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THE INDIVIDUAL AND COMBINED INFLUENCE OF HIV AND HEPATITIS C VIRUS ON DYSLIPIDEMIA IN A HIGH RISK HISPANIC POPULATION

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Summary

Objectives—To assess the effects of chronic hepatitis C (HCV) and HIV infection on dyslipidemia in a Hispanic population at high risk of insulin resistance.

Methods—We compared serum lipids and C-reactive protein (CRP) in 257 adult Hispanics including 47 HIV mono-infected; 43 HCV mono-infected; 59 HIV/HCV co-infected and 108 healthy controls. We also assessed the effect of HCV on lipid alterations associated with antiretroviral therapy (ART), and the impact of HCV and HIV on the associations among insulin resistance, triglycerides and cholesterol.

Results—HCV infection was associated with lower total and LDL cholesterol, but not HDL or triglycerides compared to healthy controls. HIV infection was associated with higher triglycerides, and lower HDL, but not total or LDL cholesterol. HCV mitigated the elevation of triglycerides associated with ART. In healthy Hispanics, insulin resistance was significantly correlated with higher triglycerides, CRP and lower HDL. HIV infection nullified the association of insulin resistance with triglycerides and HDL, and the association of triglycerides with LDL. HCV infection nullified the association of insulin resistance with triglycerides, HDL and CRP.

Conclusions—HCV co-infection alters the profile of HIV-associated dyslipidemia. The clinical significance of these findings for cardiovascular complications in HIV merits further study.

Keywords

Dyslipidemia; HCV; HIV; C-reactive protein; Hispanic

Introduction

Metabolic abnormalities are common in both HIV and hepatitis C (HCV) infections. HCV infection is associated with insulin resistance and lower levels of total cholesterol [1–11]. Attainment of HCV virologic clearance with treatment is associated with improved insulin resistance and elevations in cholesterol concentrations [11–13]. HIV infection is also

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associated with insulin resistance; mechanisms for this association may include exposure to certain antiretroviral agents, including nucleoside reverse transcriptase inhibitors (NRTI) and protease inhibitors (PI) [14–16]. However, in contrast to HCV, HIV is associated with a more atherogenic lipid profile [17–20]. Initiation of antiretroviral therapy (ART) can lead to further exacerbation of this unfavorable profile [14,21–23].

There is a growing appreciation that HCV influences the lipid response to HIV infection as well as the lipid response to ART [8–10,13]. The extent to which this has influenced our understanding of HIV-associated dyslipidemia is not clear since many studies have not accounted for HCV co-infection. An additional limitation of many studies has been the lack of a comparable healthy control group with a similar diet and lifestyle. These limitations have constrained our understanding of how HIV and HCV infections alter the associations among insulin resistance, triglycerides and cholesterol that are typically seen in uninfected persons.

Another shortcoming of this line of research is the predominance of studies conducted in whites. In the USA, HIV and HCV infections disproportionately affect minorities [24] including Hispanics, now the largest minority group in the country [25]. Hispanics have an increased risk of insulin resistance and the metabolic syndrome compared to whites [26–29], as well as dietary differences from whites that may impact serum lipids [30,31]. Since unfavorable lipid profiles promote conditions such as cardiovascular disease and fatty liver disease, it is important to understand the factors that can influence these serum parameters in high risk HIV/HCV infected groups.

Our study, locally known as the BIENESTAR study, was originally designed to examine the role of drug use as a co-factor in HIV-related nutritional status and metabolic alterations in Hispanics. The community-recruited cohort includes HIV and HCV mono-infected persons, HIV/HCV co-infected persons, as well as a group of healthy low risk Hispanics. This provided an ideal opportunity to examine the separate and combined effects of HCV and HIV on dyslipidemia in a group that shares ethnicity and diet. We examined the effects of HIV and HCV infection on metabolic parameters including insulin resistance, lipids and high sensitivity C-reactive protein (CRP), a marker of inflammation. We also measured serum retinol binding protein, a retinol (vitamin a) transport protein that has recently been identified as a possible co-factor in insulin resistance and type 2 diabetes [32–33].

