Prevalence and Risk Factors of Moderate to Severe Hepatic Steatosis in HIV Infection: The Copenhagen Co-Morbidity Liver Study

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ABSTRACT

Background

People living with HIV (PWH) may be at risk of non-alcoholic fatty liver disease (NAFLD). We compared the prevalence of moderate-to-severe hepatic steatosis (M-HS) in PWH with HIV-uninfected controls and determined risk factors for M-HS in PWH.

Methods

The Copenhagen Co-Morbidity in HIV infection Study included 453 participants and the Copenhagen General Population Study 765 participants. None had prior or current viral hepatitis or excessive alcohol intake. M-HS was assessed by unenhanced CT liver scan defined by liver attenuation ≤48 Hounsfield units. Adjusted odds ratios (aOR) were computed by adjusted logistic regression.

Results

The prevalence of M-HS was lower in PWH compared to uninfected controls (8.6% vs. 14.2%, p<0.01). In multivariable analyses, HIV (aOR:0.44, p<0.01); female sex (aOR:0.08, p=0.03); physical activity level (aOR 0.09 very active vs inactive, p<0.01); and alcohol (aOR:0.89 per unit/week, p=0.02) was protective factors, while BMI (aOR:1.58 per 1 kg/m^2, p<0.01); ALT (aOR:1.76 per 10 U/L, p<0.01); and exposure

to integrase inhibitors (aOR: 1.28 per year, p=0.02) were associated with higher odds of M-HS.

Conclusions

Moderate-to-severe hepatic steatosis is less common in PWH compared to demographically comparable uninfected controls. Besides BMI and ALT, integrase inhibitor exposure was associated with higher prevalence of steatosis in PWH.

Key words: NAFLD, NAFL, fatty liver disease, comorbidity, human immunodeficiency virus

Introduction

In the Western World, non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in adults with an estimated overall prevalence of 25 % [1]. A high prevalence of NAFLD has been reported for people living with HIV (PWH), but with a wide range from 13-73% due to substantial differences in study populations and diagnostic methods used [2–6]. A recent meta-analysis found a prevalence of NAFLD in PWH without viral hepatitis of 35% based on imaging procedures [7].

NAFLD covers a wide spectrum of liver disease from hepatic steatosis with accumulation of fat within the hepatocytes to non-alcoholic steatohepatitis (NASH) with additional inflammation and injury of the hepatocytes to liver cirrhosis, liver failure and hepatocellular carcinoma. Hepatic steatosis has been considered a benign condition, but a recent study of HIV uninfected individuals with serial liver biopsies showed that 44% of individuals with baseline hepatic steatosis progressed to NASH and 22% progressed to advanced fibrosis [8]. As liver fibrosis is the only histological feature of long-term prognosis in NAFLD [9], this is of major concern and patients at risk of progression to NASH and liver fibrosis should be identified to prevent disease progression. Risk factors for NAFLD in HIV infection have differed in previous studies. A meta-analysis found that an increase in body mass index (BMI), waist circumference, type 2 diabetes mellitus, hypertension and high levels of total-cholesterol; high-density lipoprotein (HDL); low-density lipoprotein (LDL); triglycerides; fasting glucose; alanine transaminase (ALT); aspartate transaminase (AST) and CD4+ T-cell count were all associated with higher odds of NAFLD [7]. Further, antiretroviral treatment (ART) may contribute to the development of NAFLD due to adverse metabolic effects with mitochondrial dysfunction [10–12].

The aim of this study was to determine if the prevalence of hepatic steatosis was different between PWH and matched HIV uninfected individuals. We hypothesized that PWH had a higher prevalence of hepatic steatosis compared to HIV uninfected individuals. Factors associated with hepatic steatosis were assessed in PWH and the influence of HIV infection evaluated.

Methods

Study populations

The COCOMO Study has been described in detail elsewhere [13,14]. In short, the COCOMO study is an observational, longitudinal cohort study designed to estimate prevalence and incidence of non-AIDS comorbidity in PWH living in Copenhagen, Denmark. Adult PWH were recruited consecutively from the outpatient clinics of the Departments of Infectious Diseases at Rigshospitalet and Amager Hvidovre Hospital in Copenhagen, Denmark from March 2015 through November 2016. The comparator group was retrieved from the Copenhagen General Population Study (CGPS), a prospective cohort study of >100,000 randomly selected adult individuals from the area of Copenhagen initiated in 2003 [15–17]. The comparator group was enrolled from March 2011 through April 2014 except for 20 participants enrolled from February 2004 to September 2008. The comparator group was assumed to be HIV-uninfected as the prevalence of HIV infection was estimated to be 0.1% in the Danish, adult population in 2016 [18].

