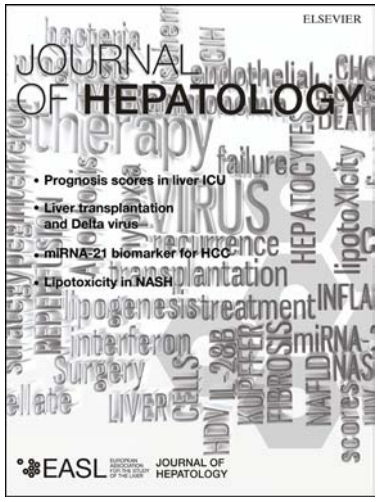

Pegylated Interferon Plus Ribavirin in HIV-infected Patients With Recurrent Hepatitis C After Liver Transplantation: A Prospective Cohort Study

Lluis Castells, Antoni Rimola, Christian Manzardo, Andrés Valdivieso, José Luis Montero, Rafael Barcena, Manuel Abradelo, Xavier Xiol, Victoria Aguilera, Magdalena Salcedo, Manuel Rodriguez, Carmen Bernal, Francisco Suarez, Antonio Antela, Sergio Olivares, Santos del Campo, Montserrat Laguno, José R. Fernandez, Gloria de la Rosa, Fernando Agüero, Iñaki Perez, Juan Gonzalez, Juan I. Esteban-Mur, Jose M. Miro the FIPSE LT-HIV investigators

PII: S0168-8278(14)00538-8
DOI: http://dx.doi.org/10.1016/j.jhep.2014.07.034
Reference: JHEPAT 5276

To appear in: *Journal of Hepatology*

Received Date: 10 June 2014
Revised Date: 22 July 2014
Accepted Date: 28 July 2014

Please cite this article as: Castells, L., Rimola, A., Manzardo, C., Valdivieso, A., Luis Montero, J., Barcena, R., Abradelo, M., Xiol, X., Aguilera, V., Salcedo, M., Rodriguez, M., Bernal, C., Suarez, F., Antela, A., Olivares, S., del Campo, S., Laguno, M., Fernandez, J.R., de la Rosa, G., Agüero, F., Perez, I., Gonzalez, J., Esteban-Mur, J.I., Miro, J.M., the FIPSE LT-HIV investigators Pegylated Interferon Plus Ribavirin in HIV-infected Patients With Recurrent Hepatitis C After Liver Transplantation: A Prospective Cohort Study, *Journal of Hepatology* (2014), doi: http://dx.doi.org/10.1016/j.jhep.2014.07.034

Title: Pegylated Interferon Plus Ribavirin in HIV-infected Patients With Recurrent Hepatitis C After Liver Transplantation: A Prospective Cohort Study

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Presented in part at the 2011 Conference on Retroviruses and Opportunistic Infections (18th CROI), Boston, Massachusetts, Abstract # Q-188.

Running head: Treatment of recurrent hepatitis C in HIV-infected liver transplant recipients

Keywords: Liver transplantation, HIV infection, HCV infection, recurrence of hepatitis C, pegylated-interferon, ribavirin, antiviral treatment, survival.

Text word count including references = 4,999

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Abbreviations

AIDS: acquired immunodeficiency syndrome

HAART: highly active antiretroviral therapy

CI: confidence interval

FIPSE: Spanish Foundation for the Investigation and Prevention of AIDS

GESIDA: Spanish Group for the Study of AIDS

HBV: hepatitis B virus

HCC: hepatocellular carcinoma

HCV: hepatitis C virus

HIV: human immunodeficiency virus

OR: odds ratio

IQR: interquartile range

MELD: Model for End Stage Liver Disease

MSM: men who have sex with men

NRTI: nucleoside reverse transcriptase inhibitor

LT: liver transplantation

SVR: sustained virological response

PI: protease inhibitor

PegIFN: pegylated interferon

RBV: ribavirin

ABSTRACT

Background & Aims: To evaluate the results of the treatment with pegylated interferon and ribavirin for recurrence of hepatitis C after liver transplantation in HCV/HIV-coinfected patients.

Methods: Prospective, multicenter cohort study including 78 HCV/HIV-coinfected liver transplant patients who received treatment for recurrent hepatitis C. For comparison, we included 176 matched HCV-monoinfected patients who underwent liver transplantation during the same period of time at the same centers and were treated for recurrent hepatitis C.

Results: Antiviral therapy was discontinued prematurely in 56% and 39% (p=0.016), mainly because of toxicity (22% and 11%, respectively; p=0.034). Sustained virological response (SVR) was achieved in 21% of coinfected patients and 36% of monoinfected patients (p=0.013). For genotype 1, SVR rates were 10% and 33% (p=0.002), respectively; no significant differences were observed for the other genotypes. A multivariate analysis based on the whole series identified HIV-coinfection as an independent predictor of lack of SVR (OR, 0.45; 95% CI, 0.24-0.85). Other predictors of SVR were donor age, pretreatment HCV viral load, HCV genotype, and early virological response. SVR was associated with a significant improvement in survival: 5-year survival after antiviral treatment was 79% for HCV/HIV-coinfected patients with SVR vs. 43% for those without (p=0.02) and 92% vs. 60% in HCV-monoinfected patients (p<0.001), respectively.

