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Evolution of Fatty Liver Disease and Relationship With Lipoproteins and Clinical Outcomes in Hepatitis B/Human Immunodeficiency Virus Coinfection

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Background. Fatty liver disease (FLD) and hepatitis B virus (HBV) infection occur commonly in human immunodeficiency virus (HIV). FLD resolution is associated with improvement in lipoproteins in HIV-uninfected patients. We evaluated changes in FLD in an HBV/HIV-coinfected cohort.

Methods. One hundred eight HBV/HIV-coinfected adults with baseline liver biopsies were followed every 24 weeks (median, 166 weeks) and 60 had follow-up biopsies. Baseline FLD categories (none, ≥5% steatosis, steatohepatitis), their change, and relationships with clinical and lipid/lipoprotein parameters were explored using multivariable modeling.

Results. Median age was 50 years, and 93% were male. At baseline 30% had FLD. With control for lipid-lowering medications and body mass index, low-density lipoprotein (LDL) cholesterol (LDL-C), LDL particle concentration (LDL-P), and apolipoprotein B (apoB) decreased and adiponectin increased over time (all $P < .05$); On follow-up (vs baseline), there was no significant difference in FLD category ($P = .85$); 60% remained without FLD, 17% had unchanged, 12% worsening, and 12% improved FLD. Baseline low-density lipoproteins (LDL-C, LDL-P, small LDL-P) and apoB appeared highest in those with unchanged FLD status (all $P < .05$). No associations between changes in FLD across follow-up (worsening/improvement vs unchanged) and lipid/lipoproteins changes were identified.

Conclusions. In this cohort, there was no significant change in FLD prevalence over a relatively short timeframe. Baseline atherogenic lipids appeared highest in those with persistent steatosis or steatohepatitis, suggesting potentially increased cardiovascular risk in this group, but an independent relationship between individual-level change in FLD status and lipid/lipoprotein levels across follow-up was not observed.

Keywords. lipids; nonalcoholic steatohepatitis; nonalcoholic fatty liver disease; cardiovascular risk; insulin resistance.

About 1.1 million Americans and 33 million individuals globally are living with human immunodeficiency virus (HIV) [1], and up to 20% are coinfected with hepatitis B virus (HBV) [2]. Liver disease remains a significant cause of morbidity and mortality in adults with HIV [3, 4]. A common contributor to the pathogenesis of liver disease in the antiretroviral therapy (ART) era is fatty liver disease (FLD) [5]. Alcoholic or nonalcoholic forms of FLD, which can coexist, have similar histologic presentations, and range from simple steatosis to steatohepatitis to advanced fibrosis and cirrhosis. Epidemiologic studies have reported an estimated nonalcoholic fatty liver disease (NAFLD) prevalence of 50% or more in persons with HIV [6, 7]. Information on the prevalence of FLD in HBV/HIV coinfection is limited. In the largest histologic study to date, approximately 30% of patients with HBV/HIV coinfection had FLD, including 10% with steatohepatitis [8]. HIV can alter the natural history of underlying liver disease. High rates of liver fibrosis are observed in hepatitis C virus (HCV)/HIV and HBV/HIV coinfection [9, 10]. While FLD also contributes to liver disease in HIV [11, 12], there are limited data on changes in FLD status in HIV monoinfection over time [13, 14] and no data in the HBV/HIV population. Furthermore, the impact of coexisting FLD on clinical outcomes in HBV/HIV is unknown.

Studies show that metabolic alterations such as changes in hepatic function, intestinal dysbiosis, and anthropometric alterations increase the risks of dyslipidemia and NAFLD in the HIV population [15]. Moreover, FLD in HIV is associated with adverse metabolic effects, including dyslipidemia

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and insulin resistance, with resultant increase in risk for cardiovascular events, a major comorbidity in an aging HIV population [16]. We have recently shown that this associated increased metabolic risk and an atherogenic lipid profile is also present in individuals with coexisting FLD and HBV/HIV coinfection [8]. However, rather than traditional lipid profiles, evaluation of atherogenic lipid subfractionation may be needed to better determine cardiovascular disease (CVD) risk in both HIV- and non-HIV-infected populations [8, 17, 18]. Importantly, studies among the HIV-uninfected population suggest that resolution of nonalcoholic steatohepatitis (NASH) is associated with improvements in lipid-related CVD risk, whereas persistent NASH may be associated with persistently elevated CVD risk [18]. Indeed, in the Pioglitazone vs Vitamin E vs Placebo for the Treatment of Nondiabetic Patients with NASH (PIVENS) trial, favorable changes in low-density lipoprotein (LDL) size with an increase in mean peak LDL particle diameter and a predominance of LDL phenotype A were observed following NASH resolution, whereas patients without NASH resolution had persistently unfavorable lipoprotein subfraction levels [18]. There is currently no information on the relationship between longitudinal changes in FLD status and change in lipoprotein profiles in the HBV/HIV-coinfected population.

In this study we aimed to evaluate the impact of histologically defined FLD on clinical, metabolic, and lipid/lipoprotein outcomes in a well-defined longitudinal HBV/HIV-coinfected cohort on dually active ART with histologic data. Additionally, we describe changes in FLD using paired liver biopsies and explore their relationship with metabolic and lipid and lipoprotein profiles on follow-up.

PARTICIPANTS AND METHODS

This is a multicenter prospective cohort study of adults with HBV/HIV as previously described (NCT01924455) [8, 10, 19]. From April 2014 to October 2017, adults (≥18 years of age) who were anti-HIV and hepatitis B surface antigen (HBsAg) positive for at least 6 months were recruited from 8 Hepatitis B Research Network (HBRN) sites in the United States and Canada. Those with detectable HCV RNA, decompensated cirrhosis, or hepatocellular carcinoma (HCC) were excluded. Study participation included evaluations at enrollment, at weeks 12 and 24, and every 24 weeks thereafter up to 192 weeks (3.7 years) or 31 January 2020, whichever came first, including a liver biopsy within 48 weeks of study entry and at study end. The institutional review board at each center approved the protocol, and participants gave written consent.

Of the 139 participants enrolled in this study, 135 were confirmed to be HBsAg positive at entry, 108 of whom had a baseline liver biopsy and were followed for at least 24 weeks. The evaluation of change in histology was limited to the 60 participants with a follow-up (paired) liver biopsy.

HISTOLOGIC AND CLINICAL, METABOLIC, AND LIPID/LIPOPROTEIN DATA

Liver biopsy sampling and detailed assessment of clinical and laboratory data definitions and metabolic and lipoprotein measurements have been reported elsewhere [8, 19] and are summarized in the Supplementary Materials. Histological findings were scored blindly with respect to clinical data by the HBRN Pathology Committee for inflammation and fibrosis using the Ishak scoring system [8, 20]. FLD categories were (1) steatohepatitis, (2) steatosis (defined as more than minimal steatosis without steatohepatitis), or (3) no FLD. Due to low frequency, the steatohepatitis and steatosis categories were collapsed as FLD for some analyses.

