

Hepatic steatosis in HIV-HCV coinfecting patients receiving antiretroviral therapy is associated with HCV-related factors but not antiretrovirals.

Valrie Martinez, Thi Ta, Zahra Mokhtari, Marguerite Guiguet, Patrick Mialhes, Marc-Antoine Valantin, Frderic Charlotte, Philippe Bertheau, Jean-Michel Molina, Christine Katlama, et al.

► **To cite this version:**

Valrie Martinez, Thi Ta, Zahra Mokhtari, Marguerite Guiguet, Patrick Mialhes, et al.. Hepatic steatosis in HIV-HCV coinfecting patients receiving antiretroviral therapy is associated with HCV-related factors but not antiretrovirals.. BMC Research Notes, BioMed Central, 2012, 5 (1), pp.180. <10.1186/1756-0500-5-180>. <inserm-00715837>

HAL Id: inserm-00715837

<http://www.hal.inserm.fr/inserm-00715837>

Submitted on 9 Jul 2012

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

RESEARCH ARTICLE

Open Access

Hepatic steatosis in HIV-HCV coinfecting patients receiving antiretroviral therapy is associated with HCV-related factors but not antiretrovirals

Valérie Martinez^{1,2*}, Thi Dieu Ngan TA^{3†}, Zahra Mokhtari^{4†}, Marguerite Guiguet⁵, Patrick Mialhes⁶, Marc-Antoine Valantin^{2,5}, Frédéric Charlotte⁷, Philippe Bertheau⁸, Jean-Michel Molina⁹, Christine Katlama^{2,5} and Eric Caumes^{2,5}

Abstract

Background: In HIV and hepatitis C virus (HCV) coinfecting patients, the role of antiretroviral therapy (ART) on hepatic steatosis (HS) remains controversial.

Methods: HIV/HCV coinfecting patients receiving ART and previously untreated for HCV who underwent a liver biopsy were included. Cumulative duration of exposure to each antiretroviral was recorded up to liver biopsy date. Logistic regression analyses evaluated factors associated with steatosis and its severity.

Results: 184 patients were included: median age 41 years, 84% male, 89% Caucasian, 61% with a past history of intravenous drug use. HCV genotypes were 1 (55%), 2 (6%), 3 (26%), and 4 (13%). Median HCV-RNA was 6.18 log₁₀ IU/ml. HIV-RNA was undetectable (<400 copies/ml) in 67% of patients. Median CD4 count was 321/mm³. All patients had been exposed to nucleoside reverse transcriptase inhibitors (median cumulative exposure 56 months); 126 received protease inhibitors (23 months), and 79 non-nucleoside reverse transcriptase inhibitors (16 months). HS was observed in 102 patients (55%): 41% grade 1; 5% grade 2, and 9% grade 3. In multivariate analysis, HCV genotype 3 and HCV viral load were moderately associated with mild steatosis but strongly with grade 2-3 steatosis. After adjustment for the period of biopsy, no association was detected between HS and exposure to any antiretroviral class or drug, or duration of ART globally or comparing genotype 3 to others.

Conclusions: Among our ART-treated HIV-HCV cohort predominantly infected with genotype 1, 55% of patients had HS which was associated with HCV-related factors, but not ART class or duration of exposure.

Keywords: HIV, HCV, steatosis, antiretroviral drugs, genotype 3

Introduction

As a result of shared transmission routes, hepatitis C virus (HCV) infection is common in patients infected with human immunodeficiency virus (HIV) [1-3]. In the USA and Western Europe, at least 30% of HIV-infected patients are also infected with HCV [1-4]. The immunosuppression

induced by HIV accelerates the natural history of HCV-related liver disease and the progression of chronic hepatitis C to cirrhosis and end-stage hepatic disease [5-10].

The introduction of highly active antiretroviral therapy has been associated with a dramatic decline in the morbidity and mortality related to specific HIV complications, whereas that related to liver disease has increased significantly in coinfecting patients [1,6,11-13]. The relative increase in morbidity and mortality due to liver disease in the HIV population is a composite of accelerated liver disease progression in HCV patients and extended survival of these individuals due to the benefit of antiretroviral therapy (ART).

Hepatic steatosis (HS), defined by the accumulation of lipid droplets in hepatocytes, is present in 24-75% of HIV

* Correspondence: valerie.martinez@abc.aphp.fr

†Equal contributors

¹Service de Médecine Interne et Immunologie Clinique, Assistance Publique-Hôpitaux de Paris, INSERM UMR_S 996, Université Paris Sud, Hôpital Antoine Bécélère, 157, rue de la Porte de Trivaux, 92141, Clamart, France

²Service des Maladies Infectieuses et Tropicales, Hôpital Pitié-Salpêtrière, Université Pierre et Marie Curie, APHP, 45/83 Boulevard de l'Hôpital, 75013, Paris, France

Full list of author information is available at the end of the article

and HCV coinfecting patients [12,14-23]. Some factors contributing to the development of HS in the general population, such as visceral obesity, alcohol consumption, hypertriglyceridemia, hypertension and diabetes mellitus remain hugely discrepant during coinfection [24-28]. In HIV and HCV coinfecting patients, HS may occur as a result of the HIV infection or as a consequence of concomitant HCV infection, as well as metabolic factors such as diabetes, obesity or antiretroviral drugs which could induce metabolic syndrome, lipodystrophy or lactic acidosis due to mitochondrial damage [12,14,15,18-20,22,29-32]. Nevertheless, the role of ART, particularly stavudine exposure, remains controversial. Moreover, in some studies, HS appears to be more common and severe in coinfecting than in HCV-monoinfecting patients [16,22] and influence by the viral genotype [16,22]. Borghi et al., showed previously that HIV related steatosis increase in genotype 3 patients and a putative role of ART in patients infected by HCV genotype other than 3 [23]. Other factors besides immunosuppression account for faster progression to ESLD in coinfecting patients (i.e. HIV hepatocyte infection, drug liver toxicity).

To assess the prevalence and risk factors of HS, particularly characteristics associated with severity, we reviewed the epidemiological, clinical and biological data of HIV-HCV coinfecting patients receiving ART, before HCV therapy and at the time of liver biopsy. Moreover, we compared the effect of ART according to the genotype.

Patients and Methods

Patients

For this study, HIV-HCV coinfecting patients were retrospectively screened in histopathology databases of two hospitals. All HIV-infected patients with detectable HCV RNA load (qualitative or quantitative detection), receiving ART but naive of HCV-specific therapy and who underwent a liver biopsy between January 1995 and January 2008, were included. When repeated liver biopsies were performed, only data associated with the first one was studied.

Patients were excluded if they were positive for hepatitis B surface antigen, had a negative plasma HCV RNA load, or other chronic liver diseases, such as autoimmune hepatitis, hemochromatosis, Wilson's disease or alpha-1 antitrypsin deficiency. All patients have been tested for all of these parameters and the patients included were negative.

At the day of liver biopsy, the following variables were assessed: age, gender, ethnicity, alcohol (reported by physician in the medical report, but no data about the quantity consumed daily), intravenous drug abuse, duration of documented HIV and HCV infections, risk factors for viral transmission, CD4 cell count, HIV and HCV plasma levels,

HCV genotype, fasting glycemia, total cholesterolemia and triglyceridemia, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT) and alkaline phosphatase. Measure of insulinemia, not performed in clinical practice, was not available in this retrospective study, nor measure of weight, body mass index and waist circumference which were not recorded in the medical report. Metabolic parameters were also recorded for each patient on a fasting state. For the purposes of this study, metabolic syndrome was defined as triglycerides >1.7 mmol/l and glycemia \geq 5.6 mmol/l as recommended by the International Diabetes Federation 2005 and diabetes as a fasting glycemia >7 mmol/l and excluded waist circumference [33].

