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Liver Retransplantation in HIV-Infected Patients: A Prospective Cohort Study

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Information regarding liver retransplantation in HIV-infected patients is scant. Data from 14 HIV-infected patients retransplanted between 2002 and 2011 in Spain (6% retransplantation rate) were analyzed and compared with those from 157 matched HIV-negative retransplanted patients. In HIV-infected patients, early (≤30 days) retransplantation was more frequently indicated (57% vs. 29%; p = 0.057), and retransplantation for HCV recurrence was less frequently indicated (7% vs. 37%; p = 0.036). Survival probability after retransplantation in HIV-positive patients was lower than in HIV-negative patients, 42% versus 64% at 3 years, although not significantly (p = 0.160). Among HIV-infected patients, those with undetectable HCV RNA at retransplantation and those with late (>30 days) retransplantation showed better 3-year survival probability (80% and 67%, respectively), similar to that in their respective HIV-negative counterparts (72% and 70%). In HIV-infected and HIV-negative patients, 3-year survival probability in those with positive HCV RNA at retransplantation was 22% versus 65% (p = 0.008); in those with early retransplantation, 3-year survival probability was 25% versus 56% (p = 0.282). HIV infection was controlled with antiretroviral therapy after retransplantation. In conclusion, HIV-infected patients taken as a whole have unsatisfactory survival after liver retransplantation, although patients with undetectable HCV RNA at retransplantation or undergoing late retransplantation show a more favorable outcome.

Key words: Chronic rejection, HBV infection, HCV infection, HCV recurrence, HIV infection, liver retransplantation, primary-graft nonfunction, Spain, survival, vascular thrombosis.

Abbreviations: AIDS, acquired immunodeficiency syndrome; CI, confidence interval; CDR, chronic ductopenic rejection; CMV, cytomegalovirus; CVA, cerebrovascular accident; FIPSE, Foundation for Research and Prevention of AIDS in Spain; GESIDA, Spanish Group for the study of acquired immunodeficiency syndrome; GESITRA, Spanish Group for the study of infections in transplanted patients; HAART, highly active antiretroviral treatment; HAS, hepatic artery stenosis; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HR, hazard ratio; IDU, intravenous drug user; IQR, interquartile range; LT, liver transplantation; MELD, model for end-stage liver disease; MOF, multiorgan failure; MSM, men who have sex with men; NRTI, nucleoside reverse transcriptase inhibitor; PNF, primary graft nonfunction; PI, protease inhibitors; reLT, liver retransplantation. SEIMC, Spanish Society of Infectious Diseases and Clinical Microbiology; SVR, sustained virological response.

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Introduction

Before the advent of highly active antiretroviral treatment (HAART) in 1996, poor outcome following liver transplantation (LT) in patients infected with human immunodeficiency virus type 1 (HIV) (1) led experts to consider HIV

Table 1: Baseline characteristics of the 14 patients who underwent liver retransplantation in Spain (2002–2011)

Case	Age at reLT	Gender	HIV risk factor	Primary liver disease	HCC	HCV genotype	HCV RNA at reLT	Indication reLT	Indication type
1	37	Male	Heterosexual	HCV cirrhosis	No	1	Positive	Vascular thrombosis	Emergency*
2	46	Male	Former IDU	HCV cirrhosis	Yes	1	Positive	Vascular thrombosis	Emergency*
3	44	Male	Former IDU	HCV cirrhosis + HBV	No	1	Positive	PNF	Emergency*
4	45	Male	Former IDU	HCV cirrhosis	No	1	Positive	Vascular thrombosis	Emergency*
5	45	Male	Former IDU	HCV cirrhosis	No	3	Positive	PNF	Emergency*
6	51	Male	Former IDU	HBV cirrhosis	No	NA	NA	Vascular thrombosis	Emergency*
7	44	Male	Former IDU	HCV cirrhosis	No	1	Positive	PNF	Emergency*
8	41	Male	Former IDU	HCV cirrhosis	No	2	Positive	Vascular thrombosis	Emergency*
9	41	Male	Former IDU	HCV cirrhosis + HBV	Yes	1	Negative	Vascular thrombosis	Elective**
10	39	Male	Former IDU	HCV cirrhosis	No	1	Negative	CDR	Elective**
11	52	Male	Former IDU	HCV cirrhosis	No	1	Negative	CDR	Elective**
12	49	Female	Heterosexual	HCV cirrhosis	Yes	1	Positive	HCV cirrhosis	Elective**
13	50	Female	Former IDU	HCV cirrhosis + HBV	No	4	Negative	CDR	Elective**
14	47	Male	Former IDU	HCV cirrhosis + OH	No	3	Negative	CDR	Elective**

CDR = chronic ductopenic rejection; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; IDU = intravenous drug user; NA = not applicable; OH = alcohol; PNF = primary graft nonfunction; reLT = liver retransplantation.
*Early reLT (≤30 days); **Late reLT (>30 days).

infection a formal contraindication for this procedure (2). However, several authors showed that HAART was able to control HIV infection after LT (3–6). Despite this success, some recent single-center reports have described reduced long-term survival after LT in patients coinfected by HIV and hepatitis C virus (HCV), mainly due to recurrence of HCV infection (7,8). Moreover, the recently published results of ongoing nationwide prospective studies conducted in Spain (funded by the Spanish Foundation for AIDS Research and Prevention [FIPSE]) and in the United States (Transplant Study for People with HIV funded by the National Institutes of Health) show that survival after LT in HIV/HCV-coinfected patients is shorter than in HIV-negative matched controls (9,10).

