Assessment of the Association of HIV Infection with Hepatic Steatosis or Fibrosis: a Cross-Sectional, Case-Control Study

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Abstract

**Background:** Human immunodeficiency virus (HIV) infection and antiretroviral therapy have been associated with non-alcoholic fatty liver disease (NAFLD), but few studies have evaluated whether HIV infection is an independent risk factor for the development of hepatic steatosis and advanced liver fibrosis.

**Objectives:** To study the prevalence and severity of hepatic steatosis and advanced fibrosis in people living with HIV and control outpatients.

**Methods:** We conducted a cross-sectional analysis of relevant data from 875 pairs of individuals belonging to an HIV-dedicated outpatient clinic and an adult primary care clinic of an inner-city hospital. Hepatic Steatosis Index (HSI) and FIB-4 index were calculated as non-invasive measures of steatosis and fibrosis, respectively. A multivariate logistic regression analysis was performed to assess predictors of steatosis and advanced fibrosis.

**Results:** The prevalence of hepatic steatosis, determined by HSI $\geq 36$, was higher in HIV-negative subjects (71.5% vs. 65.4%, $p=0.006$). The prevalence of advanced fibrosis, determined by FIB-4 index $\geq 3.25$, was higher in the HIV-positive group (7% vs. 1.7%, $p < 0.001$). Multivariable analysis did not identify HIV infection to be an independent risk factor for hepatic steatosis ($p=0.068$) and advanced fibrosis.

**Conclusions:** In this cohort, hepatic steatosis was more prevalent in non-HIV infected patients, while advanced fibrosis had a higher prevalence in people living with HIV. HIV infection was not found to be an independent risk factor for either hepatic steatosis or fibrosis.

**Introduction**

Hepatic steatosis is common in HIV infection and is associated with poor outcomes and increased mortality [1]. In the pre-antiretroviral therapy (ART) era, steatosis was the most common cause of abnormal liver function tests [2]. In the early ART era, hepatic steatosis was mainly related to the lipodystrophy syndrome with an increase in visceral fat content, and medication toxicity seen with thiamine analog nucleoside reverse transcriptase inhibitors (NRTIs) and specific protease inhibitors [3]. Advances in drug development have decreased the metabolic toxicity of antiretroviral therapy. Currently, it is uncertain whether chronic HIV infection confers an increased risk of hepatic steatosis.
Data on the prevalence and consequences of non-alcoholic fatty liver disease (NAFLD) in people living with HIV and on the risk factors for progression to fibrosis are limited. The reported prevalence of steatosis in HIV infection varies from 20–63% [2–4]. There is controversy over the prevalence compared to the general population, and only a few studies have compared HIV-infected and uninfected adults [5, 6]. Obesity contributes to the development of steatosis, though most studies of NAFLD in people living with HIV do not stress this factor [5–14]. The Bronx has a high prevalence of obesity and diabetes when compared to the other New York boroughs, both of which are well-known risk factors for hepatic steatosis [15–17].

The objective of this study was to assess the association of HIV infection with hepatic steatosis by comparing the prevalence of hepatic steatosis in people living with HIV and non-HIV individuals attending outpatient clinics at an inner-city hospital in the Bronx, New York.

Methods

Study population

This was a cross-sectional study of 875 adults living with HIV infection who were followed in the HIV-dedicated outpatient clinic at Jacobi Medical Center, Bronx, NY from January 1 through December 31, 2014. Controls included adult patients who have been tested negative for HIV and were followed in the adult primary care clinic over the same period. The Institutional Review Board at the Albert Einstein College of Medicine and the respective committee of NYC Health + Hospitals approved this study. The study was conducted according to STROBE guidelines for reporting observational studies [18]. The STROBE statement checklist is presented in the supplementary material.

