7)	−0.6	(−6.1 to 4.7)	−0.6	(−5.6 to 4.3)
BMI						
Adjusted ^a	0.2	(0.0 to 0.5)	0.3	(−1.1 to 1.8)	0.4	(0.2 to 0.6)
ALT/AST ratio						
Adjusted ^a	0.0	(−0.1 to 0.0)	−0.8	(−1.0 to −0.7)	0.1	(0.0 to 0.1)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CAP, controlled attenuation parameter; HCV, hepatitis C virus; HSI, Hepatic Steatosis Index; INSTI, integrase strand transfer inhibitor.

^aAdjusted for pretreatment age, duration of HCV infection in years, past exposure to dideoxynucleosides, and hazardous drinking.

^bRestricted to participants with all covariates measured within the year prior to starting treatment (HSI n = 360; CAP n = 85).

^cAdjusted for pretreatment age, sex, duration of HCV infection in years, diabetes, past exposure to dideoxynucleosides, BMI, and hazardous drinking.

^dAdjusted for the covariates in the main model plus a time-dependent indicator for exposure to integrase inhibitors.

study, the change in CAP was mirrored by a steady increase in BMI equivalent to an increase in mean weight of 0.7 kg per year (95% CrI, 0.0–1.4) before to 1.1 kg per year (95% CrI, 0.5–1.8) after treatment. While we cannot rule out that SVR is associated with some increase in the rate of weight gain, our participants cured of HCV appear to experience a similar trajectory of weight gain to those without HCV infection treated for HIV with modern antiretrovirals [39]. This weight gain parallels, but exceeds, trends in obesity in the general population and represents a growing clinical concern due to potential implications for metabolic consequences, including HS [40]. Integrase inhibitors have been associated with weight gain [41]; however, there is limited evidence they are associated with HS [42, 43]. We did not see such an association in our data.

With genotype 3, HS has been shown to be higher in untreated infection and lower following successful interferon treatment relative to other genotypes on paired liver biopsies [8]. Our subgroup analyses suggested there could be some difference in CAP according to HCV genotype. In contrast to other genotypes, CAP was essentially constant in those with genotype 3, neither increasing before nor decreasing after successful treatment. Relatively few participants were infected with genotype 3 and while this limits the power to detect differences between

genotypes, the precision of our response curves suggest, if there were differences, they were relatively minor.

A responsive noninvasive marker suitable for monitoring HS would help in the long-term management of people treated for HCV. Our results suggest that CAP appears to capture the behavior of HS before, during, and after DAA treatment and is therefore the diagnostic tool of choice in this setting until such time as an accessible alternative and reliable serologic measure is developed. CAP has also been shown to correlate well with important clinical outcomes, such as the incidence and severity of liver-related disease and cardiovascular disease [44, 45].

We also evaluated HSI as a simple noninvasive biomarker of HS given it may be more readily available in clinical practice and is increasingly being used for clinical and research purposes in people with HIV [46, 47] or with viral hepatitis [48]. The lack of change in HSI before and after treatment shows the inability of this marker to capture increasing HS over time. In contrast to CAP, HSI decreased markedly during the treatment period. This decrease in HSI is likely driven by a reduction in the ALT to AST ratio, because of a reduction in hepatocellular injury and liver inflammation in the context of HCV eradication [49]. HSI remained stable years after SVR, consistent with the persistent normalization of ALT and AST after HCV

