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Laurent Castéra, Marc-Arthur Loko, Brigitte Le Bail, Patrick Coffie, Victor de Lédighen, et al.. Hepatic steatosis in HIV-HCV coinfecting patients in France: comparison with HCV monoinfected patients matched for body mass index and HCV genotype.. *Alimentary Pharmacology and Therapeutics*, Wiley, 2007, 26 (11-12), pp.1489-1498. 10.1111/j.1365-2036.2007.03533.x . inserm-00177055

HAL Id: inserm-00177055

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Please cite this article as a "Postprint"; doi: 10.1111/j.1365-2036.2007.03533.x

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Hepatic steatosis in HIV-HCV coinfecting patients in France: comparison with HCV monoinfected patients matched for body mass index and HCV genotype

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Short title: Hepatic steatosis in HIV-HCV and matched HCV patients

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ABSTRACT

Background: Significance of steatosis in HIV-HCV coinfection remains controversial.

Aim: To compare the prevalence and predictors of hepatic steatosis between HIV-HCV and HCV patients matched for steatosis known determinants.

Methods: 564 naive HCV patients undergoing liver biopsy were studied: 137 with HIV-HCV coinfection and 427 with HCV mono-infection, among whom 137 were matched for age, gender, BMI and HCV genotype.

Results: Steatosis of any grade (67.1% vs. 41.6%, $p < 0.0001$), mixed steatosis (55.4% vs. 21.1%, $p < 0.0001$), severe histological activity (A2-A3: 78.1% vs. 55.5%, $p < 0.0001$), and severe fibrosis (F3-F4: 33.1% vs. 15.3%, $p < 0.0001$) were significantly more common in coinfecting than in matched mono-infected patients. In multivariate analysis, steatosis was associated only with severe histological activity (odds ratio (OR): 3.1 (95% CI: 1.3-7.1)) in coinfecting patients and with elevated BMI (OR; 1.3 (1.1-1.5)), HCV genotype 3 (OR: 5.6 (2.3-13.9)), severe histological activity (OR: 3.1 (1.3-7.3)) and severe fibrosis (OR: 4.7 (1.3-17.3)) in mono-infected patients.

Conclusions: Steatosis is significantly more common and severe in HIV-HCV coinfecting than in HCV mono-infected French patients, even after matching for BMI and HCV genotype. Steatosis is associated only with severe histological activity in coinfecting patients and with previously reported factors in mono-infected patients, thus suggesting different underlying mechanisms.

Key words: hepatic steatosis, HIV infection, HCV infection, BMI, HCV genotype

INTRODUCTION

Hepatic steatosis, defined as lipid accumulation in the hepatocyte cytoplasm, is a frequent histological finding in patients with chronic hepatitis C, occurring in more than 50 % of cases [1] and that has been suggested to be associated with fibrosis progression [2-8]. Two distinct forms of hepatocellular steatosis, “metabolic” and “viral”, can be observed in patients with chronic HCV infection [9]. Classical metabolic risk factors for steatosis such as obesity, diabetes type 2, hyperlipidaemia and excessive alcohol intake account for the vast majority of cases of steatosis in patients infected with HCV non 3 genotypes [10-12]. In contrast, in patients infected by HCV genotype 3, steatosis is thought to be induced by the virus itself through a direct cytopathic effect [13].

Liver disease is an important and increasing cause of morbidity and mortality in HIV-HCV coinfecting patients [14, 15]. The prevalence and significance of steatosis in HIV-HCV coinfecting patients have been recently investigated, and it has been suggested that it may contribute to the accelerated progression of liver disease observed in HIV-HCV coinfecting patients [16-21]. However, despite its potential clinical importance, conflicting results have been published regarding factors associated with steatosis in the context of HIV-HCV coinfection. Some studies [19, 21] suggest that predictors of steatosis in HIV-HCV coinfecting patients are the same than those observed in HCV monoinfected patients namely HCV genotype 3 and high body mass index (BMI) whereas other do not [16-18, 20]. Such discordant results may be explained by differences in the clinical features of studied populations, patients’ recruitment biases or ethnic factors. In addition, it must be stressed that two studies [18, 20] only from the US included a control group of HCV monoinfected patients and that patients of this control group were not matched for steatosis known determinants, BMI and HCV genotype.

The aim of this study was to compare the prevalence and predictors of steatosis between HIV-HCV coinfecting and HCV monoinfected French patients matched for steatosis known determinants, BMI and HCV genotype as well as age and gender.