Data Collection

The data collection has been described in detail elsewhere [13]. In short, comprehensive questionnaires were completed comprising >100 items with information on current health, dietary habits, and lifestyle. Information on food and beverages was collected by a semi-quantitative food frequency questionnaire. Study participants were instructed to report current food and beverage intake. Information on alcoholic beverages included frequency information reported as "never or almost never"; "few times a month"; "few times a week"; "daily or almost daily"; and a quantitative information reported as "average number of alcoholic units per week". Information on previous alcohol intake was not collected. Frequency information on current dietary habits was collected and reported as "times per week". HIV-specific information and status of hepatitis B and C co-infection was retrieved from medical records. Data was >95% complete unless otherwise stated. All data was collected uniformly in the COCOMO study cohort and the CGPS study cohort with identical questionnaires, laboratory equipment and physical examination techniques.

CT scan of upper abdomen

CT scan of the upper abdomen was performed on a Aquillion One scanner (Toshiba Medical Systems, Otawara-shi, Tochigi-ken, Japan) using identical scan protocols for the two cohorts[13,19]. Liver attenuation was measured for all CT scans using Vitrea 3.1 imaging software (Vital Images Inc., Minnetonka, MN, USA). A region of interest (ROI) with an area of 1500 mm^2 (+/- 100 mm^2) was placed in Coinaud liver segments 5 and 6. The average liver attenuation was calculated from the two ROIs and results presented in Hounsfield Units (HU). All analyses were performed by

trained physicians blinded to clinical and biochemical details of the study participants. A pilot study of 20 participants demonstrated a high interrater correlation (R^2=0.98 and spearman rho=0.99) with no bias.

All participants in the COCOMO study were invited to a CT scan; 921 participants (84%) attended. Participants from the CGPS aged 40 years or above were randomly invited to a CT scan; 70% accepted the invitation [20] .

Definitions of Outcome

The physiologic attenuation of the liver parenchyma ranges from 55 to 65 HU by unenhanced CT of the liver [21]. Liver attenuation is inversely correlated with liver fat content, yielding lower Hounsfield units with increasing amounts of hepatic steatosis. In this study we defined moderate-to-severe hepatic steatosis as a CT liver attenuation <48 HU with a specificity of 100%, sensitivity of 53.8%, positive predictive value of 100% and negative predictive value of 93.9% [22]. Sensitivity analyses were conducted to test a threshold of CT liver attenuation ≤40 HU, which has been used to exclude mild hepatic steatosis in previous literature [23,24].

Ethics

The study was approved by the regional ethics committee of the Capital Region of Denmark (H-15017350; H-KF-01-144/01)) and conducted in accordance with the declaration of Helsinki. All participants provided informed consent. The study has been registered at clinicaltrials.gov (NTC02382822).

Statistical analyses

PWH and uninfected controls with a CT scan of the abdomen aged 40 years or older were matched on sex and 5-years age strata in a ratio of 1:2 except for men aged 40-55 was matched 1:1 due to availability (**Supplementary Figure S1**). Baseline clinical and demographic data of the two cohorts were compared by Fisher's exact test and Chi square test (categorical variables), and Kruskal Wallis and Mann-Whitney's U-test (continuous). Univariable and multivariable logistic regression models were conducted in PWH with moderate-to-severe hepatic steatosis as outcome. Two multivariable regression models were constructed with a priori selection of independent variables. Both models were adjusted for age (per decade), sex (female vs male), and Caucasian ethnicity (no vs yes). The metabolic model was further adjusted for: body mass index (BMI, per 1 kg/m^2), plasma total cholesterol (per 1 mM), plasma triglycerides (per 1 mM), diabetes (yes vs no), plasma glucose (per 1 mM) and plasma alanine aminotransferase (ALT, per 10 IU/L). The lifestyle model was further adjusted by: smoking status (never smoker, current smoker, previous smoker), alcohol consumption (per 1 unit per week) and level of physical activity (inactive, moderate inactive, moderate active, very active). The association between a positive HIV status and moderate-to-severe hepatic steatosis was