Data collection

Clinical and laboratory data were obtained from the electronic medical record. The following variables were collected: age; gender; weight; height; ethnicity; self-reported tobacco and alcohol use, history of diabetes [defined as ongoing use of anti-diabetic medications or hemoglobin A1c (Hgb A1c) greater or equal to 6.5%], hypertension (defined as ongoing use of antihypertensive medication or documented under the problem list of the electronic medical record), and dyslipidemia (defined as current use of any lipid-lowering medication or documentation in the problem list of the electronic medical record). The diagnosis of prediabetes was defined using established American Diabetes Association (ADA) Hgb A1c criteria (5.7%-6.4%), fasting blood glucose 100–126 mg/dL, or a two-hour serum glucose 140–200 mg/dL following an oral 75 gm glucose tolerance test on patients that did not have a pre-existing diagnosis of diabetes [19]. HIV-specific data included current use of ART, duration of ART use, and years since diagnosis. Virologic suppression was defined as HIV RNA viral load < 20/ml. Body mass index (BMI) was defined as weight divided by the height in meters squared (kg/m²). Baseline laboratory investigations included aspartate aminotransferase (AST), alanine aminotransferase (ALT), total cholesterol, low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), triglyceride, Hgb A1c, platelet count, CD4 T lymphocyte (CD4) count, and HIV-1 RNA (copies/ml). Hepatitis
C serological status was determined by antibody testing (anti-HCV antibody). Hepatitis B serological status was determined by surface antigen testing (HBsAg).

**Liver steatosis and fibrosis assessment**

Hepatic Steatosis Index (HSI) and FIB-4 index were calculated for all patients as they are non-invasive, inexpensive, and readily available methods that assess steatosis and fibrosis, respectively and can be used as screening tools in inner-city HIV clinics [20]. HSI was quantified by the formula 

\[ \text{HSI} = 8 \times \frac{\text{ALT}}{\text{AST}} \times \text{BMI} \left( +2, \text{if history of diabetes}; +2, \text{if female} \right) \]

A HIS < 30 has been found to exclude NAFLD with a sensitivity of 93.1% and hold a negative predictive value of 85.2%, while HSI > 36 has been shown to detect NAFLD with a specificity of 93.1% and have a positive predictive value of 86.7% [21]. Steatosis was defined as HSI > 36. HSI has also been validated in HIV mono-infected patients with an AUROC of 0.88 and an accuracy of 84.5% when compared to ultrasound and cross-validated against \(^1\text{H}\) magnetic resonance spectroscopy [20, 21].

Advanced fibrosis was defined as a FIB-4 index higher than 3.25. FIB-4 index was calculated using the formula 

\[ \text{FIB-4} = \left[ \frac{\text{Age} \times \text{AST}}{\text{Platelets} \times \sqrt{\text{ALT}}} \right] \]

A FIB-4 index of lower than 1.45 has a negative predictive value of 94.7% to exclude a significant fibrosis (META VIR F3-F4) with a sensitivity of 74.3%, while a FIB-4 higher than 3.25 offers a positive predictive value of 82.1% to identify extensive fibrosis (META VIR F3-F4) with a specificity of 98.2% [22].

**Statistical analysis**

Variables are expressed as median and interquartile range (IQR) for continuous and percentage for categorical variables. Comparisons between continuous variables were performed using the Mann-Whitney U test and between nominal variables using the Pearson's chi-squared test. Alpha value of statistical significance was set at 0.05. Multivariate logistic regression analysis was performed to assess predictors of steatosis with his \( \geq \) 36 or advanced fibrosis. Only significant variables (p < 0.05) were then analyzed in a stepwise forward multivariate analysis model. Variables that were included in the FIB-4 and HSI equation were excluded from the analysis. HCV viral load was not included in the analysis due to the extent of missing data, particularly in the HIV-negative cohort. Odds Ratios (OR) and 95% confidence intervals (CI) were reported for p values < 0.05. Data was analyzed using the statistical software SPSS (version 23.0, IBM, New York, NY, USA).

