Published in final edited form as:

J Clin Gastroenterol. 2013 February ; 47(2): 182–187. doi:10.1097/MCG.0b013e318264181d.

Hepatic Steatosis in HIV: A Prospective Study in Patients without Viral Hepatitis, Diabetes, or Alcohol Abuse

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Abstract

Background and Aims—Abnormal liver enzymes (LE) are common in those infected with HIV. Histologic data on those with abnormal LE without viral hepatitis are lacking.

Methods—HIV positive subjects without HCV, HBV, alcohol abuse, and DM with more than 1 abnormal LE, defined as 1.25 ULN in AST, ALT, or ALP, over 6 months were included. Subjects underwent a 2 hr oral glucose tolerance test, fasting lipids, insulin and glucose for insulin resistance (IR) by HOMA-IR and DEXA for fat distribution. Biopsies were read blindly to clinical data, and scored by Ishak histologic activity index (HAI) for inflammation and fibrosis and NAFLD Activity Score (NAS).

Results—Fourteen patients underwent biopsy. All were on highly active anti-retroviral therapy (HAART) with undetectable HIV RNA and mean CD4 614. The HAI scores for inflammation and fibrosis were 3.43(1.4) and 1.71(1.26), respectively, and 2 patients had advanced fibrosis (bridging fibrosis/cirrhosis). The majority (65%) of patients had steatosis: grade 1:21%, grade 2:28%, and grade 3:14%. Hepatocyte ballooning was seen in 7 (40%) but NASH was diagnosed only in 4(26%). NAS score of all biopsies of 3.07(2.2; range 0–5). Insulin resistance (HOMA-IR) was higher in those with compared to those without steatosis (3.52 vs. 1.91; $p=.11$) and highest in those with NASH (4.89). Using multivariate logistic regression, only increased GGT ($p=.0009$) predicted steatosis while HOMA-IR ($p=.0046$) predicted NASH.

Conclusions—Although steatosis is common in HIV patients with abnormal LE without DM, alcohol, or viral hepatitis coinfection, NASH was observed in only 26%. The only clinical or laboratory feature associated with biopsy proven steatosis and NASH were GGT and a calculated measure of insulin resistance, respectively. Further studies are needed in this population to determine the long term clinical significance.

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Conflict of interest Disclosure: The authors have no financial disclosures related to this work.

Contributions:

Richard Sterling: study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; statistical analysis; obtained funding.

Paula Smith: acquisition of data; critical revision of the manuscript for important intellectual content.

Elizabeth Brunt: analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content.

Keywords

HIV; steatosis; NASH

Introduction

Human immunodeficiency virus (HIV) infection is a global health concern with an over 1,000,000 infected in the United States and 42 million worldwide. With the advent of highly active antiretroviral therapy (HAART), the morbidity and mortality related to HIV have significantly decreased (1;2). As a result, patients are now living longer with HIV infection, and other co-morbidities such as hepatic events have emerged as a key issue in the management of HIV-infected patients (3). Because the main focus on liver disease in patients with HIV has been on coinfection with HCV and HBV, there has been little attention to other liver diseases such as steatohepatitis (SH).

Abnormal liver enzymes are common and occur in 40–60% of patients on current HAART regimens even in the absence of HCV or HBV (4–6) and their management remains a challenge (7). This high proportion is far greater than expected in the general population of 8% (8). In a recent large study of almost 6000 HIV patients, the prevalence of abnormal ALT and AST in subjects without HCV was 55% and 76% respectively (9). Most clinical studies on hepatotoxicity of HAART have focused on patients with severe liver enzyme elevations (defined as ≥ 5 x the upper limit of normal (ULN) (5; 10–12). However, the majority of patients with abnormal liver enzymes have mild to moderate enzyme elevations (1.25 to $5 \times$ ULN), and there are few studies with histologic data in these individuals. Although small studies suggest the increases in liver enzymes are due to steatohepatitis, they included patients with diabetes (DM), alcohol use, and features of the metabolic syndrome (MS), all of which are known risk factors for steatosis and steatohepatitis (13–15). Therefore, histologic data in HIV subjects with increased liver enzymes without viral hepatitis, DM, MS, and alcohol is lacking. We hypothesized that increased liver enzymes in HIV patients without viral hepatitis, diabetes, or excessive alcohol use are due to steatohepatitis. To address this gap in our knowledge, we performed a prospective study to define the spectrum of histology in a cohort of HIV infected patients with abnormal liver enzymes in the absence of HCV, HBV, DM and alcohol use.

