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rs7903146 Polymorphism at Transcription Factor 7 Like 2 Gene Is Associated with Total Cholesterol and Lipoprotein Profile in HIV/Hepatitis C Virus-Coinfected Patients

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Original Article

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ABSTRACT

Transcription factor 7 like 2 (*TCF7L2*) rs7903146 polymorphism has been associated with metabolic disturbance and cardiovascular disease. The aim of this study was to analyze the association between *TCF7L2* rs7903146 polymorphism and potential disturbances on the lipid profile in human immunodeficiency virus (HIV)/hepatitis C virus (HCV)-coinfected patients. We performed a cross-sectional study on 263 HIV/HVC-coinfected patients. *TCF7L2* polymorphism was genotyped by GoldenGate assay. The analysis was performed by linear and logistic regression under a dominant model of inheritance. The variables analyzed were total cholesterol (TC), high-density lipoprotein (HDL-C), low-density lipoprotein (LDL-C), non HDL-C, and triglycerides. Patients harboring rs7903146 TT/TC genotype showed a diminished concentration of TC ($p=0.003$), LDL-C ($p=0.004$), HDL-C ($p=0.012$), non HDL-C ($p=0.013$); lower percentage of $TC \geq 200$ mg/dL ($p=0.038$) and higher percentage of $HDL \leq 40$ mg/dL ($p=0.023$). In addition, we observed that rs7903146 was differently related to fasting serum lipid levels according to HCV-genotype (HCV-GT). With regard to HCV-GT1 patients, rs7903146 TT/TC genotype was associated with lower levels of HDL-C (adjusted arithmetic mean ratio (aAMR)=0.91; $p=0.049$) and elevated percentage of patients with $HDL-C \leq 40$ mg/dL (adjusted odds ratio (aOR)=3.26; $p=0.003$). For HCV-GT3 patients, rs7903146 TT/TC genotype was associated with lower serum values of TC (aAMR=0.81; $p=0.037$), LDL-C (aAMR=0.67; $p=0.001$), non HDL-C (aAMR=0.75; $p=0.002$) and reduced percentage of $TC \geq 200$ mg/dL (aOR=0.089; $p=0.037$). In conclusion, the *TCF7L2* rs7903146 TT/TC genotype was associated with lower levels of TC, LDL, and HDL in HCV-GT3 patients, and lower levels of HDL-C in HCV-GT1 patients; suggesting a role in the cardiovascular disease and a potential use as biomarker in HIV/HCV-coinfected patients.

Key words: AIDS; chronic hepatitis C; cardiovascular risk; dyslipidemia; SNPs

INTRODUCTION

Chronic hepatitis C (CHC) has become a major cause of morbimortality in human immunodeficiency virus (HIV)/hepatitis C virus (HCV) coinfecting patients in high-income countries (1). An increased risk of dyslipidemia, atherosclerosis and cardiovascular diseases has been associated with the HCV and HIV infections, and also with the specific antiretroviral therapies (2-6). In this way, the HCV infection has been related to steatosis and metabolic abnormalities such as insulin resistance, type 2 diabetes mellitus (T2DM), and dyslipidemia (reductions in total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) (7, 8). The coinfection with HIV modify the natural history of chronic hepatitis C (CHC), generating higher rates of liver steatosis, cirrhosis and end stage liver diseases than HCV monoinfected patients (9, 10). Although the published data suggest that combination antiretroviral therapy (cART) might be beneficial for HIV/HCV-coinfecting patients (10), it has been linked to lipodystrophy, insulin resistance, type 2 diabetes mellitus, and lipid disturbances, including higher levels of TC, LDL-C, and triglyceride (TG); and decreased levels of HDL-C (11-14).

Dyslipidemia is a main risk factor of cardiovascular disease in patients with HIV infection, which is related to cART (15, 16). Thus, the risk of myocardial infarction is proportional to the time of cART (17) and it is also demonstrated that it could be partly explain by the dyslipidemia caused by these drugs (18). In this way, the increased cardiovascular risk is associated particularly with prolonged use of protease inhibitors, which are usually associated with a less favorable lipid profile, in particular elevated TG and TC (15). Moreover, nonnucleoside reverse transcriptase inhibitors show, in general, the best lipid profile of all antiretrovirals because they are associated with an increase in HDL-C and a significant reduction in TC/HDL-C ratio (15). Finally, the effects of nucleoside reverse transcriptase inhibitors on lipids are generally mild and there is a high degree of heterogeneity (11).