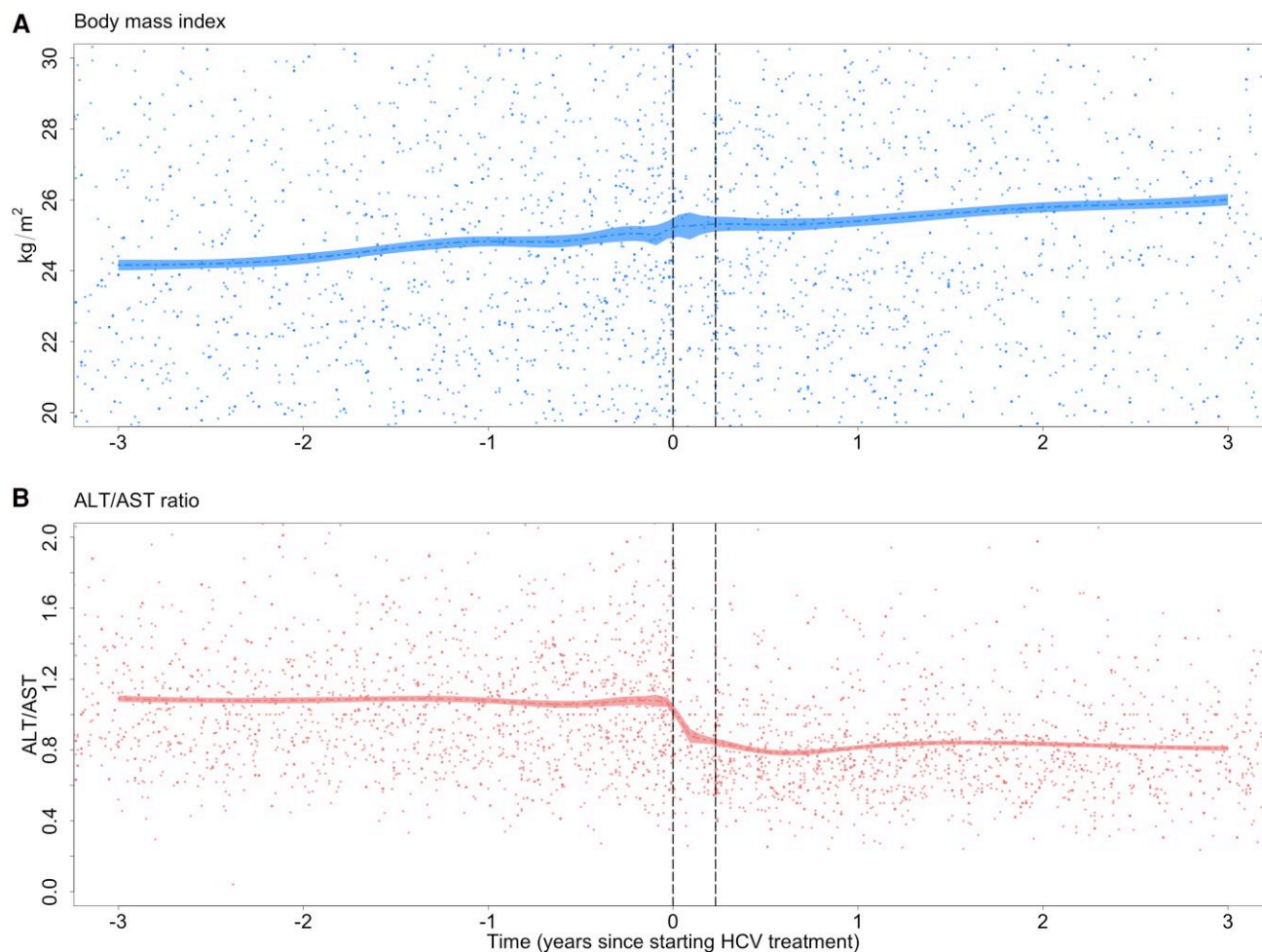


Figure 3. Mean response curves from models for (A) body mass index and (B) for the ALT to AST ratio. Vertical reference lines represent the usual 12-week treatment period. Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; HCV, hepatitis C virus.

Table 3. Model Predictions for Cohort Participants Providing Data to a Given Model

Prediction and Model	At Start of Treatment	1 y after Treatment	2 y after Treatment
CAP ≥ 248 dB/m, %			
Main model (n = 98)	19 (14–26)	23 (17–30)	27 (20–34)
HSI ≥ 36 , %			
Main model (n = 399)	34 (31–37)	27 (25–29)	28 (26–30)
BMI, kg/m ²			
Adjusted (n = 399)	25 (24–27)	25 (24–27)	26 (24–27)
ALT/AST ratio			
Adjusted (n = 399)	1.0 (0.8–1.2)	0.8 (0.7–1.0)	0.8 (0.7–1.0)

Data are the mean among individuals (95% credible interval for individual values). Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CAP, controlled attenuation parameter; HSI, Hepatic Steatosis Index.

cure [50]. BMI behaved differently, rising consistently over time. The net effect of combining these components affected differently by treatment in a single measure renders HSI a poor marker of HS in those treated for HCV.