Methods

Patients and Study Design

This is a prospective, cross-sectional cohort study in adult HIV positive subjects with more than 1 abnormal liver enzyme, defined as 1.25 to 5 times ULN in aspartate aminotransferase (AST), alanine aminotransferase (ALT), or alkaline phosphatase (ALP), over 6 months seen between 2007–2011. All patients tested negative for HCV antibody and RNA, HBV surface antigen and DNA, had normal A1AT, ceruloplasmin, and were negative for ANA, ASMA, and AMA. Additional exclusion criteria included history of DM, alcohol use (> 30 g/day in men and 20 g/day in women), hepatic decompensation (prothrombin time prolonged > 2 seconds, INR > 1.5 , ascites, hepatic encephalopathy, serum conjugated bilirubin > 3.0), thrombocytopenia (platelets $< 80,000$), concomitant use of vitamin E, thiazolidinediones, metformin, or insulin, use of medications associated with steatosis and/or steatohepatitis (amiodarone, methotrexate, corticosteroids, estrogen, and tamoxifen), renal failure (serum creatinine > 3.0), and advanced HIV disease with life expectancy less than 1 year. Alcohol consumption was assessed by AUDIT (16) and subjects with a score greater than 2 were excluded.

After informed consent, demographic (age, gender, ethnicity) and clinical (mode of acquisition of HIV, year of HIV diagnosis, duration of disease, current and past anti-retroviral therapy including nucleoside/tide reverse transcriptase inhibitor (NRTI), protease inhibitor (PI), and non-nucleoside reverse transcriptase inhibitor (NNRTI) data were collected). On the day of the biopsy, fasting serum AST, ALT, ALP, total bilirubin, albumin, gamma glutamyl transpeptidase (GGT), complete blood count (CBC) and differential, CD4 and CD8 count (absolute and %), HIV RNA (Roche Amplicor Monitor), lipid profile (serum cholesterol, triglycerides, HDL, and LDL), and free fatty acids (FFA) were collected. Anthropometric measurements (waist:hip ratio, body mass index, % body fat) were assessed by trained clinical research staff. Fasting blood glucose and insulin level for calculation of HOMA-IR, a measure of insulin resistance, were obtained prior to a 2 hour oral glucose tolerance test (OGTT). Insulin resistance was defined as a HOMA-IR > 2.5. DEXA for total body composition with analysis for regional fat distribution and peripheral lipoatrophy was obtained. (Hologic Inc., Bedford, MA) (17;18). The NCEP ATP III criteria were used to define the metabolic syndrome (19). This included 3 or more of the following factors: a waist circumference >40 inches in men and > 35 inches in women, triglyceride level 150 mg/dl, HDL < 40 mg/dl in men and < 50 mg/dl in women, blood pressure > 130/85 mm Hg, and fasting plasma glucose 110 mg/dl.

Liver Histology

All histology was obtained by percutaneous liver biopsy in the standard fashion. Formalin-fixed, paraffin-embedded liver tissue was sectioned, slides coded, and unstained slides were stained by hematoxylin-eosin, Masson's trichrome, PAS-D, Perls' Prussian blue, and reticulin stain. Additional stains for opportunistic infections (Ziehl-Nelsen, Gomori Methenamine Silver), were performed. Histology was assessed for lobular and portal inflammation, portal and perisinusoidal fibrosis, steatosis, steatosis with inflammation, SH, "cryptogenic hepatitis", HSV, CMV, granulomas, eosinophils, globules and iron deposition by a single pathologist (EMB) blinded to all identifying information as well as clinical data. Biopsies with features of chronic hepatitis were further assessed by the Ishak Histologic Activity Index (HAI) (20). Diagnostic categories of NAFLD included not NAFLD (i.e. <5% steatosis), steatosis, steatosis with inflammation and definite non-alcoholic steatohepatitis (NASH). The method of scoring the individual histologic features of NASH are detailed (21) and diagnosis and scores were performed separately (22).