The mechanisms leading to lipid disturbances are not completely understood, but there is a growing evidence that genetic background may contribute to individual differences in this pathology (19-21). The *transcription factor 7 like 2* (*TCF7L2*) is located on chromosome 10q25.3. This gene is integrated by 18 exons which suffers alternative splicing regulation. *TCF7L2* is part of the Wnt/ β -catenin signaling pathway, which is involved in glucose homeostasis and lipid metabolism (22). Recently, the rs7903146 (C>T) single nucleotide polymorphism (SNP) located at *TCF7L2* intron 5 region, has been strongly associated with metabolic syndrome (23), type 2 diabetes mellitus (24), dyslipidemia (25) and cardiovascular disease (26, 27) in general population. However, to the best of our knowledge, the effect of *TCF7L2* polymorphism has not been studied in HIV/HCV-coinfecting patients.

The aim of this study was to analyze the association between *TCF7L2* rs7903146 polymorphism and potential disturbances on the lipid profile in HIV/HCV-coinfected patients.

METHODS

Study design and patients

We carried out a cross-sectional study on 263 non-diabetic HIV/HCV-coinfected patients from Hospital Gregorio Marañón (Madrid, Spain) between September 2000 and July 2009. All subjects included in our study were HCV treatment-naïve patients who were potential candidates for HCV therapy.

The inclusion criteria for the study were HIV/HCV-coinfected patients who were over 18 years and HCV treatment-naïve, detectable HCV-RNA by polymerase chain reaction, negative hepatitis B surface antigen, availability of a DNA sample, no clinical evidence of hepatic decompensation, no diabetes mellitus, and stable cART for at least 6 months before study entry or no need for cART according to treatment guidelines used in the study period (28, 29). Patients with active opportunistic infections, pregnant women, active drug and/or alcohol addiction and other concomitant diseases or conditions were excluded. Thus, 495 HIV/HCV coinfected patients met the criteria described above, 293 of them had a DNA sample available for genotyping, but only 263 patients were included in our study (12 patients were excluded due to DNA genotyping errors and 18 due to absence of relevant clinical data). All patients were of European descent.

The study was conducted in accordance with the Declaration of Helsinki and patients gave their written consent for the study. The Institutional Review Board and the Research Ethic Committee of the Instituto de Salud Carlos III (ISCIII) approved the study.

Epidemiological and clinical data

The main clinical and epidemiological data of 263 patients analyzed were obtained from medical records. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters. The duration of HCV infection for patients with a history of intravenous drug use (IDU) was estimated starting from the first year they shared needles and other injection paraphernalia, which are the most relevant risk practices for HCV transmission (30).

Biochemical data

Biochemistry panel was measured by using an autoanalyzer Hitachi 912 (Boehringer Mannheim, Germany) in fasting patients. We collected data of TC, HDL-C, and TG. LDL-C was calculated by Friedewald estimation ($LDL-C = TC - HDL-C - (TG/5)$) (31). Non HDL-C was calculated as TC minus HDL-C (32). The degree of insulin resistance was estimated for each patient by using the homeostatic model assessment (HOMA), according the following formula (33): $\text{fasting plasma glucose (mmol/l)} \times \text{fasting serum insulin (mU/l)} / 22.5$.

Liver biopsy

Liver biopsies were performed on 211 out of 263 patients basis following the recommendations of the Patient Care Committee of the American Gastroenterological Association (34) as we previously described (35). Liver fibrosis and necroinflammatory activity were estimated according to Metavir score as follows: F0, non-fibrosis; F1, mild fibrosis; F2, significant fibrosis; F3, advanced fibrosis; and F4, definite cirrhosis. Activity grade was scored as follows: A0, non-activity; A1, mild activity; A2, moderate activity; A3, severe activity (36).

Genotyping of *TCF7L2* polymorphism

Genomic DNA was extracted from peripheral blood with Qiagen columns (QIAamp DNA Blood Midi/Maxi; Qiagen, Hilden, Germany). DNA samples were genotyped at the Spanish National Genotyping Center (CeGen; <http://www.cegen.org/>) for the rs7903146 (C>T) SNP at *TCF7L2* gene using GoldenGate® assay with VeraCode® Technology (Illumina Inc. San Diego, CA, USA).

Statistical analysis

All statistical tests were performed with the Statistical Package for the Social Sciences (SPSS) 19.0 software (IBM Corp., Chicago, USA). All p-values were two-tailed and statistical significance was defined as $p < 0.05$.