estimated in the total population. The association between HIV specific variables including ART drug classes were estimated in univariable analyses and multivariable analyses after adjustment for sex, age, ethnicity, BMI and duration of HIV infection. Results are presented as crude and adjusted odds ratios (OR) with 95% confidence intervals (CI). A p-value <0.05 was considered statistically significant. The interaction between BMI (>25 kg/m^2) and HIV status was tested to determine whether HIV modifies the effect of BMI on moderate-to-severe hepatic steatosis. We defined hepatitis B virus infection (HBV) as presence of hepatitis B surface antigen (HBsAg); hepatitis C virus infection (HCV) as presence of anti-HCV antibodies (anti-HCV); excessive alcohol intake as an average consumption of >14 alcoholic units per week for men and >7 alcoholic units per week for women; abdominal obesity as a waist-to-hip ratio of ≥0.90 for men and ≥0.85 for women according to the International Diabetes Federation [25]; and metabolic syndrome as a minimum of three of the following 5 items: (1) Waist circumference waist circumference of ≥94 cm for men and ≥80 cm for women; (2) Systolic blood pressure ≥130 mmHg and/or antihypertensive treatment; (3) plasma HDL ≤1.036 mmol/l for men, and plasma HDL ≤1.295 mmol/l for women; (4) plasma triglycerides ≥ 1.693 mmol/l; (5) self-reported diabetes mellitus and/or antidiabetic treatment and/or non-fasting plasma glucose ≥11.1 mmol/l [25]. All analyses were conducted in R version 3.4.1.

Results

A total of 1,099 participants were included in the COCOMO study. Participants were excluded due to age below 40 years (n=191), CT scan unavailability (n=143), HBV (n=23), HCV (n=82), excessive alcohol consumption (n=174) or missing information on these parameters (n=52). The final study population comprised 453 PWH. A total of 1,192 participants from the CGPS were selected for the comparator group; participants were excluded due to excessive alcohol consumption (n=415). The final control population comprised 765 individuals (**Supplementary Figure S2**).

Clinical and demographic characteristics

Clinical and demographic characteristics of PWH and uninfected controls are depicted in **Table 1**, and HIV specific characteristics of PWH in **Table 2**. In short, PWH were more likely males (86 vs 82%), of non-Scandinavian descent (25 vs 4%), with lower BMI (25 vs 26 kg/m2), less alcohol use (48 vs 72 grams/week) and higher physical activity level and educational level. The majority of PWH acquired HIV through sex between men (71%), received ART (99%), and were well-treated with HIV RNA < 50 copies/mL (97%) and a median CD4 T-cell count of 690 cells/µL (IQR: 520;884). Clinical and demographic characteristics stratified by presence of moderate-to-severe hepatic steatosis can be found in **Supplementary Table S2-S3.**

Prevalence of moderate-to-severe hepatic steatosis in PWH and uninfected controls

Thirty-nine (8.6% (95% CI: 6.4-11.6%)) of PWH had CT-defined moderate-to-severe hepatic steatosis compared to 109 (14.2% (95% CI: 11.9-16.9%)) of HIV uninfected controls (p<0.001). The distribution of liver attenuation in PWH and uninfected controls are depicted in the **Supplementary Figure S3**. The median CT liver attenuation was comparable in PWH and controls (61.3 HU (IQR: 56.5;65.6) vs 61.6 HU (IQR: 53.9;66.1), p=0.56).

HIV infection and moderate-to-severe hepatic steatosis

Compared to controls, PWH had lower odds of moderate-to-severe hepatic steatosis in unadjusted and adjusted analyses (**Figure 1**). The association between BMI and moderate-to-severe hepatic steatosis was not modified by HIV status (p=0.91 for interaction). In PWH, neither current CD4 T cell count, nadir CD4 T cell count < 200 cells/µL, plasma HIV RNA ≥50 copies/mL, nor duration of HIV infection were associated with moderate-to-severe hepatic steatosis (**Supplementary Table S3**). No association was found between moderate-to-severe hepatic steatosis and exposure to nucleoside reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI), integrase inhibitors, protease inhibitors, didanosine, or thymidine analogues (stavudine and zidovudine) (**Supplementary Table S3**). However, the cumulative duration of exposure to an integrase inhibitor was associated with higher odds of moderate-to-severe hepatic steatosis in univariate analyses (OR: 1.19 (95% CI: 1.02;1.39), per year, p=0.02) and the association increased after adjustment for age, sex, BMI, and duration of HIV infection (aOR: 1.28 (95% CI: 1.00;1.65), per year, p=0.05), although it did not reach

statistical significance. Cumulative duration of exposure to a thymidine analogue was not associated with higher odds of moderate-to-severe steatosis in univariate analyses, but after adjustment for age, sex, BMI and duration of HIV infection, a positive association was found (aOR: 1.19 (95% CI: 1.03;1.37) per year, p=0.02) (**Table 3**).

