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Direct-acting antivirals are effective and safe in HCV/HIV-coinfected liver transplant recipients who experience recurrence of hepatitis C: A prospective nationwide cohort study

Christian Manzardo[1] | Maria C. Londoño[1] | LLuís Castells[2,3] | Milagros Testillano[4] | José Luis Montero[2,5] | Judit Peñafiel[1] | Marta Subirana[1] | Ana Moreno[6] | Victoria Aguilera[7] | María Luisa González-Diéguez[8] | Jorge Calvo-Pulido[9] | Xavier Xiol[10] | Magdalena Salcedo[11] | Valentin Cuervas-Mons[12] | José Manuel Sousa[13] | Francisco Suarez[14] | Trinidad Serrano[2,15] | Jose Ignacio Herrero[2,16] | Miguel Jiménez[17] | José R. Fernandez[4] | Carlos Giménez[9] | Santos del Campo[6] | Juan I. Esteban-Mur[2,3] | Gonzalo Crespo[1,2] | Asunción Moreno[1] | Gloria de la Rosa[18] | Antoni Rimola[1,2] | Jose M. Miro[1] and the FIPSE LT-HIV investigators

[1]Hospital Clinic-IDIBAPS, University of Barcelona, Barcelona, Spain

[2]CIBEREHD, Barcelona, Spain

[3]Liver Unit, Internal Medicine Department, Hospital Vall d'Hebrón, Universitat Autónoma de Barcelona, Barcelona, Spain

[4]Servicio de Digestivo, Hospital Universitario Cruces, Barakaldo, Barakaldo

[5]Hospital Universitario Reina Sofía-IMIBIC Córdoba, Cordoba, Spain

[6]Hospital Universitario Ramón y Cajal-IRYCIS, Madrid, Spain

[7]Hospital Universitari La Fe, Valencia, Spain

[8]Hospital Universitario Central de Asturias, Oviedo, Spain

[9]Hospital Universitario Doce de Octubre, Madrid, Spain

[10]Hospital de Bellvitge-IDIBELL, University of Barcelona, L'Hospitalet de Llobregat, Barcelona, Spain

[11]Hospital General Universitario Gregorio Marañón, Madrid, Spain

[12]Hospital Universitario Puerta de Hierro, Madrid, Spain

[13]Hospital Universitario Virgen del Rocío, Sevilla, Spain

[14]Complejo Hospitalario Universitario, A Coruña, Spain

[15]Hospital Universitario Lozano Blesa, ISS Aragón, Zaragoza, Spain

[16]Clínica Universidad de Navarra, IdiSNA, Pamplona, Spain

[17]Hospital Universitario Carlos Haya, Málaga, Spain

[18]Organización Nacional de Trasplantes, Madrid, Spain

Abbreviations: AIDS, acquired immunodeficiency syndrome; CI, confidence interval; DAAs, direct acting antivirals; DCV, daclatasvir; ETR, end-of-therapy response; EVR, early (4-week) virological response; FIPSE, Spanish Foundation for the Investigation and Prevention of AIDS; GESIDA, Spanish Group for the Study of AIDS; HAART, highly active antiretroviral therapy; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IFN, interferon; INSTI, HIV integrase strand transfer inhibitor; IQR, interquartile range; LDV, ledipasvir; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; OR, odds ratio; RBV, ribavirin; RVR, rapid virological response; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained virological response.

Spanish LT in HIV-Infected Patients Working Group investigators are listed in Appendix 1.

Christian Manzardo and Maria C. Londoño contributed equally to this work.

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Correspondence: Jose M. Miro, Infectious Diseases Service, Hospital Clínic, Helios Building, Desk no. 26, Villarroel 170, 08036 Barcelona, Spain.
Email: jmmiro@ub.edu; josemaria@miromoreno.org

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Direct-acting antivirals have proved to be highly efficacious and safe in monoinfected liver transplant (LT) recipients who experience recurrence of hepatitis C virus (HCV) infection. However, there is a lack of data on effectiveness and tolerability of these regimens in HCV/HIV-coinfected patients who experience recurrence of HCV infection after LT. In this prospective, multicenter cohort study, the outcomes of 47 HCV/HIV-coinfected LT patients who received DAA therapy (with or without ribavirin [RBV]) were compared with those of a matched cohort of 148 HCV-monoinfected LT recipients who received similar treatment. Baseline characteristics were similar in both groups. HCV/HIV-coinfected patients had a median (IQR) CD4 T-cell count of 366 (256-467) cells/μL. HIV-RNA was <50 copies/mL in 96% of patients. The DAA regimens administered were SOF + LDV ± RBV (34%), SOF + SMV ± RBV (31%), SOF + DCV ± RBV (27%), SMV + DCV ± RBV (5%), and 3D (3%), with no differences between the groups. Treatment was well tolerated in both groups. Rates of SVR (negative serum HCV-RNA at 12 weeks after the end of treatment) were high and similar for coinfected and monoinfected patients (95% and 94%, respectively; P = .239). Albeit not significant, a trend toward lower SVR rates among patients with advanced fibrosis (P = .093) and genotype 4 (P = .088) was observed. In conclusion, interferon-free regimens with DAAs for post-LT recurrence of HCV infection in HIV-infected individuals were highly effective and well tolerated, with results comparable to those of HCV-monoinfected patients.