**Results**

**Baseline Characteristics**

A total of 1750 (patients living with HIV 875) patient charts were reviewed. Baseline characteristics are presented in Table 1. The median patient age (IQR) was 51.7 years (41.5–58.8); 57% were female. The majority of patients were non-Caucasian. Patients living with HIV had higher rates of tobacco use (15.5% vs 33.9%, p < 0.001). Hepatitis C seropositivity was documented in 142 HIV-infected patients compared to
24 HIV-uninfected patients (p < 0.001). Among the HIV-infected cases, 94% were on ART and 72% were virologically suppressed. The median (IQR) duration of antiretroviral therapy was 9 years (6–15).
Table 1
General characteristics of the study population a

|                                | HIV negative (N = 875) | HIV positive (N = 875) | P-value |
|--------------------------------|------------------------|------------------------|---------|
| Age (years), median (IQR)      | 52.1 (41.4–60.1)       | 51.1 (41.8–58.8)       | 0.254   |
| Sex Male, (%)                  | 371 (42.4)             | 371 (42.4)             | NA      |
| Race, (%)                      |                        |                        | < 0.001 |
| Black                          | 106 (12.1)             | 427 (48.8)             |         |
| Hispanic                       | 265 (30.3)             | 300 (34.3)             |         |
| Caucasian                      | 23 (2.6)               | 53 (6.1)               |         |
| Other                          | 56 (6.4)               | 88 (10)                |         |
| Unknown                        | 425 (48.6)             | 7 (0.8)                |         |
| BMI (kg/m²), median (IQR)      | 29.1 (25.7–34)         | 27.1 (23.6–32)         | < 0.001 |
| Normal, (%)                    | 178 (20.5)             | 292 (33.8)             | < 0.001 |
| Overweight, (%)                | 299 (34.4)             | 276 (31.9)             |         |
| Obese, (%)                     | 311 (35.8)             | 237 (27.4)             |         |
| Morbidly Obese, (%)            | 81 (9.3)               | 60 (6.9)               |         |
| Smoking, (%)                   | 134 (15.5)             | 296 (33.9)             | < 0.001 |
| Alcohol abuse, (%)             | 93 (12.1)              | 91 (10.3)              | 0.252   |
| Hepatitis B, (%)               | 9 (1.5)                | 38 (4.4)               | 0.002   |
| Hepatitis C, (%)               | 24 (3.9)               | 142 (16.3)             | < 0.001 |
| Undetectable HCV viral load (%)| 47 (33)                | 9 (60)                 | 0.045   |
| ART, (%)                       |                        | 819 (94.1)             |         |
| Viral suppression, (%)         |                        | 633 (72.4)             |         |
| Hepatic steatosis (HSI > 36), (%) | 626 (71.5)         | 572 (65.4)             | < 0.001 |
| Advanced Fibrosis (FIB 4 > 3.25), (%) | 14 (1.7)          | 61 (7)                 | < 0.001 |
| Hypertension, (%)              | 356 (40.7)             | 301 (34.4)             | 0.007   |
| Hyperlipidemia, (%)            | 160 (18.3)             | 223 (25.5)             | < 0.001 |
| Diabetes, (%)                  | 277 (31.7)             | 135 (15.4)             | < 0.001 |
| Pre-diabetes, (%)              | 207 (23.7)             | 219 (25)               | 0.504   |
|                           | HIV negative (N = 875) | HIV positive (N = 875) | P-value |
|---------------------------|------------------------|------------------------|---------|
| HSI, median (IQR)         | 41.0 (37.3–46.57)      | 38.7 (34.4–43.9)       | < 0.001 |
| Hgb a1c (%), median (IQR) | 5.7 (5.4–6.5)          | 5.5 (5.2–5.9)          | < 0.001 |
| Cholesterol (mg/dl), median (IQR) | 179 (153–209) | 171 (145–199) | < 0.001 |
| Triglycerides (mg/dl), median (IQR) | 113(79.5–171.5) | 123(84–184) | 0.022 |
| HDL (mg/dl), median (IQR) | 49 (42–58)             | 47 (38–56)             | < 0.001 |
| LDL (mg/dl), median (IQR) | 102 (80.5–126.5)       | 94 (72–117)            | < 0.001 |
| Fib 4, median (IQR)       | 1.05 (0.72–1.48)       | 1.23 (0.86–1.82)       | < 0.001 |
| AST (U/l), median (IQR)   | 24 (20–29.5)           | 26 (22–34)             | < 0.001 |
| ALT (U/l), median (IQR)   | 22 (17–32)             | 23 (17–33)             | 0.903 |
| CD4 count (cells/µl), median (IQR) | 586 (382–819) | NA                    | NA      |
| HIV RNA viral load (copies/ml), median (IQR) | 0 (0–29,000) | NA                    | NA      |