Factors associated with moderate-to-severe hepatic steatosis in PWH

Factors associated with moderate-to-severe hepatic steatosis in PWH can be found in **Table 3** and **Figure 2**. In PWH, abdominal obesity, diabetes, metabolic syndrome and higher BMI, waist circumference, plasma ALT, plasma AST, and plasma triglycerides were associated with higher odds of moderate-to-severe hepatic steatosis in unadjusted models (**Table 3**). Higher physical activity level, higher educational level, and higher plasma HDL concentration were associated with lower odds of moderate-to-severe hepatic steatosis. After adjusting for potential metabolic confounders, higher BMI and higher ALT were associated with higher odds of moderate-to-severe hepatic steatosis, while female sex was associated with lower odds. After adjusting for potential lifestyle confounders female sex and higher physical activity level were associated with lower odds of moderate-to-severe hepatic steatosis (**Figure 2**).

In PWH, a higher weekly alcohol consumption within the national recommendations for excessive alcohol intake was associated with lower odds of moderate-to-severe hepatic steatosis in univariate and multivariate analyses after adjusting for age, sex, ethnicity, BMI and physical activity level (**Table 3** and **Figure 2**). While a weekly consumption of beer seemed protective of moderate-to-severe hepatic steatosis, no

association was found with wine, liquor, sugar-sweetened beverages, coffee, fast food and type of meat product were not associated with moderate-to-severe hepatic steatosis in adjusted analysis (**Supplementary Table S4**).

Sensitivity analyses

In sensitivity analyses with a CT liver attenuation threshold of ≤40HU, the lower prevalence of moderate-to-severe hepatic steatosis in PWH compared to HIV uninfected controls persisted (3.5% (95% CI: 2.2;5.7%) vs 6.4% (95% CI: 4.9;8.4), p=0.04). Accordingly, a positive HIV status was associated with lower odds of hepatic steatosis in univariable analyses (OR: 0.54 (95% CI: 0.30;0.95), p=0.03) and after adjusting for age and sex (aOR: 0.53 (95% CI: 0.30;0.95), p=0.03).

Discussion

In this study of 453 predominantly well-treated PWH without chronic hepatitis and excessive alcohol use and 765 HIV-uninfected controls, PWH had a lower prevalence of CT-defined moderate-to-severe hepatic steatosis than HIV uninfected controls. HIV infection was independently associated with lower odds of hepatic steatosis.

In our cohort of PWH without viral hepatitis or excessive alcohol intake, 8.6% had CT-evidence of moderate-to-severe hepatic steatosis, which was considerably lower than compared to a meta-analysis of NAFLD in PWH [7]. Several reasons may account for the discrepancy. Firstly, time may play a role as 1. generation antiretroviral drugs had more liver toxicity than currently used agents. Secondly,

some studies included individuals with signs of liver disease (e.g. persistently elevated liver enzymes) [4,6,25–27] or individuals with metabolic disorders [3,28]. Thirdly, the prevalence of hepatic steatosis varies globally [29,30] due to increased adoption to a Western diet and sedentary lifestyle as well as genetic variation [20,31]. Fourth, the presence of steatosis may differ due to different diagnostic methodology used. Finally, PWH had higher rates of smoking, less alcohol use, higher physical activity, higher education level and were more frequently on antidiabetic and lipid-lowering therapies compared with controls, which may be protective factors of hepatic steatosis. Our study supports the findings of *Price et al* who found a lower prevalence of hepatic steatosis in unselected PWH compared to HIV-uninfected controls assessed by CT liver scans (13 vs 19%) [10]. Overall, our study and Price et al. question the proposed higher risk of moderate-to-severe hepatic steatosis for PWH compared to a demographically similar group of HIV uninfected individuals. Future studies should explore this in more detail because our findings do not exclude the possibility of an increased risk of mild hepatic steatosis or of more progressive NAFLD in PWH. Our study design does not permit any distinction as to whether the difference in the proportion of hepatic steatoses between the two groups is related to HIV itself or factors associated with HIV infection. Finally, residual confounding of e.g. life style cannot be precluded.