For the description of the study population, p-values were estimated with nonparametric tests: Mann-Whitney U test was used for continuous variables and Chi-square test for categorical variables.

Hardy-Weinberg equilibrium (HWE) for *TCF7L2* rs7903146 polymorphism was assessed by a Chi-square test, considering equilibrium when $p > 0.05$. The genetic association study was carried out under a dominant genetic model for T allele (CT/TT vs. CC), which was the model that best fit our data. On the one hand, lineal regression analyses were used to investigate the association between rs7903146 and continuous outcome variables, which were log₁₀-transformed. This test provides the differences between groups and the arithmetic mean ratio (AMR), which provides us the increase of the value with presence of T allele. On the other hand, logistic regression analyses were used to investigate the association of rs7903146 with categorical outcome variables. This test gives the association between groups through the odds ratio (OR), which indicates the likelihood of having the outcome in the CT/TT genotypes versus CC genotype. Each regression analysis was always adjusted by the most significant co-variables associated with each one of the outcome variables, avoiding the over-fitting of the regression. The co-variables were selected by "Stepwise" algorithm (at each step, factors are considered for removal or entry: a p-value for entry and exit of 0.15 and 0.20,

respectively), including gender, age, body mass index (BMI), nadir CD4+ T-cells, undetectable HIV viral load (<50 copies/mL), time with cART, specific antiretroviral drugs used by each patient (zidovudine, stavudine, didanosine, tenofovir, abacavir, efavirenz, ritonavir, lopinavir, saquinavir and fosamprenavir), HCV viral load $\geq 500,000$ IU/ml and significant fibrosis ($F \geq 2$). Besides, we also included two polymorphisms (*ADIPOQ* rs2241766 and *SLC30A8* rs13266634), which have been related to dyslipidemia in HIV/HCV-coinfected patients, according to two recent studies (20, 21) performed by our group in the same cohort.”

RESULTS

Characteristics of patients

The study included 263 patients, whose epidemiological and demographic characteristics are shown in **Table 1**. There were no significant differences between rs7903146 genotypes (TT/TC versus CC).

Note that patients infected with HCV-GT3 had lower serum values of TC ($p=0.013$), LDL-C ($p=0.014$), and non-HDL-C ($p=0.026$) than patients infected with HCV-GT1 (**Supplemental Figure 1**). Furthermore, liver steatosis was found in higher percentage in HCV-GT3 patients (70.6% (36/51)) than HCV-GT1 patients (52.7% (58/110); $p=0.032$) and HCV-GT4 patients (47.1% (16/34); $p=0.029$).

Frequencies of *TCF7L2* polymorphism

Allele frequencies for the *TCF7L2* rs7903146 polymorphism were 0.64 for C allele and 0.36 for T allele. Genotype frequencies for rs7903146 polymorphism were 0.42 for CC genotype, 0.43 for TC genotype and 0.15 for TT genotype. These frequencies in our dataset were in accordance with data listed on the NCBI SNP database (http://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=7903146). The rs7903146 SNP fulfilled the minimum allele frequency (MAF) >0.05 and displayed less than 5% of missing values. Furthermore, rs7903146 was in Hardy-Weinberg equilibrium ($p=0.396$).

Association of rs7903146 with lipids profile

Patients with rs7903146 TT/TC genotype showed significantly lower TC serum levels ($p=0.003$; **Figure 1A**), LDL-C ($p=0.004$; **Figure 1B**), HDL-C ($p=0.012$; **Figure 1C**), and non HDL-C ($p=0.013$; **Figure 1D**) than CC carriers. When we stratified the patients by HCV genotype, rs7903146 TT/TC carriers infected with HCV-GT3 had diminished values of TC ($p=0.019$; **Figure 1A**), LDL-C ($p=0.013$; **Figure 1B**), and non HDL-C ($p=0.020$; **Figure 1D**).

Patients with rs7903146 TT/TC genotype had diminished percentage of $TC \geq 200$ mg/dL ($p=0.038$; **Figure 2A**) and non HDL-C ≥ 130 mg/dL ($p=0.041$; **Figure 2D**) and elevated percentage of HDL-C ≤ 40 mg/dL ($p=0.028$; **Figure 2C**). When patients were stratified by HCV genotype, rs7903146 TT/TC carriers infected with HCV-GT3 had lower percentage of $TC \geq 200$ mg/dL ($p=0.001$; **Figure 2A**), whereas rs7903146 TT/TC carriers infected with HCV-GT1 had a higher percentage of HDL-C ≤ 40 mg/dL ($p=0.018$; **Figure 2C**).