The frequency of liver retransplantation (reLT) in HIV-negative patients has ranged from 6.5% to 13.4% in recent years. The most common reasons for emergency reLT are primary graft nonfunction (PNF) and vascular thrombosis; the most common reasons for elective reLT are disease recurrence and chronic rejection (11–14). Overall survival after reLT is 15–20% lower than that of primary transplant recipients (11,15,16), and the marked disparity between the number of patients awaiting their first LT and the scarcity of available organs gives cause for concern. HIV-infected recipients and HIV-negative recipients can suffer from the same complications after LT (graft dysfunction, vascular thrombosis and recurrence of liver disease), and these could eventually lead to reLT. However, published experience with reLT in HIV-infected patients is scant, and most cases are only mentioned in articles reporting single-center experiences after primary transplantation in HIV-infected patients (5,7,17–22). Consequently, the incidence and outcome of reLT in HIV-infected patients is unknown, and, since the benefit of primary LT in HIV-infected patients remains open to debate, the usefulness of reLT in this population may be even more controversial. Therefore, we describe the incidence, indications, main characteristics and outcome of reLT in HIV-infected patients included in the aforementioned Spanish prospective FIPSE study. In addition, we compare survival of reLT in HIV-infected patients with that of matched HIV-negative controls.

Methods

Study design

We performed a prospective, multicenter, cohort study of HIV-infected patients who underwent reLT between January 2002 and March 2011 in 17 centers participating in the Spanish nationwide prospective (FIPSE) study of LT in HIV-infected patients. Patients were followed until January 2012. We compared the survival of HIV-infected reLT patients and HIV-negative reLT patients (controls) selected according to frequency matching for center, period of reLT (2002–2011), and HCV or HBV infection at the first transplant. The study was approved by the Institutional Review Boards of all the participating sites. All patients signed the informed consent form.

Variables

Variables were collected for each HIV-infected patient at each site using a standardized case report form as previously described (9). Variables were recorded pre-LT, post-LT, pre-reLT and post-reLT. Donor variables were also recorded (Tables 1–3). We calculated the 1999 Rosen score, which comprises five recipient variables (age, bilirubin, creatinine, United Network for Organ Sharing status and cause of graft failure) and helps to predict survival in patients undergoing reLT (23). The modified Rosen score for patients who underwent re-LT 15 days or more after their primary LT was calculated according to the new criteria of Rosen et al. (24) published in 2003. This new score is derived from four recipient variables, namely age, bilirubin, creatinine and interval to reLT. Patient information was sent every 6 months to the coordinating center and entered into the FIPSE OLT-HIV-05-GESIDA 45–05 database (available at https://www.seif88.com/gesida/asp/login.asp), as previously described (9).

The definitions of infection by HIV, HCV and hepatitis B virus (HBV), as well as PNF, vascular thrombosis, chronic rejection, HCV recurrence and other posttransplant complications, were based on standard criteria (25,26).

Table 2: Baseline characteristics and outcome of the 14 patients who underwent liver retransplantation in Spain (2002–2011) and characteristics of their donors

Case	Days from 1st LT	MELD score at reLT	1999 Rosen score at reLT	2003 Rosen score at reLT	Donor age	Donor cause of death	Follow-up (months)	Post-reLT complications	Outcome/cause of death
1	1	32	0.12879	NA	59	Stroke	9	CDR, sepsis, MOF	Death/HCV recurrence
2	3	7	0.14025	NA	35	Stroke	13	Not reported	Death HCC recurrence
3	3	22	0.41136	NA	73	Trauma	1	Biliary leakage, perihepatic hematoma	Death/sepsis, MOF
4	6	28	0.40967	NA	51	Stroke	5	Fibrosing cholestatic hepatitis	Death/HCV recurrence
5	10	23	0.66883	NA	51	Stroke	51	Femoral vein thrombosis HAS	Alive
6	11	31	0.78222	NA	63	Stroke	0	CRA	Death/CRA
7	12	25	0.61056	NA	55	Stroke	3	PNF, hemoperitoneum, HCV recurrence, esophageal candidiasis, biliary infection	Death/stroke
8	18	25	0.33456	14.369	29	Stroke	90	Chronic renal failure	Alive
9	276	21	0.55152	14.451	54	Stroke	86	Biliary stenosis	Alive
10	281	25	0.59577	15.097	40	Trauma	26	Biliary stenosis	Alive
11	510	24	0.85927	17.773	55	Stroke	18	Not reported	Alive
12	1114	20	0.38304	12.536	46	Stroke	11	Severe HCV recurrence, SBP	Death/HCV recurrence
13	135	23	0.86024	18.603	78	Stroke	12	Esophageal herpes ulcers, CMV viremia, hypertension	Alive
14	332	22	0.48894	13.079	48	Trauma	1	Septic shock	Death/sepsis, MOF

CDR = chronic ductopenic rejection; CMV = cytomegalovirus; CRA = cardiorespiratory arrest; HAS = hepatic artery stenosis; LT = liver transplantation; MELD = Model for End-Stage Liver Disease; MOF = multiorgan failure; NA = not applicable; PNF = primary graft nonfunction; reLT = liver retransplantation; SBP = spontaneous bacterial peritonitis.

Table 3: Characteristics of HIV infection in the 14 patients who underwent liver retransplantation in Spain (2002–2011)