PATIENTS AND METHODS

Study population

This retrospective study included patients with HIV-HCV coinfection and HCV mono-infection who were referred for liver biopsy prior to HCV antiviral therapy at the University Hospital of Bordeaux between January 1999 and January 2005.

Inclusion criteria were: age over 18, positive serum antibodies to HCV by means of a second- or third-generation HCV enzyme-linked immunosorbent assay (Ortho Diagnostic, Raritan NJ, USA) and detectable serum HCV RNA (AmplicorTM HCV, Roche Molecular Systems, Pleasanton, CA, USA).

Exclusion criteria were: coinfection with hepatitis B, other known causes of liver disease, alcohol intake of more than 50g/day, previous treatment for HCV, decompensated cirrhosis, and liver biopsy specimen <10 mm.

A total of 564 patients met those criteria. They comprised 427 HCV monoinfected patients and 137 HIV-HCV coinfecting patients. This latter group is a subgroup of 148 HIV-HCV patients from the Aquitaine Cohort in whom we recently investigated the prevalence and predictors of steatosis [22]. The ANRS CO3 Aquitaine Cohort is a prospective hospital-based cohort of HIV-1-infected patients under routine clinical management which was initiated in 1987 in the Bordeaux University Hospital and four other public hospitals in the Aquitaine region, Southwestern France, by the Groupe d'Epidémiologie Clinique du SIDA en Aquitaine GECSA [23]. All adults who are in- or out- patients of the participating hospital wards with HIV-1 infection, confirmed by Western-Blot testing, and who have given an informed consent are enrolled in the cohort, whatever their clinical stage, gender or HIV transmission category. Also, information from at least one follow-up visit after the baseline assessment, or a known date of death must be available. At each hospital contact, a standardized questionnaire including epidemiological, clinical, biological and therapeutical data is filled in by clinicians

for each patient included in the Cohort and entered into the database. The schedule of follow-up visits is based on clinical practice, and an active search of patients lost to follow-up is performed annually.

Among the 427 HCV mono-infected patients, 137 were matched to the 137 HIV-HCV coinfecting patients according to age, gender, BMI and HCV genotype.

Clinical, biological and virological parameters

The following data were recorded for all patients at the time of liver biopsy: age, sex, risk factors for HCV infection, BMI, alanine aminotransferase (ALT) and HCV genotype (InnoLipa II HCV, Innogenetics, Ghent, Belgium). In addition, the following data were specifically recorded for HIV-HCV coinfecting patients: route of transmission of HIV infection, antiretroviral therapy, median CD4 lymphocyte count, and plasma HIV RNA load.

Histological studies and steatosis evaluation

Paraffin-embedded biopsy specimens of more than 10 mm were analyzed prospectively during clinical management by an experienced pathologist unaware of clinical and biological data except for the HCV or HIV status. Liver biopsy specimens were stained with hematoxylin-eosin-saffran, or picroSirius red for collagen. Data were collected in a standardized report form developed for hepatitis C before this specific study. In this report, histological activity and fibrosis are scored according to the METAVIR classification [24]. Steatosis is also graded according to METAVIR as previously validated [24]: none; mild: involving 1-10% of hepatocytes; moderate: involving 11-30% of hepatocytes; and severe: >30% of hepatocytes. In addition, the pattern of steatosis was characterized as follows: predominantly macrovesicular; predominantly microvesicular; mixed.

Statistical analysis

For univariate and multivariate statistical analysis, the outcome of interest was the presence of steatosis. Variables considered for analyses of steatosis determining factors were age at liver biopsy, gender, BMI, source of HCV infection, HCV genotype, ALT activity, use of antiretroviral treatment before liver biopsy, histological activity and fibrosis.

Continuous variables were expressed by their mean \pm standard deviation (SD) and categorical variables by absolute figures and percentages. Mann-Whitney and Chi-2 tests were used for statistical comparisons of unmatched quantitative and qualitative variables, whereas Wilcoxon test and a conditional logistic regression were used for comparing quantitative and qualitative matched variables, respectively. A p value < 0.05 was considered significant.

To assess the independent value of each parameter related to steatosis in univariate analysis with $p < 0.25$, a multivariate analysis was performed by means of a stepwise logistic regression analysis. Statistical analyses were performed using SAS software (SAS institute Inc, Cary, NC, USA, version 9.1).