HCV RNA detection was performed using a signal amplification nucleic acid probe assay (bdNA 3.0, Bayer diagnostics, Tarrytown NY) and was expressed in KIU/ml. All biological data were assessed directly to the data system of the different laboratories of the 2 hospitals. All of the parameters collected were routinely performed in HIV-HCV patients who underwent a liver biopsy and were assessed on the day of biopsy or during the week before.

History of antiretroviral therapy was assessed in the medical report and from our database (Nadis software[®]). The cumulative duration of exposure to each drug and class of drugs was recorded for each patient up to the date of liver biopsy. As patients could have received more than one ART regimen, and because of the large diversity of regimens available in France, it would be impossible to select specific drug combinations for analysis. Therefore, we hypothesized that a relationship between a combination of drugs and severity of HS would be evident by studying each component of the combination.

Histologic evaluation

Percutaneous or transjugular liver biopsy specimens were fixed in formalin and embedded in paraffin. Minimal size was 10 mm and contained at least 6 portal spaces, excepted if cirrhosis. Sections 4 μ m thick were stained with hematoxylin and eosin, with picosirius stain for collagen and Perls' stain for iron. All liver biopsy specimens were evaluated by two experienced pathologists, one in each hospital (F.C. or P.B.).

The grade of activity and the stage of fibrosis were evaluated according to the METAVIR scale [34]. Necroinflammatory activity was graded A0 (none), A1 (mild), A2 (moderate) or A3 (high). The degree of portal and septal fibrosis was assessed as F0 (none), F1 (portal fibrosis without septa), F2 (portal fibrosis with a few septa), F3 (portal fibrosis with numerous septa) or F4 (cirrhosis). HS was evaluated and graded as proposed by Brunt et al. [33]: grade 0, none; grade 1, steatosis involving <33% of hepatocytes; grade 2, 33-66% and grade 3, >66%. HS was defined as mild (grade 1) or severe (grade 2-3).

Statistical analysis

Median and interquartile ranges (IQRs) described continuous variables. Comparisons between patients found with and without steatosis were performed using Kruskal-Wallis or Wilcoxon tests for quantitative variables, and χ^2 test or Fisher's exact test for qualitative variables. Logistic regression analyses were used to identify determinants of liver steatosis, and polytomous logistic regression analyses evaluated factors associated with the presence of mild or severe steatosis.

Exposure to ART was studied after adjustment for the period of biopsy (1995-1998, 1999-2001, 2002-2008). The periods were chosen at the time of the statistical analysis according to the introduction of drugs such as abacavir in 1999 and tenofovir in 2002 to show an impact of the use of more "metabolic friendly" drugs. Exposure to ART and cumulative exposure duration (per 1 year increased) were evaluated globally for all patients and according to genotype: genotype 3 compared to others.

Variables with $p < 0.15$ in univariate analyses were included in the final model. Analyses were processed with the use of SAS software (SAS Institute, Cary, North Carolina, USA).

Results

Study population

Between January 1995 and January 2008, 250 HIV-HCV coinfecting patients who underwent a liver biopsy and fulfilled all inclusion criteria were evaluated. Sixty-six patients were not analyzed for the following reasons corresponding to exclusion criteria: hepatitis B coinfection ($n = 28$), loss of medical records ($n = 8$) or no ART at the time of biopsy ($n = 30$). Therefore, 184 patients were included. Demographic and biological characteristics are summarized in Table 1.

No correlation was observed between the duration of HIV infection and CD4 cell count in this cohort of ART-treated patients. HIV plasma viral load was undetectable (< 400 copies/ml) in 119 out of the 178 (67%) evaluable patients and median HIV viral load on average was 3.93 \log_{10} copies/ml for the remaining 33% patients. The median HCV viral load was 6.18 \log_{10} IU/ml (IQR 5.76-6.60) in the 148 (80%) patients with quantificative HCV values. The other patients ($n = 36$) had only a positive HCV RNA without quantification.

All patients had been exposed to a nucleoside reverse transcriptase inhibitor (NRTI), including zidovudine ($n = 144$), lamivudine ($n = 161$), stavudine ($n = 114$), zalcitabine ($n = 22$), didanosine ($n = 105$), tenofovir ($n = 24$) and abacavir ($n = 24$); 126 patients had received protease inhibitors (PI), including ritonavir as boosted-PI ($n = 59$), indinavir ($n = 68$), nelfinavir ($n = 47$), saquinavir ($n = 16$), lopinavir ($n = 17$) and atazanavir ($n = 8$); and 79 patients had received

Table 1 Characteristics of HIV-HCV coinfecting patients treated with antiretroviral therapy at the time of liver biopsy (parameters collected the day of the liver biopsy or during the week before)

	n = 184
Median age at biopsy (IQR), years	41 (36-45)
Male, n (%)	154 (84)
Ethnicity, n (%)	
Caucasian	163 (89)
Black	21 (11)
Intravenous drug use, n (%)	127 (61)
Alcohol use, n (%)*	67 (36)
Median duration of HIV diagnosis (IQR, years)	11 (7-14)
Median CD4 cell counts/mm ³ (IQR)	321 (227-461)
Undetectable HIV RNA ⁺ , n (%)	119 (67)
HCV genotype ⁺⁺ , n (%)	
1	98 (55)
2	10 (6)
3	47 (26)
4	24 (13)
Median HCV RNA (IQR), \log_{10} KIU/ml ⁺⁺⁺	6.18 (5.76-6.60)
Median laboratory variables (IQR), U/l	
ALT	83 (47-128)
AST	65 (43-97)
Alkaline phosphatase	89 (71-113)
GGT	80 (42-160)
Median glycemia (IQR), mmol/l	4.8 (4.3-5.3)
Glycemia ≥ 5.6 mmol/l ⁺ , n (%)	33 (19)
Glycemia ≥ 7.0 mmol/l ⁺ , n (%)	7 (4)
Median total cholesterol (IQR), mmol/l	4.20 (3.54-5.10)
Median triglyceridemia (IQR), mmol/l ^{°°}	1.49 (0.99-2.10)
Triglyceridemia ≥ 1.7 mmol/l ⁺ , n (%)	60 (36)
Median duration of antiretroviral therapy (IQR), months	58 (28-94)
Median cumulative exposure to antiretrovirals (IQR), months	
NRTI	56 (28-90)
NNRTI	16 (9-31)
PI	23 (12-40)
Combination of ART at liver biopsy, n (%)	
2 NRTI + 1 PI	93 (51)
2 NRTI + 1 NNRTI	36 (20)
1 or 2 NRTI	31 (16)
3 NRTI	17 (9)
Other regimens	7 (4)

⁺ proportions calculated on available data.

⁺ Data missing for 6 patients; ⁺⁺ Data missing for 5 patients; ⁺⁺⁺ Data missing for 36 patients; [°] Data missing for 11 patients; ^{°°} Data missing for 18 patients.

*Alcohol: no quantification was available.

Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase; IQR, interquartile range; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

non-nucleoside reverse transcriptase inhibitors (NNRTI), including efavirenz (n = 51) and nevirapine (n = 44).

