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Metabolic abnormalities and liver stiffness evaluated by Transient Elastography in HIV and HIV/HCV coinfected patients

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Metabolic abnormalities and liver stiffness evaluated by Transient Elastography in HIV and HIV/HCV coinfected patients

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Metabolic abnormalities and liver stiffness evaluated by Transient Elastography in HIV and HIV/HCV coinfected patients

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Abstract

Background

Hepatitis C Virus (HCV) infection is highly prevalent among HIV infected patients. Liver disease and metabolic complications are the major concerns about their management and the main causes of morbimortality. It is still not fully understood how the presence of coinfection affects the metabolic profile and the natural history of the liver disease.

Methods

Retrospective cohort study including 299 adults under combined antiretroviral therapy (cART) (236 HIV monoinfected and 63 HIV/HCV coinfected patients). Insulin Resistance (IR) was defined as HOMA-IR≥2. Coinfected patients were divided into 4 groups according to the presence of fibrosis defined by Liver Stiffness (LS): 1) absence of significant fibrosis, if LS≤6.0 kPa; 2) undetermined fibrosis, if 6.0<LS<9.0 kPa; 3) significant fibrosis, if 9.0≤LS<14.6 kPa; 4) cirrhosis, if LS≥14.6 kPa.

Results

HIV/HCV coinfected patients presented lower body mass index, waist circumference, hypertension and lipid levels in comparison to HIV mono-infected patients. Glucose metabolism parameters did not differ according to HCV serostatus and IR was found in approximately half of the patients in both groups.

In HIV/HCV coinfected patients, fibrosis grade was associated with differences in non-nucleoside reverse transcriptase inhibitors (NNRTI) use, duration of HCV infection and HCV genotype. Regarding metabolic characteristics, higher glutamic oxaloacetic transaminase (GOT) levels and lower total cholesterol (TC), non-high density lipoprotein cholesterol (Non-HDL-C) and albumin were observed in the presence of liver fibrosis.

NNRTI, TC, GOT(ln), albumin, glucose(ln) and age were included in the linear regression for LS. TC [β=-0.038 (-0.074;-0.001)] and albumin [β=-0.896 (-1.191;-0.602)] were found to be inversely associated with LS.

Conclusions

HIV/HCV coinfection was associated with better metabolic profile than HIV monoinfection, except for insulin resistance that was similar in both groups. Total cholesterol and albumin were independently and inversely associated with liver stiffness.

Keywords

HIV; HCV; Coinfection; Liver stiffness; Liver fibrosis; Insulin resistance; HOMA; Dyslipidemia

Background

Hepatitis C Virus infection has an extremely high prevalence among Human Immunodeficiency Virus (HIV) infected patients, affecting 4 to 5 million people worldwide [1]. In the setting of HIV/HCV coinfection, rapid rates of fibrosis progression were observed [2] and end-stage liver disease is now the primary cause of death among patients under cART [3].

HIV/HCV coinfection pathogenesis is still not fully understood. Both HIV and HCV infections give rise to glucose and lipid disorders, bringing up to discussion how the presence of coinfection influences the metabolic status. Metabolic changes in HIV/HCV coinfected patients have been associated with accelerated progression of liver

disease, lower rates of response to anti-HCV therapy as well as cardio and cerebrovascular complications [4, 5].

As a result, the development of measures that may slow down the progression of HCV related liver disease should be a priority [3]. Earlier recognition of these metabolic changes may be an important step to allow an improved therapeutic approach, both to the viral infection and to the metabolic diseases [6].

Staging and monitoring liver fibrosis is a key concern in the management of coinfected patient, which requires a tool that is reliable, relatively inexpensive and accurate. Transient Elastography (TE) is a non-invasive test to assess liver fibrosis by measuring liver stiffness, validated to predict significant fibrosis and cirrhosis in HIV/HCV coinfected patients. Besides avoiding the complications inherent to liver biopsy, it also outgrows the latter in terms of sampling errors, inter-observer variability and acceptance by the patients [7, 8].