Abbreviations: BMI, body mass index; IQR, interquartile range; HSI, hepatic steatosis index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; HIV, human immunodeficiency virus; ART, anti-retroviral therapy; HDL, high density lipoprotein; LDL, low density lipoprotein; NA, not applicable.

Missing values: BMI = 14, cholesterol = 46, HDL = 46, LDL = 69, triglycerides = 46, alcohol abuse = 105, hepatitis B serology = 283, hepatitis C serology = 254.

The median BMI for both cohorts was 29.1 kg/m² (IQR 24.7–34) in the HIV-negative group vs 27.1 kg/m² (IQR 23.6–32) in the HIV cohort. A total of 141 (8.1%) individuals of the total cohort had class III obesity (BMI ≥ 40 kg/m²) with a significantly higher percentage in the HIV-negative group (9.3% vs 6.9%, p < 0.005).

The prevalence of diabetes mellitus was significantly higher in the HIV-negative group (31.7% vs 15.4%, p < 0.001). There was no difference in the prevalence of pre-diabetes defined by Hgb A1c criteria (23.7% vs 25%, p = 0.504). The HIV-negative group had higher median Hgb A1c values, higher LDL levels, higher total cholesterol levels, and lower triglyceride levels.

**Hepatic Steatosis**

The prevalence of hepatic steatosis, defined as HSI > 36, was 68% in the entire cohort and was higher in HIV-negative individuals (71.5% vs 65.4%, p = 0.006). Self-reported alcohol use did not differ between the two groups. In the multivariable analysis, presence of HIV infection was not found to be an independent risk factor for the presence of hepatic steatosis (p = 0.068) (Table 2). Factors that were significantly associated with higher odds of steatosis were a diagnosis of hypertension and higher Hgb A1c levels.

Hepatitis C infection had a lower odds ratio for steatosis, as did tobacco use. Because of incorporation of
body mass index and the diagnosis of diabetes in the calculation of HSI, these variables were excluded from the logistic regression analysis.

### Table 2
Multivariate analysis of independent variables associated with hepatic steatosis

|                          | Odds Ratio | 95%CI     | P Value |
|--------------------------|------------|-----------|---------|
| HIV                      | -          | -         | 0.068   |
| Hypertension             | 1.5        | 1.16–1.95 | 0.002   |
| Tobacco use              | 0.59       | 0.46–0.77 | < 0.001 |
| Cholesterol              | -          | -         | 0.113   |
| LDL                      | -          | -         | 0.051   |
| Hgb A1c                  | 1.20       | 1.08–1.34 | 0.001   |
| AST                      | -          | -         | 0.101   |
| HBV serostatus           | -          | -         | 0.918   |
| HCV serostatus           | 0.58       | 0.41–0.83 | 0.003   |

N = 1198 individuals with steatosis. Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; Hgb a1c, hemoglobin a1c; AST aspartate aminotransferase; HBV, hepatitis B virus; HCV, hepatitis C virus.