Histologic findings

Overall, 102 (55%) out of the 184 patients had HS. Steatosis was grade 1 in 76 (41%) patients, grade 2 in 10 (5%), and 3 in 16 (9%). Macrovesicular fatty changes were observed in 56 patients (55%), microvesicular in 10 (10%), and mixed form in 36 (35%). Fibrosis was present in 163 patients (89%) with METAVIR F1 score in 66 (36%), F2 in 53 (29%), F3 in 39 (21%) and F4 in 4 (2%). Necroinflammatory activity was detected in 164 out of the 184 (89%) patients with A1 in 109 (59%), A2 in 50 (27%) and A3 in 5 (3%).

Factors associated with hepatic steatosis

Comparison of parameters in patients with or without HS are presented in Table 2. In univariate analysis, intravenous drug use ($p = 0.05$) and HCV genotype 3 ($p = 0.005$) were strongly linked with HS. The median HCV viral load was

significantly higher in patients with HS compared with those without ($p = 0.003$). HS was also associated with increased levels of ALT, AST and decreased levels of serum total cholesterol, but not with triglyceridemia nor available parameters of metabolic syndrome (only 7 patients have a glycemia >7 mmol/l with mild steatosis for 6 patients and 1 had no steatosis) (Table 2).

Also, there was no association with CD4 cell count or an undetectable HIV viral load. Similar results were found in patients with mild versus severe steatosis.

HS was also associated with fibrosis (Figure 1). Thus, the frequency of HS increased with the stages of fibrosis, with 76%, 54%, 32%, and 28% of patients without steatosis having fibrosis scores of F0, F1, F2, and F3–F4, respectively (Cochran-Armitage trend test, $p < 0.0001$). However, the severity of steatosis was not different among patients presenting fibrosis scoring F1, F2, or F3–F4. No association was observed between HS and necroinflammatory activity.

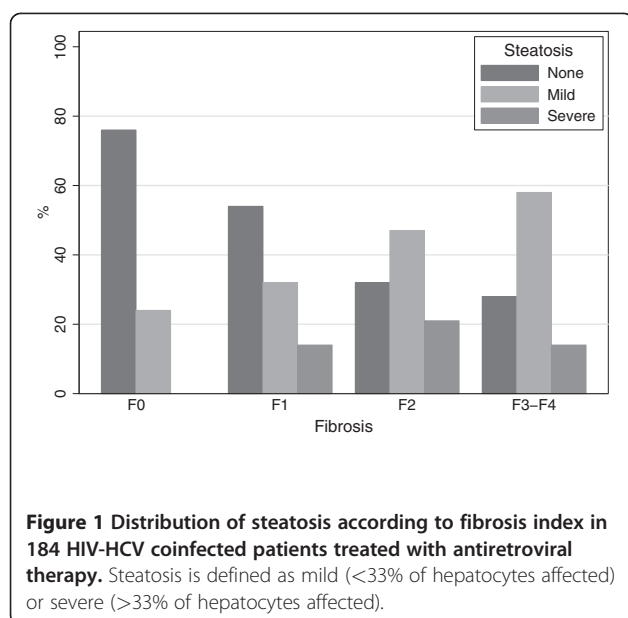
Table 2 Comparison of various parameters in patients with mild (<33% of hepatocytes affected) or severe (>33% of hepatocytes affected) steatosis and those without steatosis (univariate analysis)

	No steatosis (n = 82)	Steatosis (n = 102)	Mild steatosis (n = 76)	Severe steatosis (n = 26)	p^a	p^b	p^c
Median age (IQR), yrs	40 (36-45)	41 (37-45)	41 (36-45)	41 (37-48)	0.38	0.66	0.81
Male gender, n (%)	66 (80)	88 (86)	67 (88)	21 (81)	0.32	0.39	0.34
IVDU, n (%)	50 (62)	77 (76)	54 (71)	23 (88)	0.05	0.03	0.11
Alcohol use, n (%)	29 (35)	38 (37)	29 (38)	9 (35)	0.88	0.92	0.82
Median duration of HIV (IQR), yrs	10 (5-14)	12 (8-14)	12 (8-15)	11 (7-13)	0.17	0.23	0.30
Median CD4 cell count (IQR), /mm ³	346 (228-560)	308 (227-423)	305 (227-435)	313 (191-398)	0.10	0.24	0.67
HIV RNA < 400 copies/ml, n (%)	58 (72)	61 (63)	46 (62)	15 (65)	0.26	0.45	1.0
HCV genotype 3, n (%)	13 (16)	34 (35)	18 (25)	16 (64)	0.005	<.0001	<.0001
Median HCV RNA (IQR), logIU/ml	5.97 (5.65-6.50)	6.30 (6.00-6.72)	6.22 (5.80-6.64)	6.69 (6.27-7.06)	0.003	0.0003	0.004
Median ALT (IQR), U/l	67 (40-119)	87 (54-130)	83 (51-121)	113 (84-132)	0.04	0.01	0.03
Median AST (IQR), U/l	56 (37-78)	77.5 (50-104)	70 (48-102)	78 (59-105)	0.001	0.003	0.33
Median alkaline phosphase (IQR), U/l	90 (70-115)	89 (69-112)	90 (72-113)	80 (65-95)	0.46	0.27	0.15
Median GGT (IQR), U/l	71 (41-139)	87 (43-196)	92 (44-198)	73 (30-180)	0.09	0.09	0.19
Median glycemia (IQR), mmol/l	4.80 (4.30-5.45)	4.92 (4.30-5.22)	4.80 (4.30-5.20)	4.90 (4.35-5.26)	0.79	0.96	0.97
Glycemia ≥ 5.6 mmol/l, n (%)	16 (21)	17 (17)	12 (16)	5 (21)	0.56	0.77	0.76
Glycemia ≥ 7.0 mmol/l, n (%)	1 (1)	6 (6)	6 (8)	0 (0)	0.14	0.08	0.33
Median total cholesterol (IQR), mmol/l	4.40 (3.73-5.33)	4.00 (3.30-4.79)	4.01 (3.30-5.03)	3.72 (3.06-4.37)	0.01	0.02	0.30
Median triglycerides (IQR), mmol/l	1.47 (0.97-2.08)	1.51 (0.99-2.20)	1.53 (1.04-2.24)	1.23 (0.90-1.74)	0.86	0.51	0.28
Triglycerides ≥ 1.7 mmol/l, n (%)	30 (40)	30 (33)	23 (33)	7 (29)	0.33	0.56	0.80
Fibrosis F3-F4, n (%)	12 (15)	31 (30)	25 (33)	6 (23)	0.01	<.0001	1.0
Metavir score activity A2/A3, n (%)	21 (26)	34 (33)	29 (38)	5 (19)	0.28	0.11	0.09

p^a Comparison of patients with versus without steatosis (Kruskal-Wallis test for quantitative variables, χ^2 test or Fisher's exact test for qualitative variables).

p^b Comparison of patients with mild or severe steatosis versus without steatosis (Kruskal-Wallis test for quantitative variables, χ^2 test for qualitative variables).

p^c Comparison of patients with mild versus severe steatosis (Kruskal-Wallis/Wilcoxon test for quantitative variables, χ^2 test or Fisher's exact test for qualitative variables).



After adjustment for the period of biopsy, neither the type of ART nor the duration of exposure to a specific antiretroviral agent or class of antiretroviral was related to HS (Table 3). The same results were observed in

separate analyses among patients presenting genotype 3, or another genotype (Tables 4 and 5).

