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Higher CD163 levels are associated with insulin resistance in HCV and HIV-infected adults

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Abstract

Objectives—HIV/HCV coinfection is associated with insulin resistance, but the mechanism is unclear. We hypothesized that intestinal epithelial damage and the consequent monocyte/macrophage activation, and inflammation explain this perturbation.

Design—Cross-sectional study of 519 adults (220 HIV+/HCV−;64 HIV−/HCV+;89 HIV+/HCV+;146 HIV−/HCV−).

Methods—We used multivariable linear regression to evaluate associations of HIV and HCV with the homeostasis model assessment of insulin resistance (HOMA-IR) and if intestinal fatty acid binding protein (I-FABP, a marker of gut epithelial integrity), soluble(s)CD14 and sCD163 (markers of monocyte/macrophage activation) and interleukin-6(IL-6, an inflammatory cytokine) mediated this association.

Results—HIV+/HCV+ and HIV−/HCV+ had greater demographic-adjusted HOMA-IR (mean[95%CI]:1.96[1.51,2.54] and 1.65[1.22,2.24]) than HIV+/HCV− and HIV−/HCV−(1.41[1.18,1.67] and 1.44[1.17,1.75], respectively). After additional adjustment for lifestyle and metabolic factors, HIV+/HCV+ remained associated with 36%(95%CI:4%,80%) greater HOMA-IR relative to HIV−/HCV−, while HIV−/HCV+ and HIV+/HCV− had smaller differences. Adjustment for sCD163 substantially attenuated the difference between HIV+/HCV+ and HIV−/HCV−; adjustment for I-FABP, sCD14, and IL-6 had little effect. Higher sCD163 was independently associated with 19%[95%CI:7%,33%], 26%[95%CI:15%,39%],25%[95%CI:14%,37%], and 23%[95%CI:11%,36%] greater HOMA-IR in HIV+/HCV+, HIV−/HCV+,HIV+/HCV−, and HIV−/HCV−(all estimates per doubling of sCD163). I-FABP, sCD14, and IL-6 were not associated with HOMA-IR.

Conclusion—HIV/HCV coinfection is associated with greater HOMA-IR, even after controlling for demographic, lifestyle, and metabolic factors. sCD163, which appears independent of

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intestinal epithelial damage and inflammation, partly explains this association. Our findings that the association of sCD163 with HOMAIR occurred even in the absence of HIV and HCV, indicates that viral and non-viral factors affect sCD163 levels. Its role in insulin resistance needs elucidation.

Keywords

HIV; HCV; microbial translocation; monocyte activation; inflammation; insulin resistance

Background

The advent of effective antiretroviral therapy (ART) has led to profound improvements in survival; yet HIV-infected persons continue to experience excess morbidity and mortality. Aging-related comorbidities, such as diabetes mellitus (DM), have become increasingly important in the management of HIV-infected patients. Besides traditional risk factors for DM, HIV-infected adults have an increased risk for DM due to Hepatitis C virus (HCV) coinfection[1], use of certain antiretroviral drugs[2, 3], low testosterone[4], and HIV-related body fat changes.[5] Some have also postulated that gut microbial translocation and its consequent immune activation and inflammation, even in the setting of effective ART may be associated with DM risk.[6] Soluble markers of gut microbial translocation, innate immune activation and inflammation have been associated with mortality in treated HIV-infected individuals.[7]

During primary HIV infection, depletion of CD4+ cells in gut-associated lymphoid tissue compromises gut mucosal integrity[7], increases intestinal permeability[8], and leads to translocation of microbial products from the gut.[9, 10] This in turn triggers immune activation during the chronic phase of HIV infection and persistent inflammation through sustained translocation of gut microbial products. Plasma lipopolysaccharide (LPS), a major component of the Gram-negative bacterial cell wall and a potent immunostimulatory product[11], is elevated in HIV-infected persons and correlate with measures of innate and adaptive immune activation.[12] Levels of soluble CD14 (sCD14), a marker of monocyte activation and a co-receptor for LPS[7, 13], and intestinal Fatty Acid Binding Protein (I-FABP), a systemic marker of gut epithelial cell death, have been associated with increased mortality in persons with virologically-suppressed HIV infection.[7] Elevated levels of soluble CD163 (sCD163), which is thought to be a more specific marker of monocyte/macrophage activation marker [14], has also been associated with increased mortality in predominantly virologically-suppressed HIV-infected persons.[15] Although the root driver of elevated sCD163 in that study was unclear, it suggests that monocyte/macrophage activation plays a role in HIV pathogenesis, even among virologically-suppressed HIV-infected persons.

