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## Relationship between hepatitis C virus (HCV) and insulin resistance, endothelial perturbation, and platelet activation in HIV–HCV–coinfected patients under highly active antiretroviral treatment

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**Abstract** Insulin resistance is associated with highly active antiretroviral therapy in HIV-infected patients, and the risk of developing insulin resistance is increased in hepatitis C virus (HCV)-infected patients. The aim of the present study was to determine whether hepatitis C virus infection constitutes an additional risk factor for insulin resistance or other prothrombotic conditions in HIV–HCV–coinfected patients under highly active antiretroviral therapy. One hundred eighteen HIV-infected patients were studied: 50 who had no history of anti-HIV treatment and 68 who were receiving therapy with highly active antiretroviral treatment. The treatment-naïve group consisted of 35 HCV-negative subjects and 15 HCV-positive ones. Within the treated group, 50 patients were HCV negative and 18 were HCV positive. For each patient, the lipid profile was determined and the following values measured: glucose, soluble P-selectin (as a marker of platelet activation), soluble thrombomodulin, von Willebrand factor and soluble vascular cell adhesion molecule-1 (as endothelial markers), and insulin resistance. No significant difference ( $p>0.05$ ) for any variable was found among subjects with or without HCV coinfection in the treatment-naïve group. Among patients under highly active antiretroviral therapy, however, those with HCV coinfection showed higher values ( $p<0.05$ ) for insulin resistance

(homeostasis model assessment value: 2.65 vs. 1.79), glucose (93 vs. 86 mg/dl), endothelial markers (von Willebrand factor, 204 vs. 123%; soluble vascular cell adhesion molecule-1, 650 vs. 482 ng/ml), and platelet activation marker (soluble P-selectin, 78 vs. 51 ng/ml) in parallel with lower CD4+ cells counts (289 vs. 402 cells/mm<sup>3</sup>) and higher HIV-1 viral loads (305 vs. 50 copies/ml) compared to patients without HCV coinfection. Glucose, soluble P-selectin, and von Willebrand factor were independently related to HCV infection. The presence of HCV coinfection during HIV treatment was closely related to higher values of insulin resistance, to activated platelets, and to endothelial perturbation in parallel with lower CD4+ cell counts and higher HIV-1 viral loads compared to patients without HCV coinfection. On the basis of these results, it may be preferable to treat HCV infection prior to initiating treatment for HIV infection in HIV–HCV–coinfected patients.

### Introduction

The use of highly active antiretroviral therapy (HAART) in HIV-infected patients has helped to reduce the high mortality and morbidity caused by opportunistic infections, but potentially adverse consequences of long-term exposure to antiretroviral agents have become an increasing cause for concern [1–3]. The major long-term toxic sequelae associated with HAART include bone disease; nucleoside analogue-associated noxious effects such as neuropathy, hepatic steatosis, and lactic acidosis; and metabolic complications such as dyslipemia, abnormal fat distribution, insulin resistance (IR) and overt diabetes mellitus (especially with protease inhibitor use) [4–8]. The metabolic complications seen in HAART-treated patients seem to indicate that HIV-infected patients under HAART therapy constitute a group with a potentially elevated risk of prothrombotic complications. The need to switch to another drug to minimize the adverse effects of HAART, the development of abnormal fat distribution (android

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distribution) under HAART, and poor patient compliance with HAART all represent different forms of treatment failure.

The exact mechanism through which HAART induces certain complications is not completely understood. Besides environmental and hereditary factors, other factors such as HIV itself, immune reconstitution, or unknown components and/or agents may play a role, predisposing some patients to develop, sooner or later, metabolic complications, especially insulin resistance [9–11].

Endothelial dysfunction is the first step in the development of early atherosclerosis [12]. Several studies confirm that elevated plasma levels of endothelial markers, such as von Willebrand Factor (vWF), soluble vascular cell adhesion molecule-1 (sVCAM-1), and soluble thrombomodulin (sTM), may serve as molecular markers for atherosclerosis and are independent risk factors for the development of coronary heart disease [13, 14]. Endothelial cell perturbation is present in HIV infection and may be a consequence of different factors such as HIV-1 viral load, high plasma levels of proinflammatory cytokines, and advanced opportunistic diseases [15].

Chronic infection with hepatitis C virus (HCV) is associated with autoimmune manifestations and has been described largely in the context of the development of insulin resistance and type-2 diabetes [16–18]. Coinfection with HCV is common among HIV-infected patients, especially among those who engage in intravenous drug use, with rates of coinfection in drug users reaching up to 98% (own data). HIV–HCV coinfection has been widely studied because of the interactions between the two viruses. Rapid progression to AIDS has been described in HIV–HCV–coinfected patients [19, 20], as have higher rates of fibrosis and cirrhosis [21, 22]. The role of HCV coinfection in the development of certain metabolic complications or in the response to antiretroviral treatment in HIV patients remains uncertain and incompletely studied [23, 24].