This is the first longitudinal measurement study of CAP and HSI before and after DAA treatment in a coinfecting population, with reliable modelling of the mean response up to 3 years posttreatment. Our models for the mean response

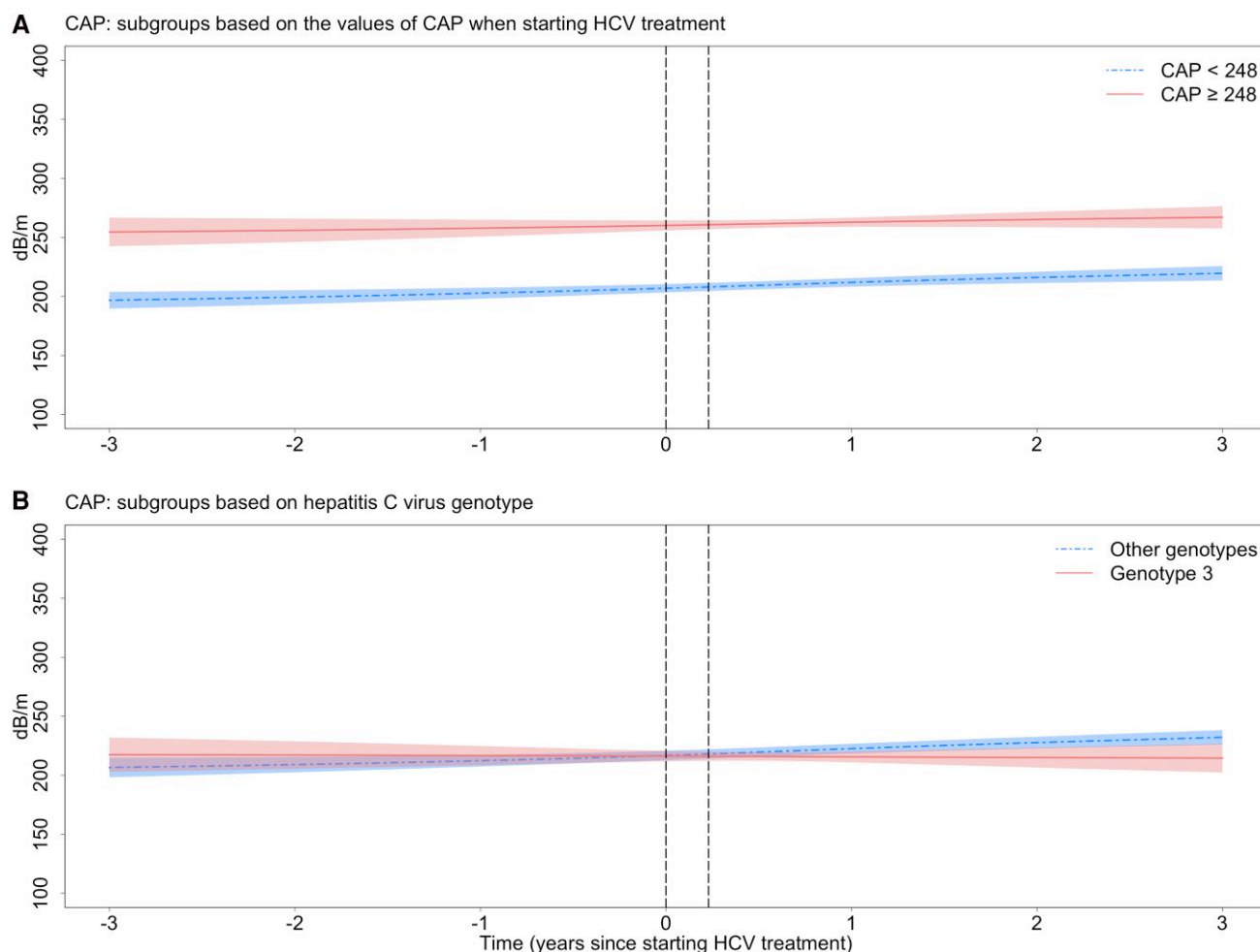


Figure 4. Mean response curves from models for CAP subgroups: (A) subgroups based on the values of CAP when starting HCV treatment; and (B) subgroups based on HCV genotype. Vertical reference lines represent the usual 12-week treatment period. Abbreviations: CAP, controlled attenuation parameter; HCV, hepatitis C virus.

reproduce mean individual values but underestimate individual variability. The estimated CAP for individual participants when starting treatment was mean 220 dB/m (95% CrI, 156–284); the observed pretreatment CAP among individual participants was mean 218 dB/m (95% CrI, 136–300). When individual variability is underestimated, the proportion predicted ≥ 248 dB/m will be too low (compare proportions in Table 1 and Table 3). However, the model provides predicted proportions that are robust to informative censoring of measurement sequences. The observed proportions are not robust: among 28 participants with CAP measurements between 0.5 and 1.5 years after treatment, 89% had HS. The high observed percentage is biased because it is the result of repeated measurement in those more at risk of liver disease.