Higher sCD163 levels have also been reported in obese persons with and without HIV infection. [16, 17] I-FABP, sCD14 and sCD163 have all been associated with DM risk in HIV-uninfected persons.[9, 10, 18, 19] Whether monocyte activation and inflammation, related to microbial translocation or independent of it, are associated with disorders of glucose metabolism in HIV-infected adults has not been established.

HCV infection is a risk factor for both insulin resistance and DM[1, 20–23] irrespective of the presence or absence of cirrhosis.[24] We previously reported that HIV/HCV-coinfected women are 1.5 times more likely to develop DM than HIV-monoinfected women.[25] However, the mechanism by which HCV infection induces disorders of glucose metabolism remains unclear. While HCV infection has been associated with higher interleukin (IL)-6 levels (a marker of systemic inflammation)[24, 26, 27], few studies have examined the relationship of markers of microbial translocation, immune activation, and inflammation with insulin resistance in the setting of HCV and HIV.

We evaluated the associations of HIV monoinfection, HCV monoinfection and HIV/HCV coinfection with insulin resistance in a cohort of ethnically diverse men and women enrolled in the Women's Interagency HIV Study (WIHS) and the Study of Visceral Adiposity, HIV and HCV: Biologic Mediators of Hepatic Steatosis (VAHH). We hypothesized that intestinal epithelial damage, monocyte/macrophage activation, and systemic inflammation is associated with insulin resistance, independent of traditional determinants of DM in the setting of HIV and HCV.

Methods

Study Population

The WIHS is a multicenter prospective cohort study that was established in 1994 to investigate the progression of HIV in women with and at risk for HIV. A total of 4,982 women (3,678 HIV-infected and 1,304 HIV-uninfected) were enrolled between 1994 and 2015 from eleven United States cities (Atlanta, Birmingham, Bronx, Brooklyn, Chapel Hill, Chicago, Jackson, LA, Miami, San Francisco, and Washington DC). Baseline socio-demographic characteristics and HIV risk factors were similar between HIV-infected and uninfected women [28, 29]. An institutional review board approved study protocols and consent forms, and each study participant gave written informed consent. Every six months, participants complete a comprehensive physical examination, provide biological specimens for CD4 cell count and HIV RNA viral load determination, and complete an interviewer-administered questionnaire, which collects information on sociodemographics, disease characteristics, and specific ART use. From December 2003 through July 2015, WIHS participants from three WIHS sites (Chicago, SF, and DC) participated in a series of substudies designed to investigate the contribution of HIV and HCV, and its metabolic and inflammatory consequences to hepatic steatosis and fibrosis. Women with hepatitis B surface antigenemia, prior HCV treatment, and decompensated cirrhosis were excluded from the substudy. From these studies, 434 women had available stored plasma for testing of markers of microbial translocation, monocyte activation, and systemic inflammation as well as fasting glucose and insulin measures.

The VAHH Study enrolled 224 participants (98% men) with HIV monoinfection (n=64), HIV/HCV coinfection (n=27), HCV monoinfection (n=55), and neither HIV nor HCV infection (n=78) between the ages of 35 and 70 from October 2010 through June 2014. Participants were recruited through posted flyers at the San Francisco VA Medical Center (SFVAMC), patient-to-patient referrals, and SFVAMC providers approaching patients in clinic. Participants with DM defined by chart review of a DM diagnosis and confirmation of

fasting glucose (FG) ≥126mg/dL, elevated hemoglobin A1C (A1C) >6.5%, or use of anti-DM medications, as well as those with evidence of hepatitis B surface antigenemia, prior HCV treatment, and history of decompensated cirrhosis were not eligible for the study. Participants provided biological specimens for CD4 cell count, HIV RNA viral load determination and fasting metabolic parameters, and completed an interviewer-administered questionnaire, which collected information on sociodemographics, disease characteristics, and specific ART use. Of the 224 participants enrolled, 190 had available stored plasma for testing of markers of microbial translocation, monocyte/macrophage activation, and systemic inflammation as well as fasting glucose and insulin measures.