Conclusions: The response to pegylated interferon and ribavirin was poorer in HCV/HIV-coinfected liver recipients, particularly those with genotype 1. However, when SVR was achieved, survival of coinfected patients increased significantly.

Word count = 236

INTRODUCTION

Since the introduction of highly active anti-retroviral therapy (HAART) in the mid-1990s and the subsequent drastic reduction in mortality of HIV infection [1], HCV-related liver disease has become a leading cause of death in HCV/HIV-coinfected individuals [2]. Consequently, in recent years, liver transplantation (LT) has been increasingly performed in selected HIV-infected patients [3, 4]. However, post-LT survival in HCV/HIV-coinfected patients has been poorer than that reported in HCV-monoinfected patients, particularly due to higher rates of graft loss and death due to HCV recurrence in the former [5-8]. In this regard, experience with antiviral treatment of recurrence in HIV-infected LT recipients with pegylated-interferon (pegIFN) and ribavirin (RBV) remains scarce, consisting of reports from small series of patients, mostly without a comparative group of HCV-monoinfected patients. In these reports, the rate of sustained virological response (SVR) was relatively low, ranging from 10% to 35% [5-7, 9-12], with the exception of the study by Wojcik et al. [13], who reported an SVR rate of 100% in a series of 4 patients. The most detailed report, a post-LT multicenter study from the United States, included 39 HCV/HIV-coinfected patients with hepatitis C recurrence treated with pegylated-interferon (pegIFN) and ribavirin (RBV) with an SVR of only 14% [14]. Unfortunately, this study did not include a control group of HCV-monoinfected patients and survival was analyzed according to whether end-of-therapy response was achieved or not instead of SVR, a more logical event for this purpose.

Since 2002 [15], most Spanish LT units have performed transplants in HIV-infected patients following the same HIV-inclusion criteria for LT [16], with the result that a sizeable cohort of HCV/HIV-coinfected patients has been prospectively followed since surgery. Based on data from this cohort, we evaluated the results of treatment with pegIFN and RBV for recurrent hepatitis C in HCV/HIV-coinfected patients. For

comparison, we included a control group comprising HCV-monoinfected patients treated for post-LT recurrence of hepatitis C.

PATIENTS AND METHODS

Study design

We performed a multicenter, cohort study based on 149 consecutive HCV/HIV-coinfected patients who underwent LT between 2002 and 2009 in Spain and who were prospectively followed until July 2012. These patients were matched with 447 HCV-monoinfected patients (1:3) who underwent LT during the same period at the same sites. Other matched criteria were calendar year (±1 year), age (±12 years), gender, presence of HBV coinfection, and presence of hepatocellular carcinoma (HCC). Only coinfected patients who had received post-transplant anti-HCV therapy with pegINF and RBV and who had matched monoinfected controls treated against HCV in the same center were included (see Figure 1). The Institutional Review Boards of all the participating sites approved the study. All patients signed the informed consent form.

As shown in Figure 1, 84 (56%) out of 149 HCV/HIV-coinfected patients and 207 (46%) out of 447 HCV-monoinfected patients (p=0.042) received antiviral therapy for recurrence of hepatitis C after LT in 13 centers. After excluding 6 coinfected patients and 31 monoinfected patients for different reasons, shown in figure 1, the final study population comprised 78 coinfected and 176 monoinfected patients.

Pre-, peri-, and post-transplant variables for coinfected patients were collected at each site using a standardized case report form as described previously [8]. Information for each patient was recorded before treatment and at 3, 6, 9, 12, and 18 months after starting anti-HCV therapy. The variables collected are presented in tables 1, 2, and 3. Patient information was sent every 6 months to the coordinating center and entered into the FIPSE LT-HIV-05-GESIDA 45-05 database (available at

https://www.seif88.com/gesida/asp/login.asp). Data from HIV-negative recipients were obtained from the Spanish Liver Transplant Registry as previously described [8]. Variables related to anti-HCV therapy not included in the registry were collected at the participating sites according to a common protocol. Data were managed and analyzed blind at the coordinating center.

Diagnosis and management of recurrent hepatitis C

During post-LT follow-up, liver biopsies were performed following the protocols of each center and were usually annual or bi-annual. Fibrosing cholestatic hepatitis (FCH) was defined according to standard histological criteria [17]. Necroinflammatory activity and fibrosis stage were established according to the METAVIR scoring system [18]. Severe histological recurrent hepatitis C was defined as the development of FCH or fibrosis stage F3/F4.

