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Liver Retransplantation in Patients With HIV-1 Infection: An International Multicenter Cohort Study

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Liver retransplantation is performed in HIV-infected patients, although its outcome is not well known. In an international cohort study (eight countries), 37 (6%; 32 coinfected with hepatitis C virus [HCV] and five with hepatitis B virus [HBV]) of 600 HIV-infected patients who had undergone liver transplant were retransplanted. The main indications for retransplantation were vascular complications (35%), primary graft nonfunction (22%), rejection (19%), and HCV recurrence (13%). Overall, 19 patients (51%) died after retransplantation. Survival at 1, 3, and 5 years was 56%, 51%, and 51%, respectively. Among patients with HCV coinfection, HCV RNA replication status at retransplantation was the only significant prognostic factor. Patients with undetectable versus detectable HCV RNA had a survival probability of 80% versus 39% at 1 year and 80% versus 30% at 3 and 5 years ($p = 0.025$). Recurrence of hepatitis C was the main cause of death in the latter. Patients with HBV coinfection had survival of 80% at 1, 3, and 5 years after retransplantation. HIV infection was adequately controlled with antiretroviral therapy. In conclusion, liver retransplantation is an acceptable option for HIV-infected patients with HBV or HCV coinfection but undetectable HCV RNA. Retransplantation in patients with HCV replication should be reassessed prospectively in the era of new direct antiviral agents.

Abbreviations: BDL, below detection limit; cART, combined antiretroviral therapy; CET, cranioencephalic trauma; CI, confidence interval; CVA, cardiovascular accident; DO, drug overdose; F, female; FAP, familial amyloid polyneuropathy; FIPSE, Spanish Foundation for AIDS Research and Prevention; HBV, hepatitis B virus; HCV, hepatitis C virus; HIVTR, Solid Organ Transplantation in HIV: Multi-Site Study; HR, hazard ratio; IDU, intravenous drug user; IQR, interquartile range; LT, liver transplantation; M, male; MELD, model of end-stage liver disease; n.a., not available; NA, not applicable; NEAT, European AIDS Treatment Network; NIH, National Institutes of Health; PNF, primary graft nonfunction; reLT, liver retransplantation; UK, United Kingdom; US, United States

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Introduction

In many developed countries, liver transplantation (LT) is performed in a growing population of selected HIV-infected patients with end-stage liver disease or hepatocellular carcinoma. Consequently, an increasing demand for liver retransplantation (reLT) could emerge because reLT is the treatment of choice for recipients with irreversible graft failure (1–3).This demand could be particularly relevant for patients coinfected with HIV and hepatitis C virus (HCV), in whom severe hepatitis C frequently recurs after LT, with an increased risk of graft failure and death (4–6).

Information on reLT in patients without HIV infection is considerable (3,7–11), and both graft and patient survival rates are lower than those in patients with primary LT (7,8). Conversely, data on reLT in HIV-infected recipients is scant. Gastaca et al (12) recently published results from a Spanish cohort study with 14 HIV-infected patients and 157 consecutive, matched, non–HIV-infected patients who underwent reLT. The reLT rate and indications for reLT were similar in both cohorts, although recurrence of HCV was significantly less common in HIV-infected recipients. Post-reLT survival in HIV-infected patients was lower than in non–HIV-infected reLT recipients: 50% versus 72%, respectively, at 1 year and 42% versus 64%, respectively, at 3 years ($p = 0.160$). Notably, survival rates for HIV-infected patients with undetectable HCV RNA at reLT or undergoing late reLT (>30 days after primary LT) were acceptable and similar to those seen in non–HIV-infected recipients. The study, however, was underpowered owing to its small sample size. The authors advocated an international registry of reLT in HIV-infected patients (12). Consequently, to draw more robust conclusions, efforts were made to increase the sample size by collecting information from countries in which reLT had been performed in HIV-infected patients. This paper aims to describe the frequency, indications, main characteristics and outcomes of reLT in patients with HIV infection, from a multicenter international cohort.