The aim of this study was to evaluate the associations between HCV infection and insulin sensitivity, serum lipids, endothelial markers, platelet markers, immunological status, and HIV viral load in a population of HIV-infected patients with and without HCV coinfection, comparing patients without prior anti-HIV treatment with those under HAART.

## Materials and methods

### Patients

We designed a cross-sectional study that included 118 patients infected with HIV-1. Of these, 50 had no history of any antiretroviral treatment (HAART-naïve group) and 68 were under HAART (HAART group), with the latter group having a median treatment length of 12 months (4–24 months). The HAART-naïve group consisted of 35 HCV-negative and 15 HCV-positive subjects. Within the HAART group, 50 patients were HCV negative and 18 were HCV positive. Seventy percent of the patients under

HAART had received protease inhibitors, and there were no statistical differences with respect to type and duration of HAART between HCV-positive and HCV-negative patients in the HAART group. The diagnosis of HCV infection was made using a serological test. Subjects were excluded if they were pregnant, less than 18 years of age, or had any of the following: an absolute neutrophil count of less than 100 cells/mm<sup>3</sup>, a hemoglobin level of less than 10 g/dl, active coinfection with other hepatotropic viruses, advanced liver disease or cirrhosis, active pancreatitis, or a history of anabolic treatment during the previous 6 months. None of the patients had ischemic heart disease, diabetes mellitus, or hypertension, and none had been abusing alcohol or drugs or had received previous treatment for HCV infection. Patients who had primary HIV infection or ongoing opportunistic infections were also excluded. Informed consent was obtained from each patient before inclusion in the study, and the hospital's ethical committee approved the protocol.

### Blood samples

Blood was obtained by clean venipuncture and collected into plastic tubes containing sodium citrate (ratio 9:1). After double centrifugation at 2,500×g for 15 min, platelet-poor plasma was immediately stored at –40°C. To prepare sera, blood collected into tubes was allowed to clot at 37°C and then centrifuged at 1,500×g. Sera were stored at –40°C until use.

### Laboratory studies

Fasting plasma glucose was assayed by a glucose-oxidase test (Randox Laboratories, Crumlin, UK). Serum insulin was measured by microparticle enzyme immunoassay (MEIA, Abbott, Chicago, IL, USA), and insulin resistance was estimated by homeostasis model assessment (HOMA). Definitive methods to assess insulin sensitivity and secretion are complicated, expensive, and difficult to apply. HOMA has been proposed as a method to assess insulin resistance by measuring fasting plasma glucose and insulin concentrations. The HOMA model may provide a useful additional tool to assess the risk of diabetes [ $HOMA = \text{fasting insulin } (\mu\text{U/ml}) \times \text{fasting glucose } (\text{mmol/l}) \div 22.5$ ]. Triglyceride serum levels were measured by enzymatic methods (Vitros 250 System; Ortho Clinical Diagnostics, Rochester, NY, USA). Low-density lipoprotein (LDL) cholesterol serum levels were measured by enzymatic methods (following pretreatment of the sample) (Biosystems, Barcelona, Spain). Plasma levels of soluble vascular cell adhesion molecule-1 (sVCAM-1) and soluble thrombomodulin (sTM), both considered markers of endothelial activation, were evaluated by enzyme immunoassays (Human sVCAM-1 Immunoassay; R&D Systems, Minneapolis, USA, and Asserachrom Thrombomodulin; Diagnostica Stago, Asnières, France, respectively). Plasma levels of von Willebrand factor (vWF), another endothelial

marker, were measured by immuno-turbidimetric assay (Liatest; Diagnostica Stago). Plasma levels of soluble P-selectin (sP-selectin), a marker of platelet activation, were evaluated by enzyme immunoassay (R&D Systems). All sera and plasma samples were thawed only once in a water bath at 37°C for 15 min before testing.

### Clinical data

We recorded CD4+ cell counts (flow cytometry) and plasma HIV viral loads (measured by branched DNA [bDNA], Versant HIV-1 RNA 3.0 Assay; Bayer, Tarrytown, NY, USA). Body mass index (BMI, weight/height<sup>2</sup>) was calculated for all patients. We also recorded age, sex, risk behavior, duration of HIV infection, status of HIV infection (A or B or C) according to the Centers for Diseases Control and Prevention (CDC), duration and type of HAART, and status of HCV infection.

### Statistical analysis

Statistical analysis was performed using SPSS for Windows (SPSS, Chicago, IL, USA). Since data were not distributed normally, they were reported as median values and quartiles (25 and 75%). Nonparametric tests (Mann-Whitney *U* test and Kruskal-Wallis test) were used to compare quantitative data, and the chi-square test was used to compare proportions. A regression binary logistic analysis based on forward linear regression was used to establish associations between HCV and a series of preselected items in HIV-HCV-coinfected patients under HAART.