	Pre-LT			Pre- reLT			Last check-up			
Case	Plasma HIV RNA viral load	CD4+ T cells/mm^3	HAART	Plasma HIV RNA viral load	CD4+ T cells/mm^3	HAART	HAART resumed (days)	Plasma HIV RNA viral load	CD4+ T cells/mm^3	HAART
1	<50	368	T-20, 3TC, NFV	ND	*ND*	Not restarted	2	40319	252	AZT, 3TC, T-20
2	<50	644	ATV/rtv, EFV	ND	*ND*	Not restarted	4	<50	866	RAL, ATV
3	<50	277	TDF, 3TC EFV	ND	*ND*	Not restarted	Not restarted	<50	67	NA
4	<50	90	TDF+3TC, LOP/r	ND	*ND*	Not restarted	12	<50	22	RAL, TDF+FTC
5	<50	172	EFV,TDF+ FTC	<50	409	Not restarted	23	<50	193	EFV+TDF+ FTC
6	<50	177	TDF+ FTC, SQV/r	ND	*ND*	Not restarted	Not restarted	ND	ND	NA
7	223	346	RAL	<50	1023	EFV,TDF+FTC	26	<50	45	AZT+3TC, MVC
8	104	108	AZT+3TC, EFV	<50	*ND*	AZT+3T, EFV	3	<50	157	DDI, RAL, FTC
9	<50	386	3TC-D4T-LOP/r	<50	313	3TC-D4T-LOP/r	8	<50	550	3TC-D4T-LOP/r
10	34700	344	No Treatment	<50	288	RAL, TDF+FTC, ETV	NA	<50	353	RAL, TDF+FTC
11	<50	252	FTC+TDF+EFV	<50	186	ABC-3TC-RAL	4	<50	239	ABC-3TC-RAL
12	<50	208	FTC+TDF, EFV	<50	336	FTC+TDF, EFV	23	<50	27	FTC+TDF, EFV
13	<50	490	3TC, DRV/r	<50	481	ABC+3TC, DRV/r	1	<50	26	ABC+3TC, DRV/r
14	<20	115	TDF+FTC, SQV/r	<20	141	TDF, FTC, RAL	Not restarted	ND	ND	NA

ATV = atazanavir; AZT = zidovudine; DDI = didanosine; D4T = stavudine; EFV = efavirenz; ETV = etravirine; FTC = emtricitabine; LOP/r = lopinavir/ritonavir; LT = liver transplantation; MVC = maraviroc; NA = not available; ND = not determined; NFV = nelfinavir; RAL = raltegravir; reLT = liver retransplantation; RTV = ritonavir; SQV = saquinavir; TDF = tenofovir; T-20 = enfurvitide; 3TC = lamivudine.

Data from HIV-negative reLT recipients were obtained from the Spanish Liver Transplant Registry, as previously described (9). Data were analyzed blind at the coordinating center.

Primary LT and reLT criteria

HIV-infected patients had to fulfill the 2005 GESIDA/GESITRA-SEIMC criteria according to their infection status (27). As for liver disease, the criteria for accepting HIV-infected patients for primary LT were the same as those followed in Spain for HIV-negative patients. Since there are no uniform criteria for reLT in Spain, each participating center followed its local protocol for indicating reLT in both HIV-infected and HIV-negative patients.

Patients who underwent reLT within the first 30 days after primary LT were classified as early reLT recipients. The remaining cases were classified as late reLT recipients.

Post-LT management

Antiretroviral therapy was administered until the day of surgery and restarted once the patient was stable and oral intake was reintroduced. Antiretroviral drugs were administered according to Spanish national guidelines (28). HIV-infected patients received the same immunosuppressive regimens as HIV-negative patients according to local protocols. Posttransplant prophylaxis and prophylaxis against HIV infection were administered according to Spanish national guidelines (29,30), as previously described (9,31). HCV recurrence was treated with pegylated interferon α-2a or α-2b and ribavirin based on the same criteria as for HCV-monoinfected LT recipients according to local protocols.

Statistical analysis

Variables are expressed as mean and standard deviation, median and interquartile range (IQR) or as proportions. The Fisher exact test and Wilcoxon test were used to assess whether the predictors were balanced between HIV-infected patients and controls. Survival analyses were performed with the date of reLT as the start date; death from any cause was treated as failure. Survival time from reLT was estimated using the Kaplan–Meier product-limit method; the curves obtained in the different groups were compared using the generalized log-rank test (univariate Cox model analysis). Statistical significance was defined as a bilateral p-value <0.05. All statistical analyses were carried out using Stata (release 9.2).

Results

During the study period, 237 HIV-infected patients underwent primary LT. Patient disposition is shown in Figure 1. Graft failure was recorded in 61 patients (26%), although only 17 out of the 61 patients (28%) were accepted and listed for reLT. Fourteen of the 17 patients underwent reLT, and the remaining three died while on the waiting list. Therefore, the frequency of reLT was 6%. The causes of graft failure and indications for reLT are shown in Figure 1. Three cases underwent reLT in 2004 and 2009, and two cases underwent reLT in 2007, 2008, 2010 and 2011.

The main clinical characteristics and the outcome of the 14 HIV-positive patients who underwent reLT are shown in Tables 1 and 2. The median (IQR) age was 45 (37–52) years and all but two patients were males (86%). At primary LT, 13 patients had HCV-related liver disease (93%) (three were coinfected with HBV) and one patient (7%) had HBV-related liver disease. Eight patients (57%) underwent

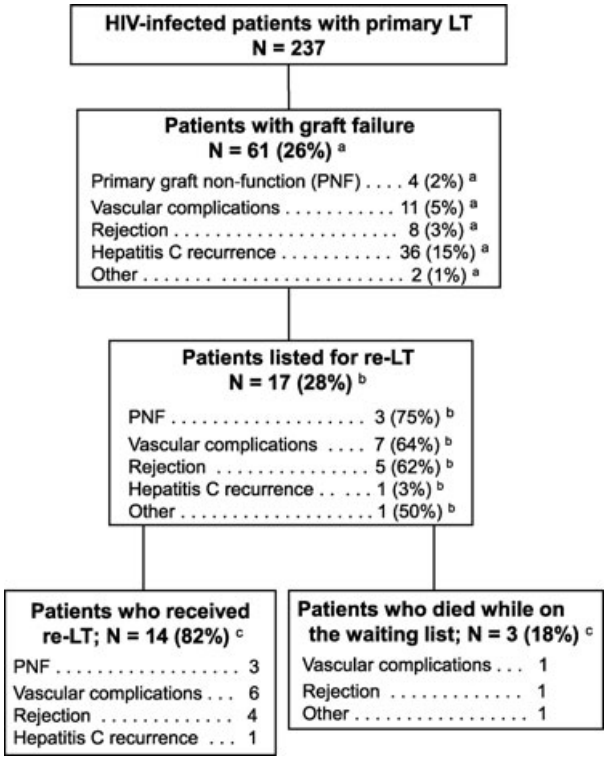


Figure 1: Progress of HIV-infected patients with graft failure after primary liver transplantation (LT).