This study has limitations: only 98 of the 687 participants achieving SVR had at least 1 CAP measure available. However, those with and without CAP measures were similar with respect to pretreatment characteristics. Some participants had to be

excluded from modelling due to missing covariate data. However, sensitivity analyses of the full data without covariate adjustment yielded similar results. Modelling choices were made to create response curves (the type of spline, the number and placement of knots); these choices may hide or exaggerate elements of a response curve. Finally, our results may not apply to people with HIV or HCV mono-infection.

In conclusion, HS progressively increased in people with HIV-HCV coinfection when measured by CAP. This increase started before DAA treatment, occurred irrespective of the presence of pretreatment HS and was unaffected by HCV cure. Future research should consider the clinical consequences of this unabated increase in HS among people cured of HCV especially in those who may have residual liver fibrosis. In particular, understanding the impact of HS on both hepatic and extrahepatic outcomes, such as cardiometabolic health and all-cause mortality, would support the need for introducing additional interventions after HCV cure.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online (<http://jid.oxfordjournals.org/>). **Supplementary materials** consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all **supplementary data** are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

Author contributions. E. T., J. Y., and M. B. K. conceptualized the study. G. S. provided expert subject knowledge informing study design and interpretation of results. S. W. and J. Y. performed all data analysis and produced reports and figures. E. T., J. Y., and M. B. K. drafted the manuscript. S. L. W., M. H., C. C., and M. B. K. recruited and followed participants in the study. All authors critically reviewed the manuscript for important intellectual content and approved the final manuscript as submitted.

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References

1. Gobran ST, Ancuta P, Shoukry NH. A tale of two viruses: immunological insights into HCV/HIV coinfection. *Front Immunol* **2021**; 12:726419.
2. Maurice JB, Patel A, Scott AJ, Patel K, Thursz M, Lemoine M. Prevalence and risk factors of nonalcoholic fatty liver disease in HIV-monoinfection. *AIDS* **2017**; 31:1621–32.
3. Lonardo A, Adinolfi LE, Loria P, Carulli N, Ruggiero G, Day CP. Steatosis and hepatitis C virus: mechanisms and significance for hepatic and extrahepatic disease. *Gastroenterology* **2004**; 126:586–97.
4. Adinolfi LE, Rinaldi L, Guerrera B, et al. NAFLD and NASH in HCV infection: prevalence and significance in hepatic and extrahepatic manifestations. *Int J Mol Sci* **2016**; 17:803.
5. Elgretli W, Chen T, Kronfli N, Sebastiani G. Hepatitis C virus-lipid interplay: pathogenesis and clinical impact. *Biomedicines* **2023**; 11:271.
6. Anstee QM, Reeves HL, Kotsiliti E, Govaere O, Heikenwalder M. From NASH to HCC: current concepts and future challenges. *Nat Rev Gastroenterol Hepatol* **2019**; 16:411–28.
7. Barré T, Protopopescu C, Bani-Sadr F, et al. Elevated fatty liver index as a risk factor for all-cause mortality in human immunodeficiency virus-hepatitis C virus-coinfected patients (ANRS CO13 HEPAVIH cohort study). *Hepatology* **2020**; 71:1182–97.
8. Chaudhari R, Fouda S, Sainu A, Pappachan JM. Metabolic complications of hepatitis C virus infection. *World J Gastroenterol* **2021**; 27:1267–82.
9. Modaresi Esfeh J, Ansari-Gilani K. Steatosis and hepatitis C. *Gastroenterol Rep* **2016**; 4:24–9.
10. Koethe JR, Lagathu C, Lake JE, et al. HIV and antiretroviral therapy-related fat alterations. *Nat Rev Dis Primers* **2020**; 6:48.
11. Eckard AR, McComsey GA. Weight gain and integrase inhibitors. *Curr Opin Infect Dis* **2020**; 33:10–9.
12. Fan R, Wang J, Du J. Association between body mass index and fatty liver risk: a dose-response analysis. *Sci Rep* **2018**; 8:15273.
13. Gitto S, Cicero AFG, Loggi E, et al. Worsening of serum lipid profile after direct acting antiviral treatment. *Ann Hepatol* **2018**; 17:64–75.
14. Iossa D, Vitrone M, Gagliardi M, et al. Anthropometric parameters and liver histology influence lipid metabolic changes in HCV chronic hepatitis on direct-acting antiviral treatment. *Ann Transl Med* **2020**; 9:35.
15. Chromy D, Mandorfer M, Bucsics T, et al. Prevalence and predictors of hepatic steatosis in patients with HIV/HCV coinfection and the impact of HCV eradication. *AIDS Patient Care STDs* **2019**; 33:197–206.