KEYWORDS
clinical research/practice, infection and infectious agents—viral: hepatitis C, infection and infectious agents—viral: human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS), liver transplantation/hepatology

1 | INTRODUCTION

Recurrence of hepatitis C virus infection after liver transplantation is universal in patients who have detectable HCV-RNA at the time of surgery.[1] The natural history of recurrence in HCV-infected patients is accelerated compared with immunocompetent patients, and 20% to 30% develop cirrhosis within 5 years of transplantation.[2] Post-LT patient and graft survival are significantly lower in HCV/HIV-coinfected than in HCV-monoinfected recipients, owing to more rapid progression of fibrosis and a higher incidence of severe forms of recurrence of HCV infection (including fibrosing cholestatic hepatitis).[3] In the interferon (IFN) era, viral eradication was associated with improved clinical and histological outcomes (reduction in portal pressure, regression of fibrosis, and resolution of clinical decompensations in cirrhotic patients).[4–6] However, IFN based therapies were associated with a low rate of sustained virological response (SVR) and a high rate of treatment discontinuation due to adverse events.[2] This was especially true for HCV/HIV-coinfected LT recipients, in whom the SVR rate was 14% to 21%, which was significantly lower than in HCV-monoinfected recipients.[7,8]

Fortunately, the emergence of direct-acting antivirals (DAAs) has completely changed treatment of HCV infection. Clinical trials and real-life cohort studies based on HCV-monoinfected LT recipients have shown excellent results in terms of efficacy and safety, especially in patients with mild fibrosis and compensated cirrhosis (SVR rate ≈ 90%).[9–12] Nevertheless, data on the efficacy and safety of DAAs in HCV/HIV-coinfected LT recipients are limited to case series and individual case reports. The largest series was published by Campos-Varela et al,[13] who evaluated the outcome of a sofosbuvir (SOF)-based compassionate use program in HCV/HIV-coinfected LT recipients. The authors found that 20 patients with early recurrence of severe HCV infection or cirrhosis received SOF-based antiviral therapy. SVR was 89% and was followed by improved liver function results (bilirubin and albumin levels) and the resolution of clinical decompensations in most of the decompensated patients. Eight patients experienced serious adverse events, although none were related to therapy. In a recent series of seven HCV/HIV-coinfected LT recipients with severe HCV recurrence taking different combinations of DAAs, all seven patients achieved SVR, and only four experienced mild adverse events.[14] In another study, one patient treated with SOF and daclatasvir (DCV) presented severe bradycardia.[13,15] In two recently published studies 24[16] and 29,[17] HIV-infected LT recipients achieved a 90% and 96% SVR rates with SOF-based DAAs regimens, respectively. However, they did not include a control group.

Despite these excellent results for effectiveness and tolerability in HCV/HIV-coinfected LT recipients, which appear to be similar

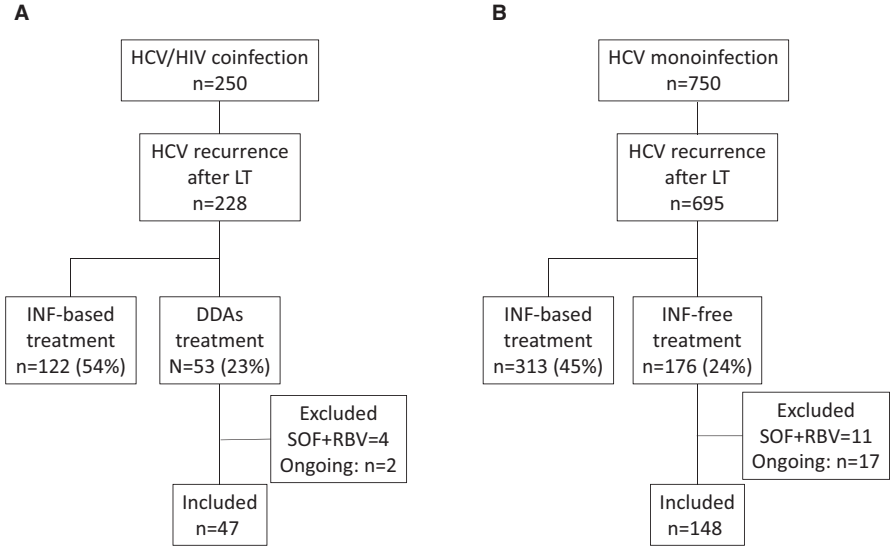

FIGURE 1 Flow-chart of HCV/HIV-coinfected (panel A) and HCV-monoinfected (panel B) liver transplant patients according to whether they received or did not receive treatment with interferon (INF)-based or INF-free treatment for recurrence of hepatitis C

to those observed for HCV-monoinfected recipients, there are no nationwide prospective studies comparing monoinfected and coinfected LT recipients. Therefore, the aim of the study was to prospectively evaluate the effectiveness of antiviral therapy with DAAs in HCV/HIV-coinfected LT recipients and to compare it with that of a matched cohort of HCV-monoinfected LT recipients.

2 | METHODS

2.1 | Study design

We performed a multicenter nationwide cohort study of 250 consecutive HCV/HIV-coinfected patients who underwent LT between 2002 and 2012 in Spain and who were prospectively followed-up until March 2017. These patients were matched with 750 HCV-monoinfected patients (1:3) who underwent LT during the same period at the same sites. Other matched variables were calendar year (±1 year), age (±12 years), gender, presence of HBV coinfection, and presence of hepatocellular carcinoma. Only coinfected patients who had received posttransplant INF-free anti-HCV therapy and for whom there were 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, 49 HCV/HIV-coinfected patients and 165 HCV-monoinfected patients received INF-free antiviral therapy for recurrence of hepatitis C following LT. After exclusion of two coinfected patients and 17 monoinfected patients who were still on treatment at the time of the analysis, the final study population comprised 47 coinfected and 148 monoinfected patients.

Pre, peri, and posttransplant variables for coinfected patients were collected at each site using a standardized case report form as previously described.[7] Information for each patient was recorded before treatment, and at 1, 3, 6, 9, and 12 months after starting anti-HCV therapy. The variables collected are presented in Tables 1–5. Patient information was sent to the coordinating center every 6 months 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.[7] 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.