Statistical Analysis

Descriptive statistics were used to report baseline characteristics of the full analysis sample and paired biopsy subsample by baseline FLD status (yes/no). All mixed models included time (days from baseline) as a continuous fixed effect, site (which was related to missing follow-up data) as a fixed effect, and a random intercept.

Relationship Between Baseline FLD Categories With Changes in Metabolic and Lipid/Lipoprotein Parameters and Clinical and Virologic Outcomes in Follow-up

Descriptive statistics were used to report select metabolic and lipid parameters at baseline, 96 weeks (1.9 years), and 192 weeks (3.7 years), overall and by baseline FLD categories. Linear mixed models were used to test for a change in these parameters over time, with each outcome as a repeated measure, with control for body mass index (BMI), diabetic medications, lipid-lowering medication, and protease inhibitor use as repeated measures. Baseline FLD status and an interaction term between FLD and time were included in each model to test whether change differed by baseline FLD status. Parameters were transformed ($\log_{10}$) as needed to normalize their distribution for modeling.

The FLD category of participants with clinical outcomes (incident cirrhosis, decompensation, HCC, and HBV death) is described; associations with FLD category or status could not be formally tested due to their low incidence. Because hepatitis B e antigen (HBeAg) loss was relatively common [19], the rate of HBeAg loss across follow-up, with 95% confidence intervals (CIs), constructed using the Poisson distribution, was compared by baseline FLD status and category.

Change in FLD

Among the paired biopsy subsample (n = 60), the distribution of histology-measured FLD-related variables are reported at baseline and follow-up. Changes in these variables were tested with ordinal logistic and binomial mixed-effects models, as appropriate, with each outcome as a repeated measure.

An Exploration of Associations With Change in FLD Status

Select baseline demographic and clinical, metabolic, and lipid/lipoprotein parameters were compared across categories representing FLD change status between entry and follow-up biopsy. Associations between FLD change status and change in lipid parameters over the same timeframe were also evaluated. These analyses are detailed in the Supplementary Materials. All analyses were conducted using SAS version 9.4 software (SAS Institute, Cary, North Carolina).

RESULTS

Baseline Participant Characteristics

In the full sample (N = 108), 32 (29.6%) participants had FLD (22 with steatosis only, 10 with steatohepatitis). Furthermore, 10 of 108 participants had cirrhosis at baseline, 4 of whom had FLD. Among the paired biopsy subsample (n = 60), 19 (31.7%) had FLD (13 with steatosis, 6 with steatohepatitis). Baseline characteristics of the full samples and subsample, by FLD status (yes/no), are reported in Table 1. As we previously reported, compared to those without FLD, patients with FLD were older and less likely to be of non-Hispanic Black race, and a higher proportion had abdominal obesity, diabetes, and hyperlipidemia [8]. Moreover, compared to no FLD, the extent of insulin resistance (Homeostatic Model Assessment for Insulin Resistance [HOMA-IR] and adipose tissue insulin resistance [Adipo-IR]) was higher in the presence of FLD. The proportion with at-risk alcohol intake was low at 12% in the full sample and 10% in the paired biopsy subsample.

Relationship Between Baseline FLD and Change in Metabolic and Lipid and Lipoprotein Parameters in Follow-up

Metabolic and lipid and lipoprotein parameters at baseline and at approximately 96 weeks (1.9 years) and 192 weeks (3.7 years) of follow-up, overall and stratified by baseline FLD categories among the full sample (N = 108), are shown in Table 2. Overall, with control for use of lipid-lowering medication and BMI at each time point, LDL cholesterol (LDL-C; mg/dL), LDL particle concentration (LDL-P; $\log_{10}$ mg/dL), and apolipoprotein B (apoB; $\log_{10}$ mg/dL) decreased and adiponectin (µg/mL) increased over time ($P < .05$ for all). Glucose ($\log_{10}$ mg/dL) and small LDL-P ($\log_{10}$ mg/dL) also appeared to decrease over time, although the trend was not statistically significant ($P = .06$ and .07, respectively). These time trends were stable across FLD categories at baseline (ie, FLD × time interaction $P > .05$). In contrast, there was not a significant change in insulin ($\log_{10}$ µIU/mL), HOMA-IR, total cholesterol (TC; $\log_{10}$ mg/dL), triglycerides (TG; $\log_{10}$ mg/dL), high-density lipoprotein cholesterol (HDL-C; $\log_{10}$ mg/dL), high-density lipoprotein particle concentration (HDL-P; µmol/L), or apolipoprotein A1 (apoA1; mg/dL) over time ($P \geq .05$ for all). Furthermore, there was a significant interaction between time and FLD category in the models of TC ($P = .01$) and HDL-C ($P = .02$). Specifically, while TC decreased in those without FLD or steatosis only, TC increased in those with steatohepatitis, and while HDL-C increased in those without FLD, HDL-C had little or no change in those with steatohepatitis and decreased in those with steatosis.

Relationship Between Baseline FLD and Clinical and Virologic Outcomes on Follow-up

During follow-up, adverse clinical outcomes (incident cirrhosis, decompensation, HCC, liver transplant, or HBV-related death) were rare, occurring in only 3 participants. One participant (of 98 without cirrhosis at baseline) was diagnosed with cirrhosis by presence of ascites, splenomegaly, and nodular liver documented by computed tomography, magnetic resonance imaging, or liver ultrasound during the third year of follow-up. Although this participant did not have FLD at baseline, steatosis was evident on their second biopsy (52 weeks after cirrhosis diagnosis). Among the full sample (N = 108), 1 participant who had steatohepatitis at baseline developed hepatic decompensation and HCC prior to an HBV-related death, while another participant who developed HCC did not have FLD per their baseline and follow-up biopsies. No participant had HBsAg loss during follow-up (Table 3).

Among 67 participants who were HBeAg positive at baseline (23 with FLD and 44 without FLD), 13 had HBeAg loss (4 with FLD and 9 without; rates of 6.75 [95% CI, 2.53–17.97] and 7.81 [95% CI, 4.07–15.02] per 100 person-years, respectively). There was not a significant difference in HBeAg loss rates, as indicated by overlapping 95% CIs, when evaluated by FLD status or FLD categories (Supplementary Table 4).

