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Statin Therapy Does Not Reduce Liver Fat Scores in Patients Receiving Antiretroviral Therapy for HIV Infection

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Abstract

Background & Aims—Therapies are needed to limit progression of fatty liver diseases in patients with HIV infection. We analyzed data from a prospective study of the effects of rosuvastatin (a statin) on hepatic steatosis in HIV-positive adults.

Methods—We performed secondary analysis of data from a double-blind trial of adult patients with HIV infection (78% male; 68% African American; mean age, 46 years; body mass index, 29 kg/m^2; HIV1 RNA<1000 copies/mL; LDL-cholesterol <130 mg/dL) receiving antiretroviral therapy. The patients were randomly assigned to groups given 10 mg daily rosuvastatin (n=72) or placebo (n=75). Demographic and clinical data were collected, and blood samples were analyzed. Changes in liver fat score (LFS, a composite score calculated from metabolic and liver function parameters) and markers of systemic inflammation and immune activation were assessed through

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96 weeks of drug or placebo administration. We performed multivariable linear and logistic regressions to study relationships among variables.

Results—The placebo and rosuvastatin groups each had significant increases in LFS, compared to baseline, at 96 weeks (P=.01 and P<.01; P=.49 for difference increase between groups). Baseline LFS was independently associated with blood level of C-X-C motif chemokine ligand 10 (CXCL10) (P=.04) and soluble CD163 molecule (P=.01). After we adjusted for baseline characteristics, an increase in LFS over time was significantly associated with blood level of CXCL10 (P=.04), insulin resistance (P<.01), and viral load (P=.02), but not rosuvastatin use (P=.06).

Conclusion—In a secondary analysis of data from a trial of patients receiving treatment for HIV infection, hepatic steatosis increased over time, regardless of statin treatment, and was independently associated with markers of immune activation. Patients who received rosuvastatin appeared to have a nonsignificant increase hepatic steatosis over 96 weeks. Despite their ability to reduce risk of cardiovascular disease, statins do not appear to reduce hepatic steatosis. Clinicaltrials.gov no: NCT01218802

Keywords

fatty liver; virus infection; ART; hepatosteatosis

Introduction

With the development of potent antiretroviral therapy (ART) and the ensuing longer life expectancies for individuals with human immunodeficiency virus (HIV)-infection[1], other causes of morbidity and mortality are becoming increasingly recognized in this group. Liver disease has emerged as one of the leading causes of death among HIV-infected patients[2].

Much of the current challenge in liver disease in HIV is related to nonalcoholic fatty liver disease (NAFLD), and effective therapies aimed at the limiting the progression of hepatic steatosis in this population are urgently needed. In the general population, NAFLD is often associated with obesity, insulin resistance, diabetes, and dyslipidemia[3]. In HIV-infected individuals, chronic inflammation and the use of ART may be associated with the development of NAFLD and progression to fibrosis[4].

Due to their immunomodulatory and anti-inflammatory properties beyond their lipid-lowering and cardioprotective utility, statins have been suggested as candidates for the treatment and prevention of NAFLD in the general population[5]. HIV-infected individuals represent a unique population, and results from the general population on the effect of statins on NAFLD cannot directly be extrapolated to HIV-infected individuals. Antiretroviral treatment is known alter lipid levels, and also interact with statin therapy[6]. This means that statins can have different lipid-lowering potencies and immunomodulatory effects in HIV-infected individuals compared to uninfected individuals[7]. Only a single recent small study assessed the effect of atorvastatin on liver fat in a group of HIV-infected individuals with NAFLD and showed an improvement in hepatic steatosis with statin therapy[8]. However, this

study was limited by very small sample size; seven participants had NAFLD and only three of them randomized to the atorvastatin arm.

Therefore, this study aims to assess the effect of rosuvastatin on hepatic steatosis and fibrosis measured by the Liver Fat Score (LFS) and the NAFLD-Fibrosis Score (NAFLD-FS) in HIV-infected adults on stable ART and to investigate the predictors of hepatic steatosis progression over time. LFS and NAFLD-FS are non-invasive biomarkers used to predict liver steatosis and fibrosis respectively. These scores are computed using clinical and laboratory parameters, allowing for the description of steatosis and fibrosis in patient populations not routinely undergoing radiographic imaging or liver biopsy[9].