The aims of this study were: 1) to present descriptive data in Hispanics, a high-risk ethnic group which has been poorly represented in previous HIV studies; 2) to contrast serum concentrations of lipids, CRP, and retinol binding protein in relation to measures of glucose homeostasis in HIV, HCV or HIV/HCV co-infection compared to healthy controls in a single racial/ethnic group, while accounting for lifestyle factors including diet, alcohol, drug use and the use of HIV antiretroviral agents. 3) To examine the influence of HIV and HCV infections on the correlations among body mass index (BMI), insulin resistance, triglycerides and lipids, and to contrast this to the pattern seen in healthy controls.

Methods

Study Population

Recruitment was done on the streets, in homeless shelters, support groups, health clinics, and hair salons. Hispanics ≥18 years of age who spoke Spanish as their first language were eligible. The majority of participants were of Puerto Rican extraction, a group that is a mix of European (predominant), Black and Amerindian race [34]. The exclusion criteria for the cohort at enrollment were: pregnancy, non-HIV associated malignancies, the use of hormones for a sex change, and refusal of consent to release of medical records. The data presented here were collected at the first visit of a sub-study designed to examine alterations in micronutrient

metabolism (n=333). Serum insulin and glucose, lipid profiles, CRP, and retinol binding protein were measured as potential confounders, modifers or mediators of the main associations of interest, and for this reason were available for the present analyses. For this study, data were excluded from the analyses if the participant was not fasting at the time of the blood draw (n=46), reported a diagnosis of diabetes mellitus (n=20), or reported taking a lipid-lowering agent (n=4). In addition, data from six participants with positive serum tests for hepatitis B surface antigen were excluded to focus on HCV infection since these viruses may have different impacts on lipids [35]. After these exclusions, data from 257 participants were available for analyses. All participants provided informed consent, and were paid a modest stipend for their participation. The study was approved by the Institutional Review Board at the Tufts Medical Center.

Study interviews were conducted in Spanish by bilingual, Hispanic personnel. Data collected by standardized interview included detailed information on the demographic profile, smoking, alcohol and drug use as well as information on HIV history and use of ART. Participants were asked to fast for a minimum of five hours prior to the clinic visit, and were asked not to drink alcohol or do strenuous physical exercise for a period of 48 hours prior to the visit. Body weight and height were measured by standardized techniques. BMI was calculated as weight in kilograms divided by height in square meters. Anthropometric measures related to fat distribution were not conducted as part of the micronutrient study and therefore were not available for these analyses. We have previously reported low rates of visceral adiposity and peripheral lipoatrophy in this cohort [36]. Dietary intake of cholesterol and saturated fats was assessed using a Hispanic food frequency questionnaire that has been validated in this population [37,38].

Serum measures

With the exception of retinol binding protein, all serum measures were conducted in the laboratories of the Tufts Medical Center using standard clinical chemistry techniques. Serum glucose cholesterol, HDL cholesterol and triglycerides were measured on a Beckman Coulter Synchron Clinical Systems Analyzer (Beckman Coulter Inc. Fullerton, CA, USA). Glucose was measured using a glucose oxidase/oxygen consumption method. Cholesterol and HDL were measured using a cholesterol esterase/cholesterol oxidase/peroxide colorimetric method. Triglycerides were measured using a lipase/glycerol kinase/glycerophosphate-oxidase/peroxidase colorimetric method Serum insulin was measured using an ADVIA Centaur Immunoassay System (Siemens Healthcare Diagnostics Inc. Deerfield IL, USA), which is a two-site sandwich immunoassay. Insulin resistance (IR) was measured using the homeostasis model assessment (HOMA), calculated as glucose (mmol/L) × fasting insulin (μU/ml)/22.5 [39]. High-sensitivity CRP was measured using a UniCel® DxC 800 Synchron® Clinical System and CRP High Sensitivity Reagent (Beckman Coulter, Fullerton, CA, USA); Retinol binding protein was measured by enzyme-linked immunosorbent assay (Alpo Diagnostics, Windham, NH).

HIV and HCV related assays

Self-reported HIV status was confirmed by enzyme immunoassay (Genetic Systems ™HIV1/HIV2 Plus O EIA, Biorad Laboratories, Redmond, WA). HIV RNA levels were measured by reverse transcriptase polymerase chain reaction (RT-PCR) using a Roche Amplicor Monitor (Roche Molecular Systems, Somerville, NJ), with a lower detection limit of 400 copies/mL. An undetectable viral load was given a value of 200 copies/mL, the midpoint between zero and the limit of detection. CD4 cell counts were determined using a specific monoclonal antibody and fluorescence-activated cell sorting (FACS) analysis. HCV infection was determined qualitatively by the presence of HCV RNA in serum (AMPLICOR Hepatitis C Virus test, Version 2.0 Roche Molecular Systems Inc., Branchburg, NJ, USA).

