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Controlled Attenuation Parameter and MR Spectroscopy-measured Liver Steatosis are Discordant in HIV-infected Adults with High Body Mass

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Abstract

Objective—Hepatic steatosis (HS) is common in HIV-infected individuals. Magnetic resonance spectroscopy (MRS) is the preferred non-invasive method for HS measurement but is expensive. Controlled attenuation parameter (CAP) also assesses HS and is conveniently performed concomitantly with transient elastography. We aimed to assess the accuracy of CAP in the setting of HIV infection.

Design—Cross-sectional study

Methods—CAP and MRS were performed in 82 subjects (39 HIV-monoinfected; 7 HCV-monoinfected; 21 HIV/HCV-coinfected; 15 with neither infection). We used concordance correlation coefficients to compare log-transformed and standardized CAP and MRS values and linear regression to examine factors associated with CAP and MRS-measured HS. The accuracy of CAP to detect mild HS, defined as MRS-liver fat fraction ≥ 0.05 , and the factors associated with discordance between CAP and MRS were evaluated.

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Author contributions:

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Results—Overall, CAP-HS and MRS-HS correlated moderately well ($r=0.60$, $p<0.001$), and correlation was strongest in the HIV-monoinfected group ($r=0.67$, $p<0.001$). Body composition factors (higher BMI, waist circumference, visceral and abdominal subcutaneous adipose tissue) and insulin resistance were significantly associated with both greater CAP-HS and MRS-HS. Using a validated CAP cut-off 238 decibels/meter, sensitivity and specificity for mild HS were 84% and 75% in the entire cohort; 89% and 80% in the HIV-monoinfected group. Higher body composition parameters were more likely to be misclassified as having HS by CAP.

Conclusions—Our findings suggest CAP is an acceptable non-invasive surrogate for HS in HIV-infected individuals but may overestimate HS prevalence, especially in individuals with high BMI. Evaluation of factors that improve CAP accuracy and determination of optimal cut-offs are warranted.

Keywords

HIV; HCV; hepatic steatosis; fatty liver; CAP; MRS

INTRODUCTION

Hepatic steatosis (HS) is common in HIV-infected individuals, and its prevalence is expected to increase with the rise of obesity and metabolic syndrome and the aging of the HIV-infected population(1–3). Although liver biopsy is the gold standard for detecting and staging HS, it is infrequently performed in HIV-infected patients without viral hepatitis coinfection. Magnetic resonance spectroscopy (MRS) is the preferred non-invasive modality to detect and quantify HS but is costly and not readily available in resource-limited settings(4).

Fibroscan®-measured transient elastography (TE) is increasingly utilized to estimate liver fibrosis. Controlled attenuation parameter (CAP) quantifies HS by measuring the attenuation of ultrasound waves traveling through the liver at the radiofrequency of the Fibroscan® probe. Because it is conveniently performed simultaneously with Fibroscan®-TE and is relatively inexpensive, CAP is an attractive method to measure HS. Indeed, CAP has been evaluated as a surrogate for histologic HS among patients with a variety of liver diseases (5–7) and is increasingly being used to screen for HS in HIV-infected persons(8–12). However, there are no published data on the accuracy of CAP in the setting of HIV infection. Therefore, the objectives of this study were to examine the correlation of CAP and MRS-measured HS in a cohort of patients with and without HIV infection and to determine whether HIV altered this correlation.

PATIENTS AND METHODS

Participants were recruited from the Northern California site of the Women’s Interagency HIV Study (WIHS) and the Study of Visceral Adiposity, HIV, and HCV: Biologic Mediators of Hepatic Steatosis (VAHH). Both WIHS and VAHH enrolled participants with HIV monoinfection, HCV monoinfection, HIV/HCV coinfection and those with neither infection. Recruitment and study design details of both studies have previously been described (13, 14).

