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Short Communication

HIV-coinfection leads to a modest increase in plasma HCV-RNA load in patients with chronic HCV infection

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ABSTRACT

The influence of HIV coinfection on plasma hepatitis C virus (HCV) RNA load has not been reliably evaluated. We analyzed plasma HCV RNA load in 396 HCV-monoinfected and 467 HIV/HCV-coinfected patients. Median HCV RNA concentrations (interquartile range) in HCV-monoinfected patients were 5.88 (5.3–6.2) $\log_{10}$ IU/mL versus 5.96 (5.6–6.5) $\log_{10}$ IU/mL in HIV/HCV-coinfected individuals ($p = 0.033$) as determined with the Cobas Amplicor Test and 6.06 (5.4–5.7) $\log_{10}$ IU/mL versus 6.3 (5.5–6.9) $\log_{10}$ IU/mL ($p = 0.026$) using the Cobas TaqMan System. The plasma HCV RNA load in patients with HIV infection and undetectable plasmatic HIV RNA was similar to that observed in HCV-monoinfected individuals [6.02 (5.45–6.61) $\log_{10}$ IU/mL versus 6.01 (5.36–6.59) $\log_{10}$ IU/mL, respectively ($p = 1.0$)]. In conclusion, HIV coinfection tends to be associated with higher plasma HCV RNA load, however, the magnitude of the differences is small and this effect can be counterbalanced with antiviral therapy.

1. Introduction

HIV coinfection considerably lowers the overall response rate to anti-hepatitis C therapy with pegylated interferon (Peg-IFN) plus ribavirin (RBV) (Carrat et al., 2004; Torriani et al., 2004). The underlying mechanism for this fact is not fully known. Differences in adherence, a poorer immune control of hepatitis C virus (HCV) replication and interactions with antiretroviral drugs have been pointed out as potential causes of this fact (Operalski and Kovacs, 2011).

Plasma HCV RNA load has been identified as a strong predictor of sustained virologic response (SVR) to Peg-IFN plus RBV in HCV-monoinfected (Fried et al., 2002) and in HIV/HCV-coinfected (Carrat et al., 2004; Torriani et al., 2004; Pineda et al., 2010) patients. It has been reported that HCV RNA levels are higher in HIV/HCV-coinfected patients than in HCV-monoinfected subjects (Gadalla et al., 2011; Di Martino et al., 2001; Sánchez-Quijano et al., 1995; Thomas et al., 2000), which may be due to a poorer immune control of HCV replication in the setting of HIV coinfection. This finding could partly explain the negative impact of HIV infection on anti-HCV treatment response. Nevertheless, this hypothesis is based on results obtained from studies that used procedures for HCV RNA load quantification that were less sensitive than the current standard TaqMan PCR (Di Martino et al., 2001; Sánchez-Quijano et al., 1995; Thomas et al., 2000), that included low sample sizes (Di Martino et al., 2001; Sánchez-Quijano et al., 1995) and/or that were conducted in a specific subset of patients, which may not be representable of the overall HIV/HCV-coinfected population (Gadalla et al., 2011). In addition, the potential effect of the control of HIV replication by means of antiretroviral therapy (ART) was not always considered in these studies. Therefore, these observations might not be extrapolable to the present state of the art. Studies applying techniques according to the current standard, with higher sample sizes and adjusting results by the effects of controlled HIV replication are needed to elucidate this matter.

This study was aimed to evaluate the influence of HIV coinfection on plasma HCV RNA load in patients bearing HCV infection by using the Cobas Amplicor HCV Monitor test or the Cobas TaqMan system with two different detection limits (DL).

2. Patients and Methods

This was a retrospective study which included all HCV-infected patients who were consecutively seen in the Infectious Diseases

Abbreviations: DL, detection limit; HCV, hepatitis C virus; Peg-IFN, pegylated interferon; RBV, ribavirin; SVR, sustained virologic response.