Recurrence was treated with pegIFN α-2a or α-2b and RBV and was based on the same criteria as for HCV-monoinfected LT recipients according to local protocols. Despite variations between centers and protocols over time, all protocols included the following 2 criteria: a) antiviral treatment was indicated in patients with both positive serum HCV RNA and histological and/or biochemical (increased serum transaminases without any other apparent reason and with stable immunosuppression) evidence of hepatitis; and b) treatment was initially planned for 48 weeks, although it could be discontinued in the absence of an early virological response (EVR), defined as a decrease of at least 2 log10/mL in plasma HCV RNA viral load at 12 weeks of therapy. End of therapy response (ETR) was defined as a negative plasma HCV RNA viral load at the end of therapy. SVR was defined as a persistently negative plasma HCV-RNA viral load at 24 weeks after the end of treatment. Biochemical response was defined as normalization of aminotransferase levels at the end of treatment, regardless of the

virological response. In patients without ETR but with marked clinical and/or biochemical improvement, maintenance therapy with pegIFN could be administered at the attending physician's discretion.

Statistical analysis

Variables are expressed as the mean and standard deviation, median and interquartile range [IQR], and as proportions, as appropriate. Outcomes after starting antiviral therapy were analyzed on an intention-to-treat basis. Patient and graft survival were calculated with the date of the initiation of anti-HCV therapy as the start date and estimated using the Kaplan-Meier method, and the curves obtained were compared using the generalized log-rank test (univariate Cox model analysis). We performed a univariate analysis of predictors of SVR using logistic regression analysis. Those associated with a p value <0.10 in the univariate analysis were considered candidate predictors for the multivariate analyses. We used both forward stepwise and backward elimination subset selection methods to identify variables that independently predicted SVR. The significance level for entering effects was <0.1, and the significance level for removing effects was <0.05. The odds ratio (OR) and the associated 95% confidence interval (CI) for each predictor of SVR were calculated. Statistical significance was defined as a bilateral p value <0.05. All statistical analyses were carried out using the Stata package (release 9.2).

RESULTS

Baseline characteristics

The main characteristics of coinfected and monoinfected patients before starting anti-HCV therapy are summarized in table 1. Coinfected patients were younger, started antiviral treatment earlier, more frequently had HCV genotype 3, and had a higher

incidence of FCH than their monoinfected counterparts. Conversely, monoinfected patients more frequently had genotype 1 and less frequently genotype 4, and higher aminotransferase levels at initiation of antiviral therapy. The two cohorts did not significantly differ in the remaining baseline variables (Table 1).

Recurrence of hepatitis C was confirmed histologically before antiviral therapy in 78% of coinfected patients and in 83% of monoinfected patients. Immunosuppressive therapy was also similar in both groups at the time of antiviral treatment.

Results of antiviral therapy

Antiviral therapy was started after a median (IQR) of 10 months (5-18) after LT in coinfected patients compared with 15 months (7-21) in monoinfected patients, p=0.023).

Thirty-four of the 78 coinfected patients (44%) and 107 of the 176 monoinfected patients (61%) completed 48 weeks of treatment, while 44 patients (56%) and 69 patients (39%), respectively (p=0.016), discontinued treatment prematurely (Table 1). Discontinuation because of toxicity related to antiviral treatment was significantly more frequent in coinfected patients (22% vs. 11%; p=0.034). The use of growth factors during antiviral treatment was similar in both groups: erythropoietin/darbepoetin in 55% and 56%, and granulocyte colony-stimulating factor in 27% and 24%, respectively.

Virological response to anti-HCV therapy with pegIFN and RBV is summarized in Table 2. The frequency of EVR, ETR, and SVR was 42%, 29%, and 21% in coinfected patients and 57%, 44%, and 36% in monoinfected patients (p<0.05 in all comparisons). When patients were classified according to genotype, EVR, ETR, and SVR were less frequent in coinfected patients for all 4 genotypes, although the differences were only

statistically significant for genotype 1 (Table 2). Of note, the rate of SVR for genotype 4 was very low: 7% in coinfected and 0% in monoinfected patients.

The negative influence of HIV coinfection on antiviral efficacy was maintained in a multivariate analysis of the whole series of HCV-infected patients, in which HCV/HIV coinfection was identified as an independent predictor of SVR (OR, 0.268; 95% CI, 0.085-0.745) after adjustment for other variables capable of affecting the antiviral response (Table 3). In this analysis, other predictive factors of SVR were donor age, pre-treatment HCV viral load and HCV genotype. EVR was also a powerful predictor of SVR ($p<0.001$ in the univariate analysis), but a statistical issue precluded the introduction of this variable in the multivariate analysis (no patient had SVR without EVR). Interestingly, the use of cyclosporine was not significantly associated with SVR.

When we restricted the analysis of predictors of SVR to the 78 coinfected patients (Supplementary Table 1), the only variables identified as predictive factors of SVR were donor age (OR, 8.82; 95% CI, 1.62-79.39) and HCV genotype (OR, 23.86; 95% CI, 5.59-136). EVR was also strongly associated with SVR in the univariate analysis ($p<0.001$), but this variable could not be introduced in the multivariate analysis owing to statistical issues (no patient reached SVR without EVR). In addition, HIV-specific variables such as previous AIDS criteria, CD4 nadir, pre-treatment CD4 count, pre-treatment plasma HIV viral load and the type of antiretroviral regimen did not influence the outcome.