From October 2013 through July 2015, 85 subjects enrolled in the WIHS MRS-Steatosis Substudy and VAHH who had both MRS and CAP measurements available within a median of 14 days (range:0–294) were included in analysis. Magnetic resonance imaging was performed on a 3T whole body scanner (General Electric Healthcare, Waukesha, WI), and MRS was acquired from an 8cc voxel similarly to prior reports, with a 64-acquisition time series of spectra(15). Spectra were automatically phase, frequency, motion and T2 relaxation time corrected(16–18). Quality was visually confirmed by an MR spectroscopist with over 20 years' experience. We calculated liver fat fraction from the corrected MRS measures of CH₂ and CH₃ lipids and of water as the total lipids/(total lipids + water). Visceral adipose tissue (VAT) and abdominal subcutaneous adipose tissue (SAT) volumes were generated based on magnetic resonance slices located at the discs between lumbar vertebrae L2-3, L3-4, and L4-5. Of 85 subjects who underwent CAP assessment (Fibroscan®, Echosens, Paris, France), 82 had valid measurements (39 HIV-monoinfected, 7 HCV-monoinfected, 21 HIV/HCV-coinfected, and 15 uninfected) and were included in the analysis.

Race, ethnicity, alcohol consumption, smoking history, marijuana use and history of injection drug use were obtained through self-report. Alcohol use was categorized as: none; light-moderate (0–12 drinks/week); or heavy (>12 drinks/week). The homeostatic model assessment of insulin resistance (HOMA-IR) was calculated using 8-hour fasting insulin and glucose values. The aspartate aminotransferase-to-platelet ratio index (APRI) and the FIB-4 score were used to estimate liver fibrosis(19, 20). Probable cirrhosis was defined as APRI>2 or FIB-4>3.25. HIV infection was defined by documentation of a positive HIV enzyme immunoassay confirmed with western blot, and chronic HCV infection was defined as serum HCV antibody and HCV RNA positive.

Both MRS-measured HS (MRS-HS) and CAP-measured HS (CAP-HS) had right-skewed distributions, and therefore results were log-transformed. In order to compare MRS-HS and CAP-HS, we standardized log-transformed values to a mean of 0 and standard deviation (SD) of 1. We used concordance correlation coefficients to compare the standardized measurements and linear regression to examine the factors associated with CAP-HS and MRS-HS. The regression coefficients and 95% confidence intervals (CI) are reported as changes in SD units of the log-transformed MRS or CAP values.

Next, we used receiver operating characteristics (ROC) analysis to evaluate the ability of the CAP cut-off 238 decibels/meter (dB/m) to detect mild HS, defined as MRS liver fat fraction 0.05. This CAP cut-off was selected because it has been validated in HIV-uninfected patients and has been used in studies of HS in HIV-infected individuals(5, 8, 10, 12). Kappa coefficient was used to measure agreement between HS diagnosed by CAP or MRS. We used the chi-squared and the Wilcoxon rank-sum tests to compare the characteristics of participants with concordant and discordant MRS and CAP values. Specifically, participants were stratified by MRS into no HS and HS groups; within these groups, participants with low CAP (no HS) and high CAP (HS) were compared. Finally, factors associated with false-positive CAP-HS were evaluated using logistic regression. Statistical analyses were performed using SAS system, version 9.4 (Cary, NC) and STATA version 12.1 (College Station, TX).

RESULTS

Table shows characteristics of the study population and factors associated with CAP-HS and MRS-HS. The median age was 56 years, 71% were women; over half were African American; 50% were overweight or obese (median: BMI 25kg/m²), and only 10% reported heavy alcohol use. The majority (98%) were on highly active antiretroviral therapy. The CAP mean was 232 dB/m and standard deviation 51 dB/m, and the MRS mean liver fat fraction was 0.04 with standard deviation 0.05. On univariate analysis, non-white, non-African American race was associated with significantly higher CAP-HS and MRS-HS, as were increasing BMI, waist circumference, VAT, SAT, and HOMA-IR (Table). These factors remained significantly associated with CAP-HS and MRS-HS after adjusting for age and sex. History of clinical AIDS was associated with significantly higher MRS-HS but not CAP-HS, but this was only borderline significant after adjusting for age and sex (p=0.05).