**Advanced fibrosis**

The overall prevalence of advanced fibrosis, defined as FIB-4 index > 3.25, was 4.4% and was higher in people living with HIV (7% vs. 1.7%, p < 0.001). In the multivariate analysis, independent factors associated with higher odds of advanced fibrosis were age (OR = 1.06, CI = 1.02–1.09, p < 0.001), HBV infection (OR = 2.82, CI = 1.02–7.85, p = 0.05), and HCV infection (OR = 8.35, CI = 4.80–14.54, p < 0.001) (Table 3). HIV was not an independent risk factor for diagnosis of advanced fibrosis. The results of a multivariate analysis were similar when FIB-4 results were expressed as absolute values. Because of incorporation of ALT and AST in the FIB-4 index calculation, these variables were excluded from the logistic regression analysis.
| Table 3                                                                 |
|----------------------------------------------------------------------|
| Multivariate analysis variables associated with hepatic fibrosis     |
| **Odds Ratio** | **95% CI** | **P Value** |
| HIV       | -           | -           | 0.226 |
| Age       | 1.05        | 1.02–1.08   | < 0.001 |
| Gender    | -           | -           | 0.719 |
| Tobacco use | -       | -           | 0.693 |
| BMI per 1 kg/m² increment | 0.94 | 0.9–0.99 | 0.018 |
| Cholesterol | -       | -           | 0.657 |
| LDL cholesterol | 0.99 | 0.98–0.99 | 0.015 |
| HDL cholesterol | -       | -           | 0.540 |
| HBV serostatus | 2.82   | 1.02–7.85  | 0.05  |
| HCV serostatus | 8.35    | 4.80–14.54 | < 0.001 |

N = 75 individuals with fibrosis. Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; BMI, body mass index; HBV, hepatitis B virus; HCV, hepatitis C virus

**Discussion**

In this cohort of patients living with HIV, we found a lower prevalence of hepatic steatosis compared to the control cohort of individuals without HIV despite a higher prevalence of HCV seropositivity. The prevalence of hepatic steatosis in both cohorts was higher than anticipated (> 50% for both groups). Notably, HIV was not associated with an increased risk of steatosis or fibrosis in this study.

The overall prevalence of hepatic steatosis in patients with HIV in our cohort was 65.4%, a finding that was higher than other studies using imaging and invasive studies as diagnostic tools [4, 7]. There are several factors that could potentially account for the higher prevalence rate of hepatic steatosis in our study. The median BMI for HIV positive cases with steatosis was 30.2 kg/m², studies with lower prevalence rates of fatty liver had a mean BMI in the normal category [5, 10], while studies showing higher prevalence rates of more than 50%, had mean BMIs in the overweight category [7]. Also, our study did not exclude patients with alcohol use or hepatitis C. The rate of self-reported alcohol use was not statistically different between both groups. Hepatitis C was found not to be associated with hepatic steatosis in the multivariate regression analysis.

While BMI is known to explain much of the variance in HSI, it is not the most accurate predictor of hepatic adiposity, as opposed to waist circumference or visceral fat content, both of which more closely reflect the presence of metabolic syndrome [23]. A prior study of liver biopsies in patients undergoing bariatric
surgery showed that the presence of steatosis was significantly related to measures of insulin resistance rather than to BMI [24]. Also, hepatic fat content, as estimated by proton spectroscopy, was a stronger predictor of insulin resistance by the Homeostasis Model Assessment (HOMA) than was visceral fat content, as determined by magnetic resonance imaging [25].

The prevalence of advanced fibrosis determined by FIB 4 > 3.25 in our HIV cohort is similar to a recent meta-analysis where the pooled prevalence was 21% with the highest reported prevalence of 35% [2, 12]. The prevalence of hepatic fibrosis in our study was higher in the HIV cohort compared to non-HIV individuals. The main factor associated with the increased prevalence of advanced fibrosis in HIV positive cases was a higher rate of HCV infection. HIV itself was not related with an increased risk of advanced fibrosis in our study. HCV infection in HIV-positive individuals has been shown to be associated with an increased risk of progression to fibrosis [26].