Change in Histologic FLD Status Among the Participants With Paired Biopsies (n = 60)

The median time between baseline and follow-up liver biopsies was 3.6 (range, 2.6–4.3) years. The distribution of steatosis grade at baseline and follow-up is shown in Figure 1. FLD-related histologic parameters on biopsies by time point and evaluation of changes are reported in Table 4. There were no significant differences in distributions of steatosis grade ($P = .91$) or FLD category ($P = .85$), although compared to initial biopsy, the percentages of participants with moderate and severe steatosis (3.3% vs 11.7%, $P = .08$) and steatohepatitis (10.0% vs 13.3%, $P = .57$) on follow-up biopsy were higher. There also were no significant differences in presence of ballooning ($P = .76$), Mallory-Denk bodies ($P = .56$), or distribution of perisinusoidal fibrosis grade ($P = .98$) by time point. Changes in FLD-related histologic parameters with >2 levels (steatosis grade, perisinusoidal fibrosis grade, and FLD category) are available at the individual level in Supplementary Tables 1–3. Of the 11 participants with "worse" steatosis, 2 were 2 grades worse, and of those with "improved" steatosis, only 1 was 2 grades better. Of the 9 participants with "worse" perisinusoidal fibrosis, the majority (n = 7) had a 1-stage increase in perisinusoidal fibrosis; similarly, of the 10 with "improved" perisinusoidal fibrosis, 7 had a 1-stage increase.

Table 1. Baseline Characteristics of Hepatitis B Virus/Human Immunodeficiency Virus–Coinfected North American Adult Sample and Paired Biopsy Subsample, Overall and by Fatty Liver Disease Status

Characteristic	Full Sample (N = 108)[a]	No FLD (n = 76)	FLD (n = 32)	Paired Biopsy Subsample (n = 60)[a]	No FLD (n = 41)	FLD (n = 19)
Demographic characteristics						
Age, y, median (IQR)	49.5 (45–55)	48 (43–54.5)	53 (47.5–55.5)	50.5 (46–54)	48 (45–54)	54 (50–57)
Sex						
Male	100 (92.6)	69 (90.8)	31 (96.9)	57 (95.0)	38 (92.7)	19 (100.0)
Female	8 (7.4)	7 (9.2)	1 (3.1)	3 (5.0)	3 (7.3)	0 (0.0)
Race	n = 105	n = 74	n = 31	n = 58	n = 40	n = 18
Non-Hispanic White	35 (33.3)	20 (27.0)	15 (48.4)	16 (27.6)	8 (20.0)	8 (44.4)
Non-Hispanic Black	54 (51.4)	45 (60.8)	9 (29.0)	31 (53.4)	26 (65.0)	5 (27.8)
Non-Hispanic Asian	5 (4.8)	4 (5.4)	1 (3.2)	4 (6.9)	3 (7.5)	1 (5.6)
Other	11 (10.5)	5 (6.8)	6 (19.4)	7 (12.1)	3 (7.5)	4 (22.2)
Alcohol consumption						
None	60 (55.6)	40 (52.6)	20 (62.5)	29 (48.3)	18 (43.9)	11 (57.9)
Moderate	35 (32.4)	28 (36.8)	7 (21.9)	25 (41.7)	20 (48.8)	5 (26.3)
At-risk	13 (12.0)	8 (10.5)	5 (15.6)	6 (10.0)	3 (7.3)	3 (15.8)
HIV parameters						
Antiretroviral medications[b]						
NRTI use	103 (95.4)	73 (96.1)	30 (93.8)	58 (96.7)	41 (100.0)	17 (89.5)
NNRTI use	36 (33.3)	25 (32.9)	11 (34.4)	21 (35.0)	14 (34.1)	7 (36.8)
Protease inhibitor use	49 (45.4)	36 (47.4)	13 (40.6)	29 (48.3)	21 (51.2)	8 (42.1)
INSTI use	51 (47.2)	30 (39.5)	21 (65.6)	25 (41.7)	13 (31.7)	12 (63.2)
HIV-related tests						
CD4, cells/mm^3	n = 96	n = 66	n = 30	n = 56	n = 38	n = 18
Median (IQR)	564.5 (367.5–712.5)	560 (369–753)	575.5 (343–673)	564.5 (358.5–675.5)	560 (374–707)	575.5 (343–673)
CD4 %	n = 97	n = 67	n = 30	n = 57	n = 39	n = 18
Median (IQR)	25 (18–36)	27 (18–37)	24.5 (19–34)	25.9 (21–36.3)	26 (18–37)	25.7 (21.2–36.3)
CD8, cells/μL	n = 62	n = 44	n = 18	n = 37	n = 27	n = 10
Median (IQR)	878.5 (592–1243)	901 (576–1198)	750.5 (595–1272)	827 (560–1070)	889 (560–1139)	680 (554–1018)
CD8 %	n = 63	n = 45	n = 18	n = 38	n = 28	n = 10
Median (IQR)	44 (35–53)	43 (35–56)	46 (39–50)	42.5 (35–56)	40.5 (35–56.5)	48 (35–50)
HIV stage	n = 96	n = 66	n = 30	n = 56	n = 38	n = 18
1 (CD4 ≥ 500 cells/mm^3)	55 (57.3)	36 (54.5)	19 (63.3)	33 (58.9)	22 (57.9)	11 (61.1)
2 (CD4 250–499 cells/mm^3)	28 (29.2)	23 (34.8)	5 (16.7)	15 (26.8)	12 (31.6)	3 (16.7)
3 (CD4 200–349 cells/mm^3)	7 (7.3)	4 (6.1)	3 (10.0)	5 (8.9)	3 (7.9)	2 (11.1)
4 (CD4 < 200 cells/mm^3)	6 (6.3)	3 (4.5)	3 (10.0)	3 (5.4)	1 (2.6)	2 (11.1)
HIV RNA, copies/mL	n = 98	n = 68	n = 30	n = 54	n = 36	n = 18
<20	77 (78.6)	52 (76.5)	25 (83.3)	46 (85.2)	29 (80.6)	17 (94.4)
20–399	9 (9.2)	8 (11.8)	1 (3.3)	4 (7.4)	3 (8.3)	1 (5.6)
400–9999	10 (10.2)	7 (10.3)	3 (10.0)	3 (5.6)	3 (8.3)	0 (0.0)
≥10 000	2 (2.0)	1 (1.5)	1 (3.3)	1 (1.9)	1 (2.8)	0 (0.0)
HBV parameter						
HBV DNA, IU/mL						
Undetectable	70 (64.8)	51 (67.1)	19 (59.4)	43 (71.7)	29 (70.7)	14 (73.7)
<1000	18 (16.7)	10 (13.2)	8 (25.0)	10 (16.7)	5 (12.2)	5 (26.3)
1000–19 999	8 (7.4)	6 (7.9)	2 (6.3)	2 (3.3)	2 (4.9)	0 (0.0)
≥20 000	12 (11.1)	9 (11.8)	3 (9.4)	5 (8.3)	5 (12.2)	0 (0.0)
Cirrhosis	10 (9.3)	6 (7.9)	4 (12.5)	5 (8.3)	2 (4.9)	3 (15.8)
Metabolic parameters						
Weight status (race-adjusted)	n = 103	n = 71	n = 32	n = 58	n = 39	n = 19
Underweight/normal	40 (38.8)	29 (40.8)	11 (34.4)	23 (39.7)	16 (41.0)	7 (36.8)
Overweight	36 (35.0)	26 (36.6)	10 (31.3)	24 (41.4)	15 (38.5)	9 (47.4)
Obese	27 (26.2)	16 (22.5)	11 (34.4)	11 (19.0)	8 (20.5)	3 (15.8)
High waist circumference	28 (32.6)	18 (28.6)	10 (43.5)	14 (28.0)	9 (25.0)	5 (35.7)
Diabetes mellitus	10 (9.3)	5 (6.6)	5 (15.6)	4 (6.7)	2 (4.9)	2 (10.5)