In the multivariate analysis, only two independent factors remained associated with an increased risk of HS: HCV genotype 3 (odds ratio [OR], 2.6; 95% confidence intervals [CI], 1.1-6.3), and HCV RNA load (OR, 2.2 per 1 log higher; 95% CI, 1.2-3.8). Using a multivariate polytomous logistic regression model, HCV genotype 3 and HCV RNA load were moderately associated with mild steatosis and strongly associated with severe steatosis (Table 6).

Discussion

Hepatic steatosis has emerged as a major comorbidity in HIV-HCV coinfecting patients [13,35]. In this retrospective observational study of 184 HIV-HCV coinfecting patients ART-treated but untreated for HCV at the time of liver biopsy, HS was present in about half patients (55%), which is similar to rates of 24-75% found in other studies of HIV-HCV coinfecting and HCV mono-infected patients [12,14-23,36]. In multivariate analysis, HS and its severity were only significantly associated with HCV genotype 3 and HCV viral load. Neither the type of ART, nor their prolonged duration of exposure with a median of near five years were related to steatosis. Moreover,

Table 3 The effects on steatosis of exposure to specific antiretroviral medication in 184 HIV-HCV coinfecting patients

Antiretrovirals	n	Exposure to ARV Adjusted OR ^a (95% CI)	p	Cumulative exposure duration (per 1 year increase) Adjusted OR (95% CI)	p
Nucleoside reverse transcriptase inhibitors	184	NE		1.05 (0.96-1.16)	0.30
zidovudine	144	1.11 (0.54-2.30)	0.77	1.03 (0.91-1.16)	0.65
lamivudine	161	1.10 (0.44-2.77)	0.82	1.01 (0.88-1.17)	0.84
stavudine	114	0.96 (0.51-1.78)	0.88	1.05 (0.90-1.24)	0.54
didanosine	105	1.20 (0.66-2.18)	0.57	1.04 (0.85-1.27)	0.70
zalcitabine	22	1.68 (0.60-4.72)	0.33	1.50 (0.68-3.34)	0.31
tenofovir	24	0.87 (0.33-2.27)	0.78	1.19 (0.69-2.07)	0.53
abacavir	24	0.55 (0.22-1.39)	0.20	0.98 (0.69-1.41)	0.94
Protease inhibitors	126	1.15 (0.59-2.24)	0.67	1.06 (0.90-1.25)	0.50
ritonavir	55	0.90 (0.46-1.75)	0.75	0.96 (0.71-1.28)	0.76
indinavir	68	0.94 (0.51-1.74)	0.84	1.14 (0.87-1.47)	0.34
nelfinavir	47	0.96 (0.48-1.89)	0.91	1.12 (0.79-1.59)	0.54
saquinavir	31	0.91 (0.41-2.00)	0.81	0.72 (0.45-1.14)	0.16
lopinavir-ritonavir	17	0.55 (0.19-1.63)	0.28	0.86 (0.54-1.37)	0.52
atazanavir	8	0.76 (0.17-3.43)	0.72	0.99 (0.35-2.81)	0.98
Non-nucleoside reverse transcriptase inhibitors	79	0.93 (0.50-1.74)	0.81	1.17 (0.88-1.55)	0.27
efavirenz	51	1.34 (0.67-2.69)	0.40	1.19 (0.88-1.63)	0.26
nevirapine	44	0.67 (0.33-1.35)	0.26	1.24 (0.77-2.00)	0.36

^a Adjusted for period of liver biopsy.

Abbreviations: OR, odds ratio; CI, confidence intervals; NE, not estimable.

Table 4 The effects on steatosis of exposure to specific antiretroviral medication in 184 HIV-HCV coinfecting patients according to the genotype

		All patients (n = 184)			Genotype 3 (n = 47)		Other genotype (n = 132)	
Antiretrovirals	n	Adjusted OR ^o (95% CI)	p	Adjusted OR ^o (95% CI)	p	Adjusted OR ^o (95% CI)	p	
NRTI	184	NE		NE		NE		
zidovudine	144	1.11 (0.54–2.30)	0.77	0.91 (0.22–3.82)	0.90	1.42 (0.58–3.49)	0.45	
lamivudine	161	1.10 (0.44–2.77)	0.82	0.50 (0.05–5.00)	0.56	1.29 (0.45–3.74)	0.64	
stavudine	114	0.96 (0.51–1.78)	0.88	0.58 (0.14–0.47)	0.46	1.05 (0.51–2.17)	0.89	
didanosine	105	1.20 (0.66–2.18)	0.57	1.02 (0.27–3.93)	0.97	1.17 (0.58–2.37)	0.66	
zalcitabine	22	1.68 (0.60–4.72)	0.33	NE		1.29 (0.41–4.06)	0.66	
tenofovir	24	0.87 (0.33–2.27)	0.78	0.15 (0.01–1.80)	0.13	1.44 (0.49–4.22)	0.51	
abacavir	24	0.55 (0.22–1.39)	0.20	0.40 (0.07–2.40)	0.32	0.58 (0.18–1.84)	0.35	
PI	126	1.15 (0.59–2.24)	0.67	0.19 (0.02–1.76)	0.15	1.46 (0.67–3.15)	0.34	
ritonavir	55	0.90 (0.46–1.75)	0.75	0.54 (0.13–2.28)	0.40	1.04 (0.48–2.27)	0.91	
indinavir	68	0.94 (0.51–1.74)	0.84	1.13 (0.29–4.41)	0.86	0.81 (0.39–1.68)	0.57	
nelfinavir	47	0.96 (0.48–1.89)	0.91	0.37 (0.09–1.56)	0.18	1.19 (0.54–2.66)	0.66	
saquinavir	31	0.91 (0.41–2.00)	0.81	0.41 (0.10–1.72)	0.22	0.94 (0.34–2.61)	0.91	
lopinavir-ritonavir	17	0.55 (0.19–1.63)	0.28	0.45 (0.02–8.11)	0.59	0.67 (0.20–2.19)	0.50	
atazanavir	8	0.76 (0.17–3.43)	0.72	NE		1.70 (0.31–9.24)	0.54	
NNRTI	79	0.93 (0.50–1.74)	0.81	0.33 (0.08–1.27)	0.11	1.38 (0.65–2.95)	0.40	
efavirenz	51	1.34 (0.67–2.69)	0.40	0.74 (0.17–3.27)	0.69	1.77 (0.79–4.00)	0.16	
nevirapine	44	0.67 (0.33–1.35)	0.26	0.34 (0.08–1.38)	0.13	0.80 (0.35–1.83)	0.60	

^o Adjusted for period of liver biopsy.

Abbreviations: OR, odds ratio; CI, confidence intervals; NE, not estimable.

ART have no differential effect on occurrence of HS according to the genotype 3 compared to others.

We confirmed previously data of higher HS associated with genotype 3 [23]. Here, the rate of severe HS (14%) was higher in our study compared with 2–9% found in US studies in HIV-HCV coinfecting individuals [12], but was similar with rates found in other studies [37,38], in particular with those conducted in France [39,40]. Several reasons may explain these discrepancies. Whereas most of our patients, and those included in the study of Bauerle et al. [37], were Caucasian and carrying HCV genotype 3, other studies have included a high proportion of Afro-American patients (47–94%) and patients infected with HCV genotype 1 [38–45]. It is well-known that HCV-infected Black people have a lower prevalence of HS than Caucasian [41,45–47], probably related to lower visceral adipose tissue [16,22].