Few studies have been able to investigate the association between HIV infection and hepatic steatosis due to lack of a HIV-uninfected comparator group. A key finding of this study was, that a positive HIV status independently was associated with lower odds of moderate-to-severe hepatic steatosis. The result was robust even after adjustment for age, sex, ethnicity, and potential metabolic and lifestyle confounders and when using a lower threshold for moderate-to-severe hepatic steatosis of

≤40HU. Interestingly, *Price et al* reported that HIV was independently associated with lower odds of hepatic steatosis (OR 0.44, p<0.002) [10], which is consistent with our findings. This may emphasize the complexity underlying the pathogenesis of hepatic steatosis in PWH [32] and warrants future studies.

Adipose tissue abnormalities leading to lipodystrophy and atrophy are associated with specific antiretroviral drugs, in particular with thymidine analogues [34]. Thymidine analogues and didanosine have hepatotoxic properties. Price et al. found an association between didanosine use and hepatic steatosis but this was not reproduced in our study [10]. A possible explanation may be that only 1 of 6 PWH in our study had been exposed to didadosine and that the exposure time was less in the COCOMO cohort compared to MACS cohort (2 vs 4 years) [10]. We did, however, see an association between use of thymidine analogues and hepatic steatosis. Interestingly, use of thymidine analogues was discontinued approximately a decade prior to inclusion in COCOMO. Similarly, low visceral and subcutaneous adipose tissue density was associated with prior exposure to thymidine analogue and/or didanosine exposure in the cohort [35]. Collectively, this suggests that the hepatotoxic effects of thymidine analogues may be long-lasting in terms of moderate-to-severe hepatic steatosis. Individuals exposed to thymidine analogues may require additional work-up for hepatic steatosis. Further, we found an association between cumulative exposure to integrase inhibitor treatment and hepatic steatosis. Of note, use of integrase inhibitors has been associated with excess weight gain [36]. It is likely that there may be a direct link between weight gain and hepatic steatosis. Alternatively, integrase inhibitors may induce hepatic steatosis regardless of overall weight gain. Future studies are warranted to study if

specific integrase inhibitors may infer an increased risk of hepatic steatosis and fibrosis.

Male gender, higher BMI and higher ALT were associated with higher odds of moderate-to-severe hepatic steatosis in PWH. These results are consistent with previous findings, and especially the association between BMI, insulin resistance and hepatic steatosis are well established [2,3,10,36]. Surprisingly, we did not find a significant association between diabetes and moderate-to-severe hepatic steatosis in PWH after adjusting for metabolic risk factors. In our study, PWH were more frequently on antidiabetic- and lipid-lowering treatment compared to controls, which may indicate more frequent physician encounters due to regular HIV care. One may speculate, that PWH initiate therapy for diabetes and dyslipidaemia at an earlier stage, which may cause a lower rate of hepatic fat accumulation. Further, there could be a synergistic effect of diabetes and increasing BMI on the development of hepatic steatosis, as the comparator group had higher BMI and more overweight individuals. A synergistic effect of excessive alcohol intake and increased BMI on liver disease has been reported previously [37], and future studies should explore these possible synergistic effects in NAFLD. Interestingly, a moderate alcohol consumption seemed to be protective of moderate-to-severe hepatic steatosis. No information on previous alcohol consumption was collected, and PWH with a history of excessive alcohol intake and potential advanced fibrosis may have affected the results. Further, previous studies have demonstrated possible protective effects of moderate beer and red wine consumption. A study by Padro et al demonstrated a positive effect of beer on the function of HDL and its capacity to protect against LDL oxidation and to increase the efflux of cholesterol [38]. Thus, a moderate beer consumption may have beneficial effects on the development of hepatic steatosis but

needs to be explored in more detail. Further, people living with HIV reported a more regular consumption of red wine compared to white wine, beer and liquor, suggesting that the high amount of e.g. polyphenols in red wine may not only have cardioprotective effects but also hepatoprotective effects with less inflammation, less insulin resistance and improved lipid profile [39]. However, our data did not support this speculation and needs to be explored in more detail. Importantly, the association between alcohol consumption and moderate-to-severe hepatic steatosis may Finally, no association was found between moderate-to-severe hepatic steatosis and wine, liquor, non-alcoholic beverages, fast-food or meat items in adjusted analyses. However, current international guidelines on treatment of NAFLD focus on changes in diet and lifestyle [40], and future studies should explore the role of different diets in randomized controlled trials.