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Unit of a tertiary care center in Southern Spain between January 2000 and May 2011 and who patients fulfilled the following criteria: (i) Older than 18 years; (ii) Detectable plasma HCV RNA; (iii) Lack of prior therapy against HCV. Up to March 2004, plasma HCV RNA load was measured in fresh plasma samples using the Cobas Amplicor HCV Monitor v2.0 (Roche Diagnostic Systems Inc., Branchburg, NJ, USA; DL: 600 IU/mL). After March 2004, samples were tested using the Cobas TaqMan AmpliPrep/TaqMan Test system (Roche Diagnostic Systems Inc., Pleasanton, CA, USA; DL: 10 IU/mL). HIV antibodies were tested by EIA (ADVIA Centaur XP, Siemens Healthcare Diagnostics S.L., Tarrytown, NY, USA) and confirmed by Western Blot. Continuous variables were compared using the Student's t-test or the one-way ANOVA test when applicable. A post hoc analysis by Bonferroni was conducted when ANOVA was used. The Chi-square test was applied to evaluate differences between categorical variables. Correlations between HCV RNA load correlations and HIV RNA levels as well as CD4 T cell counts were evaluated by means of Spearmańs ρ test. A log binomial regression analysis was conducted to identify factors that are independently associated with the HCV RNA load. The statistical analysis was carried out using the SPSS statistical software package release 19.0 (IBM Corporation, Somers, NY, USA) and STATA 9.0 (StataCorp LP, College Station, TX, USA).

3. Results

A total of 863 patients were included in this study. Of these individuals, 467 (54.1%) were HIV-coinfected. In 293 (34%) patients HCV RNA levels were determined with the Cobas Amplicor test and in 570 (66%) patients the HCV viral load was determined using the Cobas TaqMan assay. The main characteristics of the two groups are presented in Table 1.

The technique used for viral load quantification tended to have an impact on HCV RNA load, although significant differences were not reached. Thus, the median (Q1–Q3) level of HCV RNA was 5.95 (5.55–6.43) $\log_{10}$ IU/mL in patients tested with the Amplicor system versus 6.16 (5.44–6.75) $\log_{10}$ IU/mL in those tested with Taqman test ($p = 0.166$). Further analyses were conducted separately in the two subpopulations. The influence of HIV infection on plasma HCV RNA load within the two groups is shown in Table 1. Among patients tested using a test with a DL of 600 IU/mL, 156 (65%) of those bearing HIV coinfection showed HCV RNA viral load $\geqslant$600000 IU/mL as compared to 29 (57.4%) individuals without HIV infection ($p = 0.16$). The corresponding figures for subjects tested using the assay with a DL of 10 IU/mL were 155 (68.3%) and 215 (62.7%) patients, respectively ($p = 0.17$). The overall plasma HCV RNA load in patients with HIV infection and undetectable plasmatic HIV RNA was 6.02 (5.45–6.61) $\log_{10}$ IU/mL as compared to 6.01 (5.36–6.59) $\log_{10}$ IU/mL observed in patients without HIV coinfection ($p = 1.0$). The relation between the HCV RNA levels in HIV-infected patients with and without detectable plasma HIV RNA, as well as those without HIV infection, is shown in Fig. 1. No correlation between the plasma HCV RNA load and the HIV RNA levels $\rho = 0.791$) or the CD4 T cell count was observed ($\rho = 0.736$). Fig. 2 presents the CD4 cell counts among HIV-infected patients with or without undetectable plasma HIV RNA. A log binomial regression analysis, including age, the test used for HCV-RNA measurement, the transmission route and HIV infection as covariates and HCV RNA categorized with a cutoff level of 600000 IU/mL showed that older age [$p = 0.012$; odds ratio (95% confidence interval): 0.98 (0.96–0.99)] and detectable HIV viral load [$p = 0.049$; odds ratio (95% confidence interval): 1.67 (1.0–2.76)] were independently associated with a HCV-RNA load $\geqslant$600000 IU/ml.

4. Discussion

The present work confirms that HIV coinfection has a modest impact on plasma HCV viral load, regardless the procedure we use for HCV RNA quantification. However, the magnitude of the difference is low (0.24 $\log_{10}$ IU/mL when using a test with a DL of 10 IU/mL and 0.08 $\log_{10}$ IU if the DL is 600 IU/mL). The percentage of patients presenting a plasma HCV RNA load above 600000 IU/mL, a threshold with well-documented predictive value of response to HCV therapy, was only slightly higher in HIV coinfected patients, namely 7.6% and 5.6% higher for the two techniques. Importantly, the effect of HIV infection on plasma HCV RNA levels were not observed when plasma HIV RNA levels were undetectable. Currently, most HIV/HCV-coinfected patients treated

Table 1
Characteristics of the study population ($n = 863$).