Table 1. Continued

Characteristic	Full Sample (N = 108)[a]	No FLD (n = 76)	FLD (n = 32)	Paired Biopsy Subsample (n = 60)[a]	No FLD (n = 41)	FLD (n = 19)
Hyperlipidemia	34 (31.5)	17 (22.4)	17 (53.1)	17 (28.3)	8 (19.5)	9 (47.4)
Lipid-lowering medications	29 (26.9)	16 (21.1)	13 (40.6)	15 (25.0)	8 (19.5)	7 (36.8)
HOMA-IR	n = 104	n = 73	n = 31	n = 59	n = 40	n = 19
Median (IQR)	2.8 (1.6–5.0)	2.4 (1.5–3.7)	4.1 (2.4–7.8)	3.0 (1.5–5.2)	2.1 (1.3–4.3)	4.1 (2.8–6.9)
Adipo-IR	n = 104	n = 73	n = 31	n = 59	n = 40	n = 19
Median (IQR)	34.9 (17.4–57.3)	28.9 (14.2–43.3)	58.8 (43.1–80.2)	37.1 (15.0–76.5)	26.8 (12.9–44.4)	58.8 (44.2–80.2)

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: Adipo-IR, adipose tissue insulin resistance; FLD, fatty liver disease; HBV, hepatitis B virus; HIV, human immunodeficiency virus; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; INSTI, integrase strand transfer inhibitor; IQR, interquartile range; NNRTI, nonnucleos(t)ide reverse transcriptase inhibitor; NRTI, nucleos(t)ide reverse transcriptase inhibitor.

[a]Data presented among this sample unless a subset is indicated due to missing data.

[b]Only 3 patients (2.8%) among the full study sample were not on antiretroviral therapy (ART), and all 3 had no FLD at baseline. All patients within the paired biopsy subsample were on ART.

Table 2. Metabolic and Lipid and Lipoprotein Parameters Among the Full Sample by Time, Overall and Stratified by Baseline Fatty Liver Disease Category

Parameter	First Visit (Week 0)		Second Visit (≈Week 96)		Third Visit (≈Week 192)		Model P Value[a]
	No.	Median (IQR)	No.	Median (IQR)	No.	Median (IQR)	
Metabolic parameters							
Glucose, mg/dL							n = 105
Overall	107	92 (87–103)	74	88 (76–100)	68	90 (79.5–102)	.09
No FLD	75	91 (86–101)	54	86 (76–97)	49	91 (78–101)	
Steatosis	22	94 (90–103)	14	99 (86–102)	13	88 (84–100)	
Steatohepatitis	10	92.5 (88–113)	6	95.5 (82–101)	6	101 (70–118)	
Insulin, μIU/mL							n = 103
Overall	104	12.5 (7.5–19.0)	71	10.4 (6.6–18.2)	66	11.3 (5.5–20.3)	.93
No FLD	73	11.0 (7.0–16.0)	51	8.7 (6.1–14.3)	47	7.8 (4.8–18.6)	
Steatosis	22	17.0 (10.0–22.0)	14	17.8 (12.0–46.1)	12	15.7 (11.3–26.4)	
Steatohepatitis	9	29.0 (18.0–32.0)	6	34.1 (9.8–61.8)	7	19.9 (5.5–47.2)	
HOMA-IR							n = 100
Overall	104	2.8 (1.6–5.0)	26	2.2 (1.2–4.3)	28	2.9 (1.4–6.9)	.57
No FLD	73	2.4 (1.5–3.7)	19	2.1 (1.1–3.0)	20	2.2 (1.3–4.6)	
Steatosis	22	3.8 (2.4–5.2)	5	4.4 (3.2–12.1)	5	6.4 (3.8–9.1)	
Steatohepatitis	9	6.9 (4.1–11.1)	2	15.1 (2.2–28.1)	3	9.6 (1.4–14.8)	
Adiponectin, μg/mL							n = 101
Overall	102	10 (7–15)	71	20 (13–38)	68	25 (15–38.5)	<.001
No FLD	74	11 (8–15)	51	26 (16–43)	49	28 (16–39)	
Steatosis	20	8 (6.5–10.5)	14	16.5 (13–21)	12	19 (10.5–28.5)	
Steatohepatitis	8	7.5 (6.5–10.5)	6	12.5 (7–18)	7	22 (9–41)	
Lipids and lipoproteins							
Total cholesterol, mg/dL							n = 106
Overall	108	160.5 (146–197)	74	156 (136–172)	66	145 (131–166)	.61[b]
No FLD	76	158 (144–195.5)	54	152 (136–170)	47	142 (128–159)	
Steatosis	22	178.5 (148–206)	14	162.5 (153–187)	13	153 (142–176)	
Steatohepatitis	10	166 (150–211)	6	169 (161–176)	6	172 (150–179)	
Triglycerides, mg/dL							n = 106
Overall	108	118 (80–167.5)	74	112 (72–151)	66	96 (70–144)	.52
No FLD	76	113.5 (76–153.5)	54	101 (69–144)	47	85 (65–120)	
Steatosis	22	116.5 (89–218)	14	148 (80–182)	13	126 (97–190)	
Steatohepatitis	10	185 (136–218)	6	187.5 (122–293)	6	150 (96–298)	
HDL-C, mg/dL							n = 106
Overall	108	44.5 (37–54.5)	81	49 (40–59)	69	48 (41–61)	.84[b]
No FLD	76	45 (37.5–55.5)	58	50.5 (41–62)	49	50 (45–64)	
Steatosis	22	41.5 (36–56)	16	43 (37–54)	13	38 (33–44)	
Steatohepatitis	10	40.5 (39–48)	7	43 (21–63)	7	38 (21–73)	
HDL-P, μmol/L							n = 104
Overall	98	31.2 (26.7–36.1)	74	31.4 (26.2–36.1)	64	30.7 (26.8–36.0)	.12
No FLD	71	31.1 (27.2–36.2)	54	30.7 (25.6–36.1)	45	30.2 (27.6–35.3)	