Methods

The above aims were assessed utilizing data from the SATURN-HIV trial which is a randomized, double-blind, placebo-controlled study designed to measure the effect of rosuvastatin on markers of cardiovascular risk and immune activation in HIV-infected adults[10]. The results presented herein represent a secondary analysis that assessed changes in LFS and NAFLD-FS from entry to week 48 and then week 96. SATURN-HIV was approved by the Institutional Review Board of University Hospitals Cleveland Medical Center, and all participants signed a written informed consent prior to enrollment. Randomization was conducted in a 1:1 ratio to rosuvastatin 10 mg daily or matching placebo. Study drugs were provided by AstraZeneca®. SATURN-HIV is registered on clinicaltrials.gov (NCT01218802). All authors had access to study data, had reviewed and approved the final manuscript.

Study population

Participants who met inclusion criteria were ≥18 years, with HIV-1 infection, on stable ART for at least three months, HIV-1 RNA <1,000 copies/mL, fasting LDL-cholesterol ≤130 mg/dL, and triglyceride level ≤500 mg/dL. Additional entry criteria included evidence of either heightened T-cell activation and/or systemic inflammation ($CD8^+CD38^+HLA\text{-}DR^+$ ≥19%, and/or high-sensitivity C-reactive protein (hs-CRP) ≥2 mg/L). Participants were excluded if they had a history of coronary disease or diabetes, were pregnant or lactating, or had an active inflammatory condition. Further details have been previously published[10].

Study evaluations

Self-reported demographics and medical history were obtained along with a targeted physical exam. Subjects completed a substance use and physical activity questionnaires, as well as a standardized dietary assessment[11]. No lifestyle or nutritional modification counseling was done. Heavy alcohol consumption was defined as ≥ 4 drinks on any day in men and ≥ 3 drinks on any day in women.

At entry, week 48, and week 96, fasting (>12 hours) blood draws were obtained for real-time measurements of liver and lipid profiles, glucose and insulin levels. Additionally, blood was processed, and plasma, serum, and peripheral blood mononuclear cells were stored frozen at −80° C for batched measurements of inflammation and immune activation markers. HIV-1 RNA levels and CD4+ cell counts were drawn as part of clinical care. Insulin resistance was

estimated using the homeostatic model assessment of insulin resistance (HOMA-IR)[12]. All participants underwent dual-energy X-ray absorptiometry of the whole body as previously described[13].

Outcome Measure

We computed LFS and NAFLD-FS at entry, week 48, and week 96. LFS which has been validated in HIV-infected patients[14], is computed using the formula: LFS = −2.89 + 1.18 * metabolic syndrome (yes=1/no=0) + 0.45 * type 2 diabetes (yes=2/no=0) + 0.15 * fasting insulin (mU/L) + 0.04 * fasting AST (U/L) - 0.94 * AST/ALT[9]. Metabolic syndrome was defined according to criteria of the National Cholesterol Education Program[15].

An optimal cut-off value of −0.64 for LFS was previously determined[9]; values >−0.64 predict NAFLD with a sensitivity of 86% and a specificity of 71%. Increasing the cut-off to 1.257 likewise increases the specificity of the test to 95%; however, sensitivity decreases to 52%. For this analysis, we selected LFS ≥1.257 for identification of participants with NAFLD, as this cutoff has been linked with higher cardiovascular and liver-related mortality giving it clinical relevance[16].

NAFLD-FS was calculated according to the following formula: NAFLD-FS= −1.675 + 0.037 * age (years) + 0.094 * BMI (kg/m^2) + 1.13 * impaired fasting glucose or diabetes (yes=1/no=0) + 0.99 * AST/ALT - 0.013 * platelet (*10^9/l) - 0.66 * albumin (g/dl)[17]. A NAFLD-FS ≥0.676 has a positive predictive value for advance fibrosis of 90%, where as a NAFLD-FS ≤−1.455 has similar accuracy in excluding advanced fibrosis[17].

Biomarkers of inflammation and immune activation

T-cells and monocytes were phenotyped by flow cytometry as previously described[18]. Levels of interleukin-6 (IL-6), TNF receptor superfamily member 1A and 1B (TNFRSF1A and 1B), interferon γ inducible protein-10 (IP-10), vascular and intercellular cell adhesion molecule 1 (VCAM1 and ICAM1), soluble CD14 (sCD14) and soluble CD163 (sCD163) were measured by ELISA[18]. D-dimer level was determined by immuno-turbidimetric assay. Fibrinogen and hs-CRP levels were determined by particle-enhanced immunonephelometric assay[19].