2.2 | Diagnosis of recurrent hepatitis C

Patients were diagnosed with recurrent hepatitis C when they had both positive serum HCV RNA after LT, and histological and/or biochemical evidence of hepatitis (increased serum transaminases for no other apparent reason and stable immunosuppression). Fibrosis stage was established on the basis of liver histology (METAVIR scale) or liver stiffness measurement.[18] Fibrosing cholestatic hepatitis was defined according to standard histological criteria.[19] Severe histologically proven recurrent hepatitis C was defined as the development of fibrosing cholestatic hepatitis or fibrosis stage F3/F4.

2.3 | Antiviral therapy with INF-free regimens

Antiviral therapy was selected by the treating physician based on current guidelines and the regimens available at the time of treatment indication (SOF + simeprevir [SMV] ± ribavirin [RBV], SOF + DCV ± RBV, SOF/ledipasvir [LDV] ± RBV, SMV + DCV ± RBV, or ombitasvir/paritaprevir/ritonavir with dasabuvir [3D] ± RBV) and was based on the same criteria as for HCV-monoinfected LT recipients according to local protocols. DAAs were administered according to the recommendations of the package insert. The usage and dose of RBV were also decided by the treating physician according to the European treatment regimen recommendations and the

TABLE 1 Characteristics of LT recipients receiving DAAs according to HIV infection status

	ALL	HIV+	HIV-	*P* value
No. of cases	195	47	148	
Demographic data				
Male recipients	156 (80.0%)	36 (76.6%)	120 (81.1%)	.645
Age (y)	49.0 (6.15)	47.3 (6.36)	49.6 (5.99)	.023
Data at initiation of treatment				
Log_{10} HCV-RNA plasma levels (IU/mL), median [IQR]	6.37 [5.88;6.70]	6.29 [5.84;6.67]	6.38 [5.95;6.71]	.277
Fibrosis stage*				
F0	8 (4.10%)	0 (0.00%)	8 (5.41%)	.256
F1	38 (19.5%)	12 (25.5%)	26 (17.6%)	
F2	33 (16.9%)	10 (21.3%)	23 (15.5%)	
F3	37 (19.0%)	4 (8.51%)	33 (22.3%)	
F3-F4 vs F0-F2	79 (40.5%)	21 (44.7%)	58 (39.2%)	.272
F4 vs F0-F3	116 (59.5%)	25 (53.2%)	91 (61.5%)	.583
HCV genotype				
1	148 (75.9%)	27 (57.4%)	121 (81.8%)	.175
1a	41 (21.0%)	10 (21.3%)	31 (20.9%)	
1b	84 (43.1%)	8 (17.0%)	76 (51.4%)	
1a/b	3 (1.54%)	1 (2.13%)	2 (1.35%)	
Non-subtypable	20 (10.3%)	8 (17.0%)	12 (8.11%)	
3	23 (11.8%)	8 (17.0%)	15 (10.1%)	
4	22 (11.3%)	11 (23.4%)	11 (7.43%)	
Other/missing/non-typable	2 (1.03%)	1 (2.13%)	1 (0.68%)	
IFN-free treatment regimen				
SOF + DCV ± RBV	54 (27.7%)	16 (34.0%)	38 (25.7%)	.539
SOF + LDV ± RBV	66 (33.8%)	17 (36.2%)	49 (33.1%)	
SOF + SMV ± RBV	59 (30.3%)	10 (21.3%)	49 (33.1%)	
SMV + DCV ± RBV	10 (5.13%)	3 (6.38%)	7 (4.73%)	
3D ± RBV	6 (3.08%)	1 (2.13%)	5 (3.38%)	
SOF + DCV	24 (12.3%)	10 (21.3%)	14 (9.46%)	.358
SOF + LDV	19 (9.74%)	7 (14.9%)	12 (8.11%)	
SOF + SMV	13 (6.67%)	0 (0.00%)	13 (8.78%)	
SMV + DCV	3 (1.54%)	0 (0.00%)	3 (2.03%)	
SOF + DCV + RBV	30 (15.4%)	6 (12.8%)	24 (16.2%)	
SOF + LDV + RBV	47 (24.1%)	10 (21.3%)	37 (25.0%)	
SOF + SMV + RBV	46 (23.6%)	10 (21.3%)	36 (24.3%)	
SMV + DCV + RBV	7 (3.59%)	3 (6.38%)	4 (2.70%)	
3D + RBV	6 (3.08%)	1 (2.13%)	5 (3.38%)	
DDAs + RBV	136 (69.7%)	30 (63.8%)	106 (71.6%)	.393
RBV doses (mg) at treatment start	800 [600;1000]	800 [600;800]	800 [600;1000]	.397
Treatment-experienced	87 (44.6%)	22 (46.8%)	65 (43.9%)	.278
Months between LT and first anti-HCV treatment	43.8 [16.5;78.7]	41.3 [16.7;68.4]	45.0 [16.5;79.9]	.144
Months between LT and DAA-based anti-HCV treatment	76.1 [51.7;104]	71.2 [57.2;100]	78.1 [49.9;107]	.618
Length of treatment with DAA-based anti-HCV treatment (weeks)	12.4 [12.0;23.9]	12.4 [12.0;23.9]	12.4 [12.0;23.9]	.988

(Continues)

TABLE 1 (Continued)

	ALL	HIV+	HIV-	*P* value
Immunosuppression at treatment start				
Cyclosporine-based	24 (12.3%)	9 (19.1%)	15 (10.1%)	.215
Tacrolimus-based	138 (70.8%)	29 (61.7%)	109 (73.6%)	
Other regimens	33 (16.9%)	9 (19.1%)	24 (16.2%)	

LT, liver transplantation; SOF, sofosbuvir; SMV, simeprevir; DCV, daclatasvir; LDV, ledipasvir; RBV, ribavirin; DAA, direct-acting antiviral, 3D, Paritaprevir/Ritonavir/Ombitasvir.

patient's status (presence of liver and renal dysfunction and baseline hemoglobin levels). The duration of therapy was 12 or 24 weeks according to guidelines.[18] Patients who received SOF + RBV were not included in this analysis because this combination is currently considered suboptimal. Similarly, patients who received INF-containing regimens with boceprevir (BOC) and telaprevir (TRV) were excluded (see Table S1).