The aim of this study was to evaluate the prevalence of clinical and metabolic parameters, comparing HIV monoinfected with HIV/HCV coinfected patients and to identify the factors associated with significant liver fibrosis, assessed by TE in HIV/HCV coinfected patients.

Methods

Subjects

As part of a cross-sectional study, 299 non-institutionalized HIV infected Caucasian adults under cART followed in the Infectious Diseases and Endocrinology Out-patient Clinic of Centro Hospitalar de São João were included: 236 HIV monoinfected and 63 HIV/HCV coinfected patients. Only the coinfected patients who had a TE evaluation from 2013 were included. Patients with a previous diagnosis of

diabetes or hepatitis B were excluded. The study protocol was approved by the Hospital Ethics Committee and all patients provided informed consent.

Clinical assessment

For each patient, the following information was collected using a standardized protocol: demographic data (age, gender), duration of HIV and HCV infection, duration of cART, history of hypertension, use of antihypertensive or lipid lowering drugs and alcohol use. Weight, height, waist circumference and resting blood pressure were measured as previously described [9].

A venous blood sample was drawn after a 12-hour overnight fast. All the samples were analyzed at the central laboratory of our hospital. Plasma glucose, insulin, GOT, glutamic pyruvic transaminase (GPT), gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), albumin, platelets, total cholesterol (TC), high density lipoprotein cholesterol (HDL-C) and triglycerides (TGL) were determined using automatic standard routine enzymatic methods. The CD4+ cell count was determined by flow cytometry and plasma RNA-HIV and RNA-HCV were measured by a quantitative reverse transcriptase polymerase chain reaction (PCR), which had a lower limit of detection of 50 copies/mL. HCV infection was diagnosed by the presence of serum antibodies against HCV (RIBA test) and detectable serum HCV RNA PCR.

Insulin resistance

Insulin resistance was defined by the homeostasis model assessment of insulin resistance (HOMA-IR) and insulin sensitivity by the quantitative insulin sensitivity check index (QUICKI). These indexes were calculated by the following formulas: HOMA-IR index = (fasting plasma insulin [mU/L] x fasting plasma glucose [mg/dL])/450 [10]. QUICKI = 1/[log (fasting insulin [mU/L]) +log (fasting plasma glucose [mg/dL])

[11]. A threshold of HOMA-IR≥2 was considered as the clinical definition of significant IR in our study [12, 13].

Liver fibrosis

Liver fibrosis was determined by Transient Elastography (Fibroscan®, Echosens, Madrid), according to the standardized technique, by a trained physician, and results were expressed as the median value of acquisitions in kilopascals (kPa). At least 10 valid measurements were obtained for each patient. To guarantee the validity of TE results, we considered for analysis only the examination with an interquartile range (IQR) below 30% of the median value and a success rate of acquisitions above 60% [14].

LS ≥ 9.0 kPa for the presence of significant liver fibrosis shows a positive predictive value of 87% for Metavir fibrosis index F≥2. To discard F of 2 and above, a cut-off of 6.0 kPa shows a negative predictive value of 90% [15]. LS higher than 14.6 kPa for the presence of liver cirrhosis shows positive and negative predictive values of 86% and 94%, respectively [16]. According to these values, four groups were defined: 1) without significant fibrosis, if LS≤6.0 kPa; 2) undetermined fibrosis, if 6.0<LS<9.0 kPa; 3) significant fibrosis, if 9.0≤LS<14.6 kPa; 4) cirrhosis, if LS≥14.6 kPa.

Statistical analysis

Data were presented as mean and standard deviation (SD) for quantitative variables when normally distributed or as median and respective 25^{th} and 75^{th} percentiles when the variable distribution was different than the normal. For comparison between quantitative variables Student-t test and the Mann-Whitney test were used when appropriate. Categorical variables were described as counts and proportions, and compared using the chi-square or Fisher's exact test. Pearson's correlation and Spearman's non-parametric rank correlation were used to assess the association between

LS and metabolic parameters, according to the variable distribution In order to assess the independent associations between the established metabolic and clinical characteristics and LS, multivariable linear regression models were computed and β coefficients and respective 95% confidence intervals (95% CI) were estimated.