HS is a frequent histological finding in patients with chronic hepatitis C virus infection, particularly among those infected with genotype 3 strain [24,48,49]. The prevalence of 26% of genotype 3 in our study was similar to the prevalence of 18% reported in the French HepaVIH cohort [50]. It has been postulated that genotype 1 is associated with “metabolic” steatosis rather than “viral” steatosis developed through a direct cytopathologic effect observed especially in genotype 3 infected patients [51–56]. When we examined the factors impacting the level of steatosis on

ART patients, genotype 3, and high HCV viral load were two independent factors associated with HS in accordance with previous studies [15,17,19,20]. Both factors moderately increased the risk of mild steatosis, but were strongly associated with severe steatosis (grade 2 or 3).

Other factors such as greater age [18], higher body mass index (BMI) [12,15–18,20,22,38–40,42,44] [23], hyperglycemia [12], lower cholesterolemia [17], and presence of lipodystrophy [17] have also been found to be independently associated with steatosis in coinfecting patients. In our study, patients with metabolic syndrome were not more likely to present HS. However, only seven patients had diabetes, and this limited sample size could have prevented to study this risk factor. Moreover, as expected, exposure to PIs and stavudine, were associated with elevated triglycerides ($p = 0.08$ and $p < 0.0001$, respectively), but this metabolic abnormality was not a risk factors of HS in our ART-experienced population. According to the lack of data about HOMA scoring, weight and BMI, we probably missed the impact of metabolic steatosis in genotype other than 3 [23,41]. Other limitation of our retrospective study is lack of information about alcohol consumption. Nevertheless, as described by Machado et al., metabolic syndrome and alcohol were not associated to HS. BMI was considered an increasing risk factor but with small magnitude and diabetes as a possible risk factor with no data for HOMA scoring [16,22]. Moreover, the higher percentage

Table 5 The effects on steatosis of cumulative exposure duration to specific antiretroviral medication in 184 HIV-HCV coinfecting patients according to the genotype

	All patients (n = 184)		Genotype 3 (n = 47)		Other genotype (n = 132)	
Antiretrovirals	Cumulative exposure duration (per 1 year increase) Adjusted OR (95% CI)	<i>p</i>	Cumulative exposure duration (per 1 year increase) Adjusted OR (95% CI)	<i>p</i>	Cumulative exposure duration (per 1 year increase) Adjusted OR (95% CI)	<i>p</i>
Nucleoside reverse transcriptase inhibitors						
zidovudine	1.05 (0.96-1.16)	0.30	1.07 (0.85-1.35)	0.55	1.03 (0.92-1.15)	0.64
lamivudine	1.03 (0.91-1.16)	0.65	1.01 (0.81-1.27)	0.92	1.00 (0.86-1.17)	0.98
stavudine	1.01 (0.88-1.17)	0.84	0.99 (0.75-1.32)	0.97	0.99 (0.84-1.17)	0.92
didanosine	1.05 (0.90-1.24)	0.54	1.16 (0.81-1.68)	0.41	0.99 (0.81-1.22)	0.94
zalcitabine	1.04 (0.85-1.27)	0.70	1.08 (0.64-1.81)	0.77	1.04 (0.83-1.29)	0.75
tenofovir	1.50 (0.68-3.34)	0.31	NE		1.35 (0.57-3.16)	0.49
abacavir	1.19 (0.69-2.07)	0.53	0.29 (0.03-2.49)	0.26	1.46 (0.80-2.66)	0.22
Protease inhibitors	0.98 (0.69-1.41)	0.94	1.14 (0.54-2.41)	0.73	0.88 (0.56-1.41)	0.61
ritonavir	1.06 (0.90-1.25)	0.50	1.14 (0.82-1.59)	0.44	0.98 (0.80-1.21)	0.87
indinavir	0.96 (0.71-1.28)	0.76	0.88 (0.45-1.74)	0.72	1.00 (0.71-1.40)	0.98
nelfinavir	1.14 (0.87-1.47)	0.34	NE		0.89 (0.63-1.25)	0.50
saquinavir	1.12 (0.79-1.59)	0.54	1.06 (0.63-1.76)	0.83	1.11 (0.66-1.87)	0.68
lopinavir-ritonavir	0.72 (0.45-1.14)	0.16	0.67 (0.33-1.36)	0.26	0.54 (0.25-1.19)	0.13
atazanavir	0.86 (0.54-1.37)	0.52	0.90 (0.13-6.28)	0.92	0.89 (0.54-1.46)	0.64
Non-nucleoside reverse transcriptase inhibitors	0.99 (0.35-2.81)	0.98	NE		1.53 (0.43-5.47)	0.51
efavirenz	1.17 (0.88-1.55)	0.27	1.04 (0.60-1.82)	0.89	1.25 (0.90-1.75)	0.18
nevirapine	1.19 (0.88-1.63)	0.26	1.08 (0.56-2.09)	0.82	1.28 (0.89-1.83)	0.18
	1.24 (0.77-2.00)	0.36	0.47 (0.19-1.20)	0.57	1.18 (0.67-2.08)	0.56

^o Adjusted for period of liver biopsy.

Abbreviations: OR, odds ratio; CI, confidence intervals; NE, not estimable.

of genotype 3 reflect the association between HS and HCV viral parameters.

Many antiretroviral drugs have been associated with hepatic damage [57-59]. It has been suggested that steatosis due to an accumulation of fatty acids in the hepatocytes could be a consequence of mitochondrial dysfunction, secondary to drugs or viruses inducing oxidative stress [60]. The effect of the drug class and drugs within classes on HS in HIV-HCV coinfecting patients remain unclear. Previously, some studies reported no significant association between HS and ART as in our study [12,15,16,18,41]. When focusing on the use of stavudine, a medication closely linked with HS and lipodystrophy syndrome resulting from mitochondrial damage, Sulkowski et al. [45] found that stavudine exposure was a risk factor for steatosis like in the study of Borghi et al., whereas no such association was found for this

drug as well as the D-drug group of antiretrovirals (didanosine, zalcitabine) in other studies [23,38,41,42,61,62]. Recently, in a meta-analysis of the risk factors associated with HS in HIV-HCV patients, Machado et al. failed to find any association with antiretrovirals of any class and HS as well as in our study [16,22]. Moreover, Woreta et al., showed in a study including a majority of Black patients (87%) with 94% genotype 1, the lack of association with antiretroviral drugs with a median cumulative drug exposure similar to ours [41]. Despite its relatively small sample size, our study had a statistical power of 80% to detect an increased risk of steatosis of 3 for the antiretroviral drugs used less frequently such as abacavir, tenofovir and lopinavir. We could hypothesize that discrepancies with other studies were linked to the differential prevalence of Caucasian subjects, of metabolic characteristics and frequency of genotype 1

Table 6 Results from multivariate polytomous logistic regression analyses of factors associated with mild (<33% of hepatocytes affected) and severe (>33% of hepatocytes affected) steatosis in 184 HIV-HCV coinfecting patients treated with antiretroviral therapy

	Mild steatosis AOR (95%CI)	<i>p</i>	Severe steatosis AOR (95%CI)	<i>p</i>
HCV genotype 3	1.76 (0.72-4.30)	0.22	19.51 (4.49-84.73)	<0.0001
HCV RNA (per 1 log10 increase)	1.80 (1.02-3.16)	0.04	14.86 (3.79-58.22)	0.0001

Abbreviations: AOR, adjusted odds ratio; CI, confidence intervals.

and 3. Borghi et al. evocated a putative role of ART in the occurrence of HS in patients infected with genotypes other than 3 [23] but in our study, the impact of ART on HS was not different between genotype 3 and the others.