Biochemical response was less frequent in coinfected patients than in monoinfected patients (27% vs. 60%, $p<0.001$). Maintenance of pegIFN monotherapy beyond the end of the scheduled administration of the combination of pegIFN and RBV was used in a similar proportion of patients in both cohorts: 10% and 11%.

Two (3%) out of the 78 coinfected patients developed rejection during anti-HCV treatment.

Course of HIV infection during anti-HCV therapy

Median (IQR) CD4 cell counts before and at 24, 48, and 72 weeks after starting anti-HCV therapy were 315 (209-435), 180 (95-288), 226 (138-398), and 310 (214-458) cells/mm^3 respectively. Plasma HIV-RNA viral load was below 200 copies/mL at the same time points in 87%, 97%, 97%, and 93% of cases. During or within the 6 months following anti-HCV therapy, 4 patients (5%) developed an AIDS-defining disease (esophageal candidiasis, pulmonary tuberculosis, disseminated varicella-zoster, and CMV disease [1 case each]). All 4 cases were cured with appropriate antimicrobial therapy.

Survival

HCV/HIV-coinfected patients and HCV-monoinfected patients were followed up for a median of 2.50 and 2.42 years, respectively, after starting antiviral treatment. During follow-up, the mortality rate in the 2 groups was 40% and 21% (p=0.003) (Table 4). Figure 2A shows the cumulative survival in both populations, which was significantly lower for coinfected patients. When HCV/HIV-coinfected and HCV-monoinfected patients were classified according to whether or not they had SVR, those with SVR (both groups) had a significantly higher survival rate than those without, as shown in figures 2B and 2C. A trend towards lower survival was observed in coinfected patients with and without SVR in comparison to their monoinfected counterparts, although the differences did not reach statistical significance (p values of 0.1392 and 0.0915, respectively). HCV-related liver graft disease was an infrequent cause of death in

patients with SVR, whereas recurrence of hepatitis C was the most important cause of death in patients without SVR (Table 4).

The retransplantation rate was 2.6% (2/78) in coinfected patients and 3.4% (6/176) in monoinfected patients (p=1.000). Graft survival is shown in Supplementary Figure 1.

DISCUSSION

In the present study, HCV/HIV-coinfected liver recipients showed a significantly lower SVR to treatment with pegIFN and RBV than HCV-monoinfected recipients: 21% vs. 36% (Table 2). The adverse impact of HIV coinfection on treatment of recurrent hepatitis C was also supported by the results of a multivariate analysis of the whole study population, in which HIV coinfection was independently associated with lack of SVR. This is not surprising, as our results are consistent with those of large, multicenter, randomized controlled trials involving patients who did not undergo transplant in which treatment with pegIFN and RBV resulted in SVR rates of 27% to 40% in HCV/HIV-coinfected patients [19-21] and of around 60% in non-HIV-infected individuals [22].

Several explanations can be proposed for the reduced SVR observed in our coinfected population. First, the impaired immune response in many HIV-infected patients might have negatively affected anti-HCV treatment efficacy, as has been suggested for coinfected patients who did not undergo transplant [23]. Second, since adherence to treatment is thought to be one of the most important determinants of SVR in liver recipients with recurrent hepatitis C [24], the higher rate of premature discontinuation of antiviral treatment we observed in coinfected patients (56% vs. 39%; Table 1), mainly due to a higher frequency of adverse effects associated with antiviral therapy, could also have contributed to the lower antiviral efficacy in this population. Since FCH is

associated with a poor therapeutic response in LT recipients [25], another potential reason for the lower efficacy of anti-HCV therapy in coinfected patients could have been the higher frequency of FCH in this group than in the monoinfected group (13% vs. 3%, Table 1). However, we were unable to identify FCH as a significant predictive factor for SVR in any of our analyses. Other baseline differences between coinfected and monoinfected patients, such as younger age, earlier initiation of antiviral therapy, and lower serum ALT levels in the former (Table 1), can hardly explain the lower treatment efficacy attained in coinfected patients. Furthermore, it is unlikely that the different distribution of HCV genotypes in the 2 cohorts influenced the reduced efficacy of antiviral treatment in coinfected patients, because this population had a lower proportion of the unfavorable genotypes 1 and 4 (72% vs. 87%). Nevertheless, since the different genotypes strongly affected the response to antiviral therapy in coinfected liver recipients, we address this issue in greater depth below.

A noteworthy finding in our study was that anti-HCV treatment with pegIFN and RBV was poorly effective in coinfected patients with genotypes 1 and 4 (SVR rates of only 10% and 7%, respectively). In contrast, the efficacy of anti-HCV therapy in coinfected patients with genotype 3, while not ideal, was much higher (SVR rate of 59%). The value of the HCV genotype in predicting SVR in coinfected patients was maintained in a multivariate analysis adjusted for other potential predictors (Supplementary Table 1). The strong influence of HCV genotype on antiviral efficacy in the coinfected population could be expected from previously published information in monoinfected liver transplant recipients [26], as well as from our own results in the monoinfected cohort, where the rates of SVR were also lower for genotypes 1 and 4 (33% and 0%, respectively) than for genotypes 2 and 3 (80% overall). These results are particularly relevant, because genotype 1 was a frequent finding in coinfected patients, as was genotype 4, albeit to a lesser extent (54% and 18%, respectively). A low antiviral efficacy in patients with genotype 1 was also observed in the study from the United

States of America [14], with an identical SVR rate as in our study: 10%. Based on these results, better anti-HCV medication is urgently required for the management of recurrence of hepatitis C after LT.