Statistical Analysis

This is an exploratory analysis to assist in developing hypotheses for future confirmatory studies. The main objective of this study was to compare changes in LFS and NAFLD-FS scores from baseline to 48 and baseline to 96 weeks between rosuvastatin and placebo groups. Secondary objectives were to evaluate within-group changes over time in these scores and to examine associations between baseline and changes in LFS with markers of systemic inflammation, immune activation, and insulin resistance.

Non-normal biomarkers were transformed using Box-Cox methods. Baseline variables were compared between groups, and absolute changes in LFS and NAFLD-FS across study weeks were calculated for each group. Between and within group changes were tested using paired t-tests or Wilcoxon signed rank tests and unpaired t-tests or Wilcoxon rank sum tests as

appropriate for the distribution of the variables, respectively. Linear regressions were used to assess relationships between baseline and 0–96 week changes in LFS, randomization group, and clinically relevant factors. All variables with $p<0.15$ in univariable models were considered for inclusion in the multivariable models. Last, logistic regression was used to model variables associated with the progression from no steatosis (LFS <1.257) at baseline to liver steatosis (LFS ≥1.257) at 96 weeks. Randomization group was the variable of interest in these models which were adjusted for demographics, excessive alcohol, and change in HOMA-IR over 96 weeks, each in separate models.

Results

Overall, 147 participants were enrolled and randomized in SATURN-HIV study and were eligible for this analysis. A total of 28 participants (9 rosuvastatin, 19 placebo) were lost to follow up or withdrew prior to 96 weeks, none due to adverse event. Therefore, this analysis includes 128 participants at week 48 and 119 participants at week 96. The participant flow chart has been published previously[10].

Baseline Characteristics

Baseline characteristics are presented in table 1 and randomization groups were similar at baseline. Briefly, mean age and BMI were 45 years and 28.1 kg/m^2. Most were male (78%) and African American (68%). All participants were on ART by design (51% on a PI and 5% on a thymidine analog), and most participants (78%) had an undetectable HIV-1 RNA level (≤48 copies/ml). Mean current and nadir CD4+ cell counts were 640 and 200 cells/mm3, respectively; 5% of patients had HIV transmission through intravenous drug use, and the remaining were through sexual contact. At baseline, 42% of participants had a LFS >−0.64 (47% vs. 36%, for placebo vs. rosuvastatin, respectively; p=0.19). However, more participants in the placebo group had a LFS ≥1.257 than the rosuvastatin group at baseline (28% vs. 13%; p=0.02).

Changes in Liver Fat Score

Changes in LFS over 48 weeks were not statistically significant within or between groups (p=0.92 and p=0.21 for placebo and statin, respectively; p=0.54 between-groups); however, by 96 weeks, there were significant increases in LFS in both placebo (p=0.01) and statin arms (p<0.01), but the changes were similar between the groups (p=0.49).

After excluding participants with active co-infection with hepatitis B and/or C (a total of 19 participants were excluded, 8 in the rosuvastatin and 11 in the placebo group) results were qualitatively unchanged (data not shown).

Interestingly, among HIV/hepatitis C and/or B co-infected participants who were followed up at 96 weeks (n=15; 6 in the rosuvastatin group and 9 in the placebo group), there was a significant decrease in LFS in the rosuvastatin arm (p=0.046), but not in the placebo arm (p=0.2); however changes were not different between the groups (p=0.3). Individual components of LFS changes in HIV mono-infected and co-infected participants are presented in supplementary table 1.

Changes in NAFLD Fibrosis Score

NAFLD-FS increased significantly within both groups from 0 to 48 weeks (p=0.013 and p<0.001 for placebo and statin, respectively) and from 0 to 96 weeks (p=0.01 and p<0.01). At both time points, however, these changes were similar between the groups (p=0.18 and p=0.52, respectively).