Our findings of lower prevalence rates of hepatic steatosis in patients living with HIV is compatible with the only other large study done with HIV-negative controls [5]. This may be in part due to currently used ART, which unlike the previously used agents, is not implicated in medication-induced hepatotoxicity and does not serve as a risk factor for increased incidence of steatosis in HIV positive patients. In fact, data suggest that cumulative exposure to ART reduces the risk of developing hepatic steatosis [5, 27].

Cross-sectional studies in HIV positive patients have looked at the prevalence of steatosis determined by non-invasive methods, including ultrasound, CT scan, and elastography, with prevalence ranging from 13 to 55% [2–4]. Studies including HCV co-infected patients have similar prevalence rates [5, 28, 29]. These radiological techniques can be expensive and are not readily available to inner-city HIV clinics in low-income settings. There are limited liver biopsy assessment studies and they often include high-risk patients with advanced disease or unexplained elevation of transaminases [7, 11]. These diagnostic modalities are also unlikely to be readily available in low-income settings. Several non-invasive serological methods for the diagnosis of hepatic steatosis have been validated in HIV positive patients, including the liver fat score (LFS), the lipid accumulation product, and HIS [20, 30]. Previous studies with serological and diagnostic modalities were found to significantly underestimate the prevalence of NAFLD [31], but the high prevalence of steatosis in our study with the use of HSI is similar to other prevalence studies which suggests that it is adequate for use in HIV clinics where metabolic abnormalities are prevalent.

We acknowledge the strengths and limitations of our study. This is the largest study conducted to date comparing the prevalence of hepatic steatosis in people living with HIV and HIV-negative controls. This study used accessible and noninvasive clinical markers to estimate hepatic steatosis so that these markers can be easily incorporated during evaluation of patients in HIV clinics. However, we recognize that the estimation of hepatic steatosis and fibrosis were based on surrogate markers. The HSI calculation includes BMI and the diagnosis of diabetes, both of which were common in our cohort. While transient elastography and other sophisticated measurements may be more sensitive tools to estimate hepatic steatosis in both HIV-negative and positive individuals they were not available at our institution at
the time of data collection [28, 32]. Information on the use of thymidine analog NRTIs or specific PIs was not recorded. HCV and HBV viral loads were not available for many patients and treatment status was uncertain. Finally, HgbA1c testing may underestimate serum glucose in HIV-infected patients with reduced red cell survival [33].

Conclusions

In summary, while hepatic steatosis was more prevalent in non-HIV infected patients and advanced fibrosis had a higher prevalence in the HIV-positive cohort, HIV infection itself did not seem to significantly influence the development of either steatosis or fibrosis. The ability of non-invasive clinical predictors to guide therapy and improve clinical outcomes remains to be determined.

Declarations

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Conflicts of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethics approval This project was approved by the Albert Einstein College of Medicine Institutional Review Board. A consent waiver was provided.

Consent to participate Not applicable

Consent for publication Not applicable

Availability of data and material The dataset can be provided after data use agreement among Jacobi Medical Center and the requester’s institution is requested and approved.

Code availability Not applicable

Authors’ contributions Drs. Debroy, Leider, and Kotler contributed to the conception of this project. Drs. Nagraj, Chamorro-Pareja, Palaiodimos, and de Leon designed the study. Drs. Debroy, Nagraj, Chamorro-Pareja, Palaiodimos, Castro, Quintero, Mathias, Laniado, Guerson-Gil, Kladas, and Desai performed the data collection. Drs. Palaiodimos, Leider, and Kotler performed the statistical analysis. All authors evaluated the results of the analysis and substantially contributed to the interpretation of results and drafting of the article. Drs. Debroy, Kotler, Nagraj, Chamorro Pareja, and Palaiodimos critically revised the manuscript. All authors approved the final version.

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