Statistical Analyses

The data were stratified by HIV/HCV infection status. Statistical analyses were carried out using SAS version 9.1 (SAS Inc., Chicago, IL). Since several of the serum metabolic measures had highly skewed distributions, transformation with the natural logarithm (ln) was used to normalize the data for statistical analysis. The data are reported as mean and standard deviation (SD) or standard error (SE) for normally distributed continuous data, or median (25th, 75th percentile) for non-normally distributed continuous data. In table 1, between-group differences in means were tested with the least square means option in the general linear models procedure in SAS for continuous variables, using either the raw or log transformed data, where appropriate. Chi-square or Fisher's exact test was used to test between-group differences for categorical variables. In table 2, unadjusted between-group differences in means were tested by F-test on the raw or log transformed data. Multivariate analyses were then conducted to evaluate the differences in average serum metabolic measures among the infection groups while adjusting for BMI, gender, smoking, alcohol and drug use, as well as dietary cholesterol and saturated fat (table 3). Use of ART was defined as the use of any protease inhibitor (PI), or nucleoside reverse-transcriptase inhibitor (NRTI). These classes were not mutually exclusive. All participants who were taking a NRTI were also taking a NNRTI so these agents could not be evaluated separately. To control for the confounding influence of ART in models which included healthy subjects, indicator variables combining HIV/HCV group status plus ART agent use were coded as follows: HIV mono-infected plus PI use; HIV/HCV co-infected plus PI use; HIV mono-infected no PI use; HIV/HCV co-infected no PI use; or HIV-mono-infected plus NRTI use; HIV/HCV co-infected plus NRTI use; HIV mono-infected no NRTI use; HIV/HCV co-infected no NRTI use. PI and NRTI agents were evaluated in separate models. All comparisons were to the healthy control group. The correlations reported in tables 4 and 5 were done using Spearman's correlation coefficient to account for the lack of normality in several of the measures. All tests were two-tailed using a nominal alpha of 0.05.

Results

The characteristics of the participants are shown in table 1. All groups were overweight on average [40]. The HIV/HCV co-infected group had a longer history of HIV infection and lower average CD4 cell counts compared to the HIV mono-infected group, but there was no difference in average HIV RNA. Protease inhibitor (PI) use was more common among the HIV/HCV co-infected group.

Table 2 shows the unadjusted serum values in each of the four infection groups. There were significant between-group differences in total cholesterol, LDL and HDL cholesterol, triglycerides and retinol binding protein. The lowest average values of cholesterol and retinol binding protein were seen in the HCV infected groups, whereas the highest average triglyceride values were in the HIV infected groups.

Since there were significant differences among the groups in age, gender, smoking, dietary saturated fat and cholesterol, and substance abuse (Table 1), the analyses were repeated with multivariate adjustment (Table 3). These analyses demonstrated significant and differential effects of HIV and HCV on serum lipids. Total and LDL cholesterol were significantly lower in the HCV infected groups compared to the healthy controls. HDL cholesterol was lower in the HIV-infected participants compared to the healthy controls and compared to the HCV mono-infected participants. Triglycerides were significantly higher in the HIV infected groups compared with the healthy group and the HCV mono-infected group. HDL cholesterol and triglycerides were similar in the HCV mono-infected and healthy control groups.

The data were further adjusted for the use of PI and NRTI agents. Compared to the healthy controls, triglycerides were elevated in the HIV mono-infected group on NRTI (+0.60 ln

triglycerides unit, SE=0.17, p=0.0030), but not in the HIV/HCV co-infected group on NRTI (+0.19 ln triglyceride units, SE=0.17, p=0.26). Alcohol use was associated with higher HDL (+4.5 mg/dl, SE=1.7, p=0.01); smoking with lower HDL (−4.2 mg/dl, SE=2.0, p=0.04).