Factors Associated with Baseline and 0–96 Week Changes in LFS

Univariable and multivariable analysis exploring factors associated with baseline and 0–96weeks changes in LFS are presented in table 2. Although randomization group was not associated with a change in LFS in the univariable model, there was a trend toward significance in the multivariable model (p=0.06) suggesting randomization to rosuvastatin may have resulted in a greater increase in LFS over 96 weeks.

To further explore this finding, we evaluated whether randomization to rosuvastatin was associated with the progression from no steatosis at baseline to hepatic steatosis by 96 weeks. Of the 86 participants that did not have steatosis at baseline, or hepatitis B or C coinfection and had 96-week follow-up data, 13 (15%) progressed to steatosis by week 96; 10 in the rosuvastatin group, and 3 in the placebo group (p=0.13). Table 3 shows how the odds ratio for progression to steatosis in the rosuvastatin group compared to the placebo group changes when clinical factors potentially in the causal pathway are added to the model. Patients in the rosuvastatin group were nearly three times more likely to develop hepatic steatosis than patients in the placebo group, and it seems that change in insulin resistance over 96 weeks had the greatest impact on the odds ratio estimate suggesting that this factor is likely an important link between rosuvastatin and the development of steatosis.

Discussion

In this study, established markers of liver steatosis and fibrosis increased significantly over 96 weeks in HIV-infected participants on stable ART, without any apparent beneficial effect of statin. In the absence of effective pharmacotherapy for hepatic steatosis and NAFLD-related fibrosis in HIV, statin therapy has been proposed as a potentially beneficial intervention[5]; however, our preliminary findings failed to show a benefit in favor of statin. Even more, randomization to rosuvastatin may have resulted in a greater increase in hepatic steatosis over 96 weeks, a finding that highlights the need for further investigation.

Insulin resistance, oxidative stress, and inflammatory cascades are believed to play important roles in the pathogenesis and progression of NAFLD[20]. Consistent with the literature, both baseline LFS, and the increase over 96 weeks were independently associated with different metabolic factors such as trunk fat and insulin resistance[21]. We have previously reported in SATURN-HIV that 10mg of daily rosuvastatin led to significant worsening in insulin resistance when compared to the placebo group[13]. Furthermore, our results show that increase in insulin resistance over 96 weeks has the greatest impact on the development of steatosis, and as such, the increase in insulin resistance in the rosuvastatin group may have contributed to the increase in hepatic steatosis in that group.

Hepatotoxicity with increased levels of AST and ALT have been reported as a frequent side effect of statin therapy[22]. In our study, changes in AST, ALT, and AST/ALT ratio did not differ between rosuvastatin and placebo groups.

Interestingly, we found that hepatic steatosis did not change over time among HIV/hepatitis B and/or C co-infected patients in the placebo group, but decreased in the rosuvastatin arm. These findings are consistent with recent findings where hepatic steatosis was found to be higher and progress faster in HIV mono-infected patients compared to HIC/HCV co-infected patients [23, 24]. One recent study has shown beneficial effect of statins in reducing liver disease progression in HIV/HCV co-infected patients[25]; however, the mechanism behind the differential effect of statin on hepatic steatosis in mono-infected vs. co-infected patients seen in our findings is unknown, and is possibly reflecting a pathophysiological difference in hepatosteatosis between the two population (metabolic vs. virus-induced).

The direct impact of HIV was long thought to play a role in hepatic steatosis among HIV-infected individuals, though studies exploring this hypothesis have yielded inconsistent results. Interestingly, our analysis shows that baseline and change in LFS over time were independently associated with ART exposure and viral load. It is possible that antiretroviral medications or HIV itself may have directly led to the observed liver toxicity; persistent immune activation associated with chronic HIV infection or metabolic changes observed with ART (such as fat abnormalities, increased weight or changes in lipoprotein levels) might have contributed to this toxicity.

In non HIV-infected patients, circulating levels of the soluble monocyte activation marker sCD163 and IP-10 have been shown to predict the presence and severity of NAFLD[26, 27]. Consistent with these observations, our results show that hepatic steatosis was associated with higher baseline levels of sCD163 and IP-10, and the increase in LFS over time was also positively associated with baseline IP-10 levels. Elevations in sCD163 and IP-10 have also been shown previously to predict non-AIDS related comorbidities in the HIV population, including cardiovascular disease and HIV-associated neurocognitive disorder[28]. Although the enhanced systemic inflammation in HIV may be contributing to the liver steatosis, these relationships may be bi-directional, and so, the increased inflammation from hepatic steatosis may potentiate already-existing HIV-associated inflammation, further increasing the burden of other HIV-related comorbidities. Taken together, these findings might have important clinical relevance, suggesting that hepatic steatosis should be considered as part of the metabolic monitoring used to optimize cardiovascular risk profiles in this high-risk population. Further studies are warranted to determine the exact contribution of NAFLD to HIV-related comorbidities.