Materials and Methods

Study design

The cohort comprised adults (aged ≥18 years) with HIV infection who underwent reLT between January 1997 and December 2011 in eight countries: Spain, the United States, Italy, Germany, the United Kingdom, Argentina, Portugal, and Switzerland. Patients were followed until 2013. The study was approved by the institutional review boards of all participating sites. All patients signed the informed consent form. Patient data were obtained from the respective national transplant coordination centers using standardized clinical record forms and were entered into a common database. Data were recorded for sociodemographic characteristics, HIV infection, and primary LT and reLT. In addition, the most relevant events during post-reLT follow-up were recorded.

Diagnosis of HIV infection, HCV and hepatitis B virus (HBV) infections, primary graft nonfunction (PNF), vascular complications, rejection, HCV recurrence, and other posttransplant complications was based on standard criteria (13,14).

Primary LT and reLT criteria

For both primary LT and reLT, patients had to fulfill national criteria for HIV infection (15–19). With minor differences between countries, these criteria included a minimum CD4 cell count (100–200/mm^3), the possibility of effective combined antiretroviral therapy (cART) after transplantation and no unmanageable C events (Centers for Disease Control and Prevention Classification System for HIV Infection). The criteria for enlisting HIV-infected patients for primary LT were the same as those followed in each country for non–HIV-infected patients. In contrast, because there were no uniform criteria for reLT, each participating country followed its center or national protocol (if present) for indications for reLT in HIV-infected patients. The reLT was classified as early or late according to whether the interval from the primary LT was ≤30 days or >30 days, respectively.

Post-LT management

In both primary LT and reLT, cART was administered until the day of surgery and restarted once patients were stable and oral intake was reintroduced. The cART and antimicrobial prophylaxis regimens following transplantation were administered according to national or international guidelines (20–22). HIV-infected patients received the same immunosuppressive regimens as non–HIV-infected patients according to national or local protocols.

Statistical analysis

Continuous variables were expressed as the median and interquartile range (IQR). Categorical variables were expressed as a percentage and compared using either the chi-square test or the Fisher exact test. Survival analyses were performed with the date of reLT as the start date. Death from any cause was treated as a failure. Survival time from reLT was estimated by plotting Kaplan-Meier curves, which were then compared using the log-rank test. Predictors of outcomes were analyzed using Cox proportional hazards models. Statistical significance was defined as a two-tailed p value <0.05. All statistical analyses were carried out using SAS version 9.2 (SAS Institute, Cary, NC).

Results

Patient characteristics

During the study period, 600 patients with HIV infection received primary LT. Of those, 37 patients (6%) underwent reLT and compose the cohort of the present study. Their main characteristics are described in Table 1. The median age was 47 years, and most patients were male (92%). HCV-related disease was the leading indication for primary LT (32 of 37, 86%; four patients were also coinfected with HBV), whereas the remaining five patients (14%) received primary LT for HBV-related disease.

The most frequent indications for reLT were vascular complications (35%). Other indications were PNF (22%), rejection (19%), and hepatitis C recurrence (13%). The median score for the model of end-stage liver disease at reLT was 23, and the median Rosen score (23) was 16. Time from primary LT to reLT was very variable, from 8 to 388 days, with a median of 29 days. Nineteen patients (51%) underwent early reLT (≤30 days), mostly owing to vascular complications (nine cases) and PNF (eight cases), and 18 patients (49%) underwent late reLT (>30 days), mainly for rejection (seven cases) and HCV recurrence (five cases). Of the 32 patients who received primary LT for HCV-related disease, serum HCV RNA at the time of reLT was detectable in 22 patients (69%) and undetectable in 10 (31%; HCV eradication by antiviral treatment or spontaneous resolution). All but one patient who had primary LT for HBV-related disease were DNA HBV negative at the time of reLT.

Most patients were on effective cART, and HIV viral load was below the detection limit at both primary LT and reLT. All grafts for reLT were obtained from deceased donors and were whole organs. Median reLT donor age was 48 years.