RESULTS

Study population

The baseline characteristics of the 137 HIV-HCV coinfecting patients as compared with those of the 427 HCV monoinfected patients are shown in table 1. Among HIV-HCV coinfecting patients, the main source of HIV infection was intravenous drug use (68.0%). The median CD4 count was 508 cells/mm³ (78-1644 cells/mm³). A total of 125 (91%) patients were taking antiretroviral therapy: 122 (89%) were taking nucleoside reverse transcriptase inhibitors (NRTI), 55 (40%) protease inhibitors (PI), and 50 (36.5%) non nucleoside reverse transcriptase inhibitors (NNRTI). Plasma HIV RNA was undetectable (<50 copies/ml) in 60 patients (44%).

Coinfecting patients differed from monoinfected patients in that there were significantly younger, more often male, had lower BMI, were more likely to have a prior history of intravenous drug use and to be HCV genotype 3-infected. They also had higher histological activity grade and more severe fibrosis.

Prevalence, severity and patterns of steatosis in the 137 HIV-HCV coinfecting patients and the 427 HCV monoinfected patients

Steatosis of any grade was significantly more common (67.1 % vs. 49.6%, respectively) in coinfecting than in monoinfected patients (Figure 1A). Among the 92 HIV-HCV coinfecting and the 212 HCV monoinfected patients who had steatosis of any grade on liver biopsy, the pattern of steatosis differed significantly between the two groups (Figure 1B). Although the majority of HCV monoinfected patients had macrovesicular steatosis, coinfecting patients were more likely to have a mixed pattern of steatosis (55.4% vs. 23.6%, respectively) or microvesicular steatosis (6.6% vs. 0.9%, respectively). Among the 92 HIV-HCV coinfecting patients with steatosis, those with macrovesicular steatosis did not differ from those with

mixed of microvesicular steatosis for most characteristics, except for HCV genotype distribution (genotype 1: 54.3% vs. 31.6 %, respectively; p=0.01) (Table 2).

Factors associated with steatosis in the 427 monoinfected patients

In univariate analysis, steatosis was associated with age, BMI, ALT level, HCV genotype 3, severe histological activity and severe fibrosis (Table 3). In multivariate analysis, steatosis was associated with BMI (OR: 1.2 95% CI 1.1-1.2, p<0.0001), HCV genotype 3 (OR: 3.0 1.5-6.1, p=0.002), severe histological activity (A2-A3 OR: 1.7 1.1-2.6, p=0.02) and severe fibrosis (F3-F4 OR: 3.8 2.2-6.8, p< 0.0001) (Table 3).

Prevalence, severity and patterns of steatosis in the 137 HIV-HCV coinfecting patients and the 137 matched HCV monoinfected patients

The baseline characteristics according to HIV status of the 137 matched patients are shown in Table 4. Coinfecting patients were more likely to have a prior history of injection drug use, higher ALT levels, more severe histological activity and more severe fibrosis.

Steatosis of any grade was significantly more common in coinfecting patients than in monoinfected patients (67.1% vs 41.6%, p<0.0001) (Figure 2A). Among the 92 HIV-HCV coinfecting and the 57 HCV monoinfected patients who had steatosis of any grade on liver biopsy, the type of steatosis differed significantly between the two groups (Figure 2B). Although the majority of HCV monoinfected patients had macrovesicular steatosis, coinfecting patients were more likely to have a mixed pattern of steatosis (55.4% vs. 21.1%, respectively) or microvesicular steatosis (6.6% vs. 1.7%, respectively).

Factors associated with steatosis in the 137 HIV-HCV coinfecting patients and the 137 matched HCV monoinfected patients

In univariate analysis, steatosis was associated with severe histological activity A2-3, in coinfecting patients whereas it was associated with elevated BMI, HCV genotype 3, severe histological activity (A2-A3) and severe fibrosis (F3-F4) in monoinfected patients (Table 5). In multivariate analysis, steatosis was associated with severe histological activity (A2-3 OR: 3.1 95% CI 1.3-7.1, p=0.008) in coinfecting patients whereas it was associated with elevated BMI (OR: 1.3 1.1-1.5; p=0.005), HCV genotype 3 (OR: 5.6 2.3-13.9; p=0.0002), severe histological activity (OR: 3.1 1.3-7.3; p=0.009) and severe fibrosis (OR: 4.7 1.3-17.3; p=0.02) in monoinfected patients (Table 5).