Correlation of CAP and MRS by HIV and HCV Status

In the entire group, CAP-HS increased with increasing MRS-HS, and we found moderate agreement between the two continuous measurements, with a concordance correlation coefficient(r_c)=0.63 (p<0.001). When stratified by disease status, agreement between CAP-HS and MRS-HS was highest among the HIV-monoinfected (r_c =0.67;p<0.001) and HIV/HCV-coinfected groups (r_c =0.67;p<0.001)(Figure A). CAP detected mild HS, defined as MRS liver fat fraction > 0.05, with an area under the ROC curve of 0.85(95%CI:0.76–0.95) in the entire cohort and 0.88(95%CI:0.78–0.99) in the HIV-monoinfected group. Using a CAP cut-off > 238dB/m, sensitivity and specificity for mild HS were 84%(95%CI:60%–97%) and 75%(95%CI:62%–85%), respectively, in the entire cohort and 89%(95%CI:52%–100%) and 80%(95%CI:61%–92%), respectively, in the HIV-monoinfected group.

CAP-MRS Discordance

The prevalence of HS in our cohort differed depending on the modality used to assess HS: 23% had HS using MRS and 39% had HS using CAP. Among the 63 individuals *without* HS on MRS, 16 (25%) were categorized as having HS on CAP, whereas among the 19 *with* HS using MRS, 3 (16%) were identified as not having HS using CAP, yielding a Kappa coefficient of 0.47 (Figure B). Within the group without HS on MRS, the 16 with false-positive CAP values had higher median BMI (30kg/m² versus 24kg/m²; p=0.002), waist circumference (100cm versus 87cm; p=0.02), VAT volume (176cm³ versus 134cm³; p=0.01), and abdominal SAT volume (285cm³ versus 224cm³; p=0.03) compared to the 47 with true-negative CAP values. After adjusting for age, sex, and race, odds of a false-positive CAP was significantly increased with higher BMI (OR:2.05 per 5 point increase; 95%CI:1.15–3.64) and higher VAT (OR:4.18 per doubling;95%CI:1.30–13.42).

DISCUSSION

The major finding of our study was that CAP-HS and MRS-HS correlated moderately well and that HIV serostatus did not adversely alter the correlation. Furthermore, similar clinical factors were associated with both MRS- and CAP-measured HS, primarily body composition and metabolic factors known to be associated with HS. Although our cohort is

small, the findings suggest that CAP is an acceptable noninvasive surrogate for HS in large studies of HIV-infected individuals. However, CAP overestimated HS prevalence, and higher BMI and VAT were associated with increased odds of false-positive CAP.

Nonalcoholic fatty liver disease (NAFLD) refers to HS in the absence of excessive alcohol use. It is the most common cause of liver disease in Western industrialized countries, and prevalence is increasing in parallel to the obesity epidemic(21). Given the scope of the disease, affecting an estimated 30% of the US population(22), a safe, inexpensive, reliable method of HS screening is critical. This is especially important in the setting of HIV infection: several studies indicate HS is common in HIV-infected individuals, ranging from 28–54% in HIV-monoinfected groups(8, 12, 14, 23–25), but the pathophysiology and implications of HS in this population are not well understood.

Although CAP is used to screen for HS in HIV-infected populations, it has not been validated for this purpose. Multiple studies have compared CAP-HS to histologic HS in patients with a variety of underlying liver diseases– in a meta-analysis including 2,735 patients from 19 studies, CAP demonstrated good performance in detecting HS (defined as 5% of hepatocytes affected on histology) with an area under the ROC of 0.82(26). However, HIV-infected patients were not included. Moreover, the authors found that patients with NAFLD had higher CAP values than patients with other causes of liver disease such as hepatitis C or B virus, independent of histologic HS. Therefore, validation of CAP within a cohort of patients with HIV infection is important.