Women with DM **(**defined as having: 1) an elevated FG ≥126mg/dL confirmed by a subsequent FG≥126mg/dL, report of anti-DM medication, or a confirmed A1C ≥6.5%; and 2) a report of DM confirmed by a subsequent report of anti-DM medication or two FG measurements ≥126mg/dL., or FG≥126mg/dL concurrent with A1C≥6.5%) were also excluded from the analysis, leaving 519 participants (220 HIV-monoinfected, 64 HCV-monoinfected, 89 HIV/HCV-coinfected and 146 HIV and HCV-uninfected controls) in the cross-sectional analysis.

Measurement of markers of microbial translocation and inflammation

Using blood samples collected from WIHS and VAHH participants at the same time as their study visit and stored at −70 ° C, I-FABP, sCD14, and sCD163 were measured from frozen plasma and interleukin 6 (IL-6) from frozen sera. Commercially available enzyme-linked immunosorbent assays (ELISA) were used to measure I-FABP [ELISA kit (Hycult Biotech, Plymouth Meeting, Pennsylvania)]; sCD14 and sCD163 [Quantikine ELISA kit (R & D systems, Minneapolis, Minnesota, USA); and IL-6 [Quantikine HS Human IL-6 Immunoassay kit (R & D Systems, Minneapolis, Minnesota, USA)]. Samples from both cohorts were tested centrally at the same laboratories. Assays were performed in duplicate and in accordance with manufacturers' protocols.

Outcomes

The primary outcome was insulin resistance quantified using the Homeostasis Model Assessment defined as fasting insulin (μU/mL) × glucose (mg/dL)/405.[30] Fasting specimens for glucose determination were collected in tubes with glycolytic inhibitors for the WIHS and standard serum separator tubes for the VAHH. Serum for insulin determination was obtained at the same time, and all specimens were stored at −70°C until the day of assay. Plasma glucose was measured using the hexokinase method, and insulin was measured using the IMMULITE 2000 assay at the same central laboratory (Quest Diagnostics, Baltimore, MD) for both WIHS and VAHH.

Covariates

Candidate covariates included demographic characteristics (i.e., age, sex and race/ethnicity); anthropometric measures (i.e., weight, height, waist circumference, waist and hip circumference and body mass index), metabolic parameters including fasting lipids (i.e., high density lipoprotein (HDL) and low density lipoprotein (LDL)) and estimated glomerular filtrate rate; lifestyle factors [i.e., alcohol use (>0–7 drinks/week; >7–12 drinks/

week; >12 drinks/week); smoking (current vs. none) and years smoked among past and current smokers] and liver-related factors [hepatitis C virus infection (confirmed by detectable HCV RNA following a positive anti-HCV antibody result) and hepatic fibrosis estimated using the aspartate aminotransferase (AST)-to-platelet ratio index (APRI)]. HIV infection status (defined by prior documentation of a positive HIV enzyme immunoassay confirmed by Western blot) and HIV-related risk factors included current CD4 cell count, CD4 cell count nadir, current HIV RNA level, history of clinical AIDS and current use of HAART.

Statistical Analysis

We first compared sociodemographic and clinical characteristics across 4 groups: HIV/HCV-coinfected individuals, HCV-monoinfected individuals, HIV -monoinfected individuals and those with neither infection, using ANOVA model or Kruskal Wallis test for continuous variables and the chi-squared test or Fisher exact test for categorical variables.

