Pro-Inflammatory Interleukin-18 Is Associated with Hepatic Steatosis and Elevated Liver Enzymes in People with HIV Monoinfection

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Abstract

People with HIV (PWH) are at an increased risk of developing nonalcoholic fatty liver disease (NAFLD). Interleukin (IL)-18 is regulated by inflammasomes in response to pathogens and danger signals and has been implicated in both the pathogenesis of NAFLD and HIV disease progression. We hypothesized that increased IL-18 may be associated with NAFLD and liver injury in PWH. This was an observational study of 125 PWH and 59 individuals without HIV in the Boston area. Participants with known hepatitis B, hepatitis C, and excessive alcohol use were excluded. IL-18 was measured in serum by enzyme-linked immunosorbent assay. Liver lipid content was assessed by liver-to-spleen computed tomography (CT) attenuation ratio. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and IL-18 levels were higher in PWH than in controls. In PWH, $\log_{10}$ IL-18 was associated with $\log_{10}$AST ($r=0.34$, $p=.0001$), $\log_{10}$ALT ($r=0.33$, $p=.0002$), $\log_{10}$HIV RNA ($r=0.29$, $p=.002$), and inversely associated with liver-to-spleen ratio ($r=-0.24$, $p=.02$). In addition, $\log_{10}$ IL-18 was associated with $\log_{10}$ triglycerides ($r=0.26$, $p=.003$), $\log_{10}$ MCP-1 (monocyte chemoattractant protein-1; $r=0.33$, $p=.0004$), $\log_{10}$caspase-1 ($r=0.35$, $p<.0001$), $\log_{10}$LPS ($r=0.28$, $p=.004$), and inversely associated with high-density lipoprotein ($r=-0.28$, $p=.002$), and CD4$^+$/CD8$^+$ T cell ratio ($r=-0.24$, $p=.007$). In controls without HIV, $\log_{10}$ IL-18 was also associated with $\log_{10}$ALT ($r=0.44$, $p=.0005$). After adjusting for potential confounders, the relationships between IL-18 and AST ($p=.004$) and ALT ($p=.003$) remained significant, and the relationship between IL-18 and liver-to-spleen ratio ($p=.02$). Increased inflammasome activation and subsequent monocyte recruitment in PWH may contribute to the development and progression of NAFLD. Clinical Trials Registration. NCT00455793.

Keywords: NAFLD, NASH, inflammasome, interleukin-18

Introduction

WITH THE SUCCESS of antiretroviral therapy and improved life expectancy from decreased AIDS-related morbidities, metabolic complications such as nonalcoholic fatty liver disease (NAFLD) are increasing in people with HIV (PWH). NAFLD prevalence estimates range from 30% to 40% in PWH,[1] and histologic studies suggest increased severity of NAFLD in PWH compared with non-HIV patients.[2] Traditional risk factors such as insulin resistance and dyslipidemia are more common in PWH and are implicated in the development of NAFLD. In addition, chronic low-grade inflammation, which is persistent in PWH despite viral suppression, and intestinal microbial translocation and dysbiosis present in PWH are important factors that have also been associated with the pathogenesis of NAFLD.[3]

More recently, the role of inflammasomes has been elucidated in the progression of NAFLD by modulating the inflammatory response.[4] The activation of inflammasome components is evident in nonalcoholic steatohepatitis (NASH), and it is also required for the development of fibrosis.[5,6] In particular, NLRP3 inflammasomes are cytosolic multiprotein complexes located in liver immune cells and hepatocytes that sense pathogens or host cell damage to

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activate caspase-1, which in turn produces effector cytokines interleukin-1β (IL-1β) and interleukin-18 (IL-18). These cytokines create a proinflammatory and profibrotic milieu by increasing the expression of secondary proinflammatory cytokines and chemokines including tumor necrosis factor alpha and monocyte chemoattractant protein-1/chemokine ligand 2 (MCP-1/CCL2), recruiting inflammatory cells, and activating hepatic stellate cells.[4] MCP-1-mediated migration of monocytes is an important contributor to inflammation and disease progression in NAFLD.[7,8] In NAFLD, repeated exposures to endotoxins, saturated fatty acids, cholesterol esters, and reactive oxygen species are thought to perpetuate inflammation through inflammasome activation and lead to disease progression.[4]

Consistent with this mechanism, IL-18 has previously been implicated in NASH in individuals without HIV. Hepatic expression of inflammasome components including pro-IL-18 is significantly increased in individuals with NASH compared with those with simple steatosis.[6] The levels of IL-18 in circulation are also significantly increased in PWH and have been implicated in the pathogenesis of HIV disease progression and in a nonhuman primate monkey model of HIV.[9–11] To our knowledge, the relationship between fatty liver disease and proinflammatory cytokine IL-18 in PWH has not yet been reported. We hypothesized that increased levels of IL-18, as a marker of increased inflammasome activation, may be associated with noninvasive measures of NAFLD and liver injury in PWH.