16. Chuaypen N, Siripongsakun S, Hiranrat P, Tanpowpong N, Avihingsanon A, Tangkijvanich P. Improvement of liver fibrosis, but not steatosis, after HCV eradication as assessment by MR-based imaging: role of metabolic derangement and host genetic variants. *PLoS One* **2022**; 17:e0269641.
17. Saldarriaga OA, Dye B, Pham J, et al. Comparison of liver biopsies before and after direct-acting antiviral therapy for hepatitis C and correlation with clinical outcome. *Sci Rep* **2021**; 11:14506.
18. Kobayashi N, Iijima H, Tada T, et al. Changes in liver stiffness and steatosis among patients with hepatitis C virus infection who received direct-acting antiviral therapy and achieved sustained virological response. *Eur J Gastroenterol Hepatol* **2018**; 30:546–51.
19. Shimizu K, Soroida Y, Sato M, et al. Eradication of hepatitis C virus is associated with the attenuation of steatosis as evaluated using a controlled attenuation parameter. *Sci Rep* **2018**; 8:7845.
20. Ogasawara N, Kobayashi M, Akuta N, et al. Serial changes in liver stiffness and controlled attenuation parameter following direct-acting antiviral therapy against hepatitis C virus genotype 1b. *J Med Virol* **2018**; 90:313–9.
21. Karlas T, Petroff D, Sasso M, et al. Individual patient data meta-analysis of controlled attenuation parameter (CAP) technology for assessing steatosis. *J Hepatol* **2017**; 66:1022–30.
22. Panel CP, Berzigotti A, Tsochatzis E, et al. EASL clinical practice guidelines on non-invasive tests for evaluation of liver disease severity and prognosis—2021 update. *J Hepatol* **2021**; 75:659–89.
23. Lee JH, Kim D, Kim HJ, et al. Hepatic steatosis index: a simple screening tool reflecting nonalcoholic fatty liver disease. *Dig Liver Dis* **2010**; 42:503–8.
24. Busca C, Sánchez-Conde M, Rico M, et al. Assessment of noninvasive markers of steatosis and liver fibrosis in human immunodeficiency virus-monoinfected patients on stable antiretroviral regimens. *Open Forum Infect Dis* **2022**; 9: ofac279.
25. Preveden T, Veres B, Ruzic M, et al. Triglyceride-glucose index and hepatic steatosis index for the assessment of liver steatosis in HCV patients. *Minerva Gastroenterol* **2022**; 69: 254–60.
26. Babor TF, Higgins-Biddle J, Saunders JB, Monteiro M. AUDIT—the alcohol use disorders identification test: guidelines for use in primary health care. 2nd edn. Geneva, Switzerland: World Health Organization, **2001**.
27. Kronfli N, Young J, Wang S, et al. Liver fibrosis in human immunodeficiency virus (HIV)-hepatitis C virus (HCV) coinfection before and after sustained virologic response: what is the best noninvasive marker for monitoring regression? *Clin Infect Dis* **2021**; 73:468–77.
28. Thiébaud R, Walker S. When it is better to estimate a slope with only one point. *QJM* **2008**; 101:821–4.
29. Verbeke G, Molenberghs G, Rizopoulos D. Random effects models for longitudinal data. In: van Montfort K, Oud JHL, Satorra A, eds. *Longitudinal research with latent variables*. Heidelberg: Springer, **2010**: 37–96.
30. Wood S. Prediction with predict.gam. In: *Generalized additive models: an introduction with R*. 2nd ed. Boca Raton, FL: Chapman and Hall/CRC, **2017**:239–43.
31. Sebastiani G, Saeed S, Lebouche B, et al. Vitamin E is an effective treatment for nonalcoholic steatohepatitis in HIV mono-infected patients. *AIDS* **2020**; 34:237–44.
32. Nguyen Q, Wooten D, Lee D, et al. GLP-1 receptor agonists promote weight loss among people with HIV [published online ahead of print 19 March 2024]. *Clin Infect Dis* doi: [10.1093/cid/ciae151](https://doi.org/10.1093/cid/ciae151).
33. McComsey GA, Sattar A, Albar Z, et al. Effects of semaglutide on adipose tissue in HIV-associated lipohypertrophy. *Open Forum Infect Dis* **2023**; 10(Suppl 2): ofad500.111.
34. Harrison SA, Bedossa P, Guy CD, et al. A phase 3, randomized, controlled trial of resmetirom in NASH with liver fibrosis. *N Engl J Med* **2024**; 390:497–509.
35. Loomba R, Hartman ML, Lawitz EJ, et al. Tirzepatide for metabolic dysfunction-associated steatohepatitis with liver fibrosis. *N Engl J Med* **2024**; 391:299–310.
36. Siribelli A, Ceccarelli D, Galli L, et al. CAP and metabolic profile worsening post-SVR in HCV-HIV people as a sign of steatosis, abstract 615. 30th Conference on Retroviruses and Opportunistic Infections. Seattle, WA, **2023**.
37. Cespiati A, Petta S, Lombardi R, et al. Metabolic comorbidities and male sex influence steatosis in chronic hepatitis C after viral eradication by direct-acting antiviral therapy (DAAs): evaluation by the controlled attenuation parameter (CAP). *Dig Liver Dis* **2021**; 53:1301–7.
38. Trifan A, Stratina E, Rotaru A, et al. Changes in liver steatosis using controlled attenuation parameter among patients with chronic hepatitis C infection treated with direct-acting antivirals therapy who achieved sustained virological response. *Diagnostics* **2022**; 12:702.
39. Bourgi K, Jenkins CA, Rebeiro PF, et al. Weight gain among treatment-naïve persons with HIV starting integrase inhibitors compared to non-nucleoside reverse transcriptase inhibitors or protease inhibitors in a large observational cohort in the United States and Canada. *J Int AIDS Soc* **2020**; 23:e25484.
40. Chandiwana NC, Siedner MJ, Marconi VC, et al. Weight gain after HIV therapy initiation: pathophysiology and implications. *J Clin Endocrinol Metab* **2023**; 109:e478–87.
41. Bailin SS, Koethe JR. Weight gain and antiretroviral therapy. *Infect Dis Clin North Am* **2024**; 38:499–515.