In conclusion, for our Caucasian cohort predominantly infected with genotype-HCV 1, hepatic steatosis in HIV-HCV coinfecting patients receiving antiretroviral therapy is associated with HCV-related factors particularly in genotype 3 patients but not antiretrovirals. Nevertheless, as showed in our study, ART seems play a minor role in HS since the choice and use of more "metabolically friendly" antiretroviral drugs. Overall, we found only viral parameters, HCV genotype 3, and HCV RNA value, which were strongly associated with HS, particularly a severe steatosis. Among HIV-HCV coinfecting patients receiving ART and who had never been treated for HCV, neither the type of drugs nor the duration of exposure was related to HS whatever the genotype.

Abbreviations

HIV: human immunodeficiency virus; HCV: hepatitis C virus; ART: antiretroviral therapy; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase; IQR: interquartile range; NRTI: nucleoside reverse transcriptase inhibitor; PI: protease inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; OR: odds ratio; CI: confidence intervals; IVDU: intravenous drug use; AOR: adjusted odds ratio; NE: not estimable.

Competing interests

The authors declare that they have no competing interests.

Acknowledgements

English language assistance for the preparation of this manuscript was provided by Andrea Bothwell of inScience Communications.

Author details

¹Service de Médecine Interne et Immunologie Clinique, Assistance Publique-Hôpitaux de Paris, INSERM UMR_S 996, Université Paris Sud, Hôpital Antoine Bécélère, 157, rue de la Porte de Trivaux, 92141, Clamart, France. ²Service des Maladies Infectieuses et Tropicales, Hôpital Pitié-Salpêtrière, Université Pierre et Marie Curie, APHP, 45/83 Boulevard de l'Hôpital, 75013, Paris, France. ³Department of Infectious Disease, Hanoi Medical University, 01, Ton That Tung Street, Hanoi, Vietnam. ⁴Department of Internal Medicine, Hospital National Iranian oil company, Hafez Avenue, Tehran, Iran. ⁵INSERM U943, UPMC Univ Paris 06, UMR S943, Paris, F-75013, France. ⁶Service de Maladies Infectieuses et Tropicales, 103 Grande-Rue de la Croix-Rousse, Hôpital de la Croix-Rousse, Hospices Civils de Lyon, 69317 Lyon cedex 04, Paris, France. ⁷Service d'Anatomopathologie, Hôpital Pitié-Salpêtrière, Université Pierre et Marie Curie, APHP, 45/83 Boulevard de l'Hôpital, 75013, Paris, France. ⁸Service d'Anatomopathologie, Hôpital Saint-Louis, Université Denis Diderot, APHP, 1, avenue Claude Vellefaux, 75010, Paris, France. ⁹Service des Maladies Infectieuses et Tropicales, Hôpital Saint-Louis, Université Denis Diderot, APHP, 1, avenue Claude Vellefaux, 75010, Paris, France.

Authors' contributions

VM conceived the study, collected data of patients, participated in its design and coordination and drafted the manuscript. TDNT and ZM collected the data and helped to draft the manuscript. MG made the statistical analysis and helped to draft the manuscript. PM and MAV helped to draft the manuscript. FC and PB made the histological analysis of liver biopsy. CK and EC participated in the design of the study and helped to draft the manuscript. All authors read and approved the final manuscript.

Financial disclosure

The authors have no commercial links or other associations that might pose a conflict of interest (e.g. pharmaceutical stock ownership, consultancy, advisory board membership, relevant patents, or research funding) relevant to this study.

Statement naming sources of financial support (including grant numbers)

None

Received: 24 October 2011 Accepted: 10 April 2012

Published: 10 April 2012

References

1. Martin-Carbonero L, Benhamou Y, Puoti M, Berenguer J, Mallolas J, Quereda C, Arizcorreta A, Gonzalez A, Rockstroh J, Asensi V et al: Incidence and predictors of severe liver fibrosis in human immunodeficiency virus-infected patients with chronic hepatitis C: a European collaborative study. *Clin Infect Dis* 2004, **38**(1):128-133. Epub 2003 Dec 2008.
2. Mehta SH, Thomas DL, Torbenson M, Brinkley S, Mirel L, Chaisson RE, Moore RD, Sulkowski MS: The effect of antiretroviral therapy on liver disease among adults with HIV and hepatitis C coinfection. *Hepatology* 2005, **41**(1):123-131.
3. Qurishi N, Kreuzberg C, Luchters G, Effenberger W, Kupfer B, Sauerbruch T, Rockstroh JK, Spengler U: Effect of antiretroviral therapy on liver-related mortality in patients with HIV and hepatitis C virus coinfection. *Lancet* 2003, **362**(9397):1708-1713.
4. Lauer GM, Walker BD: Hepatitis C virus infection. *N Engl J Med* 2001, **345**(1):41-52.
5. Graham CS, Baden LR, Yu E, Mrus JM, Carnie J, Heeren T, Koziel MJ: Influence of human immunodeficiency virus infection on the course of hepatitis C virus infection: a meta-analysis. *Clin Infect Dis* 2001, **33**(4):562-569.
6. Macias J, Castellano V, Merchante N, Palacios RB, Mira JA, Saez C, Garcia-Garcia JA, Lozano F, Gomez-Mateos JM, Pineda JA: Effect of antiretroviral drugs on liver fibrosis in HIV-infected patients with chronic hepatitis C: harmful impact of nevirapine. *AIDS* 2004, **18**(5):767-774.
7. Qurishi N, Kreuzberg C, Luchters G, Effenberger W, Kupfer B, Sauerbruch T, Rockstroh JK, Spengler U: Effect of antiretroviral therapy on liver-related mortality in patients with HIV and hepatitis C virus coinfection. *Lancet* 2003, **362**(9397):1708-1713.
8. Mohsen AH, Easterbrook PJ, Taylor C, Portmann B, Kulasegaram R, Murad S, Wiselka M, Norris S: Impact of human immunodeficiency virus (HIV) infection on the progression of liver fibrosis in hepatitis C virus infected patients. *Gut* 2003, **52**(7):1035-1040.
9. Soriano V, Martin-Carbonero L, Garcia-Samaniego J, Puoti M: Mortality due to chronic viral liver disease among patients infected with human immunodeficiency virus. *Clin Infect Dis* 2001, **33**(10):1793-1795.
10. Thein HH, Yi Q, Dore GJ, Krahn MD: Natural history of hepatitis C virus infection in HIV-infected individuals and the impact of HIV in the era of highly active antiretroviral therapy: a meta-analysis. *AIDS* 2008, **22**(15):1979-1991.
11. Bica I, McGovern B, Dhar R, Stone D, McGowan K, Scheib R, Snydman DR: Increasing mortality due to end-stage liver disease in patients with human immunodeficiency virus infection. *Clin Infect Dis* 2001, **32**(3):492-497.
12. Sulkowski MS, Mehta SH, Torbenson M, Afdhal NH, Mirel L, Moore RD, Thomas DL: Hepatic steatosis and antiretroviral drug use among adults coinfecting with HIV and hepatitis C virus. *AIDS* 2005, **19**(6):585-592.
13. Pol S, Lebray P, Vallet-Pichard A: HIV infection and hepatic enzyme abnormalities: intricacies of the pathogenic mechanisms. *Clin Infect Dis* 2004, **38**(Suppl 2):S65-S72.
14. Sterling RK, Contos MJ, Smith PG, Stravitz RT, Luketic VA, Fuchs M, Shiffman ML, Sanyal AJ: Steatohepatitis: Risk factors and impact on disease severity in human immunodeficiency virus/hepatitis C virus coinfection. *Hepatology* 2008, **47**(4):1118-1127.
15. Bani-Sadr F, Carrat F, Bedossa P, Piroth L, Cacoub P, Perronne C, Degott C, Pol S: Hepatic steatosis in HIV-HCV coinfecting patients: analysis of risk factors. *AIDS* 2006, **20**(4):525-531.
16. Gaslightwala I, Bini EJ: Impact of human immunodeficiency virus infection on the prevalence and severity of steatosis in patients with chronic hepatitis C virus infection. *J Hepatol* 2006, **44**(6):1026-1032.