Rapid virological response and end of treatment response were defined as a negative plasma HCV RNA viral load at 4 weeks and at the end of therapy, respectively. SVR was defined as a persistently negative plasma HCV-RNA viral load at 12 weeks after the end of treatment. HCV-RNA breakthroughs were defined as one or more undetectable HCV-RNA values during treatment, but not two consecutive undetectable HCV-RNA values at the end of treatment. Relapse was defined as a positive plasma HCV-RNA viral load in a patient meeting the criteria for end of treatment response. Biochemical response was defined as the normalization of aminotransferase levels at the end of treatment.

2.4 | Statistical analysis

Analyses were primarily conducted by a modified intention-to-treat analysis, which only excluded those patients who had a virological response but had not finished treatment at the time of the analysis. Categorical variables were expressed as a frequency (percentage). Continuous variables were expressed as mean (standard deviation) or median (interquartile range). As HIV+ individuals were originally matched in a proportion 1:3 with HCV-monoinfected individuals, conditional logistic regression was used to compare variables between HCV/HIV-coinfected and HCV-monoinfected patients.[19] Confidence intervals for categorical variables were calculated with the exact binomial. To compare values between the start and end of treatment, patients whose treatment failed were excluded and a paired *t* test was used. A $P < .05$ was considered to indicate statistical significance. Statistical analyses were performed with R, version 3.3.2 (2016-10-31).

3 | RESULTS

3.1 | Characteristics of patients

The study population comprised 195 LT recipients who received antiviral therapy with an IFN-free regimen. Of these, 47 were HCV/HIV-coinfected and 148 were HCV-monoinfected. The baseline characteristics of these patients are shown in Table 1. Briefly, most of the patients were male (n = 156, 80%) with a mean age of 49 years. The median time from LT to initiation of treatment was 76.1 months (IQR: 51.7-104). At the time of antiviral therapy, most patients had significant fibrosis or cirrhosis (F2-F4, n = 95, 63.3%) and were receiving tacrolimus-based immunosuppression (n = 134, 70.8%). Most of the patients were treated with the combination of SOF/LDV with or without RBV (n = 66, 33.9%) for a median of 12.4 weeks (IQR: 12.0-23.9). There were no significant differences between coinfected and monoinfected patients.

In HCV/HIV-coinfected LT patients, the main risk factor for acquiring HIV infection was intravenous drug use (n = 30, 69.8%). Nine (20%) of the 45 coinfected recipients had AIDS (acquired immunodeficiency syndrome)-defining events. At the time of treatment with DAAs, HIV viral load was undetectable (<50 copies/mL) in 41 patients (87.2%), and median CD4+ cell count was 367 (IQR: 264-473). All but one patient (98%) was on antiretroviral therapy (cART). Table S2 summarizes the cART received during treatment with DAAs. Only five patients (11.1%) required a modification in cART before starting treatment with DAAs. All but one was switched to ART based on a nonboosted INSTI (raltegravir, two cases; dolutegravir, two cases). The other case was a patient with a multidrug-resistant virus who was receiving a PI-based regimen plus RAL and TDF/FTC before being switched to TDF/FTC/rilpivirine plus dolutegravir based on a historic genotyping analysis. The DAA dose did not have to be adjusted in any cases.

3.2 | Efficacy of antiviral therapy

The antiviral regimen administered is shown in Table 1. Combinations including SMV (SMV + SOF and SMV + DCV with or without RBV) were the most commonly administered to HIV negative recipients (82% of patients receiving SMV were HIV negative), but the difference between HIV positive and HIV negative recipients was not statistically significant ($P = .121$). Most of the patients received RBV (n = 136, 67.9%) with a median dose of 800 mg/day with no difference between HIV positive and HIV negative recipients. The only significant difference between patients taking RBV and those not was the type of antiviral regimen. As shown in Table S3, the HIV infected individuals receiving suboptimal combinations such as SMV + SOF or SMV + DCV were those on RBV ($P = .004$). The SVR rate was 94% in HCV/HIV-coinfected patients and 95% in HCV-monoinfected

TABLE 2 Virological response to IFN-free treatment in HIV/HCV-coinfected and HCV-monoinfected liver transplant recipients [95%CI]

	HIV+	HIV-	*P* value
Overall, n	47	148	
Week 4	100 [92.3;100]	75.8 [67.3;83][a]	.004
EOT	95.7 [85.5;99.5]	98 [94.2;99.6]	.239
SVR	93.6 [82.5;98.7]	95.3 [90.5;98.1]	.239
Genotype 1, n	27	120	
Week 4	100 [87.2;100]	76.5 [67;84.3]	.138
EOT	100 [87.2;100]	97.5 [92.9;99.5]	1.000
SVR	96.3 [81;99.9]	95 [89.4;98.1]	1.000
Genotype 1a, n	10	31	
Week 4	100 [69.2;100]	100 [88.8;100]	.
EOT	100 [69.2;100]	100 [88.8;100]	.
SVR	100 [69.2;100]	84 [63.9;95.5]	.239
Genotype 1b, n	8	76	
Week 4	100 [63.1;100]	72.7 [60.4;83]	.239
EOT	100 [63.1;100]	97.4 [90.8;99.7]	1.000
SVR	87.5 [47.3;99.7]	93.4 [85.3;97.8]	.462
Genotype 1a/b	1	2	
Week 4	100 [2.5;100]	50 [1.3;98.7]	1.000
EOT	100 [2.5;100]	100 [15.8;100]	.
SVR	100 [2.5;100]	100 [15.8;100]	.
Genotype 3	8	15	
Week 4	100 [63.1;100]	63.6 [30.8;89.1]	.239
EOT	100 [63.1;100]	100 [78.2;100]	.
SVR	100 [63.1;100]	100 [78.2;100]	.
Genotype 4, n	11	11	
Week 4	100 [69.2;100]	77.8 [40;97.2]	1
EOT	81.8 [48.2;97.7]	100 [71.5;100]	.476
SVR	81.8 [48.2;97.7]	90.9 [58.7;99.8]	1.000
Genotype 2/ other/ non-typable/ unknown, n	1	1	
Week 4	100 [2.5;100]	100 [2.5;100]	
EOT	100 [2.5;100]	100 [2.5;100]	
SVR	100 [2.5;100]	100 [2.5;100]	