[a] Percentage for HIV-infected patients with primary LT.

[b] Percentage for patients with graft failure.

[c] Percentage for patients listed for re-LT.

early reLT, five because of vascular thrombosis and three because of PNF. Six patients (43%) underwent late reLT because of chronic rejection in four cases and hepatic artery stenosis and HCV recurrence in one case each. Among the 13 patients with HCV infection, five were HCV RNA-negative and eight were HCV RNA-positive at the time of reLT. The median (range) Model for End-stage Liver Disease score, 1999 Rosen score and 2003 Rosen score were 23.5 (7–32), 0.52 (0.12–0.86) and 14.45 (12.54–18.60), respectively. None of the patients were high-risk in either of the 2 Rosen scores (23, 24). All liver grafts were obtained from deceased donors. Data from donors are shown in Table 2.

After a median (IQR) follow-up of 12 (3–26) months, eight of the 14 HIV-infected patients with reLT (57%) died. The causes of death were severe recurrence of HCV infection in three cases, infectious complications in two, and stroke, recurrence of HCC and intraoperative death in one case each. Survival was 25% (2/8 patients) after early reLT and 67% (4/6 patients) after late reLT, although this difference was not statistically significant ($p = 0.227$). Survival in patients who were HCV RNA-negative at reLT (80% [4/5 patients]) was higher than that in patients who were HCV

RNA-positive (25% [2/8 patients]), although the difference was not statistically significant (p = 0.103).

Data concerning HIV infection are summarized in Table 3. Twelve patients (86%) were former drug users. The median (range) CD4+ T cell counts before LT, before reLT and at the last check-up before death were 310 (90–644), 324 (141–1023) and 239 (26–550) cells/mm^3, respectively. Most patients had an undetectable viral load (<50 copies/mL) at all time points. HAART was restarted after reLT in 11 cases (79%) at a median of 6 days (1–26) after surgery. Five patients received a raltegravir-based regimen, two an efavirenz-based regimen and four other regimens.

Post-reLT survival in HIV-infected and HIV-negative recipients

During the study period, 549 reLT were performed in 6,310 HIV-negative patients with a primary LT at the same participating centers (frequency of reLT, 8.7% [HIV-negative] vs. 6% [HIV-infected]; p = 0.165). A total of 157 reLT were performed in HIV-negative and HCV-positive or HBV-positive recipients. The main clinical characteristics and outcome of the 14 HIV-infected and the 157 HIV-negative patients with reLT are summarized in Table 4. HIV-infected reLT recipients were younger (p<0.001), showed a higher proportion of early reLT (57% vs. 29%, p = 0.057) and, accordingly, had a shorter interval between the first and the second LT (15 vs. 265 days, p = 0.055). The reasons for reLT are shown in Table 4. The rate of HCV recurrence as an indication for LT was significantly lower in HIV-infected recipients (7% vs. 37%, p = 0.036). Donor characteristics were similar in both groups.

After a median (IQR) follow-up of 12 (3–26) and 17 (1.5–45) months, respectively, eight (57%) HIV-infected patients and 55 (35%) HIV-negative patients died (p = 0.176). The distribution of the causes of death was similar in both groups (Table 4), although recurrence of HCV showed a nonsignificant trend toward being more frequent in HIV-infected recipients (21% [3/14] vs. 5% [8/157], p = 0.069). Mortality rates in both groups classified according to the interval to reLT (early vs. late) and to HCV infection status (HCV RNA-positive vs. HCV RNA–negative) are shown in Table 4. The only significant difference was observed in HCV RNA-positive patients, with a higher mortality in HIV-infected patients (6/8 [75%] vs. 32/100 [32%]; p = 0.039).

The survival probability of reLT recipients according to HIV status is shown in Figure 2A. Survival at 1 and 3 years for HIV-infected and HIV-negative patients was 50% versus 72% and 42% versus 64%, respectively (p = 0.160).

Survival curves of reLT recipients according to their HCV RNA status at reLT are shown in Figure 2B and C. The survival probability at 1 and 3 years for HIV-infected and HIV-negative patients with a negative HCV RNA viral load at the time of reLT was 80% versus 82% and 80% versus 72.5%, respectively (p = 0.977). Conversely, the survival probability at 1 and 3 years for the same groups of patients with a positive HCV RNA viral load at the time of reLT was 33% versus 74% and 22% versus 65%, respectively (p = 0.008).

Survival curves after early and late reLT are shown in Figure 2D and E. Survival at 1 and 3 years for HIV-infected versus HIV-negative patients who had undergone early reLT was 37.5% versus 59% and 25% versus 56%, respectively (p = 0.282). Conversely, survival at 1 and 3 years for patients who had undergone late reLT was 67% versus 77% and 67% versus 67%, respectively (p = 0.868).

Discussion

Information on reLT in HIV-infected patients is scarce. In fact, only a few cases of liver regrafting after primary LT have been reported in this population (Table 5) (5,7,17–22). Most cases are described in case series reporting outcome after primary LT in HIV-positive patients and, therefore, have not been studied in depth. Only two studies provide an in-depth analysis of reLT in HIV-infected patients (17,20). We present detailed prospective data on clinical characteristics and outcome in 14 HIV-infected reLT recipients, making ours the most numerous series to date. We also compare these patients with 157 matched HIV-negative reLT recipients.