In addition to HCV genotype, donor age and early virological response were strongly associated with SVR in coinfected patients, a finding that is consistent with the results obtained in previous studies on predictors of anti-HCV treatment efficacy in LT recipients [27]. Contrary to what has been suggested for HCV-moninfected LT recipients [28], we did not observe any beneficial effect of cyclosporine on the response to treatment of recurrent hepatitis C in coinfected patients.

An encouraging finding from our investigation is that SVR in coinfected patients was associated with a substantial increase in survival (Figure 2B), similar to that of monoinfected recipients with recurrent hepatitis C [29-31]. Five-year survival after initiation of antiviral treatment in coinfected patients with SVR was 79%, whereas it was only 43% in patients without SVR. Coinfected patients with SVR had a lower survival probability than monoinfected patients, although the difference was not statistically significant (Figure 2B and 2C). As expected, mortality in patients without SVR in our series was mainly associated with recurrence of hepatitis C in both the coinfected cohort and the monoinfected cohort (Table 4). The strong negative impact of the lack of SVR on the survival of the coinfected population emphasizes the urgent need for improved antiviral therapy in these patients. Although data in the LT setting are scarce, preliminary results have shown higher SVR rates in LT recipients treated with triple therapy including pegIFN, RBV, and telaprevir or boceprevir, regardless the frequent side effects and drug interactions with calcineurin inhibitors leading to increased discontinuation rates and thereby limiting antiviral efficacy [32-35]. The introduction of IFN-free regimens, with a much tolerance, will presumably enable even

higher antiviral efficacy to be achieved. In this sense, a recent prospective, multicenter study of 40 HIV-negative patients with recurrent hepatitis C after LT showed that the combination of sofosbuvir and RBV had a SVR rate of approximately 70% and was very well tolerated [36]. Furthermore, recent results in HCV/HIV-coinfected non-transplanted patients treated with INF-free antiviral regimens [37] are excellent, with SVR rates close to those reported for HCV-monoinfected non-transplanted patients [38]. All these results are very promising for HCV/HIV-coinfected patients with post-LT hepatitis C recurrence.

Our study is subject to a series of limitations. First, antiviral therapy in both cohorts was based on local protocols, which changed somewhat over the study period. Nonetheless, the same therapeutic strategy was used in both HCV/HIV-coinfected patients and their HCV-monoinfected counterparts, who were matched for participating center and calendar year, thus making the comparison of the cohorts reliable. Other limitations include the lack of information on rapid virological response and genotyping of *IL28B* polymorphisms, thus precluding any valid analysis of their potential effect on antiviral efficacy. The relatively small size of the subsets of coinfected patients with and without SVR completing a prolonged follow-up could also limit evaluation of the impact of response to treatment on survival. Nevertheless, our results are robust in that they are from a nationwide multicenter study of the largest series to date of HCV/HIV-coinfected patients treated with anti-HCV therapy after transplant. Coinfected patients were matched with a control group of HCV-monoinfected liver recipients who also took anti-HCV therapy. In addition, follow-up in both cohorts was sufficiently long to evaluate the impact of response to treatment on survival.

In conclusion, the present study showed that the combination of pegIFN and RBV was less efficacious in HCV/HIV-coinfected liver recipients than in HCV-monoinfected recipients. The rate of SVR was particularly low in patients with HCV genotypes 1 and

4. However, when sustained SVR was achieved, survival of HCV/HIV-coinfected patients increased substantially.

Acknowledgments

We are indebted to the study participants and to the staff of the liver transplant units at the centers for retrieving detailed data on donors and transplantation. We dedicate this article to Dr. Iñaki Perez (Barcelona) statistician who played a key role in this project and who died recently. We also acknowledge the following organizations: "Fundación para la Investigación y Prevención del Sida en España (FIPSE)", Madrid, Spain; the National AIDS Plan Secretariat and the National Transplant Organization (ONT) of the Spanish Ministry of Health, Madrid, Spain; the Spanish Society of Liver Transplantation (SETH), Madrid, Spain; and the HIV/AIDS (GESIDA) and Infections in Transplants (GESITRA) Working Groups and the SEIMC/GESIDA Foundation (FSG) of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC), Madrid, Spain for their constant support from the beginning of the project. CIBEREHD was supported by Instituto de Salud Carlos III, Madrid (Spain).