Next, we calculated within-group marginal mean values of HOMA-IR for each disease category, adjusted for age, sex, and race/ethnicity. We used multivariable linear regression models to examine the association of disease category with HOMA-IR. Because HOMA-IR was found to have a right-skewed distribution, it was log-transformed to normalize its distribution. The regression coefficients and their confidence intervals were then exponentiated to calculate percentage differences attributable to each factor. To determine whether HIV and HCV status were independently associated with HOMA-IR, multivariable models were sequentially adjusted for (1) demographic, lifestyle, body composition and metabolic characteristics, and (2) demographic, lifestyle, body composition and metabolic variables and each of the four biomarkers, I-FABP, sCD14, sCD163 and IL-6, respectively. Biomarkers were tested individually, rather than jointly. We then used univariable and multivariable linear regression models to examine the association of I-FABP, sCD14, sCD163 and IL-6 with HOMA-IR, in separate models for each biomarker. Models were stratified by disease category in order to determine whether biomarker associations with HOMA-IR were similar in those with and without HIV and HCV infection. We adjusted sequentially for: 1) demographic factors; 2) demographic, lifestyle, body composition and metabolic parameters; and then 3) each of the 4 predictor variables. In models with missing cases, multiple imputation using the Chained Equations method[31] was used to impute missing covariates with ten repetitions. All analyses were conducted using Stata version 14 (College Station, TX).

Results

Population Characteristics

Sociodemographic and clinical characteristics are shown in Table 1, stratified by HIV and HCV status. HCV-infected participants were older than the HIV-monoinfected and uninfected participants. Over half of the HCV-monoinfected participants were White and male, whereas half or more of the HIV-infected participants (with or without HCV) were African American and female. Among the participants with neither HIV nor HCV infection, the proportion of participants that were African-American and White were evenly

distributed; as was the proportion of men and women. HCV-infected participants were more likely to report smoking than the HIV-monoinfected and uninfected participants. HIV/HCV-coinfected participants had the lowest BMI and circumferences of the waist and hip, whereas those with neither infection had the highest BMI and circumferences of the waist and hip. HIV/HCV-coinfected participants had the highest levels of I-FABP, sCD163, sCD14, and IL-6 and those with neither infection the lowest levels. Among the HIV-infected participants, HIV/HCV-coinfected had lower current and nadir CD4 cell count and were less likely to have an undetectable HIV RNA level, but were more likely to report being on HAART compared to HIV-monoinfected participants.

Association of HIV and HCV infection status with HOMA-IR—The age, sex, and race/ethnicity adjusted mean HOMA-IR was highest in the HIV/HCV-coinfected at 1.96 (95% CI: 1.51, 2.54); intermediate in the HCV-monoinfected at 1.65 (95% CI: 1.22, 2.24); and lowest in the HIV-monoinfected and controls at 1.41 (95% CI: 1.18, 1.67) and 1.44 (1.17, 1.75), respectively.

HIV/HCV coinfection was associated with significantly higher (70%, $p<0.001$) HOMA-IR levels relative to those with neither infection in analysis adjusted for demographic, lifestyle, body composition and metabolic characteristics (Table 2). HIV/HCV coinfection remained strongly associated with greater HOMA-IR after additional adjustment for I-FABP, sCD14, and IL-6. By contrast, after adjustment for sCD163, the association of HIV/HCV coinfection with greater HOMA-IR was greatly diminished (42%, $p=0.039$). HCV monoinfection was associated with a 24% elevation in HOMA-IR relative to those with neither infection, although the difference did not reach statistical significance either in models adjusted for demographic, lifestyle, body composition and metabolic characteristics or after additional adjustment for biomarkers. There was a non-significant difference in HOMA-IR between HIV-monoinfected and uninfected participants in fully adjusted analysis, and after additional adjustment for I-FABP, sCD14, IL-6, or sCD163.

Association of soluble markers with HOMA-IR in each infection group—We next evaluated the association of each soluble marker with HOMA-IR in separate multivariable models by HIV and HCV status (Table 3). Elevations in sCD163 showed strong associations with HOMA-IR, regardless of disease category. In unadjusted analysis, each doubling of sCD163 was associated with a 28%–34% increase in HOMA-IR (all $p<.001$). In fully adjusted models that controlled for demographic, lifestyle, and metabolic factors, sCD163 remained associated with a 19%–26% increase in HOMA-IR ($p\leq.001$). By contrast, elevations in sCD14 appeared to be associated with *lower* levels of HOMA-IR. In unadjusted analyses, each doubling of sCD14 was associated with an 8–11% decrease in HOMA-IR, with associations reaching statistical significance in all disease categories except for HIV monoinfection ($p=0.051$). However, in fully adjusted models that controlled for demographic, lifestyle, and metabolic factors, sCD14 did not show significant associations with HOMA-IR in any disease category. We found little association of I-FABP or IL-6 with HOMA-IR in any disease category.