Our results that CAP-HS correlated moderately well with MRS-HS are similar to other studies comparing CAP-HS and MRS-HS in HIV-uninfected populations, in which the correlation coefficients ranged from 0.50–0.69(27–29). There was no significant correlation between CAP and MRS in the HCV-monoinfected group, likely due to the very small sample size in this subgroup. Our finding that CAP-MRS was able to detect mild HS with an area under the ROC of 0.85 in the whole cohort and 0.88 in the HIV-monoinfected group is also consistent with published literature, with area under the ROC for detection of mild HS ranging from 0.80–0.88 using histology as the reference standard(27, 30–32) and 0.83–0.90 using MRS as the reference standard(33).

Notably, we found that CAP was more likely to overestimate the presence of HS as BMI increased. Others have similarly reported this; the recent meta-analysis found increasing BMI was associated with significantly higher odds of a discrepancy between CAP and histologic HS(26). This highlights a key limitation of CAP and the importance of exercising caution when comparing HS prevalence across studies and patient populations, especially when varying modalities are used to assess HS. A limitation to our study was lack of liver biopsy to correlate CAP results with histology. However, we used MRI as our reference standard, which is considered the most reliable non-invasive modality for detecting HS(4), and similar factors were associated with both CAP-HS and MRS-HS. Another limitation is that the CAP and MRS measures may not have been taken from the same location in the liver– heterogeneity of steatosis may have led to some of the discordance observed(15).

In summary, we found that CAP-HS and MRS-HS correlated moderately well in our cohort of patients with and without HIV and HCV infection. Importantly, HIV infection did not adversely impact CAP performance in detecting HS, but participants with higher BMI were more likely to be falsely identified as having HS using CAP. Our results support the use of CAP for initial HS screening in large cohorts of HIV-infected individuals. However, optimal CAP cut-offs are needed, especially if CAP results are used to make individual patient decisions. Further evaluations of factors that could improve CAP accuracy and interpretation of longitudinal changes in CAP are warranted.