Methods

This study reports on new analyses from an observational study of men and women with HIV infection and simultaneously recruited matched controls without HIV.[12,13] Participants were recruited from the Boston area from community centers and infectious disease clinics. PWH and individuals without HIV were recruited from the same communities, and family members, partners, and friends of PWH were also encouraged to enroll in an attempt to ensure the two groups would be similar with respect to demographic characteristics and cardiovascular risk factors. Other than HIV disease, inclusion and exclusion factors were identical for both groups. Participants recruited were 18–60 years of age and had no known cardiac disease or symptoms suggestive of any current or prior cardiac disease (including angina, arrhythmias, valvular disease, pericarditis, and congestive heart failure). Participants with renal disease, creatinine levels >1.0 mg/dL or creatinine clearance <60 mL/min were excluded to minimize the risk of contrast nephropathy. In addition to the eligibility criteria outlined in the original study, for this study, participants with known history of hepatitis B, hepatitis C, and excessive alcohol intake were also excluded. Excessive alcohol intake was defined as >21 standard drinks per week in men and >14 drinks per week in women.[14] All participants provided informed consent to participate. This study was approved by the institutional review board of Massachusetts General Hospital.

Alanine aminotransferase (ALT), aspartate aminotransferase (AST), glucose, hemoglobin A1c, lipids, HIV-1 RNA level (reverse transcription polymerase chain reaction [RT-PCR]; Roche Amplicor Monitor; lower limit of detection, 50 copies/mL), CD4$^+$ T cells, and CD8$^+$ T cells were measured by MGH laboratory using standard techniques. Using serum collected after an overnight fast, IL-18 was measured by enzyme-linked immunosorbent assay (ELISA; R&D, Minneapolis, MN) and caspase-1 was measured according to manufacturers' instructions (Cell Technology, Hayward, CA). MCP-1 was measured by ELISA (R&D) and LPS (Associates of Cape Cod, East Falmouth, MA) was measured according to the manufacturers' instructions. Measurements of serum markers were performed in duplicate with appropriate controls. Sample variation was acceptable with a percent coefficient of variation (%CV) of 25% or less. Samples exceeding the %CV cutoff were repeated.

To characterize hepatic steatosis, measurements of liver and spleen attenuation were measured on noncontrast computed tomography (CT) images by a reader blinded to HIV status as well as clinical and biomarker results. Three circular regions with an area of at least 2 cm^2 on three axial CT slices were measured in the liver with the spleen as an internal control.[15] The liver-to-spleen ratio was calculated from the mean liver density measurements divided by the mean spleen density measurements, and the ratio <1 was defined as NAFLD as previously described.[16,17] A lower liver-to-spleen ratio indicates higher hepatic lipid content.[18] A single-slice abdominal CT was used to derive measurements of visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) areas.

Liver enzymes, triglycerides, HIV RNA, and inflammatory markers were log$_{10}$-transformed owing to non-normal distributions. Pearson correlation coefficients were assessed for investigating relationships between continuous variables. Multivariable linear regression was performed to adjust for potential confounders that may affect liver enzymes or liver fat content. Comparisons between the two groups were analyzed using Student's t-test for normally distributed variables and by Wilcoxon rank-sum test for non-normally distributed variables. Statistical significance was defined as $p < .05$. Statistical analyses were performed using SAS JMP Pro (Cary, NC).

Results

Characteristics of participants

A total of 125 PWH and 59 matched controls without HIV were included in the current analysis. The PWH and participants without HIV were similar in age (46.5 ± 8.2 vs. 45.4 ± 7.1 years; $p = .32$), sex (69.6% vs. 66.1% male; $p = .63$), and body mass index (BMI; 27.9 ± 5.5 vs. 27.3 ± 4.9 kg/m^2; $p = .49$). Demographic, metabolic, and immunologic characteristics of participants are summarized in the Supplementary Table S1. AST [26 (21–37) vs. 23 (17–29) U/L; $p = .009$] and ALT [25 (17–38) vs. 19 (14–27) U/L; $p = .005$] were higher in PWH than in controls. IL-18 [245.8 (179.5–317.0) vs. 198.6 (141.7–246.6) pg/mL; $p = .0008$] (Fig. 1A) and MCP-1 [262.0 (179.0–358.0) vs. 223.5 (170.3–275.0) pg/mL; $p = .02$] were also higher in PWH than in controls.