17. Marks KM, Petrovic LM, Talal AH, Murray MP, Gulick RM, Glesby MJ: **Histological findings and clinical characteristics associated with hepatic steatosis in patients coinfecting with HIV and hepatitis C virus.** *J Infect Dis* 2005, **192**(11):1943–1949. Epub 2005 Nov 1942.
18. Monto A, Dove LM, Bostrom A, Kakar S, Tien PC, Wright TL: **Hepatic steatosis in HIV/hepatitis C coinfection: prevalence and significance compared with hepatitis C mono-infection.** *Hepatology* 2005, **42**(2):310–316.
19. McGovern BH, Ditelberg JS, Taylor LE, Gandhi RT, Christopoulos KA, Chapman S, Schwartzapfel B, Rindler E, Fiorino AM, Zaman MT, et al: **Hepatic steatosis is associated with fibrosis, nucleoside analogue use, and hepatitis C virus genotype 3 infection in HIV-seropositive patients.** *Clin Infect Dis* 2006, **43**(3):365–372.
20. Neau D, Winnock M, Castera L, Bail BL, Loko MA, Gerault L, Dupon M, Ragnaud JM, Lacoste D, Lafon ME, et al: **Prevalence of and factors associated with hepatic steatosis in patients coinfecting with hepatitis C virus and HIV: Agence Nationale pour la Recherche contre le SIDA et les hepatites virales CO3 Aquitaine Cohort.** *J Acquir Immune Defic Syndr* 2007, **45**(2):168–173.
21. Sanchez-Conde M, Berenguer J, Miralles P, Alvarez F, Carlos Lopez J, Cosin J, Pilar C, Ramirez M, Gutierrez I, Alvarez E: **Liver biopsy findings for HIV-infected patients with chronic hepatitis C and persistently normal levels of alanine aminotransferase.** *Clin Infect Dis* 2006, **43**(5):640–644.
22. Castera L, Loko MA, Le Bail B, Coffie P, De Ledinghen V, Trimoulet P, Winnock M, Dabis F, Neau D: **Hepatic steatosis in HIV-HCV coinfecting patients in France: comparison with HCV mono-infected patients matched for body mass index and HCV genotype.** *Aliment Pharmacol Ther* 2007, **26**(11–12):1489–1498.
23. Borghi V, Puoti M, Mussini C, Bellelli S, Angeletti C, Sabbatini F, Prati F, Cossarizza A, Esposito R: **HIV coinfection and antiretroviral therapy enhances liver steatosis in patients with hepatitis C, but only in those infected by HCV genotype other than 3.** *Antivir Ther* 2008, **13**(8):1057–1065.
24. Monto A, Alonzo J, Watson JJ, Grunfeld C, Wright TL: **Steatosis in chronic hepatitis C: relative contributions of obesity, diabetes mellitus, and alcohol.** *Hepatology* 2002, **36**(3):729–736.
25. Sanyal AJ: **Review article: non-alcoholic fatty liver disease and hepatitis C—risk factors and clinical implications.** *Aliment Pharmacol Ther* 2005, **22** (Suppl 2):48–51.
26. Hourigan LF, Macdonald GA, Purdie D, Whitehall VH, Shorthouse C, Clouston A, Powell EE: **Fibrosis in chronic hepatitis C correlates significantly with body mass index and steatosis.** *Hepatology* 1999, **29**(4):1215–1219.
27. Hu KQ, Kyulo NL, Esrailian E, Thompson K, Chase R, Hillebrand DJ, Runyon BA: **Overweight and obesity, hepatic steatosis, and progression of chronic hepatitis C: a retrospective study on a large cohort of patients in the United States.** *J Hepatol* 2004, **40**(1):147–154.
28. Sanyal AJ, Contos MJ, Sterling RK, Luketic VA, Shiffman ML, Stravitz RT, Mills AS: **Nonalcoholic fatty liver disease in patients with hepatitis C is associated with features of the metabolic syndrome.** *Am J Gastroenterol* 2003, **98**(9):2064–2071.
29. Marks KM, Petrovic LM, Talal AH, Murray MP, Gulick RM, Glesby MJ: **Histological findings and clinical characteristics associated with hepatic steatosis in patients coinfecting with HIV and hepatitis C virus.** *J Infect Dis* 2005, **192**(11):1943–1949.
30. Brinkman K: **Editorial response: hyperlactatemia and hepatic steatosis as features of mitochondrial toxicity of nucleoside analogue reverse transcriptase inhibitors.** *Clin Infect Dis* 2000, **31**(1):167–169.
31. Balasubramanyam A, Sekhar RV, Jahoor F, Jones PH, Pownall HJ: **Pathophysiology of dyslipidemia and increased cardiovascular risk in HIV lipodystrophy: a model of 'systemic steatosis'.** *Curr Opin Lipidol* 2004, **15**(1):59–67.
32. Ogedegbe AE, Thomas DL, Diehl AM: **Hyperlactataemia syndromes associated with HIV therapy.** *Lancet Infect Dis* 2003, **3**(6):329–337.
33. Brunt EM, Janney CG, Di Bisceglie AM, Neuschwander-Tetri BA, Bacon BR: **Nonalcoholic steatohepatitis: a proposal for grading and staging the histological lesions.** *Am J Gastroenterol* 1999, **94**(9):2467–2474.
34. The French METAVIR Cooperative Study Group: **Intraobserver and interobserver variations in liver biopsy interpretation in patients with chronic hepatitis C.** *Hepatology* 1994, **20**(1 Pt 1):15–20.
35. Tien PC, Grunfeld C: **The fatty liver in AIDS.** *Semin Gastrointest Dis* 2002, **13** (1):47–54.
36. Bauerle J, Miquel R, Laguno M, Mallolas J, Murillas J, Gatell JM, Walker UA: **Hepatic steatosis with stavudine in HIV/hepatitis C virus co-infection.** *AIDS* 2005, **19**(13):1441–1442.
37. Bauerle J, Miquel R, Laguno M, Mallolas J, Murillas J, Gatell JM, Walker UA: **Hepatic steatosis with stavudine in HIV/hepatitis C virus co-infection.** *AIDS* 2005, **19**(13):1441–1442.
38. Gaslightwala I, Bini EJ: **Impact of human immunodeficiency virus infection on the prevalence and severity of steatosis in patients with chronic hepatitis C virus infection.** *J Hepatol* 2006, **44**(6):1026–1032.
39. Bani-Sadr F, Carrat F, Bedossa P, Piroth L, Cacoub P, Perronne C, Degott C, Pol S: **Hepatic steatosis in HIV-HCV coinfecting patients: analysis of risk factors.** *AIDS* 2006, **20**(4):525–531.
40. Castera L, Loko MA, Le Bail B, Coffie P, De Ledinghen V, Trimoulet P, Winnock M, Dabis F, Neau D: **Hepatic steatosis in HIV-HCV coinfecting patients in France: comparison with HCV mono-infected patients matched for body mass index and HCV genotype.** *Aliment Pharmacol Ther* 2007, **26**(11–12):1489–1498.
41. Woreta TA, Sutcliffe CG, Mehta SH, Brown TT, Higgins Y, Thomas DL, Torbenson MS, Moore RD, Sulkowski MS: **Incidence and risk factors for steatosis progression in adults coinfecting with HIV and hepatitis C virus.** *Gastroenterology* 2011, **140**(3):809–817.
42. Marks KM, Petrovic LM, Talal AH, Murray MP, Gulick RM, Glesby MJ: **Histological findings and clinical characteristics associated with hepatic steatosis in patients coinfecting with HIV and hepatitis C virus.** *J Infect Dis* 2005, **192**(11):1943–1949. Epub 2005 Nov 1942.
43. Monto A, Dove LM, Bostrom A, Kakar S, Tien PC, Wright TL: **Hepatic steatosis in HIV/hepatitis C coinfection: prevalence and significance compared with hepatitis C mono-infection.** *Hepatology* 2005, **42**(2):310–316.
44. Neau D, Winnock M, Castera L, Bail BL, Loko MA, Gerault L, Dupon M, Ragnaud JM, Lacoste D, Lafon ME, et al: **Prevalence of and factors associated with hepatic steatosis in patients coinfecting with hepatitis C virus and HIV: Agence Nationale pour la Recherche contre le SIDA et les hepatites virales CO3 Aquitaine Cohort.** *J Acquir Immune Defic Syndr* 2007, **45**(2):168–173.
45. Sulkowski MS, Mehta SH, Torbenson M, Afdhal NH, Mirel L, Moore RD, Thomas DL: **Hepatic steatosis and antiretroviral drug use among adults coinfecting with HIV and hepatitis C virus.** *AIDS* 2005, **19**(6):585–592.
46. Browning JD, Szczepaniak LS, Dobbins R, Nuremberg P, Horton JD, Cohen JC, Grundy SM, Hobbs HH: **Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity.** *Hepatology* 2004, **40**(6):1387–1395.
47. Martin-Carbonero L, Soriano V: **Interplay between hepatitis C, liver steatosis and antiretroviral therapy in HIV-infected patients.** *AIDS* 2005, **19** (6):621–623.
48. Castera L, Hezode C, Roudot-Thoraval F, Lonjon I, Zafrani ES, Pawlotsky JM, Dhumeaux D: **Effect of antiviral treatment on evolution of liver steatosis in patients with chronic hepatitis C: indirect evidence of a role of hepatitis C virus genotype 3 in steatosis.** *Gut* 2004, **53**(3):420–424.
49. Kumar D, Farrell GC, Fung C, George J: **Hepatitis C virus genotype 3 is cytopathic to hepatocytes: Reversal of hepatic steatosis after sustained therapeutic response.** *Hepatology* 2002, **36**(5):1266–1272.
50. Loko MA, Salmon D, Carrieri P, Winnock M, Mora M, Merchadou L, Gillet S, Pambrun E, Delaune J, Valantin MA, et al: **The French national prospective cohort of patients co-infected with HIV and HCV (ANRS CO13 HEPAVIH): early findings, 2006–2010.** *BMC Infect Dis* 2010, **10**:303.
51. Adinolfi LE, Gambardella M, Andreana A, Tripodi MF, Utili R, Ruggiero G: **Steatosis accelerates the progression of liver damage of chronic hepatitis C patients and correlates with specific HCV genotype and visceral obesity.** *Hepatology* 2001, **33**(6):1358–1364.
52. Castera L, Chouteau P, Hezode C, Zafrani ES, Dhumeaux D, Pawlotsky JM: **Hepatitis C virus-induced hepatocellular steatosis.** *Am J Gastroenterol* 2005, **100**(3):711–715.
53. Clement S, Negro F: **Hepatitis C virus: the viral way to fatty liver.** *J Hepatol* 2007, **46**(6):985–987.
54. Hezode C, Roudot-Thoraval F, Zafrani ES, Dhumeaux D, Pawlotsky JM: **Different mechanisms of steatosis in hepatitis C virus genotypes 1 and 3 infections.** *J Viral Hepat* 2004, **11**(5):455–458.
55. Patton HM, Patel K, Behling C, Bylund D, Blatt LM, Vallee M, Heaton S, Conrad A, Pockros PJ, McHutchison JG: **The impact of steatosis on disease progression and early and sustained treatment response in chronic hepatitis C patients.** *J Hepatol* 2004, **40**(3):484–490.
56. Rubbia-Brandt L, Quadri R, Abid K, Giostra E, Male PJ, Mentha G, Spahr L, Zarski JP, Borisch B, Hadengue A, et al: **Hepatocyte steatosis is a cytopathic effect of hepatitis C virus genotype 3.** *J Hepatol* 2000, **33**(1):106–115.