Table 1: Characteristics of liver retransplantation in HIV-infected patients

Characteristics	Results
Number of patients	37
Recipient variables	
Age, years*	47 (42–50)
Male sex	34 (92)
HIV risk factor	
Former IDU	20 (54)
Sexual relations	11 (30)
Other	6 (16)
Calendar year	
1997–2007	18 (49)
2008–2011	19 (51)
Primary LT	
HCV infection	28 (76)
HCV/HBV coinfection	4 (11)
HBV infection	5 (13)
Hepatocellular carcinoma	14 (38)
HCV genotype	
1 or 4	24 (75)
2 or 3	5 (16)
Other/unknown	3 (9)
Time since primary LT (days)*	29 (8–388)
Early (≤30 days)	19 (51)
Late (>30 days)	18 (49)
Indication for reLT	
Vascular complications	13 (35)
PNF	8 (22)
Rejection	7 (19)
HCV recurrence	5 (13)
Other**	4 (11)
Serum HCV RNA at reLT***	
Detectable	22 (69)
Undetectable	10 (31)
MELD score at reLT*	23 (21–31)
Rosen score at reLT*	16 (14–17)
HIV infection at reLT	
On cART	34 (92)
CD4 cells/mm^3*	246 (126–354)
HIV RNA viral load BDL	31 (91)
ReLT donor	
Donor age, years*	48 (32–59)
Brain death by trauma	8 (22)

Data are shown as number (percentage) except as indicated.
*Median and interquartile range.
**HCV recurrence plus rejection, massive liver necrosis of indeterminate etiology, perfusion or toxic injury, and cholangiocarcinoma in one case each.
***Percentages related to patients with HCV infection.
BDL, below detection limit (<200 copies/mL); cART, combined antiretroviral therapy; HBV, hepatitis B virus; HCV, hepatitis C virus; IDU, intravenous drug user; LT, liver transplantation; MELD, model of end-stage liver disease; PNF, primary graft nonfunction; reLT, liver retransplantation.

Survival

After a median follow-up of 22 months (IQR: 2–57 months), 19 (51%) of the 37 patients died. The main characteristics and causes of death in these 19 patients are shown in Table 2. The probability of survival for the whole series was 56% at 1 year and 51% at 3 and 5 years after reLT (Figure 1A). Two (40%) of the five patients with primary LT for HBV-disease and 17 (53%) of the 32 patients with primary LT for HVC disease died after reLT. As shown in Figure 1(B), Kaplan-Maier survival estimates were lower for the latter, although the difference did not reach statistical significance ($p = 0.245$).

Analyzing the 32 patients who received primary LT for HCV disease separately, the only factor reaching significance as a predictor of mortality after reLT in this subpopulation was a detectable HCV RNA status at the time of reLT (hazard ratio of 4.59 [95% CI: 1.04–20.22]; $p = 0.044$) (Table 3). Figure 1(C) shows that the survival of patients with undetectable HCV RNA at reLT was significantly higher than that of patients with detectable HCV RNA: 80% versus 39% 1 year after reLT and 80% versus 30% at 3 and 5 years, respectively ($p = 0.025$).

Figure 2 shows the mortality rate after reLT and causes of death in patients with primary LT for HBV-related disease and in patients with primary LT for HCV-related disease with either undetectable or detectable HCV RNA at reLT. The rates of mortality related to sepsis and causes other than HCV recurrence in the three subgroups were not significantly different (20%, 10%, and 18%, respectively, for both circumstances). In the subgroup of patients with detectable HCV RNA at reLT, there was a 32% greater mortality rate due to HCV recurrence.

Table 4 shows the number, indications and year of reLT, and mortality rate and causes of death in patients from the eight participating countries.

Discussion

This is the first international multicenter cohort of HIV-infected patients who underwent reLT. The 6% rate of reLT observed in the cohort falls within the rate of 5%–10% reported in non–HIV-infected patients (3,8,10,11,24). The main indications for reLT were technical problems, namely, arterial thrombosis and PNF. Although primary LT was performed for HCV-related diseases in most patients, recurrence of HCV infection was the reason for reLT in only 13% of cases. This low frequency of reLT for recurrence of HCV infection probably reflects the reluctance of physicians to perform reLT in the HCV/HIV-coinfected population because of the poorer outcome after primary LT (4–6) and the negative impact of HCV infection on survival after reLT in non–HIV-infected recipients reported elsewhere (8,25–27).