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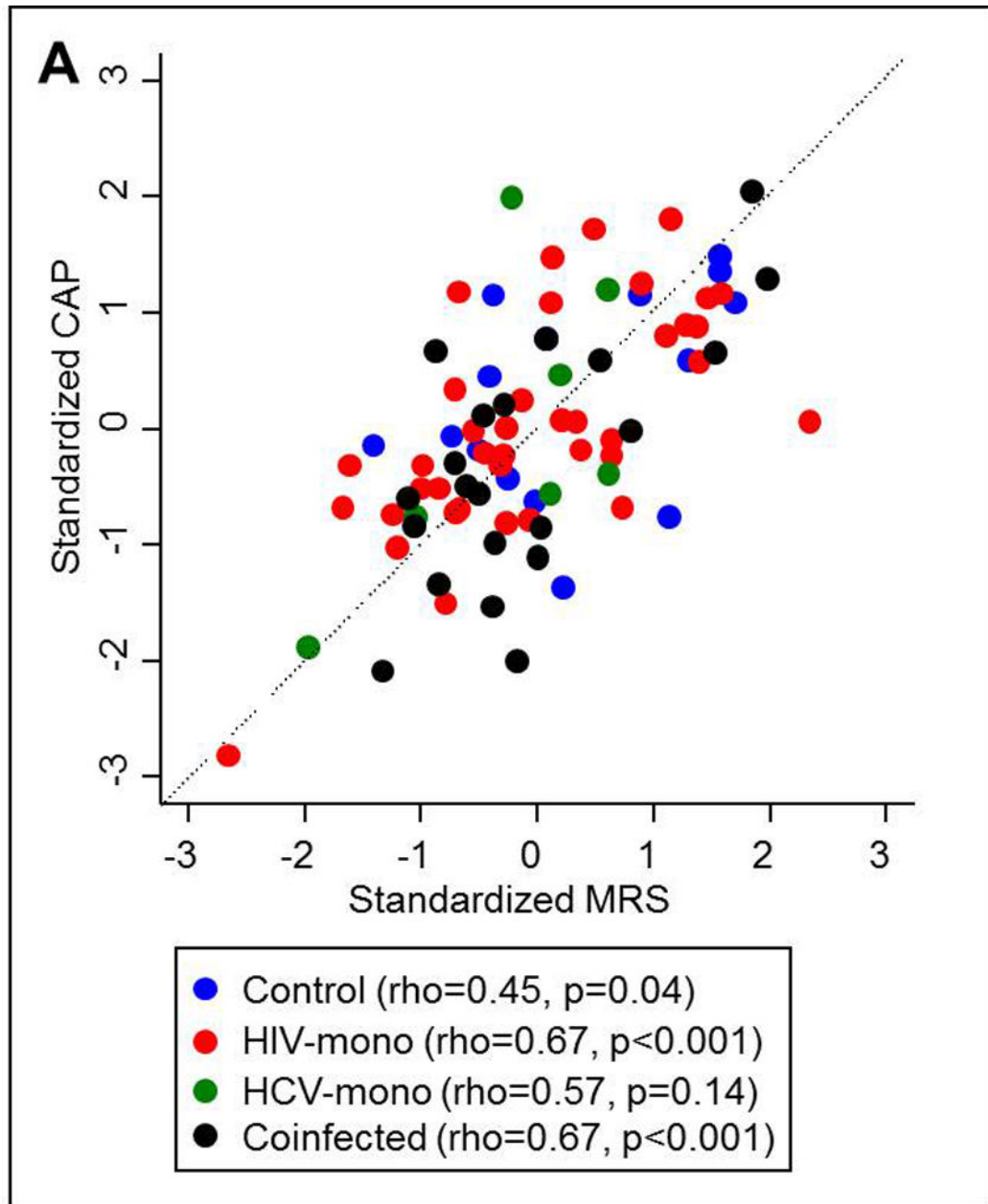