In the limited number of studies that evaluated the histological changes in the NAFLD spectrum using liver biopsy in the HIV population, hepatic steatosis did not seem to progress to NASH and cirrhosis frequently[29]. In accordance with these results, we show that among participants with baseline hepatic steatosis, although NAFLD-FS increases were observed over time, they remained below the cutoff point predictive of fibrosis in HIV-uninfected populations. However, it is unclear if these increases would be clinically significant in the HIV population.

Despite the novelty of our findings, this study has some limitations that should be acknowledged. First, we utilized previously validated scores to assess for hepatic steatosis and fibrosis recognizing that the gold standard for hepatic steatosis diagnosis remains liver biopsy. However, the invasive nature of this procedure makes it challenging to ethically justify its widespread use for assessment of liver steatosis without a specific clinical indication. More recently, imaging techniques have also been used to detect hepatic steatosis and fibrosis; however, these modalities are not widely available yet, are operator dependent, and are harder to integrate in the setting of HIV clinics. Because we recognized the limitation of the scores used, we used a higher cut-off point to detect hepatic steatosis which had more clinical relevance; this cut-off point had an increased specificity but decreased sensitivity which could have potentially underestimated hepatic steatosis in our study. Lastly, the majority of our patients were African American and men with LDL levels ≤ 130mg/dL which may make our results less generalizable to the entire HIV population.

In summary, in a 96 week randomized, double-blinded, placebo-controlled trial of rosuvastatin in HIV-infected adults on ART, hepatic steatosis increased over time and possibly to a greater degree with rosuvastatin. Both HIV related factors and markers of systemic inflammation, and immune activation were associated with baseline hepatic steatosis and with increases in LFS over time. These results call into question whether statin therapy would improve steatosis in HIV-infected adults on ART and call for further study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Background

Non-Alcoholic Fatty Liver Disease (NAFLD) has emerged as a leading cause of morbidity and mortality in HIV-infected individuals, with no effective therapeutic interventions available in this population.

Statins were shown to have a beneficial effect on NAFLD in the general population, but their role in HIV remains unclear.

Findings

In a randomized controlled trial of rosuvastatin versus placebo, 147 HIV-infected individuals on stable antiretroviral therapy were followed over 96 weeks.

We found that hepatic steatosis increased over time, regardless of statin treatment, and was independently associated with markers of immune activation.

Implications for patient care

Despite their beneficial role in cardiovascular disease risk reduction, statins do not appear effective in mitigating hepatic steatosis in HIV-infected individuals on stable antiretroviral therapy.

Table 1

Baseline Demographics and HIV-Related Factors by Randomization Group

	Rosuvastatin (n=72)	Placebo (n=75)
Age, years	45 ± 9	45 ± 11
Male	58 (81)	57 (76)
African American Race	50 (69)	50 (67)
Body Mass Index, kg/mm^2	28 ± 6.3	28.1 ± 6.7
Hemoglobin A1C, %	5.5 ± 0.4	5.5 ± 0.5
HOMA-IR	2.74 ± 3.79	3.87 ± 4.75
Non HDL cholesterol, mg/dL	118.3 ± 29.9	128.6 ± 29.0
HDL cholesterol, mg/dL	48.6 ± 16.4	48.7 ± 15.4
Triglycerides, mg/dL	155.4 ± 129.2	147.6 ± 88.4
AST (U/dL)	26.25 ± 26.1	23.26 ± 12.0
ALT (U/dL)	37.3 ± 25.9	36.5 ± 19.5
Metabolic Syndrome	16 (22)	16 (21)
CD4+ cell count, cells/mm^2	644 ± 287	636 ± 314
Nadir CD4+ count, cells/mm^2	210 ± 155	192 ± 137
HIV-1 RNA ≤ 49 copies/ml	55 (76)	57 (76)
ART duration, years	7.0 ± 5.3	7.3 ± 5.2
Didanosine, stavudine, or zidovudine use		
Current	5(7)	3(4)
Past	34(47)	35(47)
Uncertain past exposure	10(14)	16(21)
Excessive alcohol use	3(4)	1(1)
Hepatitis C co-infection	5 (7)	7 (9)
Hepatitis B co-infection	3 (4)	4 (5)
Liver Fat Score	−0.4 ± 2.6	0.2 ± 2.9
NAFLD-Fibrosis Score	−2.4 ± 1.1	−2.5 ± 1.3
Liver Fat Score > 1.257	9 (13)	21 (28)
NAFLD-Fibrosis Score > 0.676	1(1)	0