The 14 cases represent a 6% frequency of reLT in HIV-infected patients, which is not substantially different from the 8.7% frequency in the HIV-negative population (p = 0.165). The indications for reLT were similar in both groups, with the exception of HCV recurrence, which was significantly less common in HIV-infected recipients (7% vs. 37%; p = 0.036) (Table 4). This finding is consistent with the very low number of HIV-infected patients with primary LT and graft failure due to recurrence of HCV who were accepted for reLT in our series (1 of 36 patients [3%]) (Figure 1). Transplant teams may be reluctant to indicate reLT in HIV-positive patients with recurrence of severe HCV infection for the following reasons: poorer outcome after primary LT in HIV/HCV-coinfected patients, the lack of knowledge about factors affecting progression of fibrosis in this population, the relatively unsuccessful therapies available to treat HCV recurrence at present and the current shortage of organs (7,8,15). Furthermore, reduced survival after reLT in HIV-negative–HCV-positive patients may have reduced the degree of acceptance of reLT among our HIV/HCV-coinfected patients (15,16). A similar attitude was expressed by many US transplant centers in a survey conducted by Burton et al. (32) to characterize current practice in reLT for allograft failure caused by HCV recurrence in HIV-negative patients. However, the forthcoming introduction of new and highly effective anti-HCV drugs could make it easier to eradicate HCV in HIV/HCV-coinfected patients after primary LT, with the result that more patients could be considered candidates for reLT.

Table 4: Characteristics of liver retransplantation in HIV-infected and HIV-negative recipients (2002–2011)

	HIV-infected	HIV-negative	p-Value
No. of cases	14	157	
Recipient variables			
Age, y*	45(41, 49)	55.5(47.5, 62)	< 0.001
Male gender	12(86%)	111(71%)	0.354
Primary LT			
HCV infection	13(93%)	142(90%)	0.856
HBV infection	1(7%)	15(10%)	0.992
Hepatocellular carcinoma	3(21%)	54(34%)	0.490
Primary LT donor:			
Donor age, y*	53(49, 64)	50(36, 65)	0.297
Donor age ≥65, y	3(21%)	41(26%)	1.000
Donor brain death by trauma	3(21%)	38(24%)	0.696
Days from primary LT*	15(6, 281)	256(12, 1049)	0.055
Early reLT (≤30 days)	8(57%)	45(29%)	0.057
Late reLT (>30 days)	6(43%)	112(71%)	
Reasons for reLT			
Primary graft nonfunction (PNF)	3(21%)	31(20%)	0.488
Vascular complications	6(43%)	33(21%)	0.310
Rejection	4(29%)	18(11%)	0.086
HCV recurrence	1(7%)	58(37%)	0.036
Other**	–	11(8%)	0.602
Not available	–	6(4%)	1.000
ReLT donor:			
Donor age, y*	53(48, 59)	52(34.5, 62.5)	0.594
Donor age ≥65, y	2(14%)	37(24%)	0.526
Donor brain death by trauma	3(21%)	38(24%)	0.310
Length of follow-up (months)			
Overall	12(3, 26)	17(1.5, 45)	0.791
According to the interval from primary LT			
Early reLT (≤30 days)	7(2, 32)	12(1, 39)	
Late reLT (>30 days)	15(12, 26)	18(2, 49)	
According to HCV RNA at reLT			
Negative	17(12, 26)	13(3, 41)	
Positive	9(3, 13)	21(3, 49)	
Third transplantation	–	10(6%)	–
Mortality	8(57%)	55(35%)	0.176
According to the interval from primary LT			
Early reLT (≤30 days)	6/8(75%)	21/45(47%)	0.250
Late reLT (>30 days)	2/6(33%)†	34/112(30%)	0.764
According to HCV RNA at reLT			
Negative	1/5(20%)	5/23(22%)	1.000
Positive	6/8(75%)	32/100(32%)	0.039
Cause of death			
Intra-operative death	1(7%)	3(2%)	0.750
Technical complications††	–	9(6%)	0.767
Infections	2(14%)	25(16%)	0.825
HCV recurrence	3(21%)	8(5%)	0.069
Miscellaneous‡	2(14%)	8(5%)	0.418
Not available	–	3(2%)	–

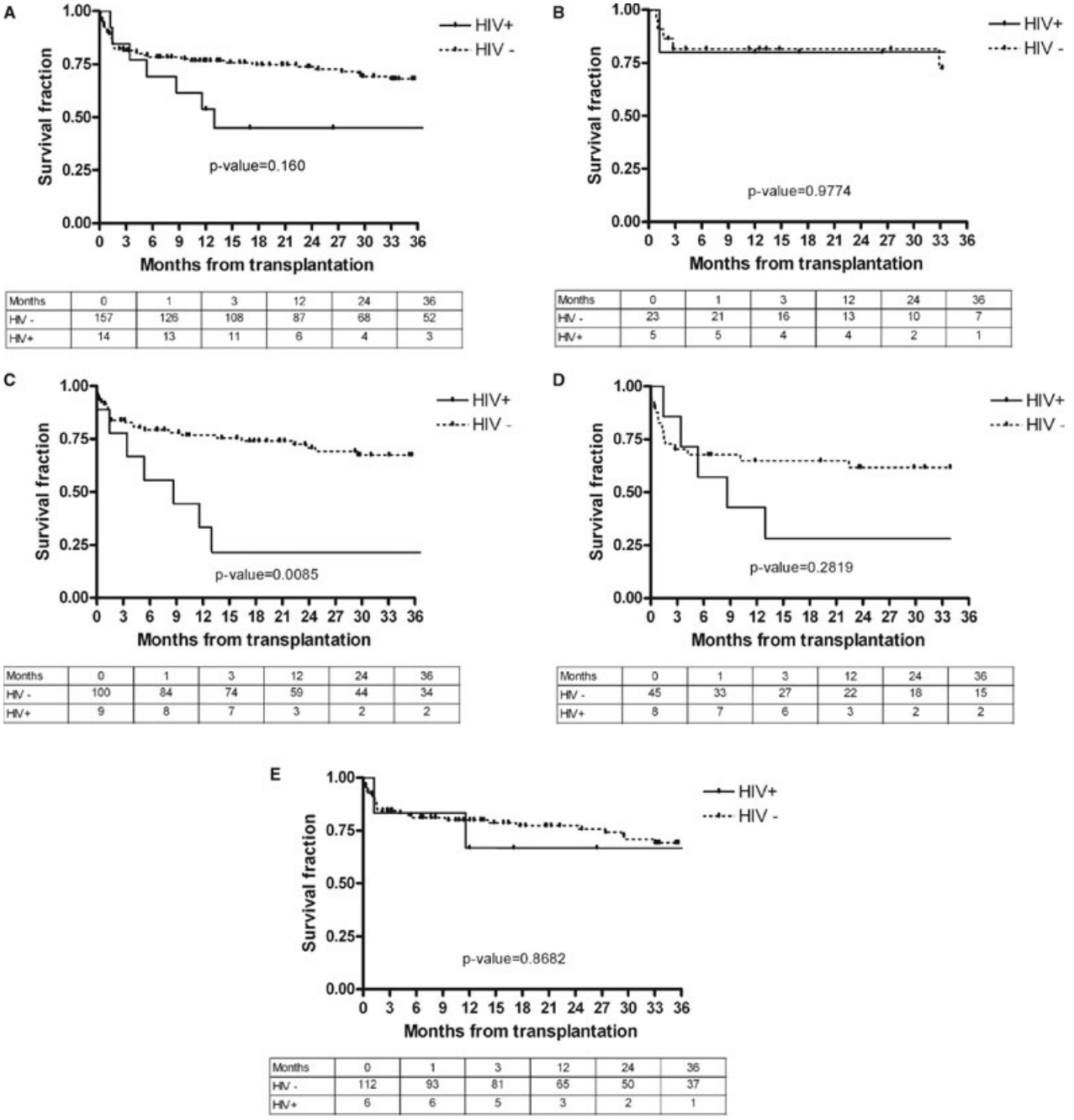
*Median and interquartile range.