Funding sources

This study was supported by grants from the Spanish Foundation for AIDS Research and Prevention (FIPSE, Madrid, Spain) (TOH-VIH/05/08/12/13/14) and the Spanish Ministry of Health (Madrid, Spain) – "Investigación Clínica Independiente" grant EC11-150. JMM held an INT10/219 Intensification Research Grant (I3SNS&PRICS programs) from the "Instituto de Salud Carlos III", Madrid (Spain) and the "Departament de Salut de la Generalitat de Catalunya", Barcelona (Spain) in 2011-2012. FA held a Rio Hortega Research Grant (CM12/00195) from the "Instituto de Salud Carlos III" and the "Ministerio de Economia and Competitividad", Madrid (Spain) in 2013-2015.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Figure Legends

Figure 1. Flow-chart of HCV/HIV-coinfected and HCV-monoinfected liver transplant patients according to whether they received or did not receive treatment with pegylated-interferon plus ribavirin for recurrence of hepatitis C. * $p<0.05$ vs. HCV-monoinfected patients.

INF, interferon; RBV, ribavirin.

Figure 2: Probability of patient survival in all patients (**2A**) and in HCV/HIV-coinfected (**2B**) and HCV-monoinfected (**2C**) liver transplant patients, classified according to whether sustained virological response (SVR) to anti-HCV therapy was achieved or not.

Supplementary Figure 1: Probability of graft survival in HCV-infected liver recipients according to HIV status.

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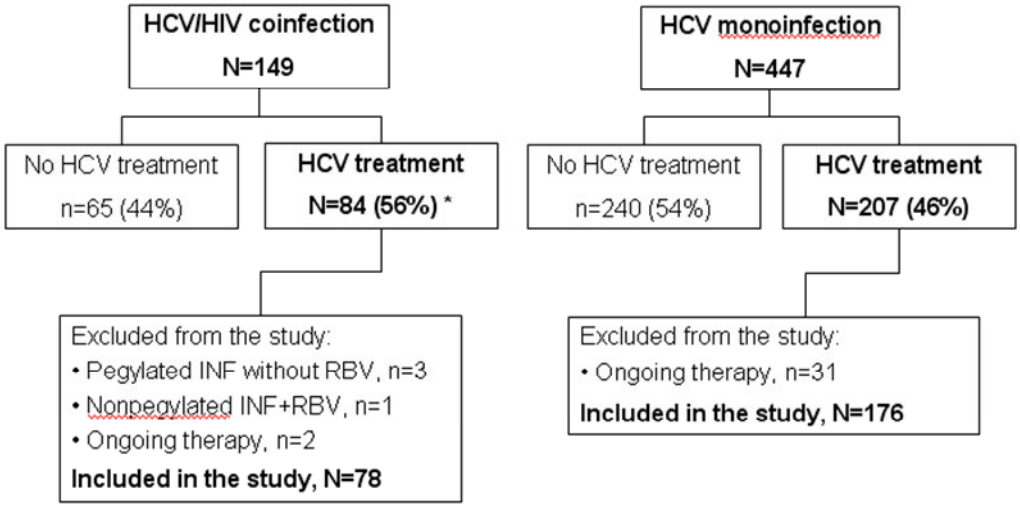
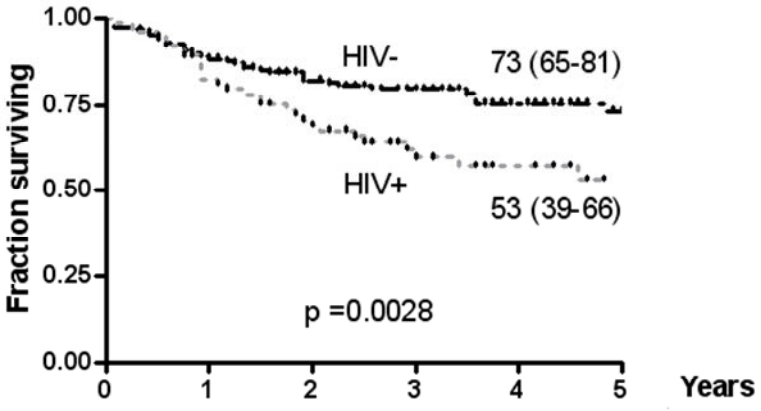


Figure 1

2A. All patients



HIV-

At risk (n)	176	146	107	75	48	32
Survival	100%	88%	82%	80%	76%	73%

HIV+

At risk (n)	78	59	43	25	19	12
Survival	100%	81%	68%	59%	56%	53%

Table 1. Characteristics and accomplishment of anti-HCV treatment of HCV/HIV-coinfected and HCV-monoinfected liver transplant recipients.