When adjusted regression was performed (**Table 2**), rs7903146 TT/TC carriers infected with HCV-GT3 were associated with lower values of TC (adjusted AMR (aAMR)=0.81; $p=0.003$), LDL-C (aAMR=0.67; $p=0.001$), non HDL-C (aAMR=0.75; $p=0.002$); and percentage of

TC \geq 200 mg/dL (adjusted OR (aOR)=0.89; p=0.037). An association between rs7903146 TT/TC genotype and diminished levels of HDL-C (aAMR=0.91; p=0.049) and elevated percentage of HDL-C \leq 40 mg/dL (aOR)=3.26; p=0.003) were found in HCV-GT1 patents.

DISCUSSION

In the present study, we evaluated for the first time the impact of the *TCF7L2* rs7903146 polymorphism on serum lipid profile in HIV/HCV-coinfected patients. The major findings were: (i) the rs7903146 TT/TC genotype (T allele) was related to lower fasting serum levels of TC, LDL-C and non HDL-C in HIV patients coinfecting with HCV-GT3; (ii) rs7903146 TT/TC genotype was linked to diminished levels of HDL-C and elevated percentage of patients with HDL-C \leq 40 mg/dL among HIV patients coinfecting with HCV-GT1.

Several reports have analyzed the *TCF7L2* polymorphism association with serum lipid disturbances in non-HIV/HCV-coinfected population, providing discordant results. Thus, the presence of rs7903146 T allele disrupted the lipid metabolism, inducing low levels of HDL-C and apolipoprotein (Apo)-A1 in healthy young men (25), high levels of TG in familial combined hyperlipidaemia patients (37) and atherogenic lipoprotein profile in nonalcoholic fatty liver disease (38). Moreover, rs7903146 T allele has been linked to severity of coronary artery disease, higher death ratio by cardiovascular event and increased cardiovascular risk in non-diabetic individuals (39). In contrast, it has been described that rs7903146 T carriers show a favorable lipid profile with lower TG and higher HDL-C concentration (40). However, other studies did not find significant association between rs7903146 and lipid metabolism (41, 42). These inconsistencies could be due to different study designs (transversal, retrospective, cohorts, etc.), patient characteristics (age, race, etc.), environmental exposure (mainly diet), or underlying comorbidities (polycystic ovary syndrome, metabolic syndrome, type 2 diabetes mellitus, etc).

The cardiovascular risk and atherosclerosis associated to CHC infection have been previously reported. For instance, HCV infection has related with carotid atherosclerosis, coronary artery stenosis and increased carotid intima-media thickness (43). According to the National Cholesterol Education Program Adult Treatment Plan Guideline III (NCEP ATP-III), the evaluation of total cholesterol, triglycerides, lipoproteins and several risk factors are useful to assess the person's risk status for CHD (44). Elevated LDL-C is considered as a major risk factor. For this reason, this is the primary target of cholesterol-lowering therapy. Patients with CHD or equivalent risks should be treated for reaching a LDL <100 mg/dL (44).

Nevertheless, the adequate interpretation of our data in the context of cardiovascular risk in coinfecting patients is complicated, due to interactions between HIV, HCV and cART. For instance: (i) HIV infection is strongly related with lipid disturbances in cART-naïve patients, including reduced levels of TC, HDL-C and LDL-C, and elevated TG levels (45); (ii) cART induces increased levels of TC, LDL-C, and TG (13); (iii) HCV replication depends on lipid metabolism of host cells, which generates an increased lipid cellular content, membrane structures alterations and induces dyslipidemia, mainly represented by low circulating levels of

TC, LDL-C (2, 46) and HDL-C (46). For these reasons, we consider that the multivariate regression with continuous values of TC and lipoproteins could be a better indicator than thresholds to evaluate the impact of TCF7L2 polymorphism on relative cardiovascular risk in HIV/HCV-coinfected patients.