Insulin resistance, measured by HOMA, was significantly higher in the HCV infected groups compared to the healthy controls. Smoking was independently associated with higher insulin (+ 0.27 ln insulin units, SE=0.12, p=0.031) and insulin resistance (+ 0.26 ln HOMA units, SE=0.13, p=0.049) and drug use was associated with lower insulin (−0.28 ln insulin units, SE=0.13, p=0.029).

There were no significant between-group differences in CRP (Table 3). Significant independent predictors of CRP included BMI (0.061, SE=0.013, p<0.0001), alcohol use (−0.43, SE=0.17, p=0.013), and drug use (+ 0.41, SE=0.20, p=0.039).

Retinol binding protein was significantly lower in the HCV infected groups compared to the HIV mono-infected group (Table 3). We examined the association between retinol binding protein and insulin resistance in each of the four study groups. There was no significant correlation between insulin resistance and retinol binding protein in any of the four groups in either crude analyses or in multivariate analyses adjusted for BMI (data not shown).

We also examined correlations among insulin resistance, triglycerides and cholesterol in the four groups to see if the presence of HIV or HCV infection altered the associations seen in the healthy controls. As expected, in the healthy control group, insulin resistance was positively associated with higher BMI and triglycerides, and lower HDL cholesterol (Table 4), the pattern typical of insulin resistance in the general population [42]. In contrast, insulin resistance was not associated with BMI, triglycerides or HDL cholesterol in the HCV infected groups. In the HIV mono-infected group insulin resistance was correlated with higher BMI, but not with triglycerides. HCV infection also nullified the correlation between insulin resistance and CRP.

The correlation of triglycerides with cholesterol was also altered in the presence of HIV and/or HCV infection (Table 5). In the healthy controls, triglycerides were significantly associated with higher BMI, total cholesterol, LDL cholesterol and lower HDL cholesterol with correlation coefficients of magnitude 0.30 or greater. The presence of HIV infection attenuated the correlation between trigycerides and LDL. Only total cholesterol was correlated with triglycerides in all four groups.

Discussion

In this study of Hispanic adults, we demonstrate that compared to healthy controls HCV infection is associated with lower levels of total and LDL cholesterol, while HIV infection is associated with lower HDL cholesterol and elevated triglycerides. These results are supported by data in HCV monoinfection, which have demonstrated a rise in total cholesterol after sustained virologic clearance [11,12]. An increase in total cholesterol after HCV eradication has also been demonstrated in HIV/HCV coinfection [13]. On the other hand, these results conflict with other studies that have compared HIV-infected subjects to healthy controls, but did not have data on HCV serostatus [43–46]. Both the Nutrition for Healthy Living study [43] and the Fat Redistribution and Metabolic Change study (FRAM) [44] found lower total and LDL cholesterol in HIV-infected subjects compared to population-based controls. Magny Bergensen et al. [45] found only HAART-naive subjects to have lower total cholesterol than control subjects. In contrast, Joy et al. [46] found higher total cholesterol among HIV-infected subjects. Triglycerides were higher in HIV infection or not different from healthy controls in all studies. The only consistent finding among these studies, including our own, was lower HDL cholesterol in HIV infection. Since intravenous drug users were not excluded from these studies, a possible explanation for the inconsistent findings is confounding due to HCV

infection. However, there were other notable differences. For example, two of these studies [44,46] recruited the HIV infected participants from other clinical metabolic research studies, and included participants on lipid lowering drugs.

Our data agree with previous reports of a mitigating effect of HCV infection on ART-induced hypertriglyceridemia [13,47,48]. Otherwise, HCV infection did not appear to significantly alter triglycerides as evidenced by the similar levels of triglycerides in the HCV mono-infected participants and healthy controls. This agrees with one previous study [49], but is at variance with a study by Flores-Moore et al. [10] who found triglycerides to be lower in HIV/HCV co-infected men compared to HIV mono-infected men.

CRP was also lower in HIV/HCV co-infected men in that study compared to HIV-infected men [10]. This result is similar to the findings from the FRAM study [50] in which, compared to controls, CRP was lower in HIV/HCV co-infected women but not in men, while CRP was higher HIV mono-infected men, but not women. We found no difference in average CRP among the groups. However, in our study, HCV infection attenuated the correlation between CRP and insulin resistance seen in the healthy controls. This suggests that differences in degrees of insulin resistance among the studies may explain the conflicting results. Current intravenous drug use was a significant predictor of elevated CRP in our study, but was not assessed in the studies cited above.