**Biliary complications (seven cases), HBV recurrence (two cases), donor-transmitted tumor (one case), massive hemorrhagic graft necrosis (one case).

†Five cases had a negative HCV RNA viral load at the time or reLT.

††Primary graft nonfunction and vascular complications in six and three cases, respectively.

‡In HIV-infected patients: stroke and recurrence of HCC. In HIV-negative patients: kidney failure in two cases and rejection, myocardial infarction, massive hemorrhagic graft necrosis, tumor, stroke and pulmonary embolism in one case each.



Months	0	1	3	12	24	36
HIV -	157	126	108	87	68	52
HIV+	14	13	11	6	4	3

Months	0	1	3	12	24	36
HIV -	23	21	16	13	10	7
HIV+	5	5	4	4	2	1

Months	0	1	3	12	24	36
HIV -	100	84	74	59	44	34
HIV+	9	8	7	3	2	2

Months	0	1	3	12	24	36
HIV -	45	33	27	22	18	15
HIV+	8	7	6	3	2	2

Months	0	1	3	12	24	36
HIV -	112	93	81	65	50	37
HIV+	6	6	5	3	2	1

Figure 2: Probability of survival in the whole cohort (A), in patients with negative HCV RNA (B) and in positive HCV RNA (C) at reLT, and in patients with early reLT (≤30 days) (D) or late reLT (>30 days) (E). Solid and dashed lines represent HIV-infected recipients and HIV-negative recipients, respectively.

In contrast, reLT for PNF or vascular complications was indicated in 67% of HIV-infected patients (10 out of 15 cases) (Figure 1), probably reflecting the reticence of physicians to deny emergency reLT when the indication is related to technical problems (PNF, vascular complications or small-for-size syndrome). In agreement with our results, most reLT in HIV-infected patients reported in the literature were also indicated because of these technical complications (Table 5). Nonetheless, LT teams from the centers participating in the current study were cautious when making decisions on early reLT in HIV-infected patients, as suggested by the fact that no patients had very high MELD or Rosen scores, which are associated with a high risk of post-reLT mortality.

Table 5: Retransplantation in HIV-infected patients: literature findings

Author, year (Reference)	Gender/age	Indication for primary LT	Indication for reLT	Interval to reLT	Outcome
Neff, 2003 (17)	F / 48	HCV cirrhosis*	Chronic rejection	28 months	Alive 7 months
Polard, 2005 (19)	M / 34	HCV cirrhosis	HAART induced FHF	22 weeks	Alive 4 years
Vogel, 2005 (18)	M / 34	HVB FHF	PNF	NA	Alive
De Vera, 2006 (7)	F / 50	HCV cirrhosis	PNF	NA	Death 7 days MOF
	M / 52	HCV cirrhosis	Cholestatic HCV recurrence	7 months	Alive 10 months
Roland, 2008 (5)	NA	N.A.	Small for size after LDLT	49 days	Death 13 months, HCV recurrence
Jao, 2010 (20)	F / 57	Nevirapine-induced FHF	PNF	7 days	Alive 2 years
Di Benedetto, 2011 (21)	NA	NA	PNF	4 days	Alive
	NA	NA	PNF	5 days	Death 34 days, sepsis
Cherian, 2011 (22)	M/9	HAART-induced FHF	PNF	29 days	Death 26 months, chronic rejection
	NA	NA	Vascular complications	11 months	NA
	NA	NA	Vascular complications	13 months	NA

*HIV infection acquired after primary LT.
reLT = liver retransplantation; HCV = hepatitis C virus; HAART = highly active antiretroviral therapy; FHF = fulminant hepatic failure; HBV = hepatitis B virus; PNF = primary graft nonfunction; MOF = multiorgan failure; LT = liver transplantation; LDLT = living donor liver transplantation; NA = not available.