To our knowledge, this is the largest study of moderate-to-severe hepatic steatosis in PWH with a comparable HIV-uninfected control group using identical methodologies. Our study is limited by a homogeneous population of PWH, which limits the generalizability to other settings. With a sensitivity of 54%, it cannot be precluded that PWH and uninfected controls may have been missed in the diagnosis of moderate-to-severe hepatic steatosis. Liver CT attenuation may not identify individuals with mild hepatic steatosis and individuals with advanced liver fibrosis. Sampling errors cannot be avoided despite the attempt to minimize this, no information on previous alcohol consumption, inflammatory markers, gut microbiota or insulin resistance (e.g. HOMA-IR) were available, and unmeasured residual confounding cannot be excluded. No testing for HIV, HBV or HCV were available for the comparator group. Finally, causality cannot be inferred in a cross-sectional study.

In conclusion, the prevalence of moderate-to-severe hepatic steatosis in this cohort of well-treated PWH was lower compared to a demographically comparable cohort of HIV uninfected individuals, and HIV infection was independently associated with lower odds of moderate-to-severe hepatic steatosis. Male sex, higher BMI and higher ALT were associated with higher odds of hepatic steatosis. Exposure to integrase inhibitor treatment was associated with moderate-to-severe hepatic steatosis and should be explored in more detail.

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Figure legends

Figure 1 Association between HIV infection and moderate to severe hepatic steatosis Odds ratio (OR) and 95% confidence interval (CI) obtained from univariate and multivariable logistic regression analyses with results shown on a log10 scale. Metabolic model adjusted for age, sex, ethnicity, BMI, plasma total cholesterol, plasma triglycerides, diabetes, plasma glucose, and ALT. The lifestyle model adjusted for age, sex, ethnicity, smoking status, weekly alcohol consumption, and physical activity level.

Figure 2 Factors associated with moderate-to-severe hepatic steatosis in people living with HIV. Odds ratio (OR) and 95% confidence interval (CI) obtained from univariate logistic regression analyses with results shown on a log10 scale. Metabolic model (A) adjusted for age, sex, ethnicity, BMI, plasma total cholesterol, plasma triglycerides, diabetes, plasma glucose, and ALT. Lifestyle model (B) adjusted for age, sex, ethnicity, smoking status, weekly alcohol consumption, and physical activity level.

Table 1 Clinical and demographic characteristics of people living with HIV (PWH) and population controls.

	PWH (n=453)	Controls (n=765)	p-value
Age (years), median (IQR)	52.4 (46.8, 61.0)	53.4 (47.7, 61.4)	0.16
Sex (male), n (%)	388 (85.7)	625 (81.7)	0.09
Ancestry, n (%)			<0.01
Scandinavian	338 (75.6)	728 (96.0)	
Other European	52 (11.6)	28 (3.7)	
Middle East and Indian	4 (0.9)	0 (0.0)	
Subcontinent			
Other	53 (11.9)	2 (0.3)	
Educational level, n (%)			<0.01
None	50 (11.5)	91 (11.9)	
Short	104 (24.0)	209 (27.4)	
Middle Length	177 (40.9)	425 (55.7)	
University	102 (23.6)	38 (5.0)	
Smoking, n (%)			<0.01
Current smoker	116 (25.6)	72 (9.4)	
Previous smoker	173 (38.2)	331 (43.3)	
Never smoker	164 (36.2)	359 (46.9)	
Alcohol (g/week), median (IQR)	48.0 (0, 108)	72.0 (36, 108)	<0.01
Physical activity, n (%)			
Inactive	39 (8.9)	49 (6.4)	
Moderate inactive	147 (33.5)	250 (32.8)	