42. Bischoff J, Gu W, Schwarze-Zander C, et al. Stratifying the risk of NAFLD in patients with HIV under combination antiretroviral therapy (cART). *EClinicalMedicine* **2021**; 40:101116.
43. Riebensahm C, Berzigotti A, Surial B, et al. Factors associated with liver steatosis in people with human immunodeficiency virus on contemporary antiretroviral therapy. *Open Forum Infect Dis* **2022**; 9:ofac538.
44. Liu K, Wong VW, Lau K, et al. Prognostic value of controlled attenuation parameter by transient elastography. *Am J Gastroenterol* **2017**; 112:1812–23.
45. Cardoso CRL, Villela-Nogueira CA, Leite NC, Salles GF. Prognostic impact of liver fibrosis and steatosis by transient elastography for cardiovascular and mortality outcomes in individuals with nonalcoholic fatty liver disease and type 2 diabetes: the Rio de Janeiro cohort study. *Cardiovasc Diabetol* **2021**; 20:193.
46. Sebastiani G, Rollet-Kurhajec KC, Pexos C, Gilmore N, Klein MB. Incidence and predictors of hepatic steatosis and fibrosis by serum biomarkers in a large cohort of human immunodeficiency virus mono-infected patients. *Open Forum Infect Dis* **2015**; 2:ofv015.
47. Fernandes SR, Leite AR, Lino R, et al. The impact of integrase inhibitors on steatosis and fibrosis biomarkers in persons with HIV naive to antiretroviral therapy. *BMC Infect Dis* **2023**; 23:553.
48. Elwan N, Elfert A, Abd-Elsalam S, et al. Study of hepatic steatosis index in patients with chronic HCV infection. *Int J Curr Microbiol App Sci* **2016**; 5:266–74.
49. Huynh T, Zhang J, Hu KQ. Hepatitis C virus clearance by direct-acting antiviral results in rapid resolution of hepatocytic injury as indicated by both alanine aminotransferase and aspartate aminotransferase normalization. *J Clin Transl Hepatol* **2018**; 6:258–63.
50. Collins LF, Adekunle RO, Cartwright EJ. Metabolic syndrome in HIV/HCV co-infected patients. *Curr Treat Options Infect Dis* **2019**; 11:351–71.