Statistical analysis was performed using the SPSS version 21.0 software (SPSS Inc., Chicago, Illinois, USA). All probabilities were two tailed and p values < 0.05 were regarded as significant.

Results

A total of 299 patients under cART were included in the study, 236 with HIV monoinfection and 63 with HIV/HCV coinfection. The main characteristics of HIV and HIV/HCV infected patients are summarized in Table 1. Coinfected patients were more often males. Age was similar in both groups. Coinfected patients presented longer HIV infection and cART cumulative exposure, as well as lower CD4 cell count. Suppressed HIV RNA replication was similar in both groups. In terms of cART regimen, HIV monoinfected patients had higher use of nucleoside reverse transcriptase inhibitors (NRTI) but the use of protease inhibitors (PI) or non-nucleoside reverse transcriptase inhibitors (NNRTI) was not statistically different between groups. The groups did not differ in terms of reported alcohol use.

Among the coinfected group, genotype 1 VHC infection was the most common (69.8%), mean duration of HCV infection was 10.6 ±5.1 years and median HCV RNA load was 6.04 (5.38-6.61) $\log10^{3}$.

Metabolic profile according to HCV serostatus

Metabolic profile in HIV and HIV/HCV coinfected groups is described in Table 2.

HIV monoinfected patients had higher body mass index (BMI), waist circumference and more prevalence of hypertension and antihypertensive medication use.

A more aterogenic lipid profile was also found in this group: higher levels of total cholesterol, low density lipoprotein cholesterol (LDL-C), Non-HDL-C and triglycerides (TGL), as well as greater use of antidyslipidemic therapy. No differences were found in high density lipoprotein cholesterol (HDL-C).

Hepatic profile was less favourable in HIV/HCV coinfected patients, characterized by higher serum levels of GOT, GPT, GGT and ALP. Both albumin and platelet count were lower in this group.

No differences were found between the groups in glucose metabolism parameters except for fasting glucose that was higher in the HIV monoinfected patients. IR was present in 44.5% and 50.8% of HIV monoinfected and HIV/HCV coinfected patients, respectively.

Absence vs Presence of Significant Liver Fibrosis

The main characteristics of HIV/HCV infected patients according to liver fibrosis stage are summarized in Table 3.

None of the epidemiologic HIV related characteristics were significantly different between groups of liver fibrosis. Fibrosis grade was associated with differences in NNRTI use and HCV genotype but no differences were found for other HCV related characteristics.

Metabolic profile according to Liver Fibrosis Stage

None of the clinic, lipid, hepatic and insulin resistance parameters mentioned above varied in the presence of significant liver fibrosis, with exception of GOT, TC, Non-HDL-C and albumin. LDL-C was marginally different between groups. No differences were found between the groups in terms of the glucose metabolism parameters (Table 4). TC, LDL-C, Non-HDL-C, glucose and albumin were negatively correlated with LS (Table 5).

Association between clinical and metabolic characteristics and Liver Stiffness

All factors previously significantly associated with LS in HIV/HCV coinfected patients, namely NNRTI, TC, GOT(ln), albumin and glucose(ln) were included in the model. Age was also included as a potential confounder. Among those, TC [β=-0.038 (95%CI: -0.074;-0.001)] and albumin [β=-0.896 (95%CI: -1.191;-0.602)] were inversely associated with LS (Table 6).

Discussion

Metabolic profile

HIV infected and cART exposed individuals are at increased risk for hyperglycaemia, insulin resistance and type 2 diabetes mellitus (T2DM), given to direct HIV effect on the pancreas, cART associated lipodystrophy, PI's effects on GLUT4 and NRTI induced mitochondrial toxicity [17, 18].