Week 4, early virological response, EOT, end of treatment response; SVR, sustained virological response.
[a]Week 4 results not available in 25 HIV-negative patients.

patients (*P* = .239) (Table 2). Interestingly, the mITT RVR (week 4 of antiviral therapy) was significantly better in HCV/HIV-coinfected patients than in HCV-monoinfected recipients (100% vs. 75.8%; *P* = .004). Treatment failures (n = 10) were due to relapse in six cases, viral breakthrough in three, and death during therapy in one case (Table 3). The three breakthrough episodes were observed exclusively in patients treated with SMV + DCV. Six patients (cases 1–4, 8, and 9 in Table 3) received a second IFN-free regimen and all achieved SVR. There were no significant differences in the baseline characteristics among patients with or without SVR (Table S4). There was a trend towards a high number of patients with F4 among those who failed antiviral therapy as compared to patients who achieved SVR (70% vs. 38.9%; *P* = .093). Interestingly, when specifically analyzing HIV-positive recipients, the SVR rate was significantly associated to the type of DAA regimen administered to the patient (*P* = .004), and especially for patients receiving SMV as part of a DAA regimen (*P* = .018). See Table S5 for details.

With regard to specific HCV genotypes, it is interesting to note that in genotype 4–infected patients, SVR tended to be lower (albeit not significantly) in HCV/HIV-coinfected patients than in HCV-monoinfected (77.8% vs. 90.9%; *P* = .566). However, the two virological failures observed in coinfected patients received antiviral therapy with SMV + DCV + RBV, which is currently considered a suboptimal combination.

The INF-free regimens were very well tolerated, and none of the HIV-infected patients needed to stop them because of adverse events. Only one HCV-monoinfected cirrhotic patient died during therapy (liver decompensation). Three out of 47 (6.38%) coinfected patients and five out of 148 (3.38%) monoinfected patients required erythropoietin or darbepoetin because of mild anemia, with no significant differences between the two groups (*P* = .40).

Adjustments in immunosuppressive (IS) medication were more frequent in HIV positive recipients (51.1% vs. 37.2% in HIV-negative patients) but the difference was not statistically significant (*P* = .11). When a detailed analysis of IS modification was performed, we observed that HIV-positive recipients more frequently underwent a decrease in calcineurin inhibitor (CNI) dose (*P* = .006) and the addition of another IS drug (*P* = .013), mainly mycophenolate (MMF). These data are shown in Table S6. Despite the need for IS adjustment, none of the patients developed T-cell mediated rejection.

3.3 | Impact of therapy on liver tests

As expected, there was a significant improvement in transaminase levels, γ-glutamyl-transpeptidase levels, and alkaline phosphatase in HCV/HIV-coinfected patients at the end of treatment compared with baseline. However, viral eradication did not have an impact on the results of liver function tests (bilirubin, albumin, INR, and MELD score). These data are reported in Table 4. Figure 2 shows the delta MELD at the time of SVR (as compared to baseline) in coinfected patients with SVR.

3.4 | Impact of therapy on hematological, renal, and HIV virological test results

As expected with the concomitant use of RBV in some patients, a significant decrease in hemoglobin levels was observed in the

TABLE 3 Characteristics of patients whose first IFN-free treatment regimen failed

Patient	HIV	Sex	HCV genotype	Fibrosis stage	Previous decomp. HVC	First IFN-free regimen	Reason for failure
1	+	M	1b	F2	No	SOF + SMV + RBV	Relapse
2	+	M	4	F4	Yes	SMV + DCV + RBV	Viral breakthrough
3	+	M	4	F4	Yes	SMV + DCV + RBV	Viral breakthrough
4	-	M	1b	F4	Yes	SMV + DCV + RBV	Relapse
5	-	M	1b	F4	No	SMV + DCV + RBV	Viral breakthrough
6	-	M	1na	F4	No	SOF + DCV	Death during treatment
7	-	M	4	F3	No	SOF + SMV	Relapse
8	-	M	1b	F4	Yes	SOF + DCV	Relapse
9	-	F	1b	F4	No	SMV + DCV + RBV	Relapse
10	-	F	1b	F4	No	SOF + LDV + RBV	Relapse

M, male; F, female; Decomp, decompensation; na, subtype not available, SVR, sustained virological response; SOF, sofosbuvir; SMV, simeprevir; DCV, daclatasvir; LDV, ledipasvir; RBV, ribavirin.

coinfected cohort, with mean values of 143 g/L at the initiation of treatment and 129 g/L at the end ($P = .001$). However, as stated above, only three patients (6.38%) required hematopoietic growth factors and none stopped antiviral treatment. There was a significant increase in the platelet count (127×10^9/L vs. 150×10^9/L, respectively; $P = .001$). No significant changes were observed in other hematological parameters, such as white blood cells, neutrophils, lymphocytes, and CD4+ T cells (Table 5) nor in renal function test (creatinine, estimated glomerular filtration rate, Table 4). DAAs did not affect plasma HIV RNA viral load, which was below detection levels at the end of treatment in most cases (Table 5).