Because our original hypothesis was that increased gut epithelial damage would lead to monocyte/macrophage activation, we included both I-FABP and sCD163 in fully adjusted

models and found that sCD163 remained associated with an 20% – 27% increase in HOMA-IR ($p<0.001$ for all groups). Other factors associated with insulin resistance that might be mediated by sCD163 including obesity and liver fibrosis also did not attenuate the association. When BMI, waist circumference, and APRI were separately added to the model, sCD163 remained associated with 23%–28% ($p<0.001$ for all groups), 20%–26%($p<0.05$ for all groups), and 18%-25% ($p<0.05$ for all groups) increase in HOMA-IR, respectively. Among the HIV-infected, the addition of CD4 or HIV RNA also did not attenuate the association between sCD163 and HOMA-IR; it remained associated with an 18%-25% increase ($p<0.05$ for all groups).

Discussion

In our large, ethnically diverse cohort of men and women, we found as expected that HIV/HCV-coinfected persons had significantly greater insulin resistance compared to those with neither HIV nor HCV infection. After demographic adjustment, there was no association of HIV monoinfection and little association of HCV monoinfection with HOMA-IR relative to those with neither infection. A strong role for macrophage activation per se was found when we examined the association of I-FABP, sCD14, sCD163, and IL-6 with HOMA-IR. We found that sCD163, but not sCD14, strongly attenuated the association of HIV and HCV infection with insulin resistance. Furthermore, sCD163 was strongly associated with HOMA-IR in all four groups and persisted after adjusting for demographic, lifestyle, metabolic and body composition factors, even in those with neither infection. Our findings are notable in that monocyte/macrophage activation independent of intestinal epithelial damage is an important mediator of the association of HIV, HCV, and HIV/HCV with HOMA-IR.

Contrary to our expectations, higher plasma I-FABP levels did not attenuate the association of HIV/HCV coinfection or HCV monoinfection with HOMA-IR. We found little association between HIV monoinfection and HOMA-IR, even though I-FABP levels were higher in those with HIV-monoinfected relative to those with neither infection. Adjustment for l-FABP did not alter this finding, suggesting that HIV-associated gut barrier dysfunction is not associated with insulin resistance. By contrast, we found that sCD163 was associated with insulin resistance consistent with studies in the general population.[18, 32, 33] To our knowledge, this is the first study demonstrating an association in HIV and HCV-infected individuals. In HIV-infected persons, this relationship was not attenuated by either the degree of immunosuppression or HIV viremia. That sCD163 was associated with greater HOMA-IR in those with neither HIV nor HCV suggests a role for factors beyond HIV and HCV infection.

There is evidence to suggest that the association of sCD163 with greater insulin resistance is mediated in part by adiposity.[16] In HIV-infected individuals on ART, obesity has been associated with greater inflammation and monocyte activation.[17] However, in our analysis, the association between sCD163 and insulin resistance was not attenuated after controlling for BMI and waist circumference, suggesting the association of sCD163 with insulin resistance is independent of surrogate markers of obesity and central obesity. Because obesity is associated with non-alcoholic steatohepatitis (NASH), we also adjusted for APRI,

a serum marker of liver fibrosis, that has previously been shown to be elevated in the setting of NASH[34] but did not find an attenuation of the association of sCD163 with HOMA-IR. HIV infection with and without HCV has also been associated with elevated APRI[35], and so our findings suggest that liver injury in the setting of HIV, HCV, and obesity does not explain the association of sCD163 with HOMA-IR. Further investigation is needed to determine not only the HIV and HCV-related but also non-viral factors that might explain the association of higher sCD163 levels with insulin resistance.

Our finding of a lack of an association between I-FABP and HOMA-IR in any infection group was contrary to a study in HIV-uninfected Pima Indians that supported a causal relationship between I-FABP and insulin resistance[36]. A possible explanation could be that non-intestinal isomers of the fatty acid binding protein (FABP), such as the adipocyte-FABP may be a better predictor of glucose tolerance than I-FABP[37]. To our knowledge, only one study has examined the association of markers of microbial translocation with insulin resistance in the HIV setting.[38] That study found a correlation between markers of microbial translocation and insulin resistance, but the median CD4 cell count was considerably lower than in our study. This supports the idea that gut microbial translocation may be an important determinant of diabetogenesis in profoundly immune-compromised patients, who are at greatest risk for the deleterious effects of translocation-mediated immune activation. Whether changes in gut microbial diversity in HIV infection are an important driver of insulin resistance is unclear and warrants further investigation.