We found that survival after reLT was lower than that reported in non–HIV-infected retransplanted patients. In our cohort of HIV-infected patients, the Kaplan-Meier estimates for survival at 1, 3, and 5 years after reLT were 56%, 51%, and 51%, respectively, compared with corresponding

Table 2: Characteristics of patients having undergone liver retransplantation who died during follow-up

Number	Sex	Age at reLT	Primary LT indication	HCV genotype	reLT indication	HCV RNA al reLT	MELD score at reLT	Interval between primary LT and reLT (days)/ type of reLT	Survival time after reLT (days)	Donor age/ cause of death	Cause of death
1	M	34	HBV	n.a.	PNF	n.a.	21	2/Early	5505	Unknown	Sepsis (undetermined organism)
2	M	51	HBV	n.a.	Vascular thrombosis	n.a.	31	11/Early	1	63/CVA	Stroke
3	M	48	HCV	3	Rejection	Negative	22	332/Late	1	48/CET	Sepsis (*E. coli*)
4	M	57	HCV	unknown	PNF	Negative	18	10/Early	47	Unknown	Acute rejection
5	M	45	HCV	1	PNF	Positive	31	14/Early	1	41/CVA	Massive perioperative bleeding
6	M	53	HCV	1	Vascular complication	Positive	34	7/Early	1	49/FAP	PNF
7	M	48	HCV	1	Massive liver necrosis	Positive	40	14/Early	30	Unknown	Sepsis (*P. aeruginosa*)
8	M	49	HCV	1	Vascular complication	Positive	40	19/Early	26	67/CVA	Sepsis (Undetermined organism)
9	M	48	HCV	1	HCV recurrence	Positive	25	304/Late	46	41/CET	Heart failure
10	M	44	HCV	1	PNF	Positive	25	1/Early	116	55/CVA	Stroke
11	M	45	HCV	1	Vascular thrombosis	Positive	28	6/Early	163	51/CVA	HCV recurrence
12	M	47	HCV	1	Perfusion/toxic injury	Positive	26	35/Early	172	31/DO	HCV recurrence
13	M	37	HCV	1	Vascular thrombosis	Positive	32	1/Early	264	59/CVA	HCV recurrence
14	M	51	HCV	2	Rejection	Positive	21	373/Late	289	46/CVA	HCV recurrence
15	F	49	HCV	1	HCV recurrence	Positive	20	1114	353	46/CVA	HCV recurrence
16	M	46	HCV	1	Vascular thrombosis	Positive	7	3/Early	389	35/CVA	HCV recurrence
17	M	45	HCV	1	HCV recurrence plus rejection	Positive	21	824/Late	662	58/CVA	HCV recurrence
18	M	44	HCV+HBV	1	PNF	Positive	22	3/Early	44	73/CET	Sepsis (*A. baumanii*)
19	M	41	HCV+HBV	1	HCV recurrence	Positive	32	1343/Late	80	Unknown	Sepsis (undetermined organism)

CET, cranioencephalic trauma; CVA, cardiovascular accident; DO, drug overdose; F, female; FAP, familial amyloid polyneuropathy; HBV, hepatitis B virus; HCV, hepatitis C virus; LT, liver transplantation; M, male; MELD, model of end-stage liver disease; PNF, primary graft nonfunction; n.a., not available; reLT, liver retransplantation.