Insulin resistant persons who are not infected by HIV or HCV typically have a lipid profile that includes elevated serum triglycerides, low HDL, and normal LDL [42]. The correlation between insulin resistance and triglycerides, seen in the healthy controls in this study reflects the regulation of triglyceride concentrations by insulin resistance [42]. The presence of hepatitis infection nullified this correlation in both HCV mono-infected and HIV/HCV co-infected persons. Similarly, the established association between triglycerides and LDL cholesterol [42] seen in the healthy controls was not present in the HIV-infected participants. The effect of HCV infection in reducing the response of pro-inflammatory markers also attenuated the correlation between CRP and insulin resistance. Thus, the factors associated with insulin resistance and the metabolic syndrome in the general population, and the interrelations among them, appear to be altered by the presence of HIV and/or HCV infection. This implies that we cannot readily generalize knowledge about the role of insulin resistance and the metabolic syndrome in chronic disease from healthy populations to those that are infected with HIV and/or HCV, and underscores the complexity of these relations. This is especially important as levels of obesity arise in these high-risk populations with corresponding concerns about morbidity due to cardiovascular disease and fatty liver disease.

Since an initial report in 2005 of elevated retinol binding protein in mice and in obese humans with type 2 diabetes [32], there have been over 50 papers published on a possible role for serum retinol binding protein in the pathogenesis of insulin resistance and type 2 diabetes. In many studies, retinol binding protein has been positively associated with factors related to insulin resistance and type 2 diabetes including, weight, waist circumference, percent trunk fat, total and LDL cholesterol, liver fat and serum liver enzymes [32,33,51–54]. However, other studies have failed to show differences in circulating retinol binding protein in relation to insulin resistance or its risk factors [55,56]. In a previous study, retinol binding protein was found be lower in chronic liver disease patients with cirrhosis and unrelated to glucose metabolism [57]. Our data support an important role for HCV infection in determining serum retinol binding protein levels. Our results do not support an association between retinol binding protein and insulin resistance in Hispanics with and without HIV or HCV infection, including healthy Hispanic adults. It is possible that the discrepant results between this and other studies are related to the etiology of insulin resistance and, possibly, the presence of fatty liver.

There are plausible explanations for the attenuation of dyslipidemia by HCV infection that include the intimate relation between HCV replication and lipid metabolism. In the blood, the virus circulates in a HCV-lipoprotein complex [58,59]. Entry of HCV into hepatic cells appears to require receptors involved with lipoprotein metabolism [60–62], including the low-density cholesterol receptor (LDLr). It has been proposed that low circulating levels of free lipids may permit greater viral infectivity by increasing LDLr expression on the hepatocyte cell surface and reducing competition for LDLr by free lipids, thereby allowing easier entry of the HCV-lipoprotein complex into hepatocytes [62]. This is an intriguing hypothesis that merits further examination.

Our study has several strengths and some weaknesses. The distribution of HIV and HCV infection allowed us to examine the independent and joint effects of these infections on dyslipidemia and contrast this to healthy controls. The participants were recruited from the community as opposed to a clinic-based sample to avoid a higher proportion of patients with complicated illness. The healthy control group was of the same ethnic/racial group, was recruited from the same community, and evaluated by the same team using the same instruments. The importance of considering race in attempts to unravel the mechanisms underlying metabolic alterations in HIV infection has been noted previously [17]. While restricting the enrollment to Hispanics favors high internal validity, it may limit the generalizability. The analyses accounted for behavioral factors of importance in lipid profiles, including diet, smoking, and alcohol use. The importance of diet as a determinant of lipid levels in HIV infection has been previously demonstrated [46]. Dietary cholesterol and saturated fat were not significant predictors of any outcome in this study possibly because of uniformity in dietary habits in the cohort, and adjustment for diet was retained in the analyses on principal. In this study, drug use, a factor that has been omitted in many studies, was assessed in detail and accounted for in the analyses. Measures of lipodystrophy were not available in the HIV-infected participants. However, we do not believe that this was an important limitation since there are low rates of visceral adiposity and peripheral lipoatrophy in this cohort [36]. Other limitations include the lack of information on the stage of chronic liver disease in the participants and no information on HCV genotype or HCV viral load. Since, in the USA, HCV genotype 1 is the predominant genotype (93%) [63], and this was a community-based cohort, we expect that the majority of participants were infected with genotype 1.