In our study, overall patient survival after reLT in HIV-infected patients was relatively poor and lower than that recorded in HIV-negative reLT recipients (50% vs. 72% at 1 year and 42% vs. 64%, at 3 years, respectively) (Figure 2A). This difference did not reach statistical significance ($p = 0.160$), probably because of the low number of HIV-infected cases. We also tried to identify subpopulations with different outcomes. Therefore, we stratified survival according to HCV RNA status (positive vs. negative) at the time of reLT and according to the interval between primary LT and reLT (early vs. late reLT) and compared the results with those of the respective HIV-negative counterparts. Survival of HIV-infected patients with a negative HCV RNA viral load at the time of reLT was almost identical to that of HIV-negative–HCV-RNA negative reLT recipients (80% vs. 72.5% at 3 years, respectively) (Figure 2B). Conversely, among patients with a positive HCV RNA viral load at the time of reLT, survival of HIV-infected patients was significantly lower than that of HIV-negative reLT recipients (22% vs. 65% at 3 years, respectively; $p = 0.008$) (Figure 2C). Survival of HIV-infected patients with a positive HCV RNA viral load at the time of reLT was poor regardless of the fact that most reLT indications were not directly related to HCV recurrence. These results, if confirmed in larger series, could prove helpful when making decisions on reLT in HIV-infected patients: reLT could reasonably be offered to patients with a negative HCV RNA viral load, whereas it might be inadequate in patients with a positive HCV RNA viral load. However, the introduction of more effective therapies against HCV could modify this approach.

In our series, the 3-year probability of survival of HIV-infected patients who underwent early reLT was only 25% (Figure 2D). Although this rate was lower than that of HIV-negative patients with early reLT (56% at 3 years) and lower than that of HIV-infected patients with late reLT (67% at 3 years), the differences did not reach statistical significance, probably owing to the small numbers of HIV-infected patients in this study. Larger series are needed before robust conclusions can be drawn. Confirmation of these results would cast serious doubts on the indication of early reLT in HIV-infected patients, even in those cases with graft failure due to technical complications directly related to the primary LT procedure. Nonetheless, most deaths after early reLT in our HIV-infected patients were caused by mid-term complications that were unrelated to the procedure, mainly HCV recurrence (Table 2). In contrast, survival after late reLT in HIV-infected patients was acceptable (67% at 3 years) and identical to that seen in HIV-negative patients receiving late reLT (67% at 3 years), thus suggesting that late reLT may reasonably be indicated in HIV-infected patients. However, it remains noteworthy that all but one patient with late reLT had a negative HCV RNA viral load at the time of the procedure (Table 1), thus precluding any conclusion on whether the acceptable survival in this subpopulation was the result of favorable HCV RNA status, the late indication of reLT, or both. A multivariate analysis could have helped to identify which variables were associated with this acceptable outcome; however, we were unable to perform an analysis of this type owing to the small number of cases included.

Control of HIV disease was adequate before and after reLT. All patients initially underwent surgery while fulfilling strict criteria for HIV disease control (27), except for one patient with a CD4 T cell count of 90 cells/mm^3 in the last test before LT. Due to the short interval, CD4 T cell count and HIV viral load were not recorded before emergency reLT; however, those with available data had an HIV viral load

below detection limits and CD4 T cell counts over 100 cells/mm^3 while on the waiting list for reLT. All patients who underwent elective reLT had suppressed plasma HIV RNA viral load and stable CD4 T cell counts before reLT. These parameters persisted after regrafting, except at the last check-up in those who died.

The main limitation of our study is its small sample size and the short follow-up of patients, which could have influenced the statistical analysis and did not allow us to investigate subpopulations of interest (e.g. subsets obtained after combining variables such as reLT indication, interval from primary LT, or HCV RNA status), thus preventing us from drawing firm conclusions. Nevertheless, our study is prospective, constitutes the most numerous series of reLT in HIV-infected patients and compares these patients with matched HIV-negative reLT recipients. Given the current low rate of reLT in most transplant centers, we believe that recording cases in a worldwide registry might be the only way to answer questions concerning this procedure in HIV-infected patients. Meanwhile, arguments for and against reLT in HIV-infected patients will necessarily be hypothetical. In this context, the main reasons for reLT are that it is the only therapeutic option for patients with allograft failure and that transplant teams find it difficult to refuse early reLT for graft failure due to technical complications. A powerful argument against reLT in HIV-infected patients is that survival after primary LT is lower in HIV/HCV-coinfected patients (7–10), thus making it difficult to justify reLT when primary LT in HIV-infected patients is still under debate. In addition, offering reLT to HIV-infected patients may be unacceptable when there are so many HIV-negative patients with better expectable outcomes waiting for their first transplant. Unfortunately, current data from both our study and the literature review are not yet sufficiently robust to resolve these doubts.

We conclude that overall survival after reLT in HIV-infected patients is unsatisfactory. Nevertheless, HIV-infected patients with a negative HCV RNA viral load at the time of reLT and patients undergoing late reLT had a more acceptable survival rate. Remarkably, HIV infection is controlled with HAART after reLT. However, since these conclusions are based on a very small sample size, a multinational registry of reLT in HIV-infected patients is necessary.

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Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