Notably, we also did not find an association of sCD14 or IL-6 with insulin resistance. The lack of an association of sCD14 with insulin resistance is consistent with our finding with IFABP, since sCD14 is thought to be a receptor for LPS. While previous studies have found an association between markers of inflammation and insulin resistance[3, 39], our participants had less advanced HIV infection, with higher current and nadir CD4 cell counts and were less likely to report a history of AIDS-defining illness. Our findings could suggest that the association of inflammation with insulin resistance is abrogated in HIV-infected persons with less advanced disease supporting recommendations for early ART initiation.

Furthermore, our finding that HIV monoinfection was not associated with insulin resistance compared to those without HIV infection was different from our previous 2008 analysis[40], when we found that HIV-infected women enrolled in the WIHS had significantly greater insulin resistance compared to HIV-uninfected women. An explanation for the difference could be the decline in use of agents such as the thymidine analogs which have been associated with insulin resistance[3], the higher CD4 counts and the higher proportion that were virologically suppressed in our study.

Our study is limited by its cross-sectional design and therefore, we cannot exclude that the causal direction might be insulin resistance leading to higher sCD163 levels. A recent study demonstrated that lowering glucose levels in ICU patients, through administration of insulin, lowered sCD163 levels over a median duration of 7 days.[41] Prospective studies are needed to better characterize the relationship of sCD163 and IR in the setting of chronic HIV and HCV infection. Because our study was observational, we used multivariable regression analysis to control for differences in characteristics between the four infection groups. We

also defined insulin resistance using the surrogate marker of HOMA-IR and not the gold standard euglycemic insulin clamp technique.[42] Given the large size of the cohort, detailed testing using the clamp technique was not possible. Furthermore, HOMA-IR has been shown to be a reasonable marker of insulin resistance in large epidemiologic studies.[43, 44] The HOMA-IR values in our cohort were also low and whether these values predict greater DM risk needs study. We also used I-FABP as a surrogate marker of microbial translocation instead of other markers such as glutathione S-transferase because I-FABP specifically measures intestinal integrity. Measurement of circulating bacterial LPS concentrations is also technically difficult and results are often inconsistent even under research conditions. [45]

In conclusion, sCD163, a marker of monocyte/macrophage activation, was strongly and independently associated with HOMA-IR in persons with HIV and HCV infection, as well as those with neither infection. The association of HIV/HCV coinfection with insulin resistance may be explained by increased monocyte/macrophage activation. By contrast, there was no evidence that intestinal epithelial damage was associated with insulin resistance. Future studies are needed to determine mechanistic pathways (other than HIV and HCV-associated gut microbial translocation) that lead to macrophage activation and insulin resistance. Elucidation of these pathways will allow the development of targeted interventions to reduce sCD163 and potentially insulin resistance in not only HIV and HCV-infected individuals, but also those with neither HIV nor HCV infection.

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Table 1

Demographic and clinical characteristics of the 519 participants included in the study stratified by HIV and HCV infection status [*]