Table 2. Continued

Parameter	First Visit (Week 0) No.	First Visit (Week 0) Median (IQR)	Second Visit (≈Week 96) No.	Second Visit (≈Week 96) Median (IQR)	Third Visit (≈Week 192) No.	Third Visit (≈Week 192) Median (IQR)	Model P Value[a]
Steatosis	19	32.3 (26.4–38.8)	14	33.4 (26.7–37.3)	13	32.9 (26.2–35.4)	
Steatohepatitis	8	30.1 (24.2–33.9)	6	33.0 (27.0–36.1)	6	33.8 (24.2–36.7)	
LDL-C, mg/dL							n = 105
Overall	107	93 (77–118)	80	78.5 (66–95)	69	71 (60–92)	.002
No FLD	75	89 (74–112)	57	76 (62–93)	49	69 (60–85)	
Steatosis	22	98.5 (81–125)	16	90.5 (71–108)	13	90 (75–110)	
Steatohepatitis	10	97 (74–132)	7	82 (69–98)	7	74.5 (52–97)	
LDL-P, nmol/L							n = 104
Overall	99	1112 (900–1428)	74	914.5 (769–1125)	64	847.5 (721.5–1028.5)	<.001
No FLD	71	1043 (876–1290)	54	901 (687–1066)	45	808 (720–891)	
Steatosis	20	1356.5 (1115–1735.5)	14	1020.5 (910–1329)	13	1062 (871–1303)	
Steatohepatitis	8	1618 (1179.5–1864)	6	1170.5 (640–1336)	6	1061.5 (448–1276)	
Small LDL-P, nmol/L							n = 104
Overall	85	623 (437–862)	74	604 (394–783)	64	555.5 (372.5–735)	.09
No FLD	58	554.5 (390–731)	54	564 (361–707)	45	516 (331–651)	
Steatosis	20	842.5 (469–976.5)	14	744 (585–859)	13	773 (559–936)	
Steatohepatitis	7	914 (436–1381)	6	1019.5 (532–1211)	6	771.5 (324–1075)	
Apolipoprotein A1, mg/dL							n = 104
Overall	106	123.5 (108–142)	74	141 (119–158)	64	132 (116.5–159)	.12
No FLD	75	123 (110–143)	54	141 (119–158)	45	135 (124–159)	
Steatosis	22	120 (103–142)	14	136 (109–152)	13	118 (108–145)	
Steatohepatitis	9	124 (93–128)	6	141 (121–164)	6	139 (107–178)	
Apolipoprotein B, mg/dL							n = 104
Overall	106	80 (68–96)	74	73.5 (63–84)	64	65.5 (53–79.5)	.01
No FLD	75	76 (66–87)	54	72 (60–78)	45	63 (53–71)	
Steatosis	22	90.5 (73–102)	14	79.5 (70–96)	13	79 (71–100)	
Steatohepatitis	9	98 (71–107)	6	88 (64–95)	6	82 (44–103)	

Abbreviations: FLD, fatty liver disease; HDL-C, high-density lipoprotein cholesterol; HDL-P, high-density lipoprotein particle concentration; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; LDL-P, low-density lipoprotein particle concentration.

[a]A series of mixed models was used to test whether lipids (the dependent variables) differed over time. Each mixed model included a random intercept and the following fixed effects: site (related to missing follow-up data), baseline FLD category, lipid-lowering medication, body mass index, diabetes medication, protease inhibitor use and time (days from baseline), and an interaction between baseline FLD and time (to evaluate whether change in lipids over time differed by baseline FLD status) as repeated measures. Variables were transformed ($\log_{10}$) as needed to normalize their distribution.

[b]Although the *P* value for time was not significant, there was a significant interaction between time and baseline FLD category in the models of total cholesterol (*P* = .02) and HDL-C (*P* = .03).

Of the 7 participants with "worse" FLD category, 5 were 1 category worse and 2 were 2 categories worse. Of the 7 participants with "improved" FLD category, 6 were 1 category better and 1 was 2 categories better.

Relationship Between Baseline Participant Characteristics, Metabolic and Lipid/Lipoprotein Parameters, and FLD Change Status

Baseline demographic, clinical, metabolic, and lipid and lipoprotein profiles are reported by change in FLD status

Table 3. Characteristics of Participants With Clinical Outcomes[a]

Patient	Age (y)/ Sex	Race	Ishak Fibrosis Score[b]/Cirrhosis ≤24 Weeks	HBeAg at Week 0	Outcomes (Timing, Week)	FLD Category[c] at Week 0/ Outcome(s)	HBV DNA, ($\log_{10}$ IU/mL) at Week 0/ Outcome(s)	ALT × ULN at Week 0/ Outcome(s)	Platelets (× 10^3/μL) at Week 0/ Outcome(s)	Anti-HBV Treatment at Week 0/ Outcome(s)
1	50/M	Asian	3/Yes	Negative	HCC (10)	Neither/Neither	BLQ/BLQ	0.9/0.9	276/276	Yes/Yes
2	52/M	White	4/Yes	Positive	Decompensation (110), HCC (112), HBV death (157)	Steatohepatitis/ No biopsy	10.1/Unknown (all 3)	2.6/1.0, 1.0, Unknown	101/67, 67, Unknown	Yes/Yes, Yes/ Unknown
3	44/M	Other[d]	3/No	Negative	Cirrhosis[b] (145)	Neither/Steatosis	BLQ/BLQ	0.8/0.8	164/123	Yes/Yes

Abbreviations: ALT, alanine aminotransferase; BLQ, below the lower limit of detection or lower limit of quantification; FLD, fatty liver disease; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; M, male; ULN, upper limit of normal.

[a]Incident cirrhosis, hepatic decompensation, HCC, liver transplant, or HBV-related death.

[b]The Ishak Fibrosis score is based on liver biopsy only while the cirrhosis diagnosis per study protocol is based on the presence of ascites, splenomegaly, and nodular liver documented by computed tomography, magnetic resonance imaging, or liver ultrasound report. Thus, the score and diagnosis may not match.

[c]FLD category is based on liver biopsy.

[d]Not White, Black, or Asian.