4 | DISCUSSION

Despite growing data on the safety and efficacy of antiviral therapy in HIV-negative HCV-infected LT recipients,[9–12,20] data on HCV/HIV-coinfected LT recipients remain scarce and are based only on small case series.[13–17] We report the results of the first nationwide, multicenter, prospective case-control study on the effectiveness and tolerability of antiviral therapy with DAAs in HCV/HIV-coinfected patients with recurrence of hepatitis C after LT and a matched cohort of monoinfected recipients. The SVR rate in HCV/HIV-coinfected recipients was high and similar to that of HCV-monoinfected LT patients (94% vs. 95%, $P = .239$). Antiviral therapy was well tolerated, and only one HIV-negative patient died (complications of cirrhosis).

In the IFN era, the SVR rate in coinfected LT recipients with recurrence of hepatitis C was significantly lower than in HCV-monoinfected patients. A prospective cohort study by our group (FIPSE Investigators)[7] showed that the SVR rate was significantly lower in coinfected than in monoinfected LT recipients (21% vs. 36%; $P = .013$).

TABLE 4 Changes in liver and kidney function counts from initiation to end of treatment in the 44 coinfected patients with SVR

	At initiation, median [IQR]	At end, median [IQR]	*P* value
ALT (U/L)	52.0 [33.0;96.2]	18.5 [16.0;24.5]	<.001
AST (U/L)	52.0 [36.8;83.5]	22.5 [20.0;29.0]	<.001
Gamma GT (U/L)	108 [66.0;177]	29.5 [21.0;45.5]	.002
AP (U/L)	112 [93.5;145]	93.0 [79.0;135]	.005
Albumin (g/L)	4.10 [3.75;4.40]	4.20 [4.00;4.42]	.067
Hemoglobin (g/dL)	14.6 [13.3;15.4]	12.6 [11.5;14.2]	<.001
INR	1.02 [1.00;1.13]	1.05 [1.00;1.13]	.954
Creatinine (mg/dL)	1.10 [1.00;1.25]	1.21 [1.00;1.39]	.247
eGFR	70.6 [57.8;86.9]	64.7 [55.2;80.4]	.126
Total bilirubin (mg/dL)	1.00 [1.00;1.20]	1.00 [1.00;1.10]	.617
MELD	8.92 [7.34;11.8]	9.73 [8.06;11.2]	.446

ALT, alanine aminotransferase; AST, aspartate aminotransferase; AP, alkaline phosphatase; eGFR, estimated glomerular filtration rate (by CKD-Epi); INR, international normalized ratio; MELD, Model for end-stage liver disease.

Treatment discontinuation was also significantly more frequent in coinfected recipients (56% vs. 39%; $P = .016$). The addition of a first-generation protease inhibitor (TVR or BOC) to the antiviral therapy regimen (triple therapy) was a major step forward in the treatment of hepatitis C, with a substantial increase in SVR rates.[3] However, in LT recipients, the use of this therapy was hampered by two relevant issues: (1) the significant number of adverse events observed in this group;

TABLE 5 Changes in lymphocyte, CD4 and CD4/CD8 T-cell counts, and plasma HIV RNA viral load from initiation to end of treatment in the 44 coinfected patients with SVR

	At initiation	At end	*P* value
Lymphocytes[a]	1505 (693)	1405 (903)	.204
CD4 T-cell count[b]	366 [256;467]	398 [264;564]	.145
CD4/CD8 ratio[a]	0.81 (0.44)	0.79 (0.47)	.784
HIV VL < 50 copies/mL	95.5%	93.2%	1.000

[a]Mean (SD).
[b]Median [IQR].

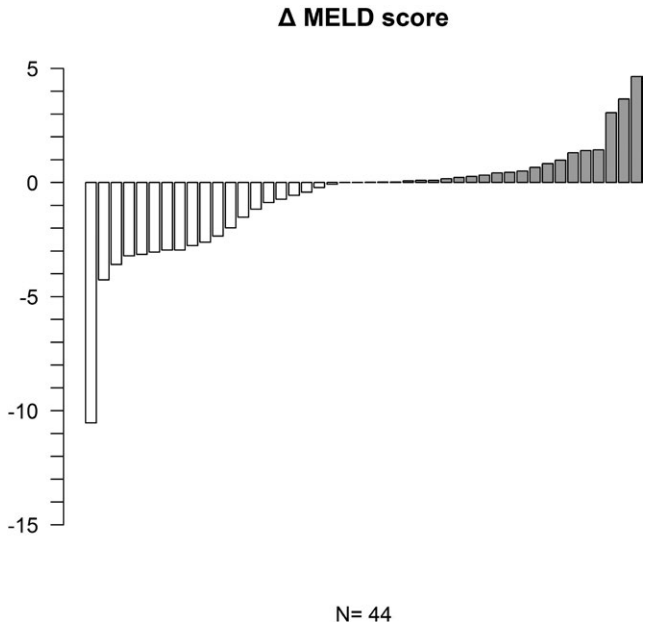

FIGURE 2 Delta MELD score from baseline to the time of SVR of the 44 HCV/HIV-coinfected patients with SVR. Median baseline and SVR MELD score were 8.92 (IQR 7.34-11.8) and 8.72 (IQR 7.47-9.83), *P* = .446

and (2) the potential for drug–drug interactions with immunosuppressive drugs, which have been shown to lead to a decrease in the dose of calcineurin inhibitors and frequent monitoring of trough levels to prevent toxicity or rejection.[21–23] Only one report addresses triple therapy with TVR or BOC in HCV/HIV-coinfected LT recipients[3]; only three of the seven patients treated achieved SVR, and six patients discontinued antiviral therapy early owing to adverse events.