Characteristics	HIV/HCV coinfected	HCV monoinfected	HIV monoinfected	Uninfected	P-value[§]
Median (IQR) or n (%)	n= 89	n=64	n=220	n=146	
Demographics					
Age, yrs	52 (48, 57)	57(53, 60)	50 (41, 53)	49 (39, 55)	**<0.001**
Female	65 (73%)	17 (27%)	173 (79%)	74 (51%)	**<0.001**
Race/ethnicity					**0.002**
White	18 (23%)	25 (52%)	63 (304%)	37 (34%)	
African American	47 (60%)	12 (25%)	104 (50%)	43 (39%)	
Hispanic	13 (17%)	9 (19%)	29 (14%)	18 (16%)	
Other[¶]	1 (1.3%)	2 (4.2%)	12 (5.8%)	12 (4.2%)	
Lifestyle					
Current Smoker	55 (63%)	32 (51%)	77 (35%)	62 (43%)	**0.001**
Smoking history, yrs	30 (23, 37)	28 (18, 33)	10 (0, 20.5)	12 (0, 23)	**<0.001**
Alcohol consumption					0.128
None	40 (46%)	20 (32%)	77 (35%)	51 (35%)	
>0–7 drinks/wk	30 (34%)	24 (38%)	103 (47%)	57 (39%)	
>7–12 drinks/wk	4 (4.6%)	6 (9.5%)	17 (7.7%)	9 (6.2%)	
>12 drinks/wk	14 (16%)	13 (21%)	23 (11%)	29 (20%)	
Metabolic					
BMI, kg/m^2	24 (22, 28)	26 (22, 29)	26 (23, 29)	28 (25,31)	**0.001**
Waist circumference, cm	88 (81, 98)	94 (83, 106)	89.5 (81, 98)	97 (86, 106)	**<0.001**
Hip circumference, cm	96 (89, 105)	98 (93, 109)	97 (91, 105)	103(96, 111)	**<0.001**
Estimated GFR, mL/min/1.73m^2	86 (73, 107)	98 (86, 109)	97 (85, 114)	99 (88, 111)	**<0.001**
APRI score[+]	0.63 (0.4, 1.1)	0.74 (0.36, 1.13)	0.29 (0.22, 0.40)	0.26 (0.21, 0.36)	**<0.001**
Immune markers					
I-FABP, pg/ml	976 (463, 1564)	761 (505, 1209)	759 (519, 1426)	520 (333, 805)	**<0.001**
sCD14,ng/ml	1628 (1354, 1924)	1351 (1083, 1585)	1514 (1225, 1837)	1105 (1008, 1360)	**<0.001**
CD163, ng/ml	908 (626, 1282)	788 (515, 1146)	402 (308, 571)	347 (269, 433)	**<0.001**

Characteristics	HIV/HCV coinfected	HCV monoinfected	HIV monoinfected	Uninfected	P-value[§]
Median (IQR) or n (%)	**n= 89**	**n=64**	**n=220**	**n=146**	
IL-6, pg/ml	1.39 (0.89, 2.1)	0.98 (0.65, 1.61)	0.8 (0.54, 1.25)	0.73 (0.44, 1.1)	**0.006**
HIV specific Parameters					
Current CD4 count, cells/mm^3	504 (285, 678)	-	588 (379, 798)	-	**<0.001**
CD4 nadir, cells/mm^3	222.5 (131, 290)	-	288 (175, 420)	-	**<0.001**
History of AIDS defining illness, (%)	50 (56)	-	81 (37)	-	**0.001**
Undetectable Viral Load (%)	53 (60)	-	149 (68)	-	0.134
Current HAART use (%)	75 (84)	-	152 (69)	-	**0.020**

HCV, hepatitis C virus; HDL, high-density lipoprotein; LDL, low-density lipoprotein,

[*] All values are median (interquartile range) unless otherwise noted.

[§] P value from Pearson χ^2 test, Wilcoxon rank-sum test or Fischer's exact test

[¶] Includes Asian, Pacific Islander, Native American, Alaskan and other study participants

[+] APRI = ((AST/Top normal AST)/Platelets) * 100

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Table 2

Association of HIV monoinfection, HCV monoinfection, HIV/HCV coinfection with HOMA-IR adjusted for demographic, lifestyle, and metabolic factors plus markers of microbial translocation, monocyte activation, and inflammation, compared to those with neither infection[¶]

Parameter	Fully-adjusted*		Fully-adjusted + I-FABP**		Fully-adjusted + sCD163**		Fully-adjusted + sCD14**		Fully-adjusted + IL-6**	
	% Estimate (95%CI)	p-value	% Estimate (95%CI)	p-value	% Estimate (95%CI)	p-value	% Estimate (95%CI)	p-value	% Estimate (95%CI)	p-value
HIV/HCV coinfection	70% (30%, 122%)	**<0.001**	81% (37%, 138%)	**<0.001**	42% (4%, 94%)	**0.029**	75% (34%,129%)	**<0.001**	70% (30%, 123%)	**<0.001**
HCV monoinfection	24% (−6%, 65%)	0.125	27% (−4%, 70%)	0.095	9% (−20%, 48%)	0.575	26% (−5%, 68%)	0.112	25% (−6%, 66%)	0.125
HIV monoinfection	18% (−3%, 43%)	0.097	**25% (2%, 54%)**	**0.036**	13% (−7%, 38%)	0.228	20% (−1%, 48%)	0.063	18% (−3%, 43%)	0.097

[¶]Multiple imputation by the Chained Equation method was used to impute missing outcome values

*Adjusted for age, gender, race, smoking, alcohol, BMI, waist circumference, and estimated glomerular filtrate rate.