In conclusion, HCV infection has an important modifying effect on metabolic derangements associated with HIV infection. This suggests that HCV co-infection needs to be considered an important co-factor in all studies of HIV-related insulin resistance and dyslipidemia. It is not yet known how HCV impacts the risk of chronic diseases such as cardiovascular disease and fatty liver disease in persons with HIV infection, though it appears that HCV co-infection has a potentially important modifying role.

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Table 1

Characteristics of the 257 study participants

Characteristic[a]	Group 1 HIV n=47	Group 2 HCV n=43	Group 3 HIV/HCV n=59	Group 4 Healthy n=108	P value
Age, years	41 (9)	38 (9)	42 (9)	37 (11)	0.0037
Male	23 (49)	39 (91)	47 (80)	47 (44)	<0.0001
BMI, kg/m^2	28.8 (8.6)	26.1 (4.4)	26.6 (3.3)	29.3 (6.4)	0.0046
Smoker	25 (53)	42 (98)	46 (77)	53 (49)	<0.0001
Alcohol use	21 (45)	23 (53)	17 (29)	64 (59)	0.0019
Drug use	4 (9)	34 (79)	28 (47)	27 (25)	<0.0001
Dietary saturated fat, g/day	23 (17, 32)	34 (23, 41)	28 (20, 37)	28 (17, 42)	0.039
Dietary cholesterol, g/day	267 (191, 436)	380 (257, 490)	396 (276, 509)	353 (219, 480)	0.030
HIV-infected:					
Years with HIV	9 (4)		12 (5)		0.0058
CD4 cells/uL	404 (229, 661)		285 (195, 574)		<0.0001
HIV RNA ($\log_{10}$ copies/mL)	3.3 (1.1)		3.2 (1.3)		0.86
ART	35 (74)		48 (81)		0.39
PI	10 (21)		27 (46)		0.0086
NRTI	35 (74)		43 (73)		0.85
NNRTI	17 (36)		16 (27)		0.32

[a] Values are mean (SD), number (%) or median (25th, 75th percentile)

BMI, body mass index; ART, antiretroviral therapy; PI, protease inhibitors, NRTI, nucleoside reverse transcriptase inhibitors; NNRTI, non-nucleoside reverse transcriptase inhibitors

Table 2

Metabolic parameters according to HIV and HCV infection status: unadjusted

Characteristic[a]	Group 1 HIV	Group 2 HCV	Group 3 HIV/HCV	Group 4 Healthy	P value[b]
Insulin, mU/L	13 (9, 19)	11 (7, 15)	13 (8, 19)	11 (7, 14)	0.080
Glucose, mg/dL	89 (83, 100)	89 (81, 99)	86 (79, 95)	83 (78, 90)	0.19
HOMA	2.7 (1.8, 4.6)	2.3 (1.5, 3.3)	2.5 (1.6, 4.3)	2.1 (1.4, 3.4)	0.081
Cholesterol, mg/dL	179 (39)	165 (35)	160 (45)	188 (40)	0.0001
LDL, mg/dL	112 (33)	107 (28)	100 (38)	126 (34)	0.0010
HDL, mg/dL	37 (11)	38 (12)	32 (9)	47 (14)	<0.0001
Triglycerides, mg/dL	122 (76, 195)	87 (68, 114)	119 (78, 190)	96 (67, 144)	0.0020
CRP, mg/L	2.6 (0.8, 6.4)	2.7 (0.8, 5.1)	2.7 (0.9, 5.4)	2.3 (0.76, 5.9)	0.95
RBP, mg/L	59 (37, 80)	37 (24, 66)	35 (21, 63)	54 (22, 95)	0.0021

HOMA: Homeostasis model assessment; LDL: low density lipoprotein; HDL: high density lipoprotein; CRP: high sensitivity C-reactive protein; RBP: retinol binding protein

[a] Values are median (25th, 75th percentile) for skewed variables or mean (SD) for normally distributed variables

[b] By F-test

Table 3

Metabolic parameters according to HIV and HCV infection status: multivariate results[a]