Glucose metabolism disturbances, ranging from IR to overt Diabetes Mellitus (DM), are also a common comorbid condition in those with HIV/HCV coinfection [19]. Nevertheless, HCV infection relevance as risk factor for T2DM is somewhat less clear in this group [20]. Previous studies found an association between HCV infection and

risk of incident diabetes in HIV patients under cART, but failed to find it when controlled for traditional risk factors and cART exposure [17, 21], strengthening the hypothesis of HCV having a permissive rather than a direct effect on the development of diabetes. On the contrary, Jain et al described that HCV related DM may have a different phenotype, as individuals who were young, lean and had no family history were twice as likely to have DM [19]. HCV is thought to have a direct role in IR development through changes in insulin signalling, glucose entry into the cell and reduced expression of PPARα, and an indirect role due to hypersecretion of proinflammatory cytokines and endoplasmic reticulum stress [17, 22]. On the other hand, given that liver and endocrine disorders have a bidirectional relationship, more severe liver disease may also play a part in the pathogenesis of IR [19, 22]. IR was present in more than a half of HIV/HCV coinfected cohort, with 50.8% having a HOMA-IR≥2 and 17.5% having very high levels of insulin resistance (HOMA-IR≥4).

Similar values of HOMA-IR, QUICKI and fasting insulin were found between groups though coinfected patients presented lower BMI and waist circumference and less frequent use of NRTI combinations, previously described as confounders in this setting [17, 20, 21]. Anthropometric parameters, preponderant risk factors for IR in the general population, might explain why HIV monoinfected patients had higher fasting glucose in this cohort. Conversely, coinfected patients were more often males and had longer exposure to cART, which are also recognized as independent factors for IR development [18, 20]. Other aggravating determinants, such as older age and PIs use, did not differ significantly between groups [18, 20].

In HIV infected patients receiving cART, there is a high but variable prevalence of hyperlipidemia across the studies, which we also found in this cohort: increased TC,

LDL-C and TGL, and decreased HDL-C, given to HIV infection itself, low grade inflammation, lipodystrophy and antiretroviral molecules [18].

There is growing evidence that HIV/HCV coinfection has a direct effect on lipid profiles and lipoprotein concentrations as the virus life cycle relies on hepatic lipid metabolism for HCV assembly and maturation [4, 6]. These changes have been described to be more pronounced in patients with HCV genotype 3 and higher HCV viraemia and seem to be present despite cART [4] and absence of advanced liver disease [23]. In our study, coinfected patients presented lower levels of TC, LDL-C, non-HDL-C and TGL and less frequent use of lipid-lowering drugs, which is in accordance to what was previously described [4, 6, 23].

GOT, GPT, GGT and ALP levels were higher in the coinfected group, which probably reflects the greater extension of the hepatic lesion and cholestasis as a consequence of more advanced fibrosis.

In summary, HIV monoinfected patients had a metabolic profile which fits metabolic syndrome's features whereas those with coinfection had lower prevalence of the traditional risk factors. It is known, however, that both infections are associated with higher risk of cardiovascular disease. Therefore, viral hepatitis status should be taken into account when evaluating cardiovascular disease risk in HIV infected patients.

Liver disease progression

Successive studies have demonstrated that HIV coinfection accelerates progression of hepatic fibrosis in HCV infected patients [24-26]. Various pathways have been implicated including: direct viral effects, immune dysregulation, profibrotic cytokine environment, depletion of gut CD4 cells and microbial translocation, oxidative stress and hepatocyte apoptosis [1, 27]. Moreover, the chronic viral state and the host

immune response both in HIV and HCV infections give rise to glucose and lipid metabolic disorders that, in turn, are risk factors for liver damage [1, 28]. cART benefits in reducing liver disease progression by improving host immunity seem to outweigh its hepatotoxicity and IR risk [3, 29, 30].

In HCV infection, low lipid levels have been correlated not only with steatosis and more advanced liver fibrosis, but also with non-response to interferon treatment [4]. This is in line with what was observed in this study: those with higher grades of fibrosis had lower TC and non-HDL-C. TC remained significantly inversely associated with LS, independently of age, NNRTI, TC, GOT and albumin.