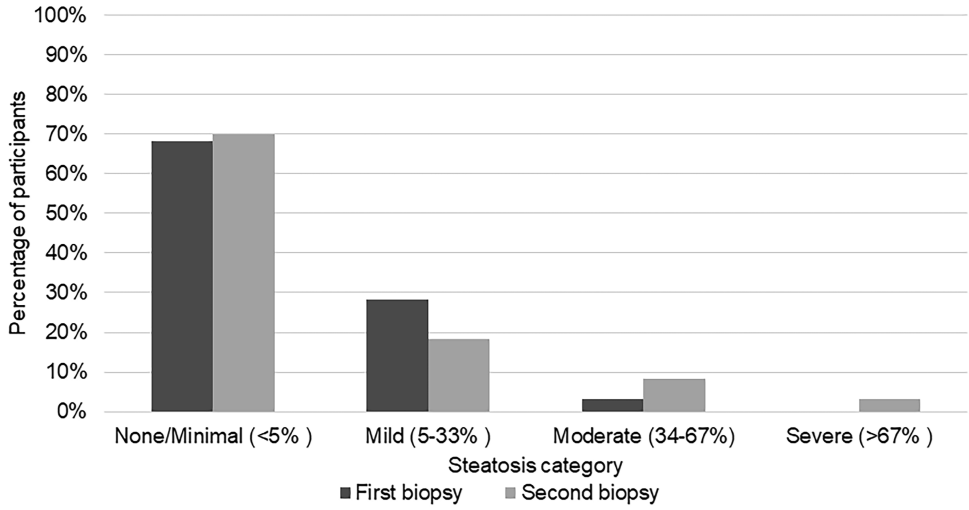

Figure 1. Distribution of steatosis severity among the paired biopsy subsample at baseline and follow-up (n = 60).

categories in Table 5. Compared to other groups, participants with worsening FLD status on follow-up appeared to have higher baseline BMI (P = .10) and waist circumference (P = .26). With respect to laboratory measures, those with no FLD at both baseline or follow-up biopsies appeared to have lower baseline liver enzymes (aspartate aminotransferase, alanine aminotransferase), insulin and free fatty acid levels, and degrees of insulin resistance (HOMA-IR and Adipo-IR), as well as higher adiponectin levels, compared to other groups; however, only Adipo-IR was significantly different by group (P = .001). With respect to baseline lipid and lipoprotein levels, TC (P = .08), low-density lipoproteins (median LDL-C [P = .03], LDL-P [P = .03], small LDL-P [P = .03]) and also TG (P = .20) and apoB (P = .007; surrogate for very low-density lipoprotein [vLDL]) appeared to be highest in those whose FLD status remained unchanged on follow-up (Table 5). The unchanged FLD group had the highest proportion with steatohepatitis (40%) compared to improved FLD (28%) and worsening FLD (0%).

Associations between FLD change status (ie, improved and worsened, respectively vs unchanged) and change in lipid and lipoprotein parameters over the same timeframe, with control for baseline age, sex, race, at-risk alcohol intake, and lipid-lowering medication use, were not statistically significant. However, the estimates were not reliable due to the small frequency of the worsening (n = 7) and improvement (n = 7), and

Table 4. Parameters of Histology-Determined Fatty Liver Disease Among the Paired Biopsy Subsample at Study Entry and at Follow-up (n = 60)

Parameter	Baseline	Follow-up	Worse	Better	Change, P Value[a]
Steatosis			11 (18.3)	6 (10.0)	.91
None/minimal (<5%)	41 (68.3)	42 (70.0)			
Mild (5%–33%)	17 (28.3)	11 (18.3)			
Moderate (34%–67%)	2 (3.3)	5 (8.3)			
Severe (>67%)	0 (0.0)	2 (3.3)			
Ballooning	5 (8.3)	6 (10.0)	2 (3.3)	1 (1.7)	.76
Mallory-Denk bodies	5 (8.3)	7 (11.7)	3 (5.0)	1 (1.7)	.56
Perisinusoidal fibrosis grade	n = 60	n = 59	9 (15.0)	10 (16.7)	.98
0	46 (76.7)	45 (76.3)			
1	6 (10.0)	8 (13.6)			
2	8 (13.3)	6 (10.2)			
FLD categories			7 (11.7)	7 (11.7)	.85
None	41 (68.3)	42 (70.0)			
Steatosis (≥5%)	13 (21.7)	10 (16.7)			
Steatohepatitis	6 (10.0)	8 (13.3)			

Data are presented as No. (%) unless otherwise indicated.

Abbreviation: FLD, fatty liver disease.

[a]Changes in histologically determined outcomes were tested with mixed-effects models (ordinal logistic for ordinal, binomial for binary outcomes) with a repeated outcome, time (ie, days since first biopsy) as a continuous fixed effect, and random intercept. The median time between biopsies was 3.6 (interquartile range, 3.1–3.7; range, 2.6–4.3) years.

Table 5. Baseline Demographic, Clinical, and Lipid Profiles, by Fatty Liver Disease Change Status