	HCV/HIV-coinfected	HCV-monoinfected	p Value
No. of cases	**78**	**176**	
Age (y)*	43 (39-46)	47 (43-53)	<0.001
Male recipients, *n* (%)	59 (76%)	135 (77%)	0.873
Data related to HIV infection			
HIV-1 risk factors, *n* (%) Drug use MSM Heterosexual relations Hemophilia Other	 59 (76%) 2 (3%) 9 (12%) 5 (6%) 3 (3%)	 NA	
Duration of HIV-1 infection (mo)	191 (134-225)	NA	
AIDS-defining events, *n* (%)	6 (8%)	NA	
Data at the time of LT			
Pre-LT anti-HCV treatment, *n* (%)	30 (38%)	48 (27%)	0.140
Hepatocellular carcinoma, *n* (%)	15 (19%)	39 (22%)	0.740
MELD score at listing	15 (12-18)	15 (12-19)	0.699
Donor characteristics			
Age (y) Cause of donor brain death, *n* (%) Vascular Cranial trauma Other	53 (43-66) 45 (58%) 19 (24%) 12(15%)	50 (36-64) 112 (64%) 53 (30%) 11 (6%)	0.148 0.066
Data at initiation and accomplishment of anti-HCV treatment			
Interval between transplantation and anti-HCV treatment (mo)	10 (5-18)	15 (7-21)	0.024
Type of HAART, *n* (%) NRTI-based PI-based Efavirenz-based Other	 11 (14%) 21 (27%) 37 (47%) 9 (12%)	 NA	
Plasma HIV-1 RNA <50 copies/mL, *n* (%)	68 (87%)	NA	
CD4 cell count	315 (209-435)	NA	
HCV genotype, *n* (%)			

1	42 (54%)	147 (84%)	0.000
2	0 (-)	2 (1%)	0.861
3	17 (22%)	13 (7%)	0.002
4	14 (18%)	6 (3.5%)	0.000
Non-typable/other	5 (6%)	8 (5%)	0.754
Plasma HCV RNA viral load (log_{10})	6.65 (6.11-7.23)	6.64 (6.08-7.10)	0.577
AST, IU/mL	127 (82-203)	156 (87-252)	0.198
ALT, IU/mL	116 (78-191)	175 (96-297)	0.007
Liver biopsy, *n (%)*	61 (78%)	147 (83%)	0.402
-Necroinflammatory activity, METAVIR grade A2-A4	56 (92%)	136 (93%)	1.000
Severe histological hepatitis	15 (25%)	22 (15%)	0.146
- Fibrosing cholestatic hepatitis	8 (13%)	4 (3%)	0.009
- METAVIR stage F3/F4 fibrosis	7 (12%)	18 (12%)	0.937
Immunosuppression before starting anti-HCV treatment, *n* (%)			0.242
- Cyclosporine-based	25 (32%)	39 (25%)	
- Tacrolimus-based	53 (68%)	118 (75%)	
- Unknown	-	19	
Type of pegylated interferon			0.281
- Alpha 2a	25 (32%)	49 (28%)	
- Alpha 2b	52 (67%)	117 (66%)	
- Not specified	1 (1%)	10 (6%)	
Accomplishment of anti-HCV treatment, *n* (%)	34 (44%)	107 (61%)	0.016
- 48-week treatment completed	44 (56%)	69 (39%)	
- Prematurely discontinued			
Reasons for premature discontinuation, *n* (%)			
- Treatment-related toxicity	17 (22%)	19 (11%)	0.034
- Lack of efficacy	20 (26%)	37 (21%)	NS
- Death during treatment	5 (6%)**	4 (2%)***	NS
- Other	2 (3%) ¶	2 (1%) ¶¶	NS
- Unknown	-	7 (4%)	-

MSM, men who have sex with men; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; HAART, highly active antiretroviral therapy; NRTI, nucleotide reverse transcriptase inhibitor; PI, protease inhibitor; AST, aspartate aminotransferase; ALT, alanine aminotransferase; NA, not applicable.
*All quantitative variables are expressed as median and interquartile range.
** Recurrent hepatitis C in 3 cases and *de novo* tumor and rejection in 2 patients (1 case each).
*** Recurrent hepatitis C in 3 cases and hepato-pulmonary syndrome in 1 case
¶ Recurrent hepatocellular carcinoma and hepato-pulmonary syndrome (1 case each).

¶¶ *De novo* tumor in 2 cases.

Table 2. Virological response to pegylated-interferon plus ribavirin in HCV/HIV-coinfected and HCV-monoinfected liver transplant recipients.

	HCV/HIV-coinfected	HCV-monoinfected	p Value
Overall	**78**	**176**	
- EVR	33 (42%)	100 (57%)	0.041
- ETR	23 (29%)	78 (44%)	0.027
- SVR	16 (21%)	64 (36%)	0.013
Genotype 1	**42**	**147**	
- EVR	11 (26%)	79 (54%)	0.002
- ETR	7 (17%)	57 (39%)	0.009
- SVR	4 (10%)	49 (33%)	0.002
Genotypes 2/3	**17**	**15**	
- EVR	15 (88%)	14 (93%)	1.000
- ETR	12 (71%)	13 (87%)	0.402
- SVR	10 (59%)	12 (80%)	0.265
Genotype 4	**14**	**6**	
- EVR	4 (29%)	3 (50%)	1.000
- ETR	2 (14%)	3 (50%)	0.131
- SVR	1 (7%)	0 (0%)	1.000

EVR, early virological response; ETR, end of therapy response; SVR, sustained virological response.

Table 3. Predictors of sustained virological response in HCV-infected liver transplant recipients.