GOT elevations are common with fibrosis progression but they are not a good marker, especially in those with HIV infection, in whom the use of cART also contributes to alterations in the hepatic profile. Normal level of GOT should not exclude the need of anti-HCV treatment because there are patients who develop fibrosis in the absence of transaminases elevation [25]. Lower albumin is an established marker of hepatic insufficiency. In our cohort, albumin levels were negatively associated with LS in our model for liver fibrosis, independently of the other variables included in the multivariated model.

Current literature is not yet accordant regarding IR importance to the pathogenesis of accelerated fibrosis progression in HIV/HCV infected individuals, as some studies described a positive correlation between IR and more advanced grades of fibrosis [12, 31, 32] and others did not find that association [13, 33]. Moreover, it was reported that IR is associated with a poor sustained virological response to HCV treatment in HIV/HCV coinfected as well as in HCV monoinfected patients [34, 35].

On the other hand, this relationship has been consistently reported for HCV monoinfection, suggesting that IR is a determinant of fibrogenesis in chronic hepatitis

C, independent of hepatic steatosis, through direct stimulation of hepatic stellate cells by hyperglycaemia and hyperinsulinemia to proliferate and to secrete extracellular matrix [36-39]. Concomitantly, IR promotes hepatic lipogenesis and it is plausible that steatosis per se contributes to fibrogenesis.

No association was found for glucose (ln) and LS in the multivariated model, similarly to what has been described by Halfon and Mechante [13, 33]. Besides the small size of our cohort that may have been responsible for the lack of association found, other factors may play a more relevant role in fibrogenesis than IR in the setting of HIV/HCV coinfection comparing to those with HCV monoinfection.

Low CD4+ cell count and history of AIDS, older age and greater length of HCV infection, HCV genotype 3, alcohol consumption, elevated GPT levels and greater waist circumference [7, 24-26] have been previously associated with increased liver fibrosis in a HIV/HCV coinfection context. Among these, only length of HCV infection was different across fibrosis stage groups.

Known risk factors for accelerate fibrosis progression are still unable to explain the wide spectrum of evolution of liver disease in HIV/HCV coinfection. Thus, further studies are required to identify other factors potentially associated with liver fibrosis in this setting.

The main limitation of our study was the small size of the population. We were unable to distinguish the temporal relationship given the cross-sectional nature of the study. Alcohol use was self reported and not quantified. Lack of data on other potential confounders, such as lipodystrophy, family history of diabetes mellitus could also affect the interpretation of our findings. Finally, the cohort may not be representative of the HIV/HCV coinfected population since the decision to undergo a TE evaluation was

made by the caring physician and only the ones who accepted to do an IR screening were included.

Conclusions

In this cohort, HIV/HCV infection was associated with better metabolic profile than HIV monoinfection, except for IR that was similar in both groups.

In HIV/HCV coinfected patients, fibrosis grade was associated with differences in NNRTI use, duration of HCV infection and HCV genotype. Patients with liver fibrosis had higher GOT levels and lower TC, Non-HDL-C and albumin. TC and albumin were independently and inversely associated with LS value.

List of abbreviations

HCV: Hepatitis C virus; HIV: Human Immunodeficiency virus; cART: Combined antiretroviral therapy; TE: Transient Elastography; LS: Liver stiffness; IR: Insulin resistance; HOMA-IR: Homeostasis model assessment of insulin resistance; QUICKI: Quantitative insulin sensitivity check index; PI: Protease inhibitors; NNRTI: Non-Nucleoside Reverse Transcriptase Inhibitors; NRTI: Nucleoside Reverse Transcriptase Inhibitors; TC: total cholesterol; LDL-C: low density lipoprotein cholesterol; HDL-C: low density lipoprotein cholesterol; TGL: triglycerides; GOT: glutamic oxaloacetic transaminase; GPT: glutamic pyruvic transaminase; GGT: Gamma-glutamyl transpeptidase; ALP: Alkaline phosphatase.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

CCB conceived the study, participated in its design, in the acquisition of data and drafted the manuscript; EL conceived the study, participated in its design and revised critically the manuscript; JO participated in its design and revised critically the manuscript; ACS performed the statistical analysis and revised critically the manuscript; LFP performed the statistical analysis; DC and AS revised critically the manuscript. PF conceived the study, participated in its design, in the acquisition of data and revised critically the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1 - Sample descriptive statistics and comparison between monoinfected HIV patients and coinfected HIV/HCV patients.