IL-18 is elevated in PWH with NAFLD defined by CT liver-to-spleen ratio

Among PWH, log$_{10}$ IL-18 was higher in the NAFLD group than in the non-NAFLD group defined by CT liver-to-spleen ratio (2.51 ± 0.15 vs. 2.36 ± 0.18; $p = .01$).
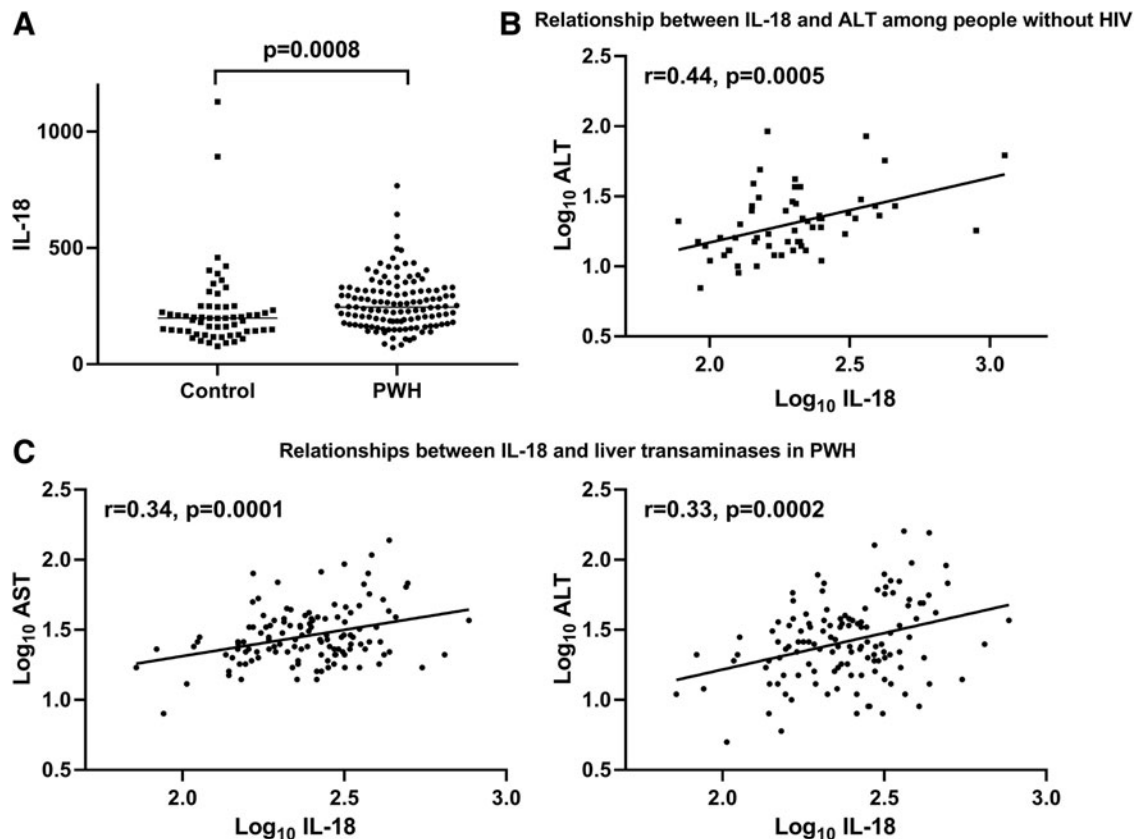
FIG. 1. (**A**) IL-18 is higher in PWH than in people without HIV. *Line* represents median. (**B**) Log_{10} IL-18 levels are associated with Log_{10} ALT in individuals without HIV. (**C**) Log_{10} IL-18 levels are associated with log_{10} AST and log_{10} ALT in PWH. ALT, alanine aminotransferase; AST, aspartate aminotransferase; IL, interleukin; PWH, people with HIV.