DISCUSSION

The results of the present study, conducted in a large cohort of French patients with chronic hepatitis C, show that, even after adjusting by design for potential confounding factors HCV genotype and BMI, hepatic steatosis is significantly more common and more severe in HIV-HCV coinfecting than in HCV monoinfected patients. In multivariate analysis, steatosis was associated only with severe histological activity in coinfecting patients whereas it was associated with already reported factors (increased BMI, HCV genotype 3, severe histological activity and severe fibrosis) in monoinfected patients.

Steatosis has been reported in HIV-HCV coinfecting patients with a prevalence ranging from 40% to 72% [16-20]. The 67% prevalence in our study is close to those reported in another French study [19] and in two recent American studies [20, 21]. A strength of the present study is that coinfecting patients were compared to a control group of HCV monoinfected patients. So far, only two studies used a similar methodology [18, 20]. Both were conducted in American patients but obtained discrepant results: Monto *et al.* [18] found that steatosis was less common in coinfecting patients than in monoinfected patients, 47% vs. 59%, respectively whereas Gaslightwala *et al.* [20] found that steatosis was more common in coinfecting patients than in monoinfected patients (72.1% vs. 52%, respectively). Difference in the studied populations might account for this discrepancy.

It must be stressed that the baseline characteristics age, gender, BMI and proportion of patients infected by HCV genotype 3 of our population of HIV-HCV coinfecting patients are similar to those reported in the Ribavirin study, a multicenter French trial having included 395 coinfecting patients [19]. In addition, the baseline characteristics as well as the prevalence and severity of steatosis in our control group of 427 HCV monoinfected patients are also similar to those previously reported [25, 26]. Finally, the factors independently associated with steatosis in multivariate analysis BMI, HCV genotype 3, severe activity and severe fibrosis

are also consistent with those of previous reports and of a recent meta-analysis in 3068 patients [27], lending further validity to our findings.

Interestingly, when compared with the total group of 427 HCV monoinfected patients, our coinfecting patients were younger, more often male, had lower BMI, and were more likely to be infected with HCV genotype 3. Also, steatosis was significantly more common and more severe in coinfecting patients, a finding in line with those reported by Gaslightwala *et al.* [20]. However, one should be cautious when interpreting such findings because the observed difference might be related to differences in the distribution of well known risk factors for steatosis such as HCV genotype 3 infection and increased BMI, between coinfecting and monoinfected patients. The only way to avoid such a bias is to match coinfecting patients with monoinfected patients according to these two risk factors, which had not been done in any study so far.

An important finding of the present study, is that, even after matching for BMI and HCV genotype, steatosis remained significantly more common and more severe in coinfecting patients than in monoinfected patients. Also, coinfecting patients were more likely to have a mixed pattern of macrovesicular and microvesicular steatosis than monoinfected patients before and after matching, a finding consistent with those of two recent studies [20, 21]. Although the reason for this finding is unclear, it suggests that different underlying mechanisms may be responsible for steatosis in coinfecting patients. Indeed, microvesicular steatosis may be induced by NRTI which inhibit mitochondrial DNA polymerase gamma [28]. Consistent also with the hypothesis of different underlying mechanisms is the fact that factors independently associated with steatosis in multivariate analysis differed between coinfecting and monoinfected patients. Indeed, steatosis was associated only with severe histological activity in coinfecting patients whereas it was associated with previously reported

risk factors such as BMI, HCV genotype 3, severe activity and fibrosis in monoinfected patients.

In HCV monoinfected patients, two distinct forms of steatosis can be observed: “metabolic” steatosis associated with risk factors such as obesity, diabetes type 2, hyperlipidaemia and excessive alcohol intake and “viral” steatosis in patients infected by HCV genotype 3, through a direct cytopathic effect. The direct responsibility of HCV in the pathogenesis of steatosis has been suggested by several lines of evidence: 1) the independent association with HCV genotype 3 infection in most studies [9, 26, 29]; 2) the correlation between severity of steatosis and HCV genotype 3 replication levels while no such relationship has been found with other HCV genotypes [2, 7, 13, 30, 31]; 3) the disappearance of steatosis in HCV genotype 3 infected patients with sustained viral clearance after antiviral therapy [7, 31-33]; 4) finally, the development of hepatic steatosis in transgenic mouse lines [34] or in cell lines [35] expressing HCV core protein and the inhibition of microsomal triglyceride transfer protein, a key enzyme for hepatic lipoprotein assembly and secretion, in both transgenic mouse [36] and human liver [37].