The development of IFN-free antiviral regimens with different combinations of DAAs has completely changed the treatment of patients who experience recurrence of hepatitis C after transplantation. In HCV-monoinfected LT recipients, the SVR rate ranged between 71% and 97% depending on the antiviral regimen, HCV genotype, and fibrosis stage.[9–12,20,24] Tolerance to antiviral therapy was excellent with all combinations, although drug–drug interactions are likely with some DAAs (3D includes ritonavir and markedly increases calcineurin inhibitor levels,[24] and SMV should not be used with cyclosporine[25]). These excellent results in monoinfected recipients have also been observed in coinfected recipients, as reported in several case series. Grant et al[26] found an SVR rate of 87% in eight patients with recurrence of mild hepatitis C treated with a SOF-based combination. Campos-Varela et al[27] reported a 100% SVR in two HCV/HIV-coinfected patients with recurrence of hepatitis C. Similarly, we reported a 100% SVR in seven patients with severe hepatitis C, four of whom had decompensated cirrhosis.[14] Castells et al[15] reported 100% SVR in six HCV/HIV-coinfected patients treated with SOF + DCV. The results from a SOF compassionate use program[13] revealed a global SVR of 89% (80% in the 10 patients treated with SOF + RBV, and 100% in patients treated either with SOF + RBV + pegylated interferon, SOF + SMV + RBV or SOF + DCV). Additional 24 cases in Italy[16] and 29 cases in France[17] treated with SOF-based DAA regimens were reported to achieve 90% and 96% of SVR, respectively. In most of these studies there was no control group.

To the authors' knowledge, this is the first nationwide cohort study to compare the effectiveness and tolerability of DAAs in coinfected and monoinfected LT recipients. As expected, the intention-to-treat SVR rate was very similar between the two groups: 94% vs. 95%. The main difference between coinfected and monoinfected recipients was observed in genotype 4–infected patients, in whom SVR rates were 74% and 91%, respectively. However, this difference did not reach statistical significance (*P* = .566), probably owing to the small number of patients in this subgroup. Overall, 10 patients failed to achieve SVR (see Table 3 for details). Interestingly, four out of the 10 patients whose treatment failed received SMV + DCV ± RBV, which is currently considered a suboptimal combination. Besides, 70% of patients who failed antiviral therapy had F4 fibrosis. This was higher (although not statistically significant) than the proportion of patients with F4 among LT recipients who achieved SVR (39%; *P* = .093). The addition of RBV to the antiviral regimen did not impact the chances of achieving SVR. This could be due to the fact that HIV-positive recipients who did not receive RBV were predominantly treated for 24 weeks. However, it is possible that liver transplant recipients receiving a potent antiviral combination (SOF plus an NS5A inhibitor) do not require RBV despite receiving a 12-week treatment duration, as shown by Houssel-Debry et al.[28]

Among the HIV-infected LT recipients, only four needed to switch their cART to two nucleot(s)ide reverse transcriptase inhibitors plus a nonboosted INSTI. None of the INF-free regimens used in these patients impacted on the CD4+ T-cell counts or the plasma HIV-RNA load, which was maintained below detection levels in most cases. Immunosuppression adjustments were more frequently observed in HIV-positive patients mainly due to decrements in CNI doses and the addition of another drug (MMF). This was probably related with potential interaction with antiviral and antiretroviral regimens. Despite the need for IS adjustment, no patients developed rejection, indicating that under close supervision by a multidisciplinary team, antiviral therapy with DAAs is safe in HIV-positive recipients.

As expected after viral eradication, we observed an improvement in liver enzyme values. However, this improvement was not noted in tests to assess liver function, such as bilirubin, albumin, INR, and MELD score. This discrepancy could have been due to the short period over which these parameters changed, namely, from the

initiation to the time of achieving SVR. It is probable that a longer follow-up will reveal an improvement in liver function.

Our study has several limitations. First, the number of patients included is relatively small (only 47 cases). Nevertheless, the 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 INF-free therapies after LT. In addition, the results were similar to those found in matched HCV-monoinfected LT recipients treated with the same INF-free regimens at the same sites. Second, a significant proportion of patients received a suboptimal combination (SMV + SOF or SMV + DCV) because it was the only choice available at the time of treatment. This had a negative impact on SVR results, especially in genotype 4–infected liver recipients. Finally, several data are lacking in the HCV-monoinfected cohort, mainly adverse events during antiviral therapy and changes in the results of liver function tests after viral eradication, thus precluding a robust comparison of monoinfected patients with their coinfected counterparts.

In conclusion, treatment of post-LT recurrence of hepatitis C in HIV-infected individuals IFN-free regimens (ie, DAA-based regimens) was highly effective and well tolerated. The results were comparable to those observed for HCV-monoinfected patients.