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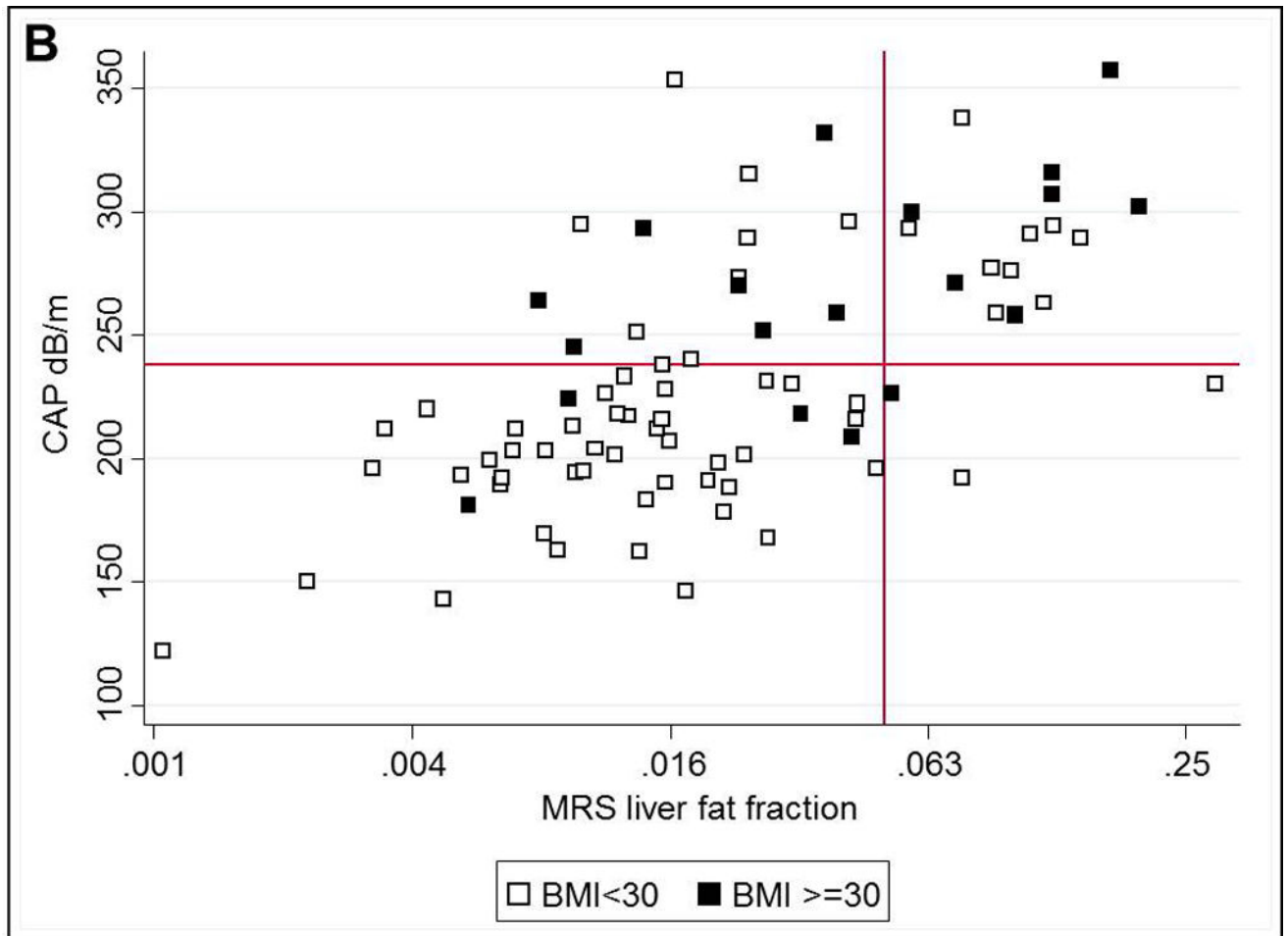