Interestingly, despite the significant proportion of coinfecting patients with HCV genotype 3 infection (30.7%) in our study, which is higher than that reported in studies from the US [16-18, 20] but similar to that reported in a recent French study [19], no correlation was found between genotype 3 and steatosis in coinfecting patients. Histological activity was the only factor associated with steatosis. An association between histological activity and steatosis has been reported in HCV monoinfected patients [27, 38] as well as in HIV-HCV coinfecting patients [17]. Several mechanisms may account for the relationship between steatosis and histological activity. HCV infection is associated with increased cytokines production enhancing histological inflammation and leading to increased lipid peroxidation [39]. Also, HCV core protein has been shown to induce oxidative stress *in vitro* and *in vivo* [40]. In HIV-

HCV coinfecting patients, histological inflammation may be related not only to HCV infection but also to the use of antiretroviral drugs. Antiretroviral therapy has clearly been implicated in the development of steatosis in patients with HIV [41] and HIV-HCV coinfection [17, 21]. Although no relationship was found between steatosis and antiretroviral treatment in the present study, we cannot rule out the implication of the latter. Indeed, given the fact that nearly all patients were on antiretroviral therapy, we cannot exclude the fact that we did not have enough statistical power to demonstrate a significant relationship between steatosis and antiretroviral treatment. Finally, the retrospective design of our study did not allow to take into consideration the cumulative duration of exposure to antiretroviral drug which may also play an important role.

In conclusion, steatosis is significantly more common and more severe in HIV-HCV coinfecting than in HCV monoinfected French patients, even after matching for BMI and HCV genotype. Steatosis is associated only with severe histological activity in coinfecting patients and with already reported factors BMI, HCV genotype 3, severe histological activity and fibrosis in monoinfected patients. These results suggest different underlying mechanisms which deserve further investigation.

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Figure 1A. Severity of steatosis in the 137 HIV-HCV coinfecting and 427 HCV monoinfected patients.

Figure 1B. Type of steatosis in the 92 HIV-HCV coinfecting and 212 HCV monoinfected patients who had steatosis of any grade on liver biopsy.

Figure 2A. Severity of steatosis in the 137 HIV-HCV coinfecting and 137 matched HCV monoinfected patients.

Figure 2B. Type of steatosis in the 92 HIV-HCV coinfecting and 57 matched HCV monoinfected patients who had steatosis of any grade on liver biopsy.

Table 1. Characteristics of the 564 HCV-infected patients at the time of liver biopsy according to HIV status.

	HIV-HCV (n=137)	HCV (n=427)	P Value
Age (yrs) (mean \pm SD)	39.3 \pm 5.8	48.5 \pm 12.8	<0.0001
Gender (male) (%)	65.0	50.0	0.002
Body mass index (kg/m ²) (mean \pm SD)	22.1 \pm 3.2	24.4 \pm 4.0	<0.0001
Source of HCV infection (%)			<0.0001
IVDU	68.0	26.0	
ALT levels (x ULN)	2.3 \pm 2.0	2.1 \pm 1.9	0.13
HCV genotype (%)			<0.0001
1	44.5	61.6	
2	3.6	16.6	
3	30.7	10.6	
4 and others	21.2	11.2	
Histological lesions (METAVIR)			
Activity (%)			0.0018
A0-1	21.9	36.4	
A2	56.9	51.2	
A3	21.2	12.4	
Fibrosis (%)			0.0045
F0-1	23.4	39.0	
F2	44.5	39.4	
F3	13.1	10.1	
F4	19.0	11.5	

IVDU: intravenous drug use; ULN upper limit of normal value
SD: standard deviation

Table 2. Characteristics of the 92 HIV-HCV coinfecting patients with steatosis of any grade at liver biopsy, according to the type of steatosis.