Markers of fatty liver disease are associated with IL-18 and MCP-1

Among PWH, log_{10} IL-18 had a positive relationship with log_{10} AST ($r=0.34$, $p=.0001$) and log_{10} ALT ($r=0.33$, $p=.0002$) (Table 1 and Fig. 1). The relationship between log_{10} IL-18 and log_{10} ALT was also significant in individuals without HIV ($r=0.44$, $p=.0005$). Similarly, log_{10} MCP-1 had a positive correlation with log_{10} AST ($r=0.27$, $p=.004$) and log_{10} ALT ($r=0.26$, $p=.006$) among PWH. Log_{10} IL-18 showed a significant correlation with liver-to-spleen ratio ($r=-0.24$, $p=.02$) in PWH.

IL-18 and MCP-1 are associated with triglycerides and high-density lipoprotein

Among PWH, log_{10} IL-18 had a positive correlation with log_{10} triglycerides ($r=0.26$, $p=.003$) and inverse correlation with high-density lipoprotein (HDL; $r=-0.28$, $p=.002$). The inverse correlation between log_{10} IL-18 and HDL was also significant in HIV-negative individuals ($r=-0.27$, $p=.04$). Log_{10} MCP-1 had a positive correlation with log_{10} triglycerides ($r=0.25$, $p=.007$) and inverse correlation with HDL ($r=-0.25$, $p=.009$).

IL-18 is associated with markers of inflammation, microbial translocation, and HIV disease parameters

In PWH, log_{10} IL-18 was associated with log_{10} MCP-1 ($r=0.33$, $p=.0004$), log_{10} caspase-1 ($r=0.35$, $p<.0001$), and

log_{10} LPS ($r=0.28$, $p=.004$). There was a significant positive correlation with log_{10} IL-18 and log_{10} HIV viral load ($r=0.29$, $p=.002$) and an inverse relationship between log_{10} IL-18 and log_{10} CD4$^+$/CD8$^+$ ratio ($r=-0.24$, $p=.007$) in PWH.

Multivariable analysis

The relationship between log_{10} IL-18 with log_{10} AST ($\beta=0.31$, $p=.004$) remained significant after adjusting for age, gender, BMI, log_{10} triglycerides, statin use, log_{10} HIV RNA, and log_{10} CD4 count. The relationship between log_{10} IL-18 with log_{10} ALT ($\beta=0.43$, $p=.003$) remained significant after adjusting for age, gender, BMI, log_{10} triglycerides, statin use, log_{10} HIV RNA, and log_{10} CD4 count.

In a model that also included MCP-1, the relationship between log_{10} IL-18 with log_{10} AST ($\beta=0.36$, $p=.007$) remained significant after adjusting for age, gender, BMI, log_{10} triglycerides, statin use, log_{10} HIV RNA, log_{10} CD4 count, and log_{10} MCP-1. The relationship between log_{10} IL-18 with log_{10} ALT ($\beta=0.52$, $p=.002$) remained significant after adjusting for age, gender, BMI, log_{10} triglycerides, statin use, log_{10} HIV RNA, log_{10} CD4 count, and log_{10} MCP-1.

Adjusting for relevant metabolic parameters, the relationship between log_{10} IL-18 with liver-to-spleen ratio ($\beta=-0.63$, $p=.02$) remained significant after adjusting for age, gender, BMI, log_{10} triglycerides, fasting glucose, and log_{10} VAT area.

To assess if HIV status affected the relationship of IL-18 with ALT, AST, or liver-to-spleen ratio, we performed an analysis among all participants including HIV status, log_{10}

TABLE 1. RELATIONSHIPS OF LIVER, METABOLIC,
AND INFLAMMATORY INDICES WITH INTERLEUKIN-18
AND MONOCYTE CHEMOATTRACTANT PROTEIN-1
IN PEOPLE WITH HIV