**Adjusted for age, gender, race, smoking, alcohol, BMI, waist circumference and estimated glomerular filtrate rate and each of the stated biomarkers

Table 3

Associations of markers of microbial translocation, monocyte activation, and inflammation with HOMA-IR by HIV and HCV status[¶]

Parameter	HOMA-IR Unadjusted % Estimate (95% CI)	HOMA-IR Demographic-adjusted[*] % Estimate (95% CI)	HOMA-IR Fully adjusted[**] % Estimate (95% CI)
HIV/HCV coinfected			
I-FABP (per doubling)	−3% (−11%, 5%) p=0.428	**−8% (−15%, 0%) p=0.044**	−5% (−12%, 2%) p=0.174
sCD163 (per doubling)[§]	**30% (17%, 45%) p<0.001**	**25% (12%, 40%) p<0.001**	**19% (7%, 33%) p=001**
sCD14 (per doubling)[§]	**−11% (−18%, −4%) p=0.002**	**−9% (−15%, −2%) p=0.014**	0% (−6%, 8%) p=0.833
1L-6 (per doubling)[§]	1% (−7%, 8%) p=0.884	2% (−5%, 11%) p=0.510	1% (−6%, 9%) p=0.758
HCV monoinfected			
I-FABP (per doubling)	−2% (−10%, 6%) p=0.597	−7% (−14%, 1%) p=0.097	−3% (−10%, 4%) P=0.397
sCD163 (per doubling)[§]	**30% (18%, 44%) p<0.001**	**28% (16%, 42%) p<0.001**	**26% (15%, 39%) p<0.001**
sCD14 (per doubling)[§]	**−9% (−14%, 0%) p=0.025**	−7% (−14%, 0%) p=0.61	4% (−4%, 12%) p=−0.341
1L-6 (per doubling)[§]	3% (−4%, 12%) p=0.392	4% (−4%, 13%) p=0.279	3% (−4%, 10%) P=0.359
HIV monoinfected			
I-FABP (per doubling)	−1% (−9%, 8%) p=0.931	−6% (−14%, 2%) p=0.182	−3% (−10%, 5%) p=0.49
sCD163 (per doubling)[§]	**28% (16%, 41%) p<0.001**	**26% (14%, 39%) p<0.001**	**25% (14%, 37%) p<0.001**
sCD14 (per doubling)[§]	−8% (−14%, 0%) p=0.051	−6% (−13%, 1%) p=0.089	1% (−6%, 10%) p=0.688
IL-6 (per doubling)[§]	3% (−5%, 10%) p=0.473	3% (−4%, 14%) p=0.343	3% (−4%, 11%) p=0.387
Uninfected			
I-FABP (per doubling)	−3% (−11%, 6%) p=0.560	−8% (−16%, 0%) p=0.052	−6% (−14%, 2%) p=0.113
sCD163 (per doubling)[§]	**34% (21%, 49%) p<0.001**	**29% (16%, 43%) p<0.001**	**23% (11%, 36%) p=001**
sCD14 (per doubling)[§]	**−10% (−16%, −3%) p=0.009**	**−9% (−15%, −2%) p=0.014**	−4% (−8%, 6%) p=0.684
1L-6 (per doubling)[§]	3% (−4%, 12%) p=0.398	4% (−4%, 12%) p=0.302	3% (−5%, 10%) p=0.493

[¶]Multiple imputation by the Chained Equation method was used to impute missing outcome values

[*]Adjusted for gender, age, race

** Adjusted for age, gender, race, smoking, alcohol, BMI, waist circumference and estimated glomerular filtrate rate.

§ All markers of inflammation added individually not sequentially.