Test used for HCV RNA determination	Amplicor[a]		*P*	TaqMan[b]		*P*
	HIV (+) $n = 240$	HIV (−) $n = 53$		HIV (+) $n = 227$	HIV (−) $n = 343$	
Age (years)[c]	32.9 (29.2–36.5)	38.5 (34.4–48.6)	<0.0001	40.5 (36.5–44.1)	42.3 (37.4–48.3)	<0.0001
Male gender, No. (%)	210 (87.5)	42 (79.2)	0.117	182 (80.2)	290 (84.5)	0.176
Transmission route, No. (%)						
IDU[d]	221 (92.1)	26 (49.1)	<0.0001	190 (83.7)	232 (67.6)	<0.0001
Sexual	0	0		7 (3.1)	0	
Blood transfusion	0	8 (15.1)		0	35 (10.2)	
Unknown	19 (7.9)	19 (35.8)		30 (13.2)	76 (22.2)	
Duration of infection (years)[c]	14.4 (9.2–17.6)	15 (10.5–19.5)	0.092	20.8 (16.7–25)	21.4 (15.5–26.1)	0.151
HCV genotype, No. (%)[e]						
1	124 (62.6)	32 (66.7)	0.146	116 (54)	196 (58.2)	0.274
2	0	1 (2.1)		2 (0.9)	5 (1.5)	
3	45 (22.7)	11 (22.9)		53 (24.7)	88 (26.1)	
4	29 (14.6)	4 (8.3)		44 (20.5)	48 (14.2)	
IL28B genotype CC, No. (%)[f]	22 (41.5)	4 (28.6)	0.377	53 (41.1)	76 (45.5)	0.447
LDLR genotype CC, No. (%)[g]	31 (66)	4 (44.4)	0.222	64 (57.7)	85 (62)	0.483
HCV viral load ($\log_{10}$ IU/ml)[c]	5.97 (5.56–6.5)	5.88 (5.3–6.16)	0.033	6.3 (5.46–6.85)	6.06 (5.37–6.65)	0.026

[a] Analyzed with Cobas Amplicor Monitor, limit of detection: 600 IU/mL.
[b] Analyzed with Cobas TaqMan System, limit of detection:10 IU/mL.
[c] Median (interquartile range).
[d] IDU: injecting drug user.
[e] Available in 798 patients.
[f] IL28B: interleukin 28B (rs12979860), available in 363 patients.
[g] LDLR: low-density lipoprotein receptor (rs14158), available in 304 patients.

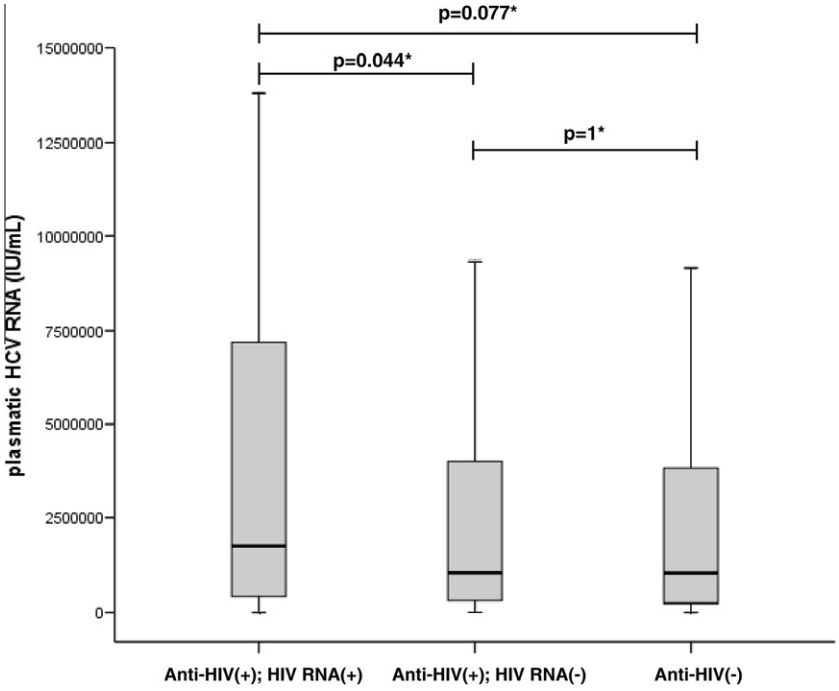

Fig. 1. Relation between the HCV RNA levels in HIV infected patients with and without detectable HIV RNA, as well as those without HIV-infection (p for the overall comparison = 0.036). *Bonferroni post hoc analysis.