				Univariate analysis		*Multivariate analysis*	
	Category	*n*	SVR N (%)	*OR (95% CI)*	*p Value*	*OR (95% CI)*	*p Value*
Calendar year*	Early	89	32 (36)	1.37 (0.79-2.37)	0.262		
	Late	165	48 (29.1)				
HIV status	Positive	78	16 (20)	0.45 (0.24-0.85)	0.013	0.17 (0.06-0.42)	<0.001
	Negative	176	64 (36)				
Recipient age	<40 years	45	10 (22.2)	0.57 (0.27-1.21)	0.143		
	≥40 years	209	70 (33.5)				
Recipient gender	Male	194	57 (29.4)	0.67 (0.37-1.23)	0.193		
	Female	60	23 (38.3)				
Pre-LT anti-HCV treatment	Missing	6	2 (33.3)				
	No	170	55 (32.4)	1.14 (0.64-2.05)	0.652		
	Yes	78	23 (29.5)				
Donor age	<60 years	171	68 (39.8)	3.91 (1.97-7.74)	<0.001	7.30 (3.18-19.05)	<0.001
	≥60 years	83	12 (14.5)				

				Univariate analysis		*Multivariate analysis*	
	Category	*n*	SVR N (%)	*OR (95% CI)*	*p Value*	*OR (95% CI)*	*p Value*
Cause of donor brain death	Missing	2	0 (0)				
	Cranial trauma	72	26 (36.1)	1.32 (0.74-2.35)	0.527		
	Other	180	54 (30)				
Interval between LT and anti-HCV treatment	Missing	1	0 (0)				
	< 1 year	111	33 (29.7)				
	≥1 year	142	47 (33.1)	1.17 (0.68-2.00)	0.568		
Pre-treatment plasma HCV RNA viral load¶	Missing	24	6 (25)				
	Low	114	48 (42.1)	2.52 (1.42-4.47)	0.002	2.56 (1.33-5.04)	0.005
	High	116	26 (22.4)				
HCV genotype	1 and 4	209	54 (25.8)				
	2 and 3	32	22 (68.8)	6.31 (2.81-14.18)	<0.001	24.47 (7.71-92.8)	<0.001
Severe histological hepatitis #	Missing	46	9 (19.6)				

				Univariate analysis		*Multivariate analysis*	
	Category	*n*	SVR N (%)	*OR (95% CI)*	*p Value*	*OR (95% CI)*	*p Value*
	0 No	171	59 (34.5)				
	1 Yes	37	12 (32.4)	0.91 (0.43-1.94)	0.810		
Fibrosing cholestatic hepatitis	Missing	46	9 (19.6)				
	0 No	196	69 (35.2)				
	1 Yes	12	2 (16.7)	0.37 (0.08-1.73)	0.205		
METAVIR F3/F4 fibrosis stage	Missing	46	9 (19.6)				
	0 No	183	61 (33.3)				
	1 Yes	25	10 (40.0)	1.33 (0.57-3.14)	0.511		
Type of immunosuppression	CsA- based	62	17 (27.4)	0.76 (0.40,1.45)	0.408		
	Non CsA-based	169	56 (33.1)				
Erythropoietin/darbepoetin use	No	106	28 (26.4)				
	Yes	135	46 (34.1)	1.44 (0.82-2.52)	0.202		

				Univariate analysis		*Multivariate analysis*	
	Category	*n*	SVR N (%)	*OR (95% CI)*	*p Value*	*OR (95% CI)*	*p Value*
G-CSF use	No	183	57 (31.1)				
	Yes	61	19 (31.1)	1.00 (0.53-1.87)	1.00		
Early virological response	No	121	0 (0)				
	Yes	133	80 (60.2)	NA	<0.001[+]		

SVR, sustained virological response; LT, liver transplantation; CsA, cyclosporine A; G-CSF, granulocyte colony-stimulating factor; NA, not applicable.

* Early, 2002-June 2007; late, July 2007-2010.

¶ Below (low) or above (high) the median (4,400,000 u/L)

[+] Fisher exact test. Variable not introduced in the multivariate analysis because no patient reached an SVR without an early virological response.

#

Table 4. Mortality rate and causes of death in HCV/HIV-coinfected and HCV-monoinfected liver transplant recipients after starting anti-HCV therapy.

	HCV/HIV-coinfected	HCV-monoinfected	p Value
No. of cases	**78**	**176**	
Mortality	31 (40%)	37 (21%)	0.003
Mortality in patients with SVR	3/16 (19%)	4/64 (6%)	0.139
Causes of death			
- HCV recurrence	1 (6%)	2 (3%)	
- Infection	-	1 (1%)	
- HCC recurrence	-	1 (1%)	
- Miscellaneous	2 (12%)	-	
Mortality in patients without SVR	28/62 (45%)	33/112 (29%)	0.056
Causes of death			
- HCV recurrence	23 (37%)	27 (24%)	
- Infection	1 (1%)	2 (2%)	
- Miscellaneous	4 (6%)	4 (4%)	

SVR, sustained virological response; HCC, hepatocellular carcinoma.