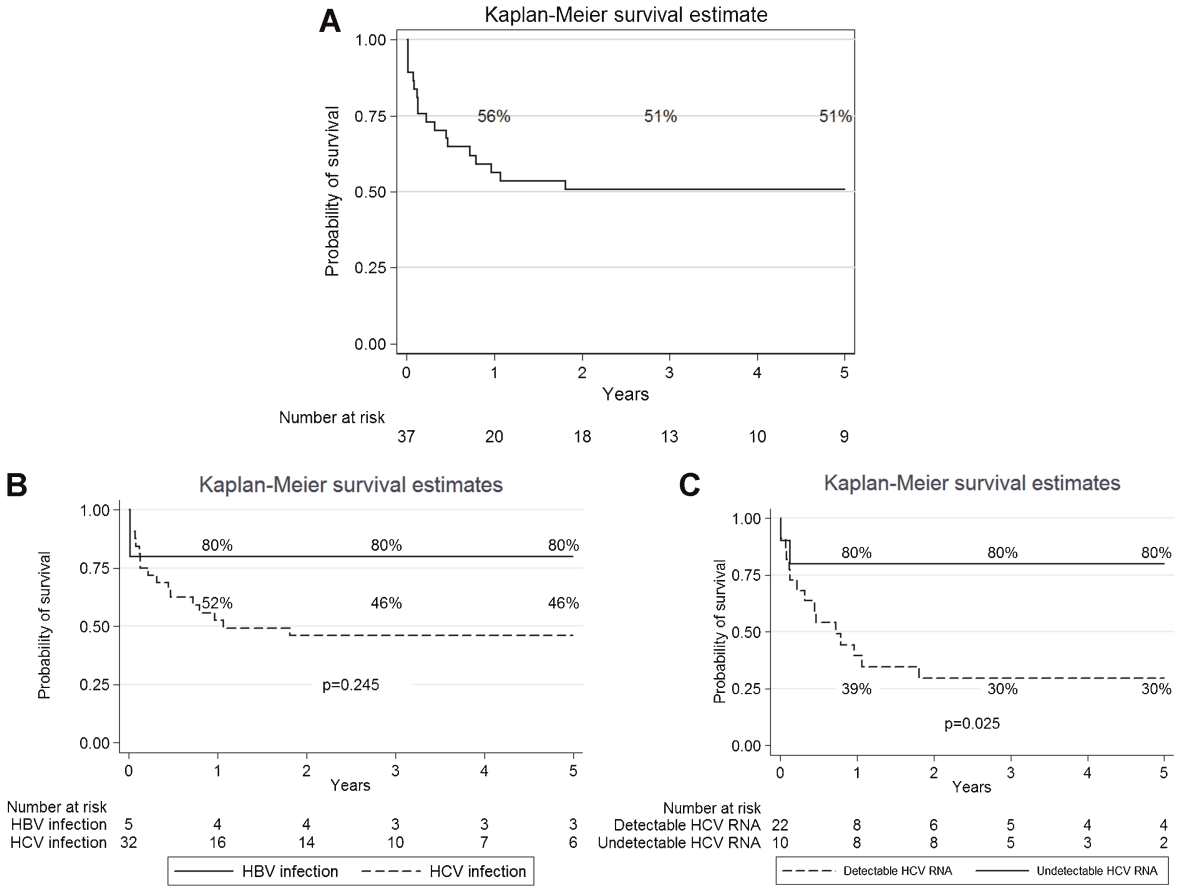

Figure 1: Probability of survival after liver retransplantation in HIV-infected recipients. (A) Whole cohort of patients. (B) Patients with primary liver transplantation for an HBV- or HCV-related disease. (C) Patients with primary liver transplantation for an HCV-related disease, classified according to whether or not serum HCV RNA at liver retransplantation was detectable. HBV, hepatitis B virus; HCV, hepatitis C virus.

figures reported in large national or multinational series of non–HIV-infected patients, which are ≈70% at 1 year, 60% at 3 years, and 55% at 5 years after reLT (9,28) (Table 5). Consequently, concerns about the suitability of reLT in non–HIV-infected patients—mainly, the poorer outcomes observed in reLT than in primary LT and the increasing number of patients waiting for their first transplant in the setting of donor scarcity—are also pertinent for HIV-infected patients.