	<u>Macrovesicular steatosis (n=35)</u>	<u>Mixed or microvesicular steatosis (n=57)</u>	<u>P Value</u>
<u>Age (yrs) (mean ±SD)</u>	40.6 ± 6.3	38.9 ± 5.6	0.26
<u>Gender (male) (%)</u>	62.9	66.7	0.71
<u>Body mass index (kg/m²)(mean ± SD)</u>	22.4 ±2.7	22.6 ± 3.4	0.91
<u>Source of infection (%)</u>			
IVDU	68.6	61.4	0.49
<u>ALT levels (x ULN) (mean ± SD)</u>	2.0 ± 1.0	2.7 ± 2.2	0.37
<u>HCV genotype (%)</u>			0.01
1	54.3	31.6	
2	5.7	0	
3	17.1	43.9	
4 and others	22.9	24.5	
<u>CD4 cell count (/mm³) (%)</u>			
= 200	5.7	3.5	0.61
<u>HIV plasma RNA (%)</u>			
Undetectable (<50copies/ml)	41.2	40.3	0.94
<u>Antiretroviral treatment (%)</u>	97.1	89.5	0.18
<u>Histological lesions (METAVIR)</u>			
Activity (%)			0.25
A0-1	20	12.3	
A2	60	52.6	
A3	20	35.1	
Fibrosis (%)			0.25
F0-1	25.7	14.0	
F2	48.6	42.1	
F3	8.6	21.1	
F4	17.1	22.8	

IVDU: intravenous drug use; ULN upper limit of normal value
SD: standard deviation

Table 3. Factors associated with steatosis in the 427 HCV monoinfected patients in univariate and multivariate analysis.

	Univariate analysis (OR (95% CI))	P Value	Multivariate analysis (OR (95% CI))	P Value
Age (yrs/10)	1.3 (1.1-1.5)	0.0003		
Gender (male)	1.3 (0.9-1.96)	0.13		
Body mass index	1.1 (1.05-1.2)	<0.0001	1.2 (1.1-1.2)	<0.0001
Source of HCV infection				
IVDU vs. Other	0.9 (0.6-1.4)	0.60		
ALT level	1.1 (1.0-1.3)	0.04		
HCV genotype	2.5 (1.3-4.8)	0.0078	3.0 (1.5-6.1)	0.002
3 vs. Other				
Histological activity	2.5 (1.6-3.7)	<0.0001	1.7 (1.1-2.6)	0.02
A2-3 vs. A0-1				
Fibrosis	4.7 (2.8-8.1)	<0.0001	3.8 (2.2-6.8)	<0.0001
F3-4 vs. F0-1-2				

IVDU: intravenous drug use

OR: odds ratio

CI: confidence interval

Table 4. Characteristics of the 137 matched pairs of HCV-infected patients at the time of liver biopsy according to HIV status.

	HIV-HCV (n=137)	HCV (n=137)	P Value
Age (yrs) (mean \pm SD)	39.3 \pm 5.8	40.1 \pm 6.2	NS
Gender (male) (%)	65.0	65.0	NS
Body mass index (kg/m ²) (mean \pm SD)	22.1 \pm 3.2	22.5 \pm 2.8	NS
Source of infection (%)			
IVDU	68.0	51.0	0.005
ALT levels (x ULN)(mean \pm SD)	2.3 \pm 2.0	1.8 \pm 1.5	0.01
HCV genotype (%)			
1	44.5	44.5	NS
2	3.6	3.6	
3	30.7	30.7	
4 and others	21.2	21.2	
Histological lesions (METAVIR)			
Activity (%)			<0.0001
A0-1	21.9	44.5	
A2	56.9	48.2	
A3	21.2	7.3	
Fibrosis (%)			<0.0001
F0-1	23.4	48.2	
F2	44.5	36.5	
F3	13.1	8.0	
F4	19.0	7.3	

IVDU: intravenous drug use; ULN upper limit of normal value
SD: standard deviation

Table 5. Factors associated with steatosis in the 137 HIV-HCV coinfecting patients and in the 137 matched HCV monoinfected patients in univariate and multivariate analysis.