Moderate active	194 (44.2)	385 (50.5)	
Very active	59 (13.4)	78 (10.2)	0.07
Abdominal obesity, n (%)	314 (71.5)	469 (61.5)	<0.01
Waist circumference (cm), median (IQR)	94.0 (87.0, 104.0)	93.0 (86.0, 101.0)	0.04
Body mass index (kg/m^2), median (IQR)	24.7 (22.4, 27.5)	26.0 (23.7, 28.4)	<0.01
WHO BMI category, n (%)			
Underweight, < 18.4 kg/m^2	10 (2.2)	2 (0.3)	
Normal weight, 18.5-24.9 kg/m^2	229 (50.8)	287 (37.5)	
Overweight, 25-29.9 kg/m^2	158 (35.0)	349 (45.6)	
Obese ≥ 30 kg/m^2	54 (12.0)	127 (16.6)	<0.01
Diabetes, n (%)	33 (7.3)	31 (4.1)	0.02
Metabolic syndrome, n (%)	183 (43.4)	261 (35.1)	0.01
Lipid lowering treatment, n (%)	80 (18.2)	88 (11.5)	
Antidiabetic treatment, n (%)	25 (5.5)	26 (3.4)	0.10
Biochemistry, median (IQR)			
Plasma ALT (IU/L)	26 (20, 34)	22 (17, 29)	<0.01
Plasma total cholesterol (mM)	4.9 (4.2, 5.7)	5.4 (4.8, 6.1)	<0.01
Plasma triglycerides (mM)	1.8 (1.3, 2.8)	1.5 (1.0, 2.2)	<0.01
Plasma LDL (mM)	2.8 (2.2, 3.5)	3.2 (2.7, 3.9)	<0.01

Abbreviations: IQR: interquartile range; BMI: body mass index; ALT: alanine aminotransferase; LDL: low-density lipoprotein.

Missing variables for COCOMO (CGPS): Ancestry: 6 (7); educational level: 20 (2); physical activity: 14 (3); abdominal obesity: 14 (2); waist circumference: 14 (2); BMI 2 (0); Metabolic syndrome 31 (21); lipid lowering treatment 13(1); ALT 30 (9); Cholesterol 21 (9).

Table 2 Characteristics of people living with HIV (n=453)

Route of HIV transmission	
MSM	316 (70.7)
HSX	101 (22.6)
IDU	2 (0.4)
Other	28 (6.3)
Blood CD4 T-cell count (cells/µL), median (IQR)	690 (520, 884)
< 200	4 (0.9)
200-349	25 (5.6)
350-500	71 (15.8)
> 500	349 (77.7)
Blood CD4 nadir T-cell count (cells/ µL), median (IQR)	220 (110;320)
Plasma HIV RNA ≥50 copies/mL, n (%)	14 (3.1)
Duration of HIV infection (years), median (IQR)	16.0 (8.3, 23.1)
cART, n (%)	445 (98.9)
ART exposure, n (%)	
NRTI	441 (97.4)
NNRTI	353 (77.9)
Integrase inhibitors	141 (31.1)
Protease inhibitors	258 (57.0)
Didanosine	76 (16.8)
Thymidine analogue	261 (57.6)
Duration of ART exposure (years), median (IQR)	
NRTI	15.1 (7.2, 22.4)
NNRTI	7.4 (3.6, 11.5)

Integrase inhibitors	1.9 (0.9, 5.2)
Protease inhibitors	10.6 (4.8, 19.2)
Didanosine	2.5 (0.8, 5.8)
Thymidine analogue	6.2 (3.5, 9.1)

Abbreviations: HIV: human immunodeficiency virus; IQR: interquartile range; ART: antiretroviral therapy; NRTI: nucleoside reverse transcriptase inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor

Table 3 Factors associated with moderate-to-severe hepatic steatosis in people living with HIV

Variable	Crude OR (95% CI)	p-value
Sex (female vs male)	0.30 (0.07;1.28)	0.10
Age (per decade)	1.12 (0.80;1.57)	0.51
Age groups		
< 50 years	Ref	
50-60 years	1.12 (0.51;2.46)	0.78
61-70 years	1.06 (0.43;2.64)	0.89
> 70 years	1.80 (0.55;5.90)	0.33
Ancestry		
Scandinavian	Ref	
Other European	1.79 (0.74;4.36)	0.20
Middle East and Indian Subcontinent	3.84 (0.39;38.18)	0.25
Educational level		
None	Ref.	
Short	0.30 (0.11;0.79)	0.02
Middle length	0.17 (0.06;0.44)	<0.01
University	0.39 (0.15;0.98)	0.05
Smoking		
Never smoker	Ref	
Current smoker	0.64 (0.27;1.54)	0.32
Previous smoker	0.76 (0.36;1.60)	0.47
Alcohol (per 1 unit/week)	0.89 (0.81;0.97)	0.01
Physical activity		
Inactive	Ref	
Moderate inactive	0.33 (0.13;0.81)	0.02
Moderate active	0.16 (0.06;0.41)	<0.01
Very active	0.10 (0.02;0.50)	<0.01
Abdominal obesity (yes vs no)	3.79 (1.32;10.91)	0.01
Waist circumference (per 1 cm)	1.16 (1.11;1.20)	<0.01