	HIV (n = 236)	**HIV/HCV (n = 63)**	***p***
Gender [1]			<0.001
Female	95 (40.3)	7 (11.1)	
Male	141 (59.7)	56 (88.9)	
Age years [2]	44 (11.48)	43 (6.54)	0.074
Duration of HIV infection years [3]	8 (5-10)	13 (9-17)	<0.001
CD4 cell count [3]	504 (338-716)	366 (285-566)	0.001
<50 HIV RNA copies/mL [1]	211 (89.4)	56 (88.9)	0.906
cART cumulative exposure years [3]	6 (3-10)	9 (5-12)	<0.001
ART [1]			
PI	136 (57.6)	41 (65.1)	0.285
NNRTI	110 (46.6)	21 (33.3)	0.059
NRTI	232 (98.3)	57 (90.5)	0.007
Duration of HCV infection years [2]		10.6 (5.05)	
HCV RNA log10 [3]		6.04 (5.38-6.61)	
Genotype [1]			
1		44 (69.8)	
3		13 (20.6)	
4		6 (9.5)	
Alcohol consumption [1]	85 (36.0)	27 (42.9)	0.319

1 – number (%); 2 – mean (SD); 3 – median (IQR)

Table 2 - Clinical and metabolic features and comparison between monoinfected HIV patients and coinfected HIV/HCV patients.

	HIV	HIV/HCV	*p*
BMI kg/m² [1]	25.2 (4.3)	22.9 (2.9)	<0.001
Waist circumference cm [1]	91.6 (11.3)	85.3 (8.4)	<0.001
High blood pressure[2]	82 (34.7)	5 (7.9)	<0.001
Antihypertensive medication[2]	31 (13.1)	1 (1.6)	0.008
Total cholesterol mg/dL [1]	227.5 (56.4)	167.3 (35.8)	<0.001
LDL cholesterol mg/dL [1]	136.4 (48.5)	97.5 (25.0)	<0.001
HDL cholesterol mg/dL [1]	47.2 (13.8)	46.5 (15.1)	0.717
Non-HDL Cholesterol mg/dL [3]	180.0 (142.0-214.0)	127.0 (104.0-139.0)	<0.001
Triglycerides mg/dL [1]	266.0 (193.5)	146.3 (71.8)	<0.001
Antidyslipidemic therapy [1]	114 (48.3)	9 (14.3)	<0.001
GOT U/L [3]	24.0 (19.3-32.8)	41.0 (29.0-68.0)	<0.001
GPT U/L [3]	24.0 (18.0-37.0)	56.0 (36.0-95.0)	<0.001
GGT U/L [3]	40.0 (26.0-76.5)	95.0 (46.0-165.0)	<0.001
ALP U/L [3]	82.50 (64.0-105.0)	93.0 (76.0-115.0)	0.008
Total bilirubin U/L [3]	0.98 (0.96)	0.93 (0.59)	0.068
Albumin g/L [1]	44.1 (3.3)	43.0 (4.4)	<0.001
Platelets x10⁹/L [1]	215.9 (58.1)	172.4 (65.9)	0.039
Prothrombin time mg/dL [1]	---	12.3 (1.4)	
Fibrinogen mg/dL [1]	---	335.2 (92.1)	
Liver stiffness kPa [3]	---	7.1 (5.4-9.8)	
HOMA-IR [3]	1.8 (1.2-3.1)	2.0 (1.0-3.3)	0.855
HOMA-IR ≥ 2 [2]	105 (44.5)	32 (50.8)	0.372
HOMA-IR ≧4 [2]	37 (15.7)	11 (17.5)	0.732
QUICKI [3]	0.35 (0.32-0.37)	0.34 (0.32-0.38)	0.855
Glucose mg/dL [3]	90.5 (83.0-98.8)	84.0 (78.0-95.0)	0.001
Insulin mU/L [3]	8.1 (5.3-13.1)	9.6 (5.1-14.6)	0.347
HbA1C % [1]	5.3 (0.49)	5.1 (0.63)	0.055