Characteristic	FLD Change Status				P Value[d]
	No FLD (n = 36)	Improved FLD (n = 7[a])	Unchanged FLD (n = 10[b])	Worsened FLD (n = 7[c])	
Demographics					
Age, y	n = 36	n = 7	n = 10	n = 7	.07
Median (25th, 75th percentile)	48.5 (45.5, 54)	54 (53, 57)	53 (50, 58)	47 (44, 54)	
Range	28–64	46–58	45–67	34–54	
Race, No. (%)	n = 35	n = 7	n = 9	n = 7	.13
Non-Hispanic White	8 (22.9)	3 (42.9)	4 (44.4)	1 (14.3)	
Non-Hispanic Black	22 (62.9)	2 (28.6)	2 (22.2)	5 (71.4)	
Non-Hispanic Asian	3 (8.6)	1 (14.3)	0 (0.0)	0 (0.0)	
Other	2 (5.7)	1 (14.3)	3 (33.3)	1 (14.3)	
Clinical parameters					
Alcohol use, No. (%)	n = 36	n = 7	n = 10	n = 7	.20
None	16 (44.4)	3 (42.9)	6 (60.0)	4 (57.1)	
Moderate	17 (47.2)	4 (57.1)	1 (10.0)	3 (42.9)	
At risk	3 (8.3)	0 (0.0)	3 (30.0)	0 (0.0)	
BMI, kg/m^2	n = 36	n = 7	n = 10	n = 6	.10
Median (25th, 75th percentile)	24.9 (22.5, 27.8)	27.0 (23.9, 27.5)	26.2 (22.8, 28.8)	32.8 (29.8, 37.7)	
Range	17.7–42.9	22.9–29.3	21.1–37.5	21.1–37.8	
High waist circumference, No. (%)	n = 33	n = 6	n = 6	n = 5	.26
Yes	7 (21.2)	2 (33.3)	2 (33.3)	3 (60.0)	
HBV DNA, No. (%)	n = 36	n = 7	n = 10	n = 7	.63
Undetected	25 (69.4)	4 (57.1)	8 (80.0)	6 (85.7)	
Detected	11 (30.6)	3 (42.9)	2 (20.0)	1 (14.3)	
ALT, U/L	n = 36	n = 6	n = 10	n = 7	.17
Median (25th, 75th percentile)	22.5 (16, 28)	28 (18, 37)	37.5 (18, 71)	32 (20, 42)	
Range	8–104	16–61	16–86	19–99	
AST, U/L	n = 36	n = 6	n = 10	n = 7	.29
Median (25th, 75th percentile)	25.5 (21, 30)	39 (20, 51)	31.5 (24, 57)	28 (22, 54)	
Range	14–80	14–54	18–67	15–65	
Metabolic parameters					
Glucose, mg/dL	n = 36	n = 7	n = 10	n = 7	.41
Median (25th, 75th percentile)	92.5 (87.5, 99.5)	91 (85, 100)	97 (90, 110)	90 (81, 109)	
Range	52–198	75–118	89–115	78–110	
Insulin, μIU/mL	n = 35	n = 7	n = 10	n = 7	.07
Median (25th, 75th percentile)	9 (6, 17)	18 (9, 19)	17.5 (13, 32)	18 (6, 36)	
Range	1–34	6–21	8–44	2–53	
Free fatty acids, mmol/L	n = 36	n = 7	n = 10	n = 7	.06
Median (25th, 75th percentile)	0.3 (0.3, 0.5)	0.5 (0.5, 0.6)	0.6 (0.4, 0.7)	0.8 (0.3, 1.0)	
Range	0.1–0.9	0.3–0.7	0.2–0.9	0.1–1.1	
HOMA-IR	n = 35	n = 7	n = 10	n = 7	.09
Median (25th, 75th percentile)	2.1 (1.3, 3.7)	3.8 (2.1, 4.6)	4.5 (3.0, 7.8)	4.9 (1.2, 7.1)	
Range	0.2–12.6	1.1–6.0	1.8–12.2	0.5–14.4	
Adipo-IR	n = 35	n = 7	n = 10	n = 7	.001
Median (25th, 75th percentile)	24.4 (12.6, 42.0)	58.8 (25.0, 76.5)	66.0 (50.0, 100.8)	87.5 (14.2, 132.5)	
Range	1.3–108.3	20.8–79.2	23.6–175.6	10.4–154.9	
Adiponectin (μg/mL)	n = 32	n = 6	n = 7	n = 7	.07
Median (25th, 75th percentile)	12.0 (8.5, 15.5)	8.5 (4.0, 16.0)	7.0 (6.0, 11.0)	8.0 (6.0, 9.0)	
Range	4.0–30.0	4.0–17.0	4.0–12.0	6.0–22.0	
Lipids and lipoproteins					
Total cholesterol, mg/dL	n = 36	n = 7	n = 10	n = 7	.08
Median (25th, 75th percentile)	157.5 (145, 193.5)	151 (122, 190)	185.5 (172, 208)	136 (116, 196)	
Range	96–245	111–220	150–252	113–287	
Triglycerides, mg/dL	n = 36	n = 7	n = 10	n = 7	.20
Median (25th, 75th percentile)	106.5 (74.5, 150.5)	90 (58, 291)	156 (101, 193)	120 (98, 156)	
Range	45–233	51–682	82–614	55–189	
HDL-C, mg/dL	n = 36	n = 7	n = 10	n = 7	.39

Table 5. Continued

Characteristic	FLD Change Status				P Value[d]
	No FLD (n = 36)	Improved FLD (n = 7[a])	Unchanged FLD (n = 10[b])	Worsened FLD (n = 7[c])	
Median (25th, 75th percentile)	45.5 (36.5, 54.5)	40 (36, 44)	45.5 (39, 53)	49 (40, 65)	
Range	27–80	29–57	35–72	31–91	
HDL-P, µmol/L	n = 36	n = 7	n = 10	n = 6	.50
Median (25th, 75th percentile)	31.2 (27.3, 36.0)	32.3 (25.4, 34.6)	33.8 (29.8, 41.5)	32.2 (26.4, 36.5)	
Range	13.4–39.3	15.6–38.8	22.9–50.5	25.0–52.8	
LDL-C, mg/dL	n = 36	n = 7	n = 10	n = 7	.03
Median (25th, 75th percentile)	88.5 (78.5, 112)	81 (64, 98)	114 (99, 136)	70 (55, 90)	
Range	35–170	51–123	74–145	45–152	
LDL-P, nmol/L	n = 36	n = 7	n = 10	n = 6	.03
Median (25th, 75th percentile)	1057 (934, 1267)	1039 (892, 1518)	1523.5 (1169, 1761)	945.5 (621, 1112)	
Range	378–1935	841–1770	698–2537	578–1428	
Small LDL-P, nmol/L	n = 30	n = 6	n = 10	n = 4	.09
Median (25th, 75th percentile)	539.5 (382, 731)	553.5 (373, 981)	861 (498, 989)	663.5 (487, 724)	
Range	237–978	278–1056	380–1761	351–744	
Apolipoprotein A1, mg/dL	n = 36	n = 7	n = 10	n = 7	.29
Median (25th, 75th percentile)	123 (111, 138)	111 (100, 129)	131 (110, 148)	126 (115, 175)	
Range	74–167	99–139	92–180	101–195	
Apolipoprotein B, mg/dL	n = 36	n = 7	n = 10	n = 7	.007
Median (25th, 75th percentile)	75 (67.5, 85)	72 (69, 95)	97.5 (86, 114)	66 (55, 75)	
Range	39–123	65–106	68–145	50–112	

Abbreviations: Adipo-IR, adipose tissue insulin resistance; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; FLD, fatty liver disease; HBV, hepatitis B virus; HDL-C, high-density lipoprotein cholesterol; HDL-P, high-density lipoprotein particle concentration; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; LDL-C, low-density lipoprotein cholesterol; LDL-P, low-density lipoprotein particle concentration.

[a]One participant changed from steatohepatitis to steatosis, 1 from steatohepatitis to none, and 5 from steatosis to none.

[b]Six participants with steatosis and 4 with steatohepatitis remained.

[c]Three participants changed from none to steatosis, 2 from none to steatohepatitis, and 3 from steatosis to steatohepatitis.

[d]Kruskal-Wallis test for continuous variables; Fisher exact test for categorical variables.

no FLD/unchanged FLD groups (n = 46), resulting in large CIs (Supplementary Table 5).