## Results

BMI values, sex distribution, age, and status of HIV infection were similar for all four groups of HIV-infected patients (Table 1). As shown in Table 2, no significant differences were found among subjects in the HAART-naïve group, with or without HCV infection, for all variables evaluated. Among subjects under HAART,

however, HCV-positive patients showed higher levels of insulin resistance (HOMA values), glucose, sVCAM-1 and vWF (markers of endothelial activation), and sP-selectin (marker of platelet activation), together with lower CD4+ cell counts and higher HIV viral loads compared to HCV-negative patients. However, there were no significant differences in triglyceride or LDL cholesterol values.

Multivariate analysis was used to assess the characteristics associated with HCV infection in the HAART group. We considered all variables that presented statistical differences as independent variables: HOMA, glucose level, CD4+ cell count, HIV viral load, sP-selectin level, and sVCAM-1 and vWF levels. Glucose (OR=1.103, *p*=0.036; 95% confidence interval [CI] 1.006–1.209), sP-selectin (OR=1.022, *p*=0.0058; 95%CI 0.999–1.045), and vWF (OR=1.016, *p*=0.007; 95%CI 1.004–1.028) levels were independently related to HCV infection. No significant association was found between HCV infection and insulin resistance status, CD4+cell count, HIV viral load, or sVCAM-1 level.

## Discussion

HIV-HCV-coinfected patients under HAART clearly showed higher levels of glucose, insulin resistance, HIV viral load, endothelial activation markers, and platelet activation marker as well as lower CD4+ cell counts compared to patients with only HIV infection. Among HIV patients under HAART, hyperglycemia, endothelial perturbation, and platelet activation were independent factors closely associated with HCV coinfection.

In several studies before the HAART era, HCV infection showed a limited effect on the progression of HIV disease. However, studies conducted since the HAART era began have presented conflicting results [19–24]. Our study showed lower CD4+ cell counts and higher HIV viral loads in HIV-HCV-coinfected patients under HAART compared with HAART patients infected with HIV alone. Some studies have reported that HIV-infected subjects with HCV coinfection experience a delay in the CD4+ response, despite treatment to suppress HIV [25, 26]. Cytokine deregulation associated with HCV infection, direct infection

**Table 1** Clinical data of HIV-infected patients. Data are given as number of cases or median and quartiles (25 and 75%)

Characteristic	HAART-naïve group		HAART group		<i>p</i> value
	HCV negative ( <i>n</i> =35)	HCV positive ( <i>n</i> =15)	HCV negative ( <i>n</i> =50)	HCV positive ( <i>n</i> =18)	
Male/female	20/15	10/5	36/14	15/3	0.054*
Age in years	35 (29–39)	35 (29–42)	37 (32–42)	37 (32–40)	0.402**
BMI (kg/m <sup>2</sup> )	24.4 (21.7–26.4)	23.9 (21.6–29.5)	23.6 (21.8–26.4)	23.8 (21.3–27.4)	0.907**
CDC category for HIV infection					0.054*
A+B	30	9	38	10	
C	5	6	12	8	

HAART highly active antiretroviral therapy, BMI body mass index, CDC Centers for Diseases Control and Prevention

\*Chi-square test

\*\*Kruskal-Wallis test

**Table 2** Comparison of lipid profile and immunological, hemostatic, and prothrombotic parameters between HAART-naïve and HAART patients with or without HCV coinfection

	HAART-naïve group		<i>p</i> value	HAART group		<i>p</i> value*
	HCV negative	HCV positive		HCV negative	HCV positive	
LDL cholesterol (mg/dl)	93 (76–128)	85 (64–100)	0.200	144 (106–186)	139 (83–154)	0.310
Triglycerides (mg/dl)	121 (80–159)	124 (105–233)	0.300	181 (120–243)	224 (145–379)	0.130
Glucose (mg/dl)	88 (80–95)	94 (84–102)	0.156	86 (79–93)	93 (87–104)	0.006
HOMA value	2.10 (1.30–2.70)	2.13 (1.10–4.07)	0.949	1.79 (1.26–2.90)	2.65 (1.71–5.14)	0.022
CD4+ count (cells/mm <sup>3</sup> )	298 (191–430)	240 (84–398)	0.125	402 (309–595)	289 (200–447)	0.057
Viral load (copies/ml)	113,942 (50,684–413,628)	83,393 (25,000–234,569)	0.553	50 (25–400)	305 (50–35,902)	0.019
sP-Selectin (ng/ml)	62 (45–85)	43 (33–70)	0.092	51 (40–63)	78 (52–101)	0.001
sVCAM-1 (ng/ml)	680 (516–860)	680 (577–882)	0.568	482 (414–601)	650 (463–836)	0.003
vWF (%)	166 (120–224)	170 (136–264)	0.253	123 (104–179)	204 (140–299)	0.003
sTM (ng/ml)	45 (35–53)	50 (35–55)	0.490	45 (39–58)	51 (44–59)	0.231