Figure.

A. Correlation of standardized CAP and MRS-measured steatosis, by HIV and HCV status. Dotted black line indicates identical correlation. B. Concordance and discordance of CAP and MRS-measured steatosis, by BMI. Y-axis reference line indicates CAP 238 dB/m and X-axis reference line indicates MRS liver fat fraction 0.05

Table

Demographic and clinical characteristics of study population and factors associated with CAP-HS and MRS-HS

Variable	Study Population (N=82) [§]	CAP-HS SD (95%CI) [£]	MRS-HS SD (95%CI) [£]
Demographics			
Age	56 (51, 59)	0.01 [¶] (-0.35, 0.33)	0.22 [¶] (-0.12, 0.56)
Male	24 (29%)	-0.13 (-0.61, 0.36)	0.08 (-0.40, 0.57)
Race			
African American	49 (60%)	0.16 (-0.34, 0.65)	0.002 (-0.49, 0.50)
White	21 (26%)	Reference	Reference
Other	12 (15%)	1.03 (0.31, 1.72)	0.96 (0.27, 1.64)
Hispanic	12 (15%)	0.17 (-0.45, 0.80)	0.29 (-0.34, 0.91)
Infection status			
Uninfected	15 (18%)	Reference	Reference
HIV-monoinfected	39 (48%)	-0.26 (-0.87, 0.34)	-0.34 (-0.95, 0.27)
HCV-monoinfected	7 (9%)	-0.29 (-1.20, 0.62)	-0.57 (-1.48, 0.35)
HIV/HCV-coinfected	21 (26%)	-0.60 (-1.27, 0.07)	-0.41 (-1.09, 0.27)
Lifestyle			
Alcohol			
None	33 (40%)	Reference	Reference
Light-Moderate	41 (50%)	-0.25 (-0.72, 0.22)	-0.03 (-0.50, 0.44)
Heavy	9 (10%)	-0.42 (-1.21, 0.36)	-0.09 (-0.89, 0.70)
Current smoker	40 (49%)	-0.23 (-0.67, 0.21)	-0.23 (-0.67, 0.21)
Current marijuana use	35 (43%)	-0.24 (-0.68, 0.21)	-0.26 (-0.71, 0.18)
Injection drug use, ever	22 (27%)	-0.25 (-0.74, 0.25)	-0.01 (-0.50, 0.49)
Metabolic			
BMI (kg/m ²)	25 (22, 30)	0.37[*] (0.21, 0.52)	0.26[*] (0.10, 0.43)
Waist Circumference (cm)	91 (83, 103)	1.95[‡] (1.04, 2.87)	1.54[‡] (0.58, 2.49)
VAT (cm ³)	163 (114, 204)	0.71[‡] (0.43, 1.00)	0.74[‡] (0.46, 1.02)
Abd SAT (cm ³)	254 (161, 379)	0.46[‡] (0.24, 0.69)	0.33[‡] (0.10, 0.57)
HOMA-IR	1.38 (0.73, 2.58)	0.27[‡] (0.09, 0.45)	0.28[‡] (0.11, 0.46)
Liver-related			
ALT (U/L)	19 (14, 31)	-0.01 [‡] (-0.28, 0.26)	0.11 [‡] (-0.16, 0.37)
Platelet (10 ⁹ /L)	232 (194, 280)	0.06 [‡] (-0.34, 0.47)	-0.16 [‡] (-0.57, 0.24)
APRI	0.31 (0.21, 0.51)	-0.06 [‡] (-0.25, 0.13)	0.08 [‡] (-0.11, 0.26)
Cirrhosis	8 (10%)	0.04 (-0.70, 0.79)	0.22 (-0.52, 0.97)

Variable	Study Population (N=82) [§]	CAP-HS SD (95%CI) [£]	MRS-HS SD (95%CI) [£]
HIV-related			
Undetectable HIV RNA	46 (78%)	0.10 (-0.53, 0.72)	0.16 (-0.48, 0.80)
Current CD4 (cells/mm ³)	658 (429, 828)	-0.01 [¶] (-0.31, 0.29)	-0.01 [¶] (-0.32, 0.29)
CD4 nadir (cells/mm ³)	214 (124, 327)	-0.05 [¶] (-0.25, 0.14)	0.003 [¶] (-0.20, 0.20)
History of clinical AIDS	21 (36%)	0.40 (-0.14, 0.93)	0.59 (0.057, 1.12)

Bold signifies statistical significance (p<0.05);

[§] Continuous variables are presented as median (interquartile range)

[£] MRS and CAP values were each standardized to a mean of 0 and standard deviation (SD) of 1. Therefore, the regression coefficients and 95% confidence intervals (CI) are reported as changes in SD units of the log-transformed MRS and CAP values. Positive values refer to more steatosis and negative values refer to less steatosis. For example, with each 5 point increase in BMI, logCAP values are 0.37 SD higher and logMRS values are 0.26 SD higher.

The CAP mean (SD) was 232 dB/m (51) and the logCAP mean (SD) was 2.36 (0.10).

The MRS mean (SD) was 0.04 (0.05) and the logMRS mean (SD) was -1.68 (0.49).

CAP mean (SD) by infection status: uninfected 247 dB/m (47), HIV-infected 234 dB/m (48), HCV-monoinfected 236 dB/m (69), HIV/HCV-coinfected 218 dB/m (54)

MRS mean (SD) by infection status: uninfected 0.05 (0.05), HIV-monoinfected 0.04 (0.05), HCV-monoinfected 0.02 (0.02), HIV/HCV-coinfected 0.04 (0.05)

[¶] Per decade;

* Per 5 point increase;

[‡] Per doubling