DISCUSSION

In this prospective cohort study of participants with HBV/HIV coinfection, we observed that FLD status was relatively stable over 3–4 years of follow-up. Certain clinical and laboratory observations that tracked changes in FLD status were noted. First, a higher proportion with worsening FLD status on follow-up had central obesity with elevated waist circumference at baseline compared to those with improvement or unchanged FLD status. Second, as anticipated, those with no FLD at both baseline or follow-up appeared to have lower baseline liver enzymes, degree of insulin resistance, and higher adiponectin levels compared to other groups with FLD. Insulin resistance and low adiponectin levels are associated with obesity and metabolic disorders that are known risk factors for FLD and its progression. Third, while certain lipid and lipoprotein levels changed over time, these changes were generally stable across baseline status of no FLD, steatosis, or steatohepatitis. An exception was that TC decreased and HDL-C increased in those without FLD, while the inverse was true for those with steatohepatitis. Last, baseline TC, low-density lipoproteins (LDL-C, LDL-P, small LDL-P), and TG and apoB (a surrogate for vLDL) appeared highest in those whose FLD remained unchanged on follow-up. However, we were unable to identify an independent relationship between improvements or worsening of FLD status and changes in lipid or lipoprotein levels.

We have previously shown that FLD is common in the setting of HBV/HIV coinfection, occurring at about 30%, of whom nearly one-third had evidence of steatohepatitis [8]. In addition, worsening fibrosis was uncommon among those with paired biopsy and longitudinal follow-up [19]. Here, we show that on longitudinal analysis, the proportion of moderate and severe steatosis appeared to increase (3.3% vs 11.7%) at follow-up. However, while some had worsening of their FLD status, a similar proportion had improvement on follow-up. The most common increase in severity of perisinusoidal fibrosis was by 1 grade, which may be related to the relatively short time between biopsies; nevertheless, among the 9 participants with worsening perisinusoidal fibrosis, 2 had a 2 grade increase in severity. Importantly, of the 8 patients with steatohepatitis in follow-up biopsy, 4 had steatohepatitis at baseline and 4 progressed to steatohepatitis, 2 of whom had no FLD at baseline. Considering coexisting HBV infection, FLD management in conjunction with optimal HBV control is critical to prevention of disease progression in this population. Indeed, nearly 10%

(10 patients) of this cohort had cirrhosis at baseline (4 with FLD), and 3 either progressed to cirrhosis or developed hepatic decompensation or HCC in follow-up.

In the earlier cross-sectional analysis of our cohort, we found FLD to be associated with known metabolic risks and also worse atherogenic lipid profiles [8]. While not necessarily evident by traditional lipid profiles, similar to other studies of HIV-uninfected individuals [17, 18, 21], there was an increase in atherogenic lipoprotein levels, namely small LDL-P and small dense LDL-C, and lower HDL2-C in the FLD group compared to those without FLD in the prior evaluation of our HBV/HIV cohort [8]. We also noted that increase in TG levels correlated with these lipid risk profiles, serving as a potential proxy for assessment of atherogenic risk [8]. In this study, while we observed a general decrease in LDL and its subfractionation over time in each of steatosis, steatohepatitis, and no FLD categories, significant changes in TG was not observed. Importantly, HDL-C increased in those without FLD at baseline, whereas these parameters either decreased or remained unchanged in other groups, suggesting a potential protective effect of HDL levels on FLD risk.

Cross-sectional studies of HIV-uninfected populations have shown differences in lipoprotein levels among patients with steatosis and NASH compared to controls [17, 21–24]. In the post hoc analysis of the PIVENS trial constituting a longitudinal HIV-uninfected cohort of 117 patients, resolution of NASH with or without treatment at 96 weeks of follow-up was associated with a favorable change in LDL size with an increase in mean peak LDL particle diameter despite lack of changes in standard LDL-C levels, while those without resolution had persistently unfavorable lipoprotein fractionation levels [18]. Although an independent relationship between improvement or worsening of FLD and lipid/lipoprotein profiles could not be determined in our study due to small frequency of these events over the 3–4 years of follow-up and a relatively short follow-up period, the fact that LDL and its subfractionation as well as TG levels appeared to be highest in those whose FLD status remained unchanged suggests a potential persistence of cardiovascular risk in this subgroup, similar to observations from the PIVENS trial [18].

This study has several limitations. Only a subgroup of the full cohort had follow-up liver biopsies. Although the clinical and laboratory parameters among this subgroup and the full sample was similar, there may be potential for selection bias toward those with potential risk or likelihood of disease progression. However, the paired biopsy sample represented those without FLD at baseline, and the majority continued to have no FLD on follow-up. Studies of nonalcoholic fatty liver disease have excluded those with heavy alcohol use. We opted to include those with alcohol intake due to high prevalence of coexisting alcohol and metabolic liver disease [25] and to fully represent the spectrum of FLD in our cohort. The proportion with at-risk drinking was low at 10%, and was similar among the FLD and no FLD groups. Additionally, we accounted for at-risk alcohol use in our analysis. Finally, the low proportion of patients with changes in FLD (7 worsened and 7 improved) resulted in limited power to detect differences in baseline characteristics, as well as change in lipid parameters by categories of change in FLD, and led to less reliable estimates of effect on lipoprotein profiles as reflected by large CIs. Nevertheless, this is the largest study of an HBV/HIV-coinfected cohort to date, allowing for longitudinal histopathologic changes in FLD and metabolic and lipid parameters over time.

In conclusion, although most patients had unchanged FLD status, improvement and worsening of FLD was observed in a subgroup, and importantly some without FLD at baseline had steatohepatitis within 4 years. Certain lipids and lipoproteins changed over time. While these time trends were generally stable across various FLD categories, some statistically significant patterns were observed—namely, TC increased in those with steatohepatitis and HDL-C in those with no FLD compared to decreases/unchanged in other groups. Nevertheless, unfavorable lipid and lipoprotein profiles, specifically LDL subfractionation and TG, were highest at baseline in those with unchanged FLD status (the group with the highest proportion of steatohepatitis), suggesting a potential for increased cardiovascular risk in this group. Lack of an independent relationship between changes in FLD and changes in lipid and lipoproteins in our cohort, however, may reflect the potential known influence of HIV infection and ART on these parameters or the small sample size and insufficient follow-up time for changes to occur [26–28].

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author Contributions. M. K. contributed to study design, data collection, data analysis, and interpretation; wrote the manuscript; and approved final submission. W. K. and A. S. H. performed statistical analyses; contributed to writing, review, and editing of the manuscript; and approved final submission. D. E. K., R. T. C., A. K. B., M. G. G., M. S. S., M. L.-M., M. K. J., H. L. A. J., and A. J. S. contributed to study design, data collection, and data interpretation; reviewed and edited the manuscript; and approved the manuscript for final submission. R. K. S. designed the study, provided material support, contributed to data collection and data interpretation, reviewed and edited the manuscript, and approved final submission.

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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