Nevertheless, it is important to remark that we were able to identify three different subsets in our cohort according to both the indication of primary LT and the respective survival rates. As shown in Figures 1(B), 1(C), and 2, survival in patients with primary LT for HBV-related disease and in patients with primary LT for an HCV-related disease who were HCV RNA negative at the time of reLT was very acceptable, with Kaplan-Meier estimates of 80% at 1, 3 and 5 years after reLT. These figures compare favorably with survival reported in the national and multinational series of non–HIV-infected reLT patients mentioned above (9,28) (Table 5). In contrast, the third subset in our cohort, consisting of patients with primary LT for HCV-related disease and detectable HCV RNA at reLT, had much shorter survival rates, with Kaplan-Meier survival estimates as low as 39% at 1 year after reLT and 30% at 3 and 5 years (Figure 1C). This subgroup had a mortality risk 4.6 times higher than patients with primary LT for HCV disease but undetectable HCV RNA at reLT (Table 3). Interestingly, mortality caused by sepsis and reasons other than HCV recurrence was not significantly different among the three subsets (10%–20% in each subgroup), whereas a 32% greater mortality due to HCV recurrence was observed among patients with HCV RNA detectable at reLT (Figure 2). Of note, most deaths due to HCV recurrence occurred within the first year after reLT (Table 2), thus emphasizing the negative influence of active HCV infection at the time of reLT. Because of the paramount importance of HCV replication status in HIV-infected reLT recipients, eradication of HCV prior to reLT

Table 3: Predictors of mortality in the 32 HIV/HCV-coinfected patients undergoing liver retransplantation included in the study

Predictors	HR (95% CI)	p value
Age (1-year increase)	1.03 (0.93–1.13)	0.623
Male sex	2.28 (0.30–17.25)	0.424
Former IDU	0.86 (0.33–2.23)	0.756
reLT during 2008–2011	1.50 (0.57–3.95)	0.199
Indication for reLT		
Vascular complications	1.02 (0.36–2.90)	0.970
PNF	1.34 (0.44–4.14)	0.605
Rejection	0.38 (0.09–1.67)	0.200
HCV recurrence	1.33 (0.38–4.69)	0.653
HCV genotype 1 or 4	1.66 (0.38–7.33)	0.503
Detectable HCV RNA at reLT	4.59 (1.04–20.22)	0.044
Early reLT (≤30 days)	1.50 (0.57–3.95)	0.410
MELD score at reLT (1-unit increase)	1.02 (0.97–1.08)	0.372
Rosen score at reLT (1-unit increase)	1.01 (0.83–124)	0.922
CD4 <200 cells/mm^3	0.96 (0.35–2.64)	0.932
On cART	0.59 (0.15–2.96)	0.665
HIV RNA viral load BDL*	NA	
Donor age (1-year increase)	1.02 (0.99–1.05)	0.249
Donor brain death by trauma	1.26 (0.36–4.43)	0.713

*Cox regression was not performed because there were no events in the group of patients with HIV RNA viral load >200 copies/mL.
BDL, below detection limit (<200 copies/mL); cART, combined antiretroviral therapy; CI, confidence interval; HCV, hepatitis C virus; HR, hazard ratio; IDU, intravenous drug user; MELD, model of end-stage liver disease; NA, not applicable; PNF, primary graft nonfunction; reLT, liver retransplantation.

in these patients appears essential to achieving favorable post–reLT outcomes. In this context, the improved efficacy and tolerability of the new direct antiviral agents against HCV are very encouraging, especially in interferon-free combinations (29).

In the study by Gastaca et al (12) including all reLTs performed in Spain (also included in the current study), late reLT was significantly better than early reLT. In the present investigation, a nonsignificant trend toward better survival in late reLT than in early reLT was also observed (61% vs. 39%, p = 0.200; data not shown).

HIV infection was adequately controlled. Most patients were receiving cART, and HIV-related parameters were acceptable at the moment of reLT. Moreover, no patients died as a result of AIDS-defining events.

This study was subject to a series of limitations. Although the cohort included the vast majority of HIV-infected patients who underwent reLT worldwide, thus making it more robust than the previously published Spanish study involving only 14 reLT patients (12), the sample size was still small (37 patients). In