	HIV-HCV univariate (OR (95% CI))	P Value	HIV-HCV multivariate (OR (95% CI))	P Value	HCV univariate (OR (95% CI))	P Value	HCV multivariate (OR (95% CI))	P Value
Age (yrs/10)	1.2 (0.6-2.3)	0.55			1.7 (0.97-3.0)	0.06		
Gender (male)	1.0 (0.5-2.2)	0.9			1.2 (0.9-4.1)	0.07		
Body mass index	1.12 (1-1.3)	0.065			1.2 (1.1-1.4)	0.0036	1.3 (1.1-1.5)	0.005
Source of HCV infection IVDU vs. other	0.6 (0.3-1.3)	0.18			1.6 (0.8-3.2)	0.18		
ALT level	1.2 (0.9-1.5)	0.16			1.0 (0.8-1.2)	0.94		
HCV genotype 3 vs. Other	1.6 (0.7-3.5)	0.27			5.3 (2.4-11.7)	<0.0001	5.6 (2.3-13.9)	0.0002
Histological activity A2-3 vs. A0-1	3.1 (1.3-7.1)	0.008	3.1 (1.3-7.1)	0.008	3.8 (1.8-7.9)	0.0004	3.1 (1.3-7.3)	0.009
Fibrosis F3-4 vs. F0-1-2	2.0 (0.9-4.7)	0.086			8.1 (2.5-25.6)	0.0004	4.7 (1.3-17.3)	0.02
Treatment with NNRTI Yes vs. No	0.6 (0.3-1.3)	0.18						
Treatment with NRTI Yes vs. No	1.9 (0.6-5.7)	0.23						
Treatment with PI Yes vs. No	1.3 (0.6-2.8)	0.44						
<u>Plasma HIV RNA (copies/ml)</u> <u>=50 vs. <50</u>	<u>1.5 (0.7-3.1)</u>	<u>0.25</u>						
<u>CD4 cell count (/mm³)</u> <u>=200 vs. >200</u>	<u>0.98 (0.2-5.5)</u>	<u>0.98</u>						

IVDU: intravenous drug use; NNRTI: non nucleoside reverse transcriptase inhibitors; NRTI: nucleoside reverse transcriptase inhibitors; PI: protease inhibitors
OR: odds ratio CI: confidence interval

Figure 1A.

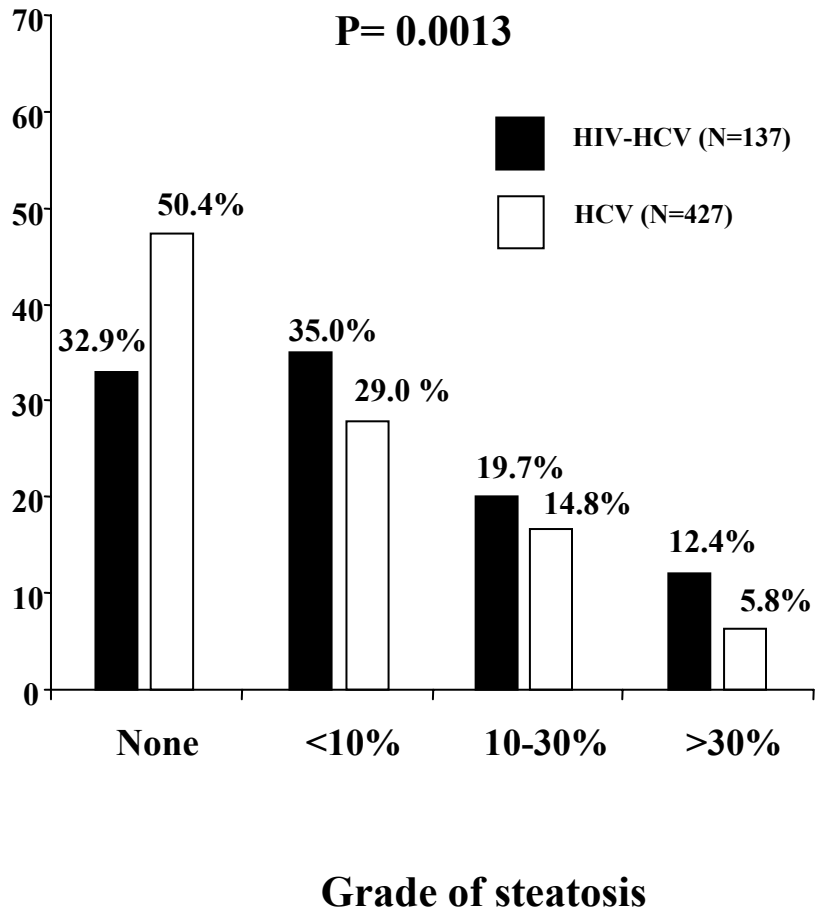


Figure 1B.