BMI (per 5 kg/m^2)	6.84 (4.11;11.40)	<0.01
BMI ≥25 kg/m^2 (yes vs no)	15.56 (4.71;51.39)	<0.01
Diabetes (yes vs no)	4.86 (2.08;11.39)	<0.01
Metabolic syndrome (yes vs no)	6.24 (2.67;14.60)	<0.01
Biochemistry		
Plasma ALT (per 10 IU/L)	1.73 (1.42;2.10)	<0.01
Plasma AST (per 10 IU/L)	1.44 (1.16;1.78)	<0.01
Plasma total cholesterol (per 1 mM)	1.31 (0.97;1.76)	0.07
Plasma triglycerides (per 1 mM)	1.40 (1.18;1.65)	<0.01
Plasma HDL (per 1 mM)	0.10 (0.03;0.31)	<0.01
Plasma LDL (per 1mM)	1.17 (0.83;1.64)	0.38
Duration of ART exposure (per year)		
Integrase inhibitors	1.19 (1.02;1.39)	0.02
Thymidine analogue	1.07 (0.98;1.17)	0.14
Stavudine	1.42 (1.08;1.88)	0.01

Abbreviations: IQR: interquartile range; BMI: body mass index; ALT: alanine aminotransferase; ART: antiretroviral therapy; LDL: low-density lipoprotein; OR: odds ratio.

Figure 1

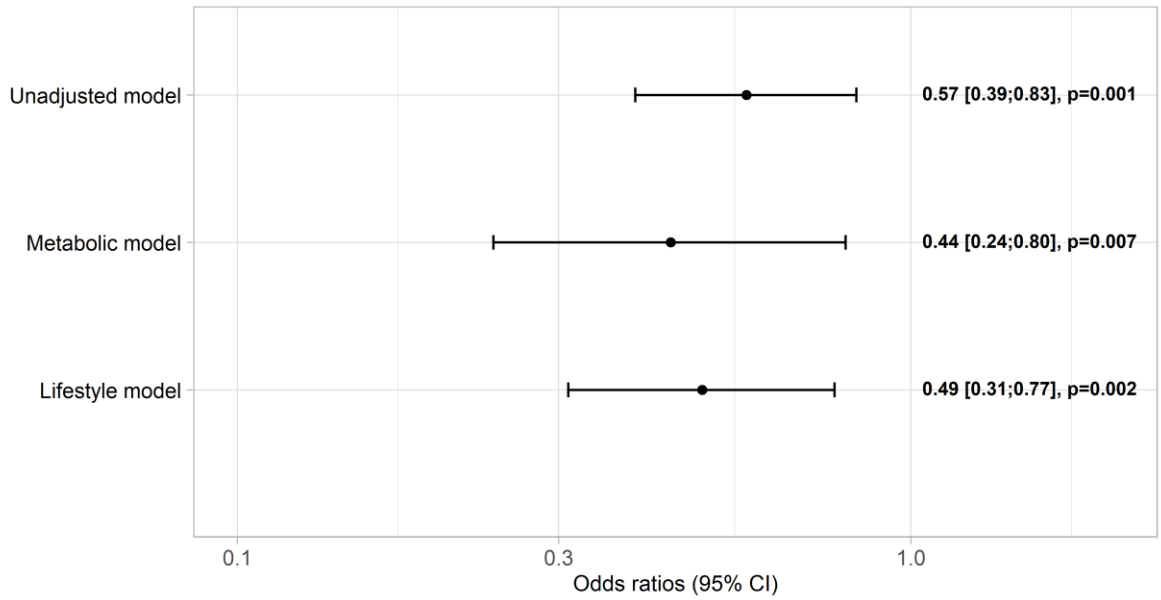

Figure 2