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DISCLOSURE

The authors of this manuscript have conflicts of interest to disclose as described by the *American Journal of Transplantation*. Jose M. Miró has received consulting honoraria and/or research grants from AbbVie, Bristol-Myers Squibb, Cubist, Genentech, Medtronic, Novartis, Gilead Sciences, and ViiV Healthcare outside the submitted work. MCL has received advisory fees from Janssen, Abbvie, Gilead, BMS and MSD outside the submitted work. The other authors have no conflicts of interest to disclose.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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APPENDIX 1

List of Investigators of the Spanish LT in HIV-Infected Patients Working Group

F. Suárez, M.A. Castro, S. López, J.D. Pedreira, P. Vázquez, Complejo Hospitalario Universitario, A Coruña; J.M. Miro, F. Agüero, J. Blanch, M. Brunet, D. Calatayud, C. Cervera, G. Crespo, E. de Lazzari, C. Fondevila, A. Forner, J. Fuster, X. Forns, J.C. García-Valdecasas, A. Gil, J.M. Gatell, M. Laguno, A. Lligoña, M.C. Londoño, J. Mallolas, C. Manzardo, M. Monrás, A. Moreno, J. Murillas, M. Navasa, D. Paredes, J. Peñafiel, I. Pérez†, M. Subirana, F. Torres, C. Tural, M. Tuset, A. Rimola and P. Ruiz, Hospital Clínic-IDIBAPS, University of Barcelona, Barcelona; A. Antela, E. Losada, E. Molina, E. Otero, E. Varo, Hospital Clínico Universitario, Santiago de Compostela; T. Serrano, J.J. Araiz, E. Barrao, J. Larraga, S. Letona, R. Lozano, P. Luque, A. Navarro, I. Sanjoaquín, E. Tejero, Hospital Clínico Universitario Lozano Blesa, Zaragoza; M. Salcedo, R. Bañares, J. Berenguer, G. Clemente, J. Cosín, J.P. Ferreiroa, J.L. García-Sabrido, I. Gutiérrez, J.C. López, P. Miralles, M. Ramírez, D. Rincón, M. Sánchez, Hospital General Universitario Gregorio Marañón, Madrid; M. Jiménez, J. de la Cruz, J.L. Fernández, J.M. Lozano, J. Santoyo, J.M. Rodrigo, M.A. Suárez, Hospital Regional Universitario Carlos Haya, Málaga; M. Rodríguez, M.P. Alonso, V. Asensi, M.L. González-Diéguez, I. González-Pinto, Hospital Universitario Central de Asturias, Oviedo; A. Rafecas, C. Baliellas, J. Carratalá, J. Fabregat, N. Fernández, R. Jorba, L. Lladó, X. Xiol, Hospital de Bellvitge-IDIBELL, University of Barcelona, Hospitalet de Llobregat, Barcelona; M. Montejo, J. Bustamante, J.R. Fernández, M. Gastaca, J. González, E. Montejo, J. Ortiz de Urbina, P. Ruiz, M.J. Suárez, M. Testillano, A. Valdivieso, A. Ventoso, Hospital de Cruces, University of the Basque Country, Baracaldo, Vizcaya; M. Abradelo, J. Calvo, J.R. Costa, A. García-Sesma, C. Jiménez, A. Manrique, J.C. Meneu, E. Moreno, V. Moreno, S.P. Olivares, F. Pulido, R. Rubio, Hospital Universitario Doce de Octubre, Madrid; M. Blanes, V. Aguilera, M. Berenguer, J. López, R. López, M. Prieto, Hospital Universitari La Fe, Valencia; M.C. Fariñas, F. Casafont, S. Echevarria, E. Fábrega, M. Gomez-Fleitas, C. Armiñanzas, J.L. Herrera-Noreña, Hospital Universitario Marqués de Valdecilla, Santander; S. Moreno, R. Barcena, S. del Campo, J. Fortún, A.M. Moreno, P. Martín-Dávila, Hospital Universitario Ramón y Cajal-IRYCIS, Madrid; J. Torre-Cisneros, P. Barrera, J. Briceño, J.J. Caston, G. Costan, M. de la Mata, R. Lara, P. López-Cillero, J.L. Montero, A. Rivero, S. Rufian, Hospital Universitario Reina Sofía-IMIBIC, Córdoba; G. Sánchez-Antolín, F. García Pajares, P. Bachiller, C. Almohalla, A. Barrera, R. Conde, Hospital Universitario Río Hortega, Valladolid; L.I. Castells, I. Bilbao, I. Campos-Varela, R. Charco, J.I. Esteban, J. Gavaldá, O. Len, A. Pahissa, E. Ribera, V. Vargas, Hospital Vall d'Hebrón, Universitat Autonoma de Barcelona, Barcelona; J.A. Pons, Hospital Universitario Virgen de la Arrixaca, El Palmar, Murcia; E. Cordero, C. Bernal, J.M. Cisneros, M.A. Gómez, J.M. Pascasio, M.J. Rodríguez, M. Sayago, J.M. Sousa, G. Suárez, Hospital Universitario Virgen del Rocío, Sevilla; J. González-García, Hospital Universitario La Paz-IdiPAZ, Madrid, E. Aznar, H. Esteban, and B. Moyano, SEIMC-GESIDA Foundation, Madrid; G. de la Rosa, G. Garrido, B. Mahillo, B. Dominguez-Gil, Organización Nacional de Trasplantes, Madrid

Steering Committee: J.M. Miro (Chair), L. Castells, G. de la Rosa, J. Torre-Cisneros, J. Fortún, J. González-García, L. Guerra (FIPSE), M. Manzanera (FIPSE), J. Berenguer, P. Miralles, A. Moreno, A. Rafecas, A. Rimola (Vice-Chair), and A. Valdivieso. The external advisors of the committee P. Stock (University of San Francisco, San Francisco, California, USA), M. Roland (University of San Francisco, San Francisco, California, USA), and D. Samuel (Hôpital Paul Brousse, Paris, France).

Follow-up Committee: J.M. Miro (Chair), S. del Campo, H. Esteban, J. González-García, C. Manzardo, M. Subirana, B. Moyano, and M. Manzanera (FIPSE). Coordinating Center Staff: E. Aznar, H. Esteban, J. González-García, and B. Moyano from the SEIMC-GESIDA Foundation, Madrid.

Methodological Committee: J.M. Miro, I. Perez†, M. Subirana, C. Manzardo, A. Moreno, and A. Rimola from Hospital Clínic-IDIBAPS, Universitat de Barcelona, Barcelona.