Characteristic[b]	Group 1 HIV	Group 2 HCV	Group 3 HIV/HCV	Group 4 Healthy
Insulin (ln mU/L)[c]	2.5 (0.14)	2.6 (0.14)[d]	2.6 (0.12)[d]	2.3 (0.08)
Glucose (ln mg/dL)[c]	4.5 (0.03)[e]	4.5 (0.03)	4.5 (0.03)	4.4 (0.02)
HOMA (ln)[c]	1.0 (0.16)	1.1 (0.15)[f]	1.1 (0.13)[f]	0.74 (0.090)
Cholesterol, mg/dL	178 (6.4)	167 (7.0)[g]	163 (5.6)[g]	187 (4.6)
LDL, mg/dL	111 (6.0)[h]	108 (5.9)[h]	101 (4.8)[h]	124 (5.2)
HDL, mg/Dl	34 (1.8)[ij]	41 (1.8)[i]	33 (1.5)[i, j]	45 (1.6)
Triglycerides, (ln mg/dL)[c]	5.0 (0.09)[k, l]	4.4 (0.10)	4.9 (0.08)[k, l]	4.5 (0.09)
CRP, (ln mg/L)[c]	0.84 (0.19)	0.74 (0.21)	0.69 (0.17)	0.70 (0.14)
RBP (ln mg/L)[c]	4.1 (0.10)[m]	3.5 (0.10)[m, n]	3.6 (0.09)[n]	3.8 (0.11)

HOMA: Homeostasis model assessment; LDL: low density lipoprotein; HDL: high density lipoprotein; CRP: high sensitivity C-reactive protein; RBP: retinol binding protein

[a] Adjusted for body mass index, gender, smoking, alcohol and drug use, dietary cholesterol and saturated fat

[b] Values are multivariate adjusted mean (SE)

[c] Values are transformed on the natural log (ln) scale due to skewed distribution

[d] Group 2 and 3 vs. 4, p=0.036, p=0.023 respectively

[e] Group 1 vs. 4, p=0.075

[f] Group 2 and 3 vs. 4, p=0.029, p=0.021

[g] Group 2 and 3 vs. 4, p=0.023, p=0.0022, respectively

[h] Group 1, 2 and 3 vs. 4, p=0.086, p=0.039, p=0.0020, respectively

[i] Group 1, 2 and 3 vs. 4, p<0.0001, p=0.090, p<0.0001, respectively

[j] Group 1 and 3 vs. 2, p=0.023, p=0.0013, respectively

[k] Group 1 and 3 vs. 4, p=0.0009, p=0.0098, respectively

[l] Group 1 and 3 vs. 2, p=0.0005, p=0.0007, respectively

[m] Group 1 and 2 vs. 4, p=0.081, p=0.065, respectively

[n] Group 2 and 3 vs. 1, p=0.0008, p=0.0003, respectively

Table 4

Correlation [a] of insulin resistance (HOMA) with metabolic parameters

Characteristic	Group 1 HIV	Group 2 HCV	Group 3 HIV/HCV	Group 4 Healthy
BMI	0.54*	0.03	0.16	0.59*
Triglyceride	−0.14	−0.03	0.07	0.40*
Cholesterol	−0.13	−0.11	−0.19	0.05
LDL	−0.01	−0.20	−0.08	0.07
HDL	−0.23	0.10	−0.11	−0.40*
CRP	0.48*	0.12	0.02	0.41*

HOMA: Homeostasis model assessment; LDL: low density lipoprotein; HDL: high density lipoprotein; CRP: high sensitivity C-reactive protein

[a] Correlation coefficient is Spearman's r

* $p<0.05$

Table 5

Correlation [a] of triglycerides with metabolic parameters

Characteristic	Group 1 HIV	Group 2 HCV	Group 3 HIV/HCV	Group 4 Healthy
Cholesterol	0.43*	0.54*	0.34*	0.40*
LDL	<-0.01	0.36*	0.08	0.38*
HDL	−0.18	−0.22	−0.36*	−0.45*
CRP	−0.01	−0.01	−0.18	<-0.01

LDL: low density lipoprotein; HDL: high density lipoprotein; CRP: high sensitivity C-reactive protein

[a] Correlation coefficient is Spearman's r

* $p<0.05$