1 – mean (SD); 2 – number (%); 3 – median (min, max | IQR)

Table 3 - Main features of the HIV/HCV coinfected patients according to liver fibrosis stage.

	Without Significant Fibrosis (n=22)	Undetermined Fibrosis (n=21)	Significant Fibrosis (n=14)	Cirrhosis (n=6)	*p*
Gender [1]					0.700
Female	4 (18.2)	2 (9.5)	1 (7.1)	0 (0.0)	
Male	18 (81.8)	19 (90.5)	13 (92.9)	6 (100.0)	
Age [2]	44.3 (6.7)	40.1 (6.4)	44.1 (5.8)	42.3 (6.5)	0.163
Duration of HIV infection years [2]	13.1 (6.2)	12.3 (5.0)	12.6 (5.8)	12.2 (4.1)	0.959
CD4 cell count [3]	444 (297-642)	367 (291-560)	327 (236-507)	346 (143-375)	0.344
<50 HIV RNA copies/mL [1]	19 (86.4)	20 (97.2)	12 (85.7)	5 (83.3)	0.887
cART cumulative exposure years [2]	9.4 (4.7)	9.2 (4.9)	9.1 (5.2)	6.0 (4.4)	0.492
ART [1]					
PI	11 (50.0)	16 (76.2)	10 (78.6)	4 (66.7)	0.349
NNRTI	12 (54.5)	6 (28.6)	3 (21.4)	0 (0)	0.040
NRTI	20 (90.2)	19 (90.5)	12 (85.7)	6 (100.0)	0.933
Duration of HCV infection years [2]	11.7 (5.8)	8.6 (4.1)	9.9 (4.5)	15.0 (2.4)	0.022
HCV RNA log10 [3]	6.3 (5.6-6.9)	5.8 (5.0-6.5)	6.2 (5.5-6.7)	5.7 (4.8-6.3)	0.410
Genotype [1]					0,017
1	14 (63.6)	12 (57.1)	12 (85.7)	6 (100.0)	
3	3 (13.6)	9 (42.9)	1 (7.1)	0 (0.0)	
4	5 (22.5)	0 (0.0)	1 (7.1)	0 (0.0)	
Alcohol consumption[1]	9 (40.9)	8 (38.1)	7 (50.0)	3 (50.0)	0.887

1 – number (%); 2 – mean (SD); 3 – median (IQR)

Table 4 - Clinical and metabolic features of the HIV/HCV coinfected patients according to liver fibrosis stage.