Statistical Analysis

We defined abnormal liver enzymes according to the NIH-NIAI Guidelines (AIDS Clinical Trial Group) as follows: grade 0: < 1.25 × ULN, grade 1: 1.25–2.5 ULN, grade 2: 2.6–5.0 ULN, grade 3: 5.1–10 × ULN, and grade 4: > 10 × ULN. At our center, ULN values were: AST 50 U/L, ALT 60 U/L for men and 50 U/L for women, and ALP 120 U/L. Clinical variables were determined at the time biopsy. All data were assessed for normality and presented as mean (±SD), median (IQR) or proportions as appropriate. The primary endpoint was to determine the prevalence and factors associated with hepatic steatosis, defined as > 5%. A diagnosis of NASH was based on the histopathologic pattern of lesions of steatosis, ballooning and lobular/portal inflammation (21; 22).

Subjects with and without steatosis and with and without NASH were compared. Differences were assessed by T-test, chi-square, or Fisher's exact test as appropriate. Univariate analysis was used to determine factors associated with steatosis. Analysis of variance was used to compare continuous variables and Pearson chi square to compare categorical variables. Multivariable logistic regression (MLR) was then used to identify independent predictors of steatosis. All tests were two-sided and a p value < 0.05 was considered statistically significant. All analyses were performed by JMP IN 8.0 (SAS

Institute, Cary, NC). This study was approved by the Institutional Review Board (IRB) for the study of Human Subjects at VCUHS.

Results

During the study period, 31 subjects with HIV, abnormal liver enzymes, and no evidence HCV or HBV were evaluated, of which 14 met inclusion/exclusion criteria and underwent biopsy. The reasons for exclusion were refused liver biopsy (n=6), excess alcohol use (n=3), cryptococcal infection (n=2), DM (n=1), or normalization of liver enzymes over a 6 month observation period, and active substance abuse, medication induced, and HIV associated cholangiopathy (1 each). Subjects who did not undergo biopsy were more likely women but otherwise similar in other demographic, clinical and laboratory characteristics to subjects included in the analysis. Table 1 shows the demographic and clinical characteristics of the cohort. The mean age was 45 years, 71% were men, and 57% were Caucasian. All subjects were on HAART with 85% on a NRTI, 57% on a NNRTI, and 42% were on a PI. The mean BMI and percent body fat were 29.9 kg/m² and 33.5%, respectively. Although no patients included had a prior clinical history of DM, 3 subjects had an abnormal OGTT.

Table 2 shows the summary laboratory and histology characteristics of the cohort. All subjects had undetectable HIV RNA and the mean CD4 count was 614mm³/L. The mean AST, ALT, and ALP values were 76 U/L, 94 U/L, and 114 U/L, respectively. The mean HOMA-IR was 2.95 ± 1.83; 57% had a HOMA-IR > 2.5. Using the Ishak HAI, the mean total inflammation and fibrosis scores were 3.42 and 1.71, respectively. Table 3 shows the specific histologic pattern for each patient. Five patients had non-specific hepatitis without steatosis. Hepatic steatosis >5% was present in 9 (65%) of patients: grade 1 (5–33%): 21%, grade 2 (34–66%): 28%, and grade 3 (>67%): 14%. The overall NAS in the cohort was 3.07, and ranged from 0 (in 2) to 5 (in 5). While 9 had steatosis with inflammation with or without hepatocellular ballooning, only 4 (26%) met histologic diagnostic criteria for NASH. No patient had evidence of other pathologic findings (see methods) except 2 patients had increased iron (2+ hepatocellular in zone 1). Neither of these patients had biochemical evidence of iron overload (iron saturation <40%). Two patients had advanced fibrosis (bridging fibrosis or cirrhosis).