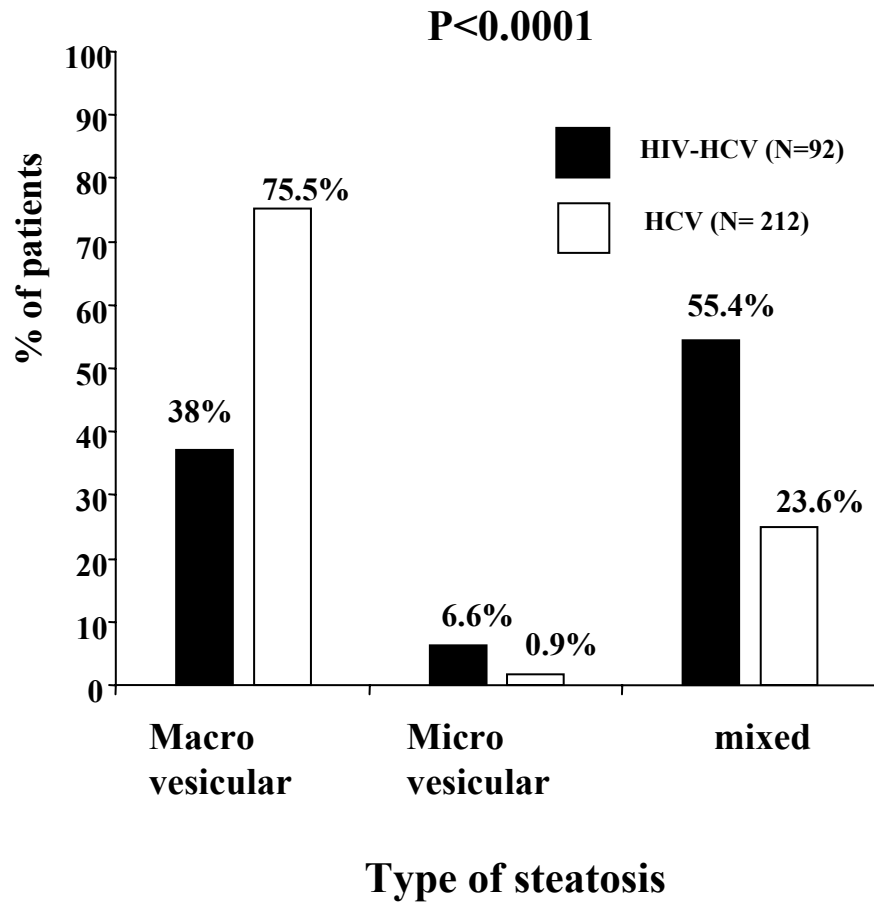
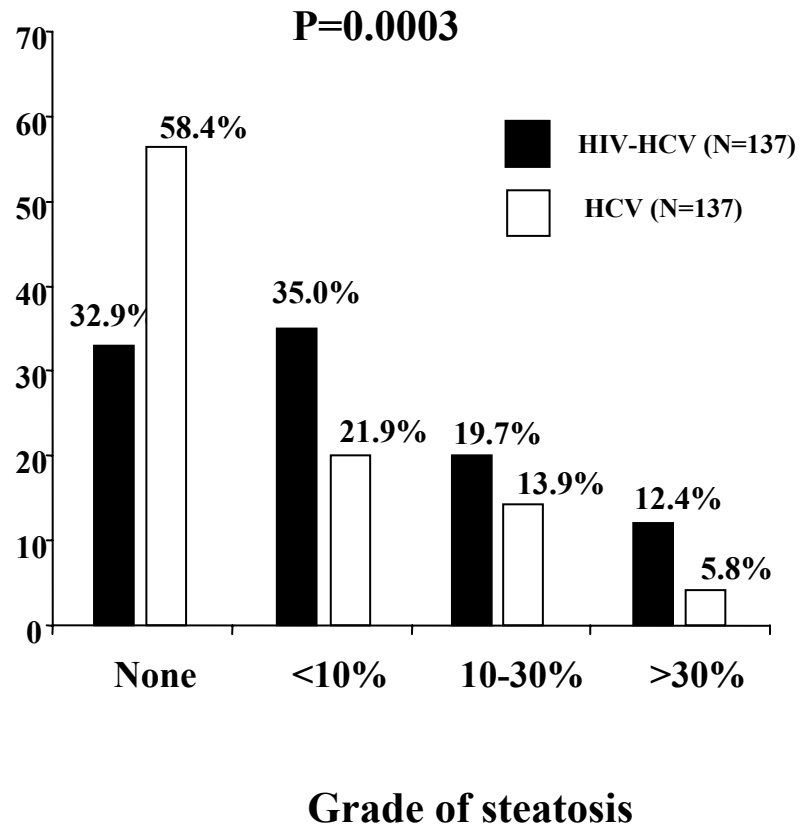


Figure 2A.**Figure 2B.**