	Log_{10} (IL-18)		Log_{10} (MCP-1)	
	r	p	r	p
Liver				
Log_{10} (AST)	0.34	**.0001**	0.27	**.004**
Log_{10} (ALT)	0.33	**.0002**	0.26	**.006**
Liver/spleen ratio	−0.24	**.02**	−0.20	.06
Glucose				
Fasting glucose	0.08	.40	0.09	.33
Log_{10} (hemoglobin A1c)	−0.09	.32	−0.001	.99
Lipids				
Total cholesterol	−0.02	.83	−0.06	.52
LDL	−0.01	.87	−0.05	.63
HDL	−0.28	**.002**	−0.25	**.009**
Log_{10} (triglycerides)	0.26	**.003**	0.25	**.007**
Fat distribution				
BMI	−0.04	.64	0.06	.53
Log_{10} (VAT)	0.12	.19	0.22	**.02**
Log_{10} (SAT)	−0.15	.09	−0.004	.97
Inflammatory markers				
Log_{10} (MCP-1)	0.33	**.0004**	—	—
Log_{10} (IL-18)	—	—	0.33	**.0004**
Log_{10} (LPS)	0.28	**.004**	0.02	.86
Log_{10} (caspase-1)	0.35	**<.0001**	0.15	.13
HIV disease parameters				
Log_{10} (viral load)	0.29	**.002**	−0.03	.74
Log_{10} (CD4$^+$ T cell count)	−0.17	.06	0.12	.21
Log_{10} (CD8$^+$ T cell count)	0.13	.16	0.24	**.01**
Log_{10} (CD4$^+$/CD8$^+$ ratio)	−0.24	**.007**	−0.05	.61
Adjusted relationships with log_{10} (IL-18)	β	p		
Log_{10} (AST)[a]	0.31	**.004**		
Log_{10} (ALT)[a]	0.43	**.003**		
Liver-to-spleen ratio[b]	0.63	**.02**		

Bold values denote statistical significance at *p*-value <0.05.

[a]Multivariate analysis adjusting for age, gender, BMI, log_{10} triglycerides, statin use, log_{10} HIV RNA, and log_{10} CD4 count.

[b]Multivariate analysis adjusting for age, gender, BMI, log_{10} triglycerides, fasting glucose, and log_{10} VAT area.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; HDL, high-density lipoprotein; IL, interleukin; LDL, low-density lipoprotein; MCP-1, monocyte chemoattractant protein-1; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.

IL-18 as covariates as well as the interaction term (HIV× log_{10} IL-18) for the outcomes of log_{10} ALT, log_{10} AST, and liver-to-spleen ratio, and we did not see significant interaction of HIV status on the relationships of log_{10} IL-18 with ALT (*p* = .76 for interaction), AST (*p* = .18 for interaction), or liver-to-spleen ratio (*p* = .32 for interaction).

Sensitivity analysis

In a sensitivity analysis excluding individuals with detectable HIV RNA, we observed similar findings including higher IL-18 in PWH than in controls [232.0 (171.3–300.2) vs. 198.6 (141.7–246.6) pg/mL; *p* = .008] and higher MCP-1 in PWH than in controls [251.5 (176.8–364.8) vs. 223.5 (170.3–275.0) pg/mL; *p* = .04]. We also observed similar relationships between log_{10} IL-18 with log_{10} ALT (*r* = 0.39, *p* < .0001), log_{10} AST (*r* = 0.40, *p* < .0001), and liver-to-spleen ratio (*r* = −0.24, *p* = .04) among PWH with undetectable HIV RNA.

Discussion

In this observational study of PWH who do not have known hepatitis B, hepatitis C, or excessive alcohol use, we observed that circulating IL-18 was higher in individuals with evidence of NAFLD by CT liver-to-spleen ratio <1, and that IL-18 was positively related to ALT and AST levels and inversely associated with CT liver-to-spleen ratio, even after controlling for relevant covariates. Furthermore, IL-18 was positively associated with MCP-1, a marker of an important inflammatory mechanism in the development of steatohepatitis that is activated downstream of inflammasome activation. These findings suggest a potential role of the inflammasome/IL-18 pathway and downstream MCP-1 pathway in NAFLD progression through hepatic inflammation in PWH. The relationship of IL-18 with liver transaminases and hepatic steatosis assessed by CT scan remained significant even after controlling for traditional risk factors for NAFLD. To our knowledge, this is the first report to support the potential role of inflammasome activation in NAFLD in PWH.