Table 4 compares cases with ≥5% steatosis to those with <5% steatosis. Although cases with steatosis had more total hepatic inflammation (4.11 vs. 2.20; p=.007), there were no differences when comparing mean fibrosis scores (2.1 vs. 1.0; p=0.11). Both of the subjects with advanced fibrosis had steatosis. As expected, the NAS was significantly higher in cases with steatosis compared to cases without (4.4 vs. 0.6; p<.001). Subjects whose biopsies had NASH had the highest HOMA-IR (4.49; p=.04) compared to those without NASH. Further, all subjects with biopsy-diagnosed NASH had a HOMA-IR > 2.5. Using multivariate logistic regression, only increased GGT (p=.09) predicted steatosis while only increased HOMA-IR (p=.0046) predicted NASH.

Discussion

Abnormal liver enzymes in patients with HIV are common and occur in 40–76% of patients on current HAART regimens even in the absence of HCV or HBV (4–6) and are common in those without HCV (9).

Because the majority of these patients have mild to moderate liver enzyme elevations (1.25 to 5 × ULN), there are few histologic data in individuals with mild to moderate elevations in liver enzymes and no viral hepatitis.

In HIV uninfected individuals, a major cause for abnormal liver enzymes in the absence of viral hepatitis and alcohol is nonalcoholic fatty liver (23). The majority of these individuals have features of the metabolic syndrome and insulin resistance (24). Most histology data on steatosis in subjects with HIV have been limited to patients coinfecting with HCV and found a high proportion (40–75%) with steatosis (25–33) that is greater than expected from the general population. Several independent factors have been associated with steatosis in coinfecting patients including Caucasian race (25), increased body mass index (25, 27–30), glucose intolerance (25; 29), use of DDII or D4T (25; 31), increased lipids (32; 33), and HCV genotype 3 (27–31; 33). However, a recent meta-analysis comparison found no significant difference (OR 1.61; 95% CI 0.84–3.10) in steatosis between coinfecting patients (n=489) compared to those with HCV alone (n=1540) (34). Similar to studies in NAFLD (24), they identified increased BMI (OR 1.13; 95% CI 1.07–1.19) and DM (OR 2.32; 95% CI 1.32–4.07) as factors associated with steatosis. Therefore, although certain HIV factors, such as DDI or D4T can be associated with steatosis, most studies identified factors commonly associated with the metabolic syndrome in all patients with steatosis, irrespective of HIV. Furthermore, most studies did not assess the impact of prior alcohol use.

Data on steatosis in HIV-infected patients without HCV are limited (35). In a study using ultrasound, Crum-Cainflone and colleagues observed that 31% of 216 HIV patients without HCV or HBV coinfection had steatosis (13). Similar to coinfection studies, they identified increased waist, triglycerides, low HDL, and Caucasian race as factors associated with steatosis. Guaraldi and associates used liver-spleen attenuation on computed tomography in 225 HIV subjects attending a metabolic clinic without viral hepatitis or excess alcohol use and found steatosis in 37% (14). In this study, steatosis was associated with higher liver enzymes, male gender, increased waist circumference, and longer exposure to NRTIs. There are few histologic data in HIV infected patients without HCV coinfection. Ingiliz studied 30 French HIV patients with increased ALT in the absence of alcohol abuse, HCV or HBV coinfection, or other known liver disease (15). The majority (22/30) had abnormal liver histology and 18/30 (60%) had steatosis. Of these, steatosis was classified as severe in 9; NASH was diagnosed in 16 (overall prevalence of steatosis: 53%). They also found fibrosis in 18/30, which was severe (bridging fibrosis or cirrhosis) in 6 (20%).