	Without Significant Fibrosis	Undetermined Fibrosis	Significant Fibrosis	Cirrhosis	*p*
BMI kg/m² [1]	23.0 (3.5)	21.8 (2.4)	22.7 (3.4)	22.2 (1.6)	0.942
Waist circumference cm [1]	85.6 (9.3)	85.3 (7.7)	87.7 (8.5)	79.0 (4.0)	0.215
High blood pressure[2]	2 (9.1)	1 (4.8)	2 (14.3)	0 (0)	0.839
Antihypertensive medication[2]	1 (4.5)	0 (0)	0 (0)	0 (0)	1.000
Total cholesterol mg/dL [1]	179 (31)	173 (30)	157 (40)	131 (37)	0.015
LDL cholesterol mg/dL [1]	103 (20)	102 (21)	91 (32)	74 (24)	0.057
HDL cholesterol mg/dL [1]	50 (16)	45 (16)	47 (16)	37 (5)	0.299
Non-HDL Cholesterol mg/dL [1]	128 (25)	128 (30)	110 (34)	94 (37)	0.035
Triglycerides mg/dL [1]	155 (67)	157 (72)	121 (72)	135 (89)	0.458
Antidyslipidemic therapy[1]	4 (18.2)	4 (19.0)	2 (14.3)	0 (0)	0.915
GOT U/L [3]	37 (22-61)	37 (26-68)	48 (37-78)	82 (44-167)	0.036
GPT U/L [3]	49 (17-75)	55 (37-107)	66 (44-109)	75 (28-148)	0.234
GGT U/L [3]	55 (32-164)	95 (48-180)	99 (72-116)	161 (44-180)	0.537
ALP U/L [3]	94 (75-115)	92 (71-106)	89 (75-121)	108 (91-142)	0.498
Total bilirubin U/L [3]	0.68 (0.53-0.90)	0.80 (0.53-1.37)	0.74 (0.46-1.15)	1.12 (0.73-1.78)	0.186
Albumin g/L [1]	43 (41-45)	44 (43-46)	42 (42-45)	41 (33-44)	0.005
Platelets x10⁹/L [1]	184 (55)	181 (80)	156 (63)	137 (46)	0.314
Prothrombin time mg/dL [1]	11.6 (1.0)	12.4 (1.6)	12.7 (1.5)	13.4 (1.0)	0.103
Fibrinogen mg/dL [1]	348 (115)	380 (82)	288 (38)	313 (79)	0.310
HOMA-IR [3]	2.1 (1.5-2.9)	2.2 (1.0-4.2)	2.0 (0.9-3.4)	1.1 (0.7-2.8)	0.593
HOMA-IR ≥ 2 [2]	12 (54.5)	11 (52.4)	7 (50.0)	2 (33.3)	0.876
HOMA-IR ≧4 [2]	2 (9.1)	6 (28.6)	3 (21.4)	0 (0)	0.272
QUICKI [3]	0.34 (0.33-0.36)	0.34 (0.31-0.39)	0.34 (0.32-0.39)	0.38 (0.33-0.41)	0.593
Glucose mg/dL [3]	85.5 (81.8-95.0)	89.0 (79.5-92.0)	79.0 (73.0-86.8)	83.5 (75.8-101.3)	0.182
Insulin mU/L [3]	9.9 (7.2-12.5)	13.1 (5.2-18.4)	9.4 (4.5-16.9)	6.2 (3.5-12.0)	0.511

1 – mean (SD); 2 – number (%); 3 – median (min, max | IQR)

Table 5 - Correlations between metabolic characteristics and liver stiffness.

	Liver Stiffness	
	r	***p***
Total cholesterol mg/dL	-0.427	<0.001
LDL cholesterol mg/dL	-0.332	0.009
HDL cholesterol mg/dL	-0.237	0.062
Non-HDL Cholesterol mg/dL	-0.373	0.003
Triglycerides mg/dL	-0.144	0.261
HOMA-IR	-0.143	0.265
QUICKI	0.143	0.265
Glucose mg/dL	-0.302	0.016
Insulin U/L	-0.092	0.471
HbA1c %	0.122	0.553
GOT U/L	0.338	0.007
Albumin g/L	-0.643	<0.001

Table 6 - Association between clinical and metabolic characteristics and liver stiffness.

	Liver stiffness	
	β*	**(95% CI)**
Age years	-0.144	(-0.336 to 0.048)
NNRTI	-2.298	(-4.887 to 0.292)
Total cholesterol mg/dL	-0.038	(-0.074 to -0.001)
TGO ln	2.111	(-0.101 to 4.324)
Albumin g/L	-0.896	(-1.191 to -0.602)
Glucose ln	-0.110	(-8.327 to 8.107)

*** β coefficients adjusted for all the variables in the table.**

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Anexos

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Porto, 18 de Março de 2014

O Secretário da Comissão de Ética para a Saúde

Pedro Brito