Mean ± standard deviation and frequency (%).

HOMA-IR, homeostatic model assessment of insulin resistance; ART, antiretroviral therapy; NAFLD, nonalcoholic fatty liver disease

Table 2

Factors Associated with Baseline LFS and 0 to 96 Week Change in LFS in Univariable and then Multivariable Linear Regression

	Baseline LFS		0 to 96 Week Change in LFS	
	Univariable Models[a]	**Multivariable Model[b]**	**Univariable Models[a]**	**Multivariable Model[b]**
Group (1=statin)	-	-	0.094 (p=0.49)	0.165 (p=0.06)
Baseline Liver Fat Score [c]	-	-	1.426*	0.777*
Sex (1=male)	−0.088 (p=0.09)	-	-	-
BMI, per kg/mm2	0.012*	-	0.041*	
Waist to hip ratio	1.496*	-	3.275*	-
Trunk fat[c]	0.005*	0.003*	0.001*	-
Insulin Resistance	0.042*	0.032*	0.045*	0.104*
Hemoglobin A1C, per %	0.190*	-	0.332 (p=0.03)	-
Hepatitis C co-infection		0.11 (p=0.03)	-	-
Hepatitis B co-infection	0.21 (p=0.03)	0.01 (p=0.09)	-	-
≥4 alcohol drinks per day	−0.199 (p=0.13)	-	-	-
Nadir CD4+, per 100 cells	−0.022 (p=0.13)	-	-	-
ART duration, per month	0.001*	0.001 (p=0.05)	-	-
HIV-1 RNA ≤48 copies/ml)	-	-	−0.278 (p=0.10)	−0.256 (p=0.02)
Interleukin-6[c]	-	-	0.181 (p=0.13)	-
C-X-C motif chemokine ligand 10[c]	1.636*	0.853 (p=0.02)	5.361*	2.579 (p=0.04)
TNFRSF1A[c]	5.519 (p=0.07)	-	-	-
ICAM1[c]	0.003 (p=0.04)	-	-	-
%CD8+CD38+HLA-DR+[c]	-	-	0.270 (p=0.06)	-
Soluble CD14[c]	−0.628 (p=0.05)	−0.487*	-	-
Soluble CD163[c]	0.857*	0.376 (p=0.02)	1.225 (p=0.09)	-
%CD14dimCD16+[c]	0.043 (p=0.05)	-	0.159 (p=0.03)	-
0–96 week change LDL-C			−0.004 (p=0.12)	-
0–96 week change in HOMA-IR			0.054*	0.13*

Values shown are parameter estimate (p-value);

*p≤0.01

[a]Only randomization group and those variables with p<0.15 are shown.

[b]Multivariable models selected using backwards elimination from all variables with p<0.15 in univariable analysis.

[c]Box cox transformed variable

BMI, body mass index; TNFRSF1A, TNF receptor superfamily member 1A; ICAM1, intercellular cell adhesion molecule 1.

Table 3

Odds Ratio for LFS Progression Adjusting For Clinically-Relevant Factors

Model	OR for Group (95% Confidence Interval)
Randomization Group only	2.6 (0.6–10.2)
Group + age, sex, race, BMI	2.4 (0.5–10.7)
Group + age, sex, race, BMI, HOMA-IR	2.8 (0.5–17.0)
Group + excessive alcohol use	2.8 (0.7–11.1)
Group + 0–96 week change in HOMA-IR	1.3 (0.2–8.0)
Group + 0–96 week change in AST	2.2 (0.5–8.9)
Group + 0–96 week change in ALT	2.3 (0.6–9.0)