Our results are the first prospective study in North America to define liver histology in this population without viral hepatitis, DM, alcohol use as confounding risks. Similar to Ingiliz (15) we found that the majority (65%) of patients had steatosis with 26% fulfilling histologic criteria for NASH (21;22). We also showed, for the first time, that increased GGT is associated with steatosis and calculated insulin resistance is associated with NASH in this population independently of current HAART use and abdominal fat, a marker of lipodystrophy. Of those with steatosis, hepatocellular ballooning was present in 40% and higher than reported in those with coinfection (29) but similar to studies in NAFLD (24). Similar to the study by Ingiliz (15), 14% in our cohort had significant fibrosis. However, because of small numbers and differences assessment or unrecognized use of alcohol and the demographics of the populations (European vs. North American) makes direct comparisons difficult.

The main strengths of our exploratory study are the prospective design, the careful exclusion of patients with known risk factors for steatosis (diabetes and alcohol use), and blinded histologic review by an experienced histopathologist (EMB) that assessed for not only hepatic steatosis, but for patterns of both lobular and portal inflammation, hepatocellular ballooning, and diagnostic criteria for NASH (21;22). Weaknesses include the small number of patients which limited our power, selection bias of patients referred or willing to undergo biopsy, incomplete records on past HAART use, sampling error inherent in all biopsy-based studies, the possibility of underreported alcohol use, and lack of a HIV negative control

group. Furthermore, if lower cut offs for liver enzymes were used (30 U/L for men and 19 U/L for women), our results may have differed. Therefore, our results may not translate to the general population of HIV-infected patients, including those with normal liver enzymes or those not on HAART. Nevertheless, our results support the high prevalence of steatosis and NASH in HIV infected patients with elevated liver enzymes in absence of viral coinfection and its association with insulin resistance. This observation is important because as HIV patients continue to live longer, unrecognized steatohepatitis may become a significant cause of morbidity and mortality similar to that observed in HIV negative subjects (36) and given the established relationship of NAFLD to cardiovascular disease (37), it may explain the prevalence of increased cardiovascular disease in HIV patients (38).

We conclude that steatosis and NASH are common in HIV patients with abnormal liver enzymes who do not have DM, alcohol abuse, viral hepatitis or coinfection. Both are associated with increased GGT and insulin resistance. Further studies are needed in this population to determine the long term clinical significance.

Acknowledgments

I would like to thank the VCU Infectious Disease/HIV Clinic for their support and referral of patients, Dr. Robert Downs who performed and interpreted the DEXA scans, and the General Clinical Research Center Staff who helped in the care of these patients.

Funding: This study was supported by the grants from the National Institutes of Health to RKS (R03 DK075416) and to the General Clinical Research Center of Virginia Commonwealth University (CCTR-UL1RR031990). This study was registered at Clinical [Trials.gov](https://www.trials.gov) (NCT00575757).

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Table 1

Patient Characteristics

Characteristic	N = 14
Age (years)	45 ± 10
Male	71 %
Caucasian	57 %
Weight (kg)	89 ± 18
Body Mass Index	29.9 ± 7.4
Waist (cm)	99.9 ± 7.9
Waist:Hip ratio	0.94 ± 0.06
% body fat (skin fold)	33.5 ± 8.1
Abdominal fat (g)	4148 ± 2060
Abdominal:gynoid fat ratio	1.36 ± 0.78
HAART use	100%
NRTI use	85%
NNRTI use	57%
PI use	42%
Abnormal OGTT	3/14 (21%)

Data presented as mean ± SD or %

Table 2

Laboratory and Histologic findings

Characteristic	N = 14
AST (U/L)	76 ± 46
ALT (U/L)	94 ± 58
ALP (U/L)	114 ± 45
CD4 (cells/uL)	614 ± 357
GGT (U/L)	137 ± 147
CD4%	29 ± 14
HIV < 50 copies/mL	100%
Total Cholesterol	172 ± 38
HDL mg/dL	40 ± 10
LDL mg/dL	89 ± 28
Triglyceride mg/dL	235 ± 180
HOMA-IR	2.95 ± 1.83
HOMA-IR > 2.5 (%)	57
Total Inflammation	3.43 ± 1.39
Piecemeal necrosis *	0.93 ± 0.61
Lobular inflammation *	1.5 ± 0.76
Portal inflammation *	0.93 ± 0.47
Fibrosis *	1.71 ± 1.26
Advanced fibrosis (%)	14
Steatosis grade (% 0/1/2/3)	0: 36 1: 21 2: 28 3: 14
Hepatocyte ballooning	50%
NAS (0–8)	3.07 ± 2.2
Steatohepatitis	26%