57. Fortgang IS, Belitsos PC, Chaisson RE, Moore RD: **Hepatomegaly and steatosis in HIV-infected patients receiving nucleoside analog antiretroviral therapy.** *Am J Gastroenterol* 1995, **90**(9):1433–1436.
58. Sulkowski MS, Mehta SH, Chaisson RE, Thomas DL, Moore RD: **Hepatotoxicity associated with protease inhibitor-based antiretroviral regimens with or without concurrent ritonavir.** *AIDS* 2004, **18**(17):2277–2284.
59. Y B: **Systemic overview of HAART-associated liver enzyme elevations in patients infected with HIV and co-infected with HCV.** In: *13 th Conference on Retroviruses and Opportunistic Infections 2006. Denver, CO, US; 2006.*
60. Day CP, James OF: **Steatohepatitis: a tale of two "hits"?** *Gastroenterology* 1998, **114**(4):842–845.
61. Bauerle J, Laguno M, Mauss S, Mallolas J, Murillas J, Miquel R, Schmutz G, Setzer B, Gatell JM, Walker UA: **Mitochondrial DNA depletion in liver tissue of patients infected with hepatitis C virus: contributing effect of HIV infection?** *HIV Med* 2005, **6**(2):135–139.
62. Monto A, Alonzo J, Watson JJ, Grunfeld C, Wright TL: **Steatosis in chronic hepatitis C: relative contributions of obesity, diabetes mellitus, and alcohol.** *Hepatology* 2002, **36**(3):729–736.

doi:10.1186/1756-0500-5-180

Cite this article as: Martinez et al.: Hepatic steatosis in HIV-HCV coinfecting patients receiving antiretroviral therapy is associated with HCV-related factors but not antiretrovirals. *BMC Research Notes* 2012 **5**:180.

Submit your next manuscript to BioMed Central and take full advantage of:

- Convenient online submission
- Thorough peer review
- No space constraints or color figure charges
- Immediate publication on acceptance
- Inclusion in PubMed, CAS, Scopus and Google Scholar
- Research which is freely available for redistribution

Submit your manuscript at
www.biomedcentral.com/submit