References

1. Tzakis AG, Cooper MH, Dummer JS, Ragni M, Ward JW, Starzl TE. Transplantation in HIV+ patients. Transplantation 1990; 49: 354–358.
2. Wiesner RH. Current indications, contraindications and timing for liver transplantation. In: Busuttil RW, Klintmalm GB, eds. Transplantation of the liver. 1st Ed. Philadelphia: W.B. Saunders Company, 1996: pp. 71–84.
3. Ragni M, Belle SH, Im K, et al. Survival of human immunodeficiency virus-infected liver transplant recipients. J Infect Dis 2003; 183: 1112–1115.
4. Castells L, Escartin A, Bilbao I, et al. Liver transplantation in HIV-HCV coinfected patients: A case-control study. Transplantation 2007; 83: 354–358.
5. Roland ME, Barin B, Carlson L, et al. HIV-infected liver and kidney transplant recipients: 1- and 3-year outcomes. Am J Transplant. 2008; 8: 355–365.
6. Testillano M, Fernandez JR, Suarez MJ, et al. Survival and hepatitis C virus recurrence after liver transplantation in HIV- and hepatitis C virus-coinfected patients: Experience in a single center. Transplant Proc 2009; 41: 1041–1043
7. de Vera ME, Dvorchik I, Tom K, et al. Survival of liver transplant patients coinfected with HIV and HCV is adversely impacted by recurrent hepatitis C. Am J Transplant 2006; 6: 2983–2993.
8. Duclos-Vallée JC, Feray C, Sebagh M, et al. Survival and recurrence of hepatitis C after liver transplantation in patients coinfected with human immunodeficiency virus and hepatitis C virus. Hepatology 2008; 47: 407–417.
9. Miro JM, Montejo M, Castells L, et al. Outcome of HCV/HIV-coinfected liver transplant recipients: A prospective and multicenter cohort study. Am J Transplant 2012; 12: 1866–1876.
10. Terrault NA, Roland ME, Schiano T, et al. Outcomes of liver transplantation in HCV-HIV coinfected recipients. Liver Transpl 2012; 18: 716–726.
11. Spanish Transplant Registry. Organización Nacional de Trasplantes (ONT); 2009: Available from: http://www.ont.es
12. Yao FY, Saab S, Bass NM, et al. Prediction of survival after liver retransplantation for late graft failure based on preoperative prognostic scores. Hepatology 2004; 39: 230–238.

13. Pfitzmann R, Benscheidt B, Langrehr JM, et al. Trends and experiences in liver retransplantation over 15 years. Liver Transpl 2007; 13: 248–257.
14. Marti J, Charco R, Ferrer J, et al. Optimization of liver grafts in liver retransplantation: A European single-center experience. Surgery 2008; 144: 762–769.
15. 2009 Annual report of the U.S. Scientific Registry for Transplant Recipients and the Organ Procurement and Transplantation Network–Transplant Data: 1999–2008. Rockville, MD: Health resources and Services Administration, Healthcare Systems Bureau, Division of Transplantation.
16. Carrión JA, Navasa M, Forns X. Retransplantation in patients with hepatitis C recurrence after liver transplantation. J Hepatol 2010; 53: 962–970.
17. Neff GW, Bonham A, Tzakis AG, et al. Orthotopic liver transplantation in patients with human immunodeficiency virus and end-stage liver disease. Liver Transpl 2003; 9: 239–247.
18. Vogel M, Voigt E, Schäfer N et al. Orthotopic liver transplantation in human immunodeficiency virus (HIV)-positive patients: Outcome of 7 patients from the Bonn cohort. Liver Transpl 2005; 11: 1515–1521.
19. Polard E, Camus C, Abault AY, et al. Retransplantation for acute liver failure due to combined antiviral agents in an HIV-HCV coinfected liver transplant recipient. Transplantation 2005; 80: 1136–1138.
20. Jao J, Sturdevant M, del Rio Martin J, Schiano T, Fiel MI, Huprikar S. Nevirapine-induced stevens johnson-syndrome and fulminant hepatic failure requiring liver transplantation. Am J Transplant. 2010; 10: 1713–1716.
21. Di Benedetto F, Di Sandro S, De Ruvo N, et al. Human immunodeficiency virus and liver transplantation: Our point of view. Transplant Proc 2008; 40: 1965–1971.
22. Cherian PT, Alrabih W, Douiri A, et al. Liver transplantation in human immunodeficiency virus-infected patients: Procoagulant, but is antithrombotic prophylaxis required? Liver Transpl 2012; 18: 83–89.
23. Rosen HR, Madden JP, Martin P. A model to predict survival following liver retransplantation. Hepatology 1999; 29: 365–370.
24. Rosen HR, Prieto M, Casanovas-Taltavull T, et al. Validation and refinement of survival models for liver retransplantation. Hepatology. 2003; 38: 460–469.
25. Mandell GL, Bennett JE, Dolin R. *Principles and practice of infectious diseases*. 7th Edition. Philadelphia, PA. Churchill Livingston, Elsevier 2010.
26. Busuttil RW, Klintmalm GK. Transplantation of the liver, 2nd Ed. Philadelphia: Elsevier Saunders, 2005.
27. Miro JM, Torre-Cisneros J, Moreno A, et al. GESIDA/GESITRA-SEIMC, PNS and ONT consensus document on solid organ transplant (SOT) in HIV-infected patients in Spain (March, 2005). Enferm Infecc Microbiol Clin 2005; 23: 353–362.
28. Iribarren JA, Labarga P, Rubio R, et al. [Spanish GESIDA/Nacional AIDS Plan Recommendations for antiretroviral therapy in HIV-infected Adults (October 2004)]. Enferm Infecc Microbiol Clin 2004; 22: 564–642.
29. Panel de expertos de Grupo de Estudio del Sida; Plan Nacional sobre el Sida. [2008 prevention of opportunistic infections in HIV-infected adolescents and adults guidelines. Recommendations of GESIDA/National AIDS Plan AIDS Study Group (GESIDA) and National AIDS Plan]. Enferm Infecc Microbiol Clin 2008; 26: 437–464.
30. Ayats-Ardite J, Cisneros-Herreros JM, Pérez-Sáenz JL, de la Torre-Cisneros J. Infectious disease assessment in solid organ transplant candidates. Enferm Infecc Microbiol Clin 2002; 20: 448–461.
31. Moreno A, Cervera C, Fortún J, et al. Epidemiology and outcome of infections in human immunodeficiency virus/hepatitis C virus-coinfected liver transplant recipients: A FIPSE/GESIDA prospective cohort study. Liver Transpl 2012; 18: 70–81.
32. Burton JR, Rosen HR. Liver transplantation for Hepatitis C virus recurrence: A survey of liver transplant programs in the United States. Clin Gastroenterol Hepatol 2005; 3: 700–704.

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