Data expressed as mean (± SD) or %

* Ishak scoring system

Advanced fibrosis = bridging fibrosis or cirrhosis

Table 3

Histologic characteristics of the cohort

CASE #	Ishak Grade 0-18	Ishak Fibrosis Score 0-6	Steatosis 0-3	Steatosis Location	Lobular Inflammation 0-3	Hepatocellular Ballooning 0-2	NAS 0-8	NAS Fibrosis Score 0-4	Iron score pos/neg	RE: 0-4	Histologic Diagnoses
1	1+0+1+1=3	5	1	Azonal	1	2	4	3	punctate RE		NASH
2	1+0+2+1+4	1	2	Zone 3	2	1	5	1b	neg		NASH
3	2+0+1+1=4	1	0	Azonal	1	0	1	1c	2+ zone 1 hepatocytes		Non-specific inflammation
4	1+0+2+1=4	4	3	Panacinar	1	0	4	3	rare KC		Steatosis with inflammation
5	2+0+2+2=6	2	2	Zone 3	1	0	3	2	neg		Steatosis with inflammation
6	0+0+1+0=1	1	0	Azonal	0	0	0	1c	neg		Non-specific inflammation
7	1+0+3+1=5	2	1	Azonal	3	1	5	2	neg		Steatosis with inflammation
8	0+0+1+0=1	1	0	Azonal	1	0	1	1b	neg		Non-specific inflammation
9	1+0+2+1=4	1	2	Azonal	1	1	4	1b	neg		Steatosis with inflammation
10	1+0+1+1=3	1	0	Azonal	0	0	0	1b	neg		Non-specific inflammation
11	1+0+2+1=4	1	1	Zone 3	2	2	5	1b	punctate RE		NASH
12	1+0+1+1=3	2	3	Panacinar	1	1	5	2	neg		Steatosis with inflammation
13	0+0+1+1=2	1	0	Azonal	1	0	1	1c	2+ zone 1 hepatocytes		Non-specific inflammation
14	1+0+2+1=4	1	2	Panacinar	2	1	5	1b	neg		NASH

Table 4

Comparison of those with and without Steatosis

Characteristic	Steatosis Absent (<5%) (n=5)	Steatosis Present (≥ 5%) (n=9)	P value
Age	42 ± 11	47 ± 9	0.42
Gender (% male)	60	77	0.48
Caucasian (%)	40	66	0.33
AST (U/L)	56 ± 37	87 ± 48	0.24
ALT (U/L)	67 ± 66	109 ± 50	0.20
ALP (U/L)	103 ± 40	121 ± 49	0.51
Total cholesterol mg/dL	153 ± 36	183 ± 37	0.17
HDL mg/dL	39 ± 4.7	40 ± 10	0.83
Triglyceride mg/dL	143 ± 46	287 ± 209	0.16
LDL mg/dL	85 ± 20	91 ± 32	0.70
GGT U/L	49 ± 17	186 ± 165	0.09
Abnormal OGTT (%)	0	33	0.07
Hepatic inflammation (Ishak)	2.20 ± 1.30	4.11 ± 0.93	0.007
BMI	27 ± 4.32	31 ± 8.7	0.
Body fat (%)	32.7 ± 3.7	33.9 ± 8.7	0.80
Abdominal fat (g)	3659 ± 984	4454 ± 2539	0.52
HOMA-IR	1.91 ± 1.14	3.52 ± 1.94	0.11
HOMA-IR >2.5 (%)	40	66	0.33
Fibrosis	1.0 ± 0.0	2.1 ± 1.45	0.11
Advanced fibrosis (%)	0	22	0.16
NAS	0.60 ± 0.55	4.44 ± 0.73	<.0001

There were no differences in HAART use or CD4 count (data not reported)