IL-18 and the inflammasome have been implicated in the pathogenesis of chronic liver diseases including NAFLD in the general population. Knockout mouse models of NLRP3 inflammasome or IL-18 are spared from the development of significant steatohepatitis and fibrosis, whereas knockin models of inflammasome or IL-18 lead to significant liver damage.[6,19,20] In a previous study by Wree *et al.*, inflammasome components including pro-IL-18 expression in the liver were significantly increased in individuals with NASH compared with those with hepatic steatosis in non-HIV-infected population.[6] Serum levels of IL-18 trended to be higher in a population with NAFLD than in controls in one study although it did not reach statistical significance,[21] and increases in IL-18 have been associated with metabolic risk factors closely related to NAFLD such as obesity, insulin resistance, and hypertriglyceridemia.[22–24] Our findings are consistent with this body of work in the non-HIV population demonstrating that IL-18 may contribute to the progression of NAFLD. As expected, serum IL-18 was positively associated with serum caspase-1 levels, which is upstream in the inflammasome pathway. Indeed, in this study, we observed strong relationships between IL-18 and ALT, indicative of hepatic inflammation in NASH, among individuals without HIV and in PWH, suggesting that the inflammasome pathway is associated with liver injury among individuals with or without HIV. Among PWH who have even higher IL-18 levels suggestive of heightened inflammasome activation, the greater degree of inflammasome activation may further contribute to the severity of NAFLD progression seen in PWH.

Similarly, the MCP-1/CCR2 pathway has been implicated in the pathogenesis of NAFLD,[7,25] and the blockade of CCR2 and CCR5 is being studied as a therapeutic target for NAFLD.[26] In HIV, monocyte activation in NAFLD progression and fibrosis development has been demonstrated by

Maurice *et al.* with increased levels of sCD163 and sCD14 in PWH with NAFLD compared with PWH without liver disease.[27] Our data showing an association between MCP-1 and noninvasive markers of NAFLD add to the evidence that monocyte recruitment and infiltration are important steps in the pathogenesis of NAFLD in PWH. Furthermore, association of IL-18 with both LPS and MCP-1 in our study may underscore the ability of inflammasome to sense danger signals such as endotoxins from increased microbial translocation and its known role in activating MCP-1-mediated monocyte recruitment to drive NAFLD progression.

This study is hypothesis generating and has limitations. It was not specifically designed to recruit participants with diagnosed NAFLD, and the assessments for NAFLD did not include liver biopsy, which is the gold standard to assess the degree of both steatosis and fibrosis, or magnetic resonance imaging-derived proton density fat fraction to assess hepatic steatosis radiographically. Second, our study measured circulating IL-18 and MCP-1 levels and did not assess tissue-specific expression in the liver and liver-specific inflammasome components. Finally, owing to the cross-sectional nature of the study, the causal directionality of the associations is uncertain. Nevertheless, the initial observations brought forth by this study may provide novel insights into the key inflammatory components of NAFLD in PWH.

Future studies using liver biopsies are needed to confirm our findings and also to elucidate precise mechanisms involving the inflammasome pathways in NAFLD development and progression in PWH. In addition, these findings may aid in the development of effective therapies. Among current investigational therapeutic studies targeting the MCP-1/CCR2 pathway, cenicriviroc, a dual antagonist of CCR2 and CCR5, has been shown to prevent progression of liver fibrosis in participants with NASH and is currently undergoing a phase 3 trial for the treatment of NASH with fibrosis in the general population.[26] Investigational therapies modulating the inflammasome pathway to prevent NAFLD progression are in preclinical stages. In one study with NASH murine models, a selective NLRP3 inflammasome inhibitor MCC950 reduced markers of inflammasome activation, MCP-1, ALT/AST, and the severity of liver inflammation and fibrosis.[28] If demonstrated to be effective, these investigational pharmacotherapies targeting specific inflammatory pathways may also be relevant for study in the treatment of NASH in PWH, who have a heightened risk of developing liver disease and metabolic complications linked to ongoing inflammation.

Conclusion

In conclusion, the proinflammatory cytokine, IL-18, which is a component of inflammasomes, has been known to be higher in PWH, and in this study, we identified a new relationship between IL-18 and liver enzymes and hepatic steatosis. These findings from this hypothesis-generating study suggest that increased inflammasome activation may be a potential mechanism in the pathogenesis of hepatic inflammation and NAFLD in PWH warranting further future investigation.

Authors' Contributions

J.H.S., J.B.S., and J.L. contributed to design and concept of the study analysis. K.V.F., S.E.L., J.A.R., M.T.L., T.H.B., and J.L. conducted data collection. J.H.S., J.B.S., and J.L. conducted data analysis. J.H.S. and J.B.S. wrote the first draft of the article. J.H.S., J.B.S., T.L.S., K.E.C., M.T.L., T.H.B., and J.L. critically reviewed and finalized the article. All authors contributed to subsequent drafts, reviewed, and approved the final version of the article.

Supplementary Material

Supplementary Table S1

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