It is previously described that patients with CHC have a lipid profile similar to familiar hypobetalipoproteinemia. These diminished levels on beta-lipoproteins are more commonly present in HCV-GT3 infection than HCV-GT1 (47). These facts are in agreement to our results, which reveal a key role of the rs7903146 polymorphism on beta-lipoprotein metabolism in patients infected with HCV-GT3. We observed that the presence of minor T allele at rs7903146 polymorphism was associated with a favorable cardiovascular profile represented by diminished serum levels of TC, non HDL-C and LDL-C among HCV-GT3 patients. In contrast, the rs7903146 T allele was correlated with lower levels of HDL-C and an elevated percentage of patients with T allele showed HDL-C \leq 40 mg/dL among the HCV-GT1 patients, which is considered as an independent risk factor by NCEP ATP-III (44).

Considering that the presence of the rs7903146 T allele was related with dislipidemia, the genotyping of TCF7L2 rs7903146 polymorphism could help to identify the individuals with lipid disturbances, opening the possibility to implement early treatment for these patients. However, the analysis of rs7903146 T allele for prediction of dyslipidemia according the NCEP ATP-III thresholds revealed a low diagnostic performance [area under the receiver operating characteristic curves (AUC-ROCs) <0.6 (data not shown)]. Thus, the utility of the rs7903146 polymorphism for prediction of dyslipidemia is limited according to our data, even though further extensive clinical research studies will be needed to clarify the impact of this SNP on cardiovascular disease of HIV/HCV coinfecting patients.

Many studies have described the interaction of HIV, HCV infection, and antiretroviral therapy to increase the risk of insulin resistance and T2DM (48, 49), although the mechanisms are not completely understood. Moreover, there is growing evidence that genetic background may contribute to differences between individuals in complex diseases (19, 50). A strong association between T2DM risk and TCF7L2 SNPs was reported by Grant et.al. (51). Next, genetic variations in TCF7L2 (particularly rs7903146) were related to T2DM (52) and glucose metabolism (53, 54). Later, the association between minor T allele of rs7903146 and T2DM was replicated in multiple different populations, as it is shown in independent meta-analyses by Cauchi et al. (55), Luo et al. (56), Tong et al. (57) and Peng et al. (24). Furthermore, T allele has been associated with increased proinsulin/insulin ratio, impaired beta cell function and hyperglycemia (54, 58-60). The participants of the present study were non diabetic HIV/HCV patients, but 34.6% showed insulin resistance (HOMA \geq 3.0). Nevertheless, an exhaustive analysis showed that the rs7903146 polymorphism was not related to HOMA values

in our HIV/HCV coinfecting population (data not shown). This lack of association with glucose metabolism could be due to the limited number of patients used in the stratified analysis, or also to the possible distortive effect of direct and indirect factors related to both HIV and HCV infections, and cART (48). Moreover, we must not discount the fact that our patients had a relatively low BMI (median: 22.5 kg/m²).

The present study has several limitations that must be taken into account for the correct interpretation of the data: (i) this is a cross-sectional study with a limited number of patients, which could limit achieving statistically significant; (ii) lipid disturbances may be caused by several interacting genetic and environmental determinants, being complicated to find the true individual effects of each disease-associated factor; (iii) our study must also be performed in mono-infected and untreated patients in order to evaluate the effect of chronic hepatitis C, HIV infection and cART separately; (iv) our study was carried out entirely in Caucasians, therefore as the allele frequency differs among ethnicities (24), it would be necessary to perform an independent replication of this study in different ethnicities.

CONCLUSIONS

The *TCF7L2* rs7903146 TT/TC genotype was associated with lower levels of TC, LDL, and HDL in HCV-GT3 patients, and lower levels of HDL-C in HCV-GT1 patients; suggesting a role in the cardiovascular disease and a potential use as biomarker in HIV/HCV-coinfecting patients. Nevertheless, we consider that further analyses on a large population are needed to conclusively corroborate these results.

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STATEMENT OF INTERESTS

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Table 1. Clinical and epidemiological characteristics of all HIV/HCV-coinfected patients stratified by *TCF7L2* genotype. Categorical variables were expressed in absolute numbers (%). Continuous variables were expressed in median (percentile 25; percentile 75).

Characteristics	All Patients	rs7903146		(*) p-value
		TT/TC	CC	
N	263 (100%)	152 (57.6%)	111 (42.1%)	-
Male	197 (74.9%)	117 (77%)	80 (72.1%)	0.365
Age, years	40.8 (37.9; 44.7)	41.2 (38.2; 44.7)	40.2 (37.5; 44.8)	0.280
BMI, kg/m²	22.5 (20.9; 24.7)	22.3 (20.8; 24.5)	22.9 (21.5; 25.1)	0.142
BMI ≥25 kg/m ²	61 (23.3%)	33 (21.9%)	28 (25.9%)	0.527
HOMA	2.1 (1.3; 3.7)	2 (1.3; 3.8)	2.3 (1.3; 3.5)	0.215
HOMA ≥3	91 (34.6%)	51 (33.6%)	40 (36%)	0.676
Years since HCV infection	20.9 (14.6; 24.4)	20.7 (15.4; 25.1)	21.7 (17.5; 24.0)	0.904
Prior AIDS	77 (29.3%)	48 (31.6%)	29 (26.1%)	0.337
cART	222 (84.4%)	130 (85.5%)	92 (82.9%)	0.559
Time on cART, years	4.7 (2.9; 7.8)	4.9 (3; 8)	4.7 (2.5; 7.4)	0.235
Current cART protocols,				
Any NRTIs + any PI	64 (24.3%)	37 (24.3%)	27 (24.3%)	0.997
Any NRTIs + PI + NNRTI	3 (1.1%)	2 (1.3%)	1 (0.9%)	0.754
Any NRTIs + any NNRTI	134 (51%)	82 (53.9%)	52 (46.8%)	0.255
Only NRTIs	20 (7.6%)	8 (5.3%)	12 (10.8%)	0.094
Antiretroviral drugs				
Zidovudine	72 (27.4%)	42 (27.6%)	30 (27%)	0.914
Stavudine	67 (25.5%)	38 (25.0%)	29 (26.1%)	0.836
Didanosine	43 (16.3%)	21 (13.8%)	22 (19.8%)	0.193
Tenofovir	72 (27.4%)	43 (28.3%)	29 (26.1%)	0.698
Abacavir	43 (16.3%)	25 (16.4%)	18 (16.2%)	0.960
Efavirenz	80 (30.4%)	48 (31.6%)	32 (28.8%)	0.632
Ritonavir (r)	16 (6.1%)	12 (7.9%)	4 (3.6%)	0.150
Lopinavir/r	32 (12.2%)	17 (11.2%)	15 (13.5%)	0.568
Saquinavir	3 (1.1%)	1 (0.7%)	2 (1.8%)	0.388
Fosamprenavir	6 (2.3%)	3 (2.0%)	3 (2.7%)	0.696
HIV markers				
Nadir CD4+, cells/μL	208 (92.3; 314.8)	191.5 (93.8; 301.5)	228 (83; 349)	0.351
Nadir CD4+ <200 cells/μL	128 (48.7%)	80 (52.6%)	48 (43.2%)	0.132
CD4+ T, cells/μL	462 (338; 667)	464.5 (323.3; 657.8)	461 (363; 684)	0.688
CD4+ ≥500 cells/μL	113 (43.1%)	67 (44.1%)	46 (41.8%)	0.715
HIV-RNA <50 copies/mL	202 (77.1%)	112 (73.7%)	90 (81.8%)	0.122
HCV markers, n (%)				
HCV-GT 1	142 (55.7%)	83 (56.8%)	59 (54.6%)	0.665
HCV-GT 2	5 (2%)	4 (2.7%)	1 (0.9%)	0.299
HCV-GT 3	65 (25.5%)	38 (26%)	27 (24.8%)	0.820
HCV-GT 4	43 (16.8%)	21 (14.4%)	22 (20.2%)	0.221
HCV-RNA ≥500.000 IU/ml	189 (75.3%)	110 (75.9%)	79 (74.5%)	0.809
Metavir score				
Liver biopsy patients	211 (80.3%)	119 (93%)	92 (92%)	0.782
Significant fibrosis (F≥2)	103 (48.8%)	52 (43.7%)	51 (55.4%)	0.092
Moderate activity (A≥2)	108 (51.9%)	56 (47.5%)	52 (57.8%)	0.140

Abbreviations: AIDS, acquired immunodeficiency syndrome; BMI, body mass index; cART, combination antiretroviral therapy; HCV, hepatitis C virus; HCV-RNA, HCV plasma viral load; GT, genotype; HIV, human immunodeficiency virus; HIV-RNA, HIV plasma viral load; HOMA, homeostatic model assessment; IVDU, intravenous drug users; NNRTI, no nucleoside analog reverse-transcriptase inhibitors; NRTI, nucleoside analog reverse-transcriptase inhibitors; PI, protease inhibitors.

Table 2. Summary of adjusted association between rs7903146 TT/TC genotype and lipid profile stratified by HCV genotype in HIV/HCV coinfecting patients.

Concentration ^(a)	All Patients		HCV-GT1		HCV-GT3		HCV-GT4	
	AMR (95% CI)	p-value	AMR (95% CI)	p-value	AMR (95% CI)	p-value	AMR (95% CI)	p-value
TC, mg/dL	0.91 (0.84; 0.97)	0.006	0.93 (0.85; 1.02)	0.133	0.81 (0.70; 0.93)	0.003	0.91 (0.75; 1.01)	0.325
LDL-C, mg/dL	0.88 (0.79; 0.98)	0.016	0.93 (0.81; 1.06)	0.263	0.67 (0.54; 0.84)	0.001	0.85 (0.66; 1.11)	0.227
HDL-C, mg/dL	0.91 (0.84; 0.98)	0.012	0.91 (0.82; 1.00)	0.049	0.89 (0.80; 1.00)	0.052	0.89 (0.76; 1.03)	0.107
Non HDL-C, mg/dL	0.90 (0.82; 0.98)	0.016	0.94 (0.84; 1.05)	0.255	0.75 (0.63; 0.90)	0.002	0.91 (0.71; 1.17)	0.460
TG, mg/dL	0.99 (0.91; 1.10)	0.925	1.00 (0.89; 1.13)	0.970	1.12 (0.96; 1.30)	0.147	0.89 (0.70; 1.11)	0.291
ATP III Classification ^(b)	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
TC≥200 mg/dL	0.49 (0.21; 1.09)	0.079	1.01 (0.34; 2.99)	0.983	0.89 (0.09-0.86)	0.037	0.47 (0.06; 3.38)	0.450
LDL-C≥100 mg/dL	0.77 (0.44; 1.37)	0.374	0.86 (0.40; 1.88)	0.707	0.77 (0.21; 2.83)	0.690	1.72 (0.39; 7.65)	0.475
HDL-C≤40 mg/dL	1.96 (1.15-3.36)	0.014	3.26 (1.49-7.16)	0.003	1.72 (0.53-5.55)	0.364	2.05 (0.41-10.12)	0.380
Non HDL-C≥130 mg/dL	0.61 (0.35-1.07)	0.087	0.71 (0.34-1.47)	0.360	0.62 (0.17-2.21)	0.464	0.61 (0.15-2.45)	0.487
TG≥150 mg/dL	0.59 (0.33-1.04)	0.067	0.72 (0.33-1.55)	0.399	0.27 (0.06-1.23)	0.091	0.16 (0.02-1.30)	0.087

(a), Multivariate lineal regression was performed to compare the serum lipid values, which were log10-transformed; (b), Logistic regression was performed to compare categorical variables. Both tests were adjusted by significant epidemiological and clinical factors [age, gender, BMI, nadir CD4+, CD4+ T cells/μL, HIV plasma viral load, HCV plasma viral load, time on CART, specific antiretroviral drugs and related SNPs]. Statistically significant differences are shown in bold.

Abbreviations: AMR, arithmetic mean ratio (how many times greater is the value in the presence of TT/TC genotype versus CC genotype); OR, odds ratio (likelihood of having the outcome in the CT/TT genotype versus CC genotype); CI, confidence interval; GT, genotype; HCV, hepatitis C virus; HDL-C, High-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

Figure 1. Summary of the unadjusted association between *TCF7L2* rs7903146 and the concentration of serum lipid profile among HIV/HCV-coinfection. Variables were expressed in median (interquartile range). P-values were calculated by univariate linear regressions. Statistically significant differences were shown in bold.

Abbreviations: GT, genotype; HCV, hepatitis C virus; HDL-C, High-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Figure 2. Summary of the unadjusted association between *TCF7L2* rs7903146 and the NCEP ATP-III characteristics among HIV/HCV-coinfection. Variables were expressed in percentages. P-values were calculated by univariate logistic regressions. Statistically significant differences were shown in bold.

Abbreviations: GT, genotype; HCV, hepatitis C virus; HDL-C, High-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Supplemental Figure 1. Serum lipid profile in HIV/HCV coinfecting patients according to HCV genotype. Variables were expressed in median (interquartile range). P-values were calculated by Mann Whitney U test. Statistically significant differences were shown in bold.

Abbreviations: GT, genotype; HCV, hepatitis C virus; HDL-C, High-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.