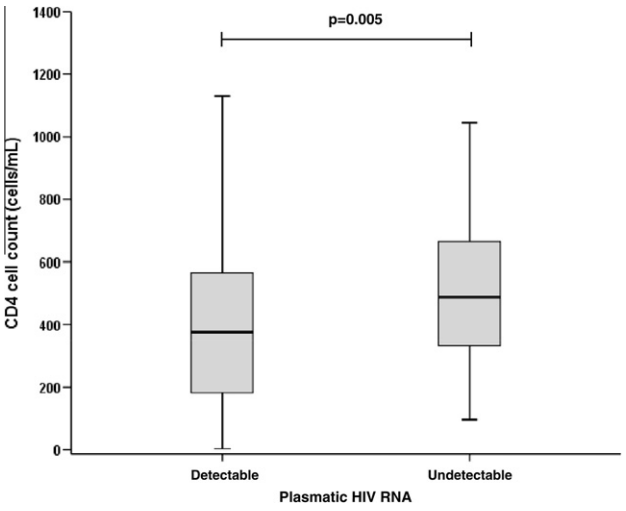

Fig. 2. Relation between the CD4 cell count and HIV RNA indetectability in the subpopulation of HIV infected patients.

against HCV receive effective ART, however, the response rates in these patient are still lower than in those without HIV infection (Pineda et al., 2007). Therefore, it is unlikely that poorer response in HIV infected individuals can be attributed to HCV RNA levels. Finally, the results of this study also suggest that ART-driven immunerestoration has a beneficial effect on controlling the replication of HCV. This is supported by the fact that CD4 cell counts were significantly higher in patients with effective ART, i.e. with undetectable plasma HIV RNA. Thus, these findings may explain in part the positive effect of antiretroviral therapy on the evolution of liver disease caused by chronic hepatitis C (Rohrbach et al., 2010) .

Slightly higher HCV RNA levels were observed in HIV/HCV-coinfected patients using two different PCR techniques. This is in accordance with previous studies conducted with less sensitive techniques and/or in smaller populations (Di Martino et al., 2001; Sánchez-Quijano et al., 1995; Thomas et al., 2000). In addition, our findings are similar to those reported in a recent study (Gadalla et al., 2011), where HIV coinfection was also associated with higher HCV viremia in a subset of HCV-infected patients with hemophilia.

Plasma HCV viremia below the cut-off value of 600000 IU/mL has been demonstrated to be a potent predictor of treatment response, both in HCV-monoinfected and in HIV/HCV-coinfected patients. This marker predicts SVR to Peg-IFN plus RBV independently of HCV genotype and interleukin 28B genotype (Neukam et al., 2012). After categorizing viral load according to this level, only a small difference, which did not reach the level of statistical significance in the univariate analysis, was observed between patients with or without HIV coinfection in both groups analyzed in this study. This finding also support that, it is unlikely that the poorer response to Peg-IFN plus RBV observed in HIV-coinfected individuals as compared to the HCV-monoinfected population can be explained to a large extent as a consequence of higher plasma HCV RNA levels in the former patients.

This study has a limitation. Determinations were conducted throughout a wide period of time and thus external conditions might have varied. However, the methods applied are widely accepted and reproducibility is well established. In addition, differences found in the first and the second study period in HIV-infected and uninfected patients were similar. It is therefore unlikely that the external variations had an influence on the results obtained.

In conclusion, HIV coinfection leads to a mild increase in plasma HCV RNA burden. However, the magnitudes of the differences are low and are not observed in patients receiving effective antiviral therapy. Therefore, it is unlikely that differences in HCV RNA burden contribute significantly to the poorer response rates to anti-HCV therapy observed in HIV/HCV-coinfected patients.

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