Data are shown as median and quartiles (25 and 75%)

HAART highly active antiretroviral therapy, LDL low-density lipoprotein, HOMA homeostasis model assessment, sP-selectin soluble P-selectin, sVCAM-1 soluble vascular cell adhesion molecule-1, vWF von Willebrand factor antigen, sTM soluble thrombomodulin

\*Mann–Whitney *U* test

of CD4+ T cells by HCV, persistent immune activation, and/or direct lymphocyte apoptosis may impair immune recovery despite adequate control of HIV. Furthermore, HCV coinfection is an independent risk factor for the development of severe hepatotoxicity under HAART [27]. In view of these points, several authors have considered the possibility of treating HIV–HCV coinfection with anti-HCV therapy prior to HAART, and the results seem to be promising [28].

Besides the poorer immunological and virological response to the HCV coinfection in HIV–HCV–coinfected patients under HAART, there are other factors to be considered. Our HIV–HCV–coinfected patients under HAART showed the highest levels of insulin resistance and glucose, although only hyperglycemia remained independently related to the HCV infection. Contrarily, HAART-naïve HIV-infected patients did not show any significant differences in HOMA or glucose values in relation to HCV status. Recently, Shintani et al. [29] used transgenic mouse models that specifically express the HCV core protein at high levels in hepatocytes. At a young age, mice developed insulin resistance before the development of steatosis, which finally led to the development of type-2 diabetes. This study has made a major contribution by showing that insulin resistance can be induced by HCV infection. Other recent publications [24, 30] showed that both HCV infection and the use of protease inhibitors appeared to increase the risk of new-onset hyperglycemia during HAART. Both of these factors were independent of other risk factors for hyperglycemia such as age, race, and BMI. In our cohort, only patients under HAART showed differences in HOMA and glucose values, raising speculation about the possibility of a synergistic effect of both HAART and HCV infection on glucose homeostasis. There is evidence of a close association between coronary atherosclerosis and both impaired glucose tolerance and insulin resistance.

Endothelial dysfunction and inflammation represent important components in the genesis of atherosclerosis [12, 31, 32]. In the current study, it was possible to show that some endothelial markers were associated with the presence of HCV infection. In fact, our HIV–HCV–coinfected patients under HAART showed the highest values of vWF, and indeed, vWF was independently related to HCV infection. The same group of patients showed high sVCAM-1 values as compared with patients infected with HIV alone. Chronic inflammation, the presence of cryoglobulinemia (which is very common and rather often associated with rheumatoid factor), and persistent liver injury associated with HCV infection may play a role in disturbing the endothelium [33].

Another interesting finding was the high level of platelet activation marker (sP-selectin) seen in HIV–HCV–coinfected patients under HAART. Increased platelet activation is well known to represent a potential risk factor for thrombotic complications. Indeed, we showed that activated platelets were independently related to HCV infection. Moreover, our previous work showed a relationship between sP-selectin values and levels of PAI-1, another indirect marker of insulin resistance [34].

One of the limitations of our study is that HOMA is a mathematical modeling tool for assessing insulin sensitivity based on a single fasting glucose or insulin value, which may correlate poorly with a direct measurement of insulin sensitivity at lower BMI ranges (BMI<25) [35]. Therefore, since our study groups are relatively small, results are preliminary.

As a whole, the presence of HCV coinfection during HIV treatment was closely related to higher values of insulin resistance, activated platelets, and endothelial perturbation in parallel with lower CD4+ cell counts and higher HIV-1 viral loads than those observed in patients without HCV coinfection. Some of these findings could indicate therapy failure; however, if that is not the case, the results indicate that HCV coinfection may confer a strong

risk for thrombotic complications. The possibility to treat HCV infection before treating HIV infection appears to be very attractive. In addition, strategies to prevent venous and/or arterial thrombotic disease from developing in these patients should be considered, as is done in the case of other risk groups. Prospective studies will be necessary to clarify some of these uncertainties.

A new challenge will be to determine an optimal HCV treatment strategy for HIV–HCV–coinfected patients based on the HCV genotype, hepatic fibrosis, HCV viral load, CD4+ cell counts, and familial or personal history of diabetes, dyslipemia, or thrombosis. Even at present, some concern still remains about which HIV–HCV–coinfected patients should be treated and how and when they should receive therapy. Further studies to provide detailed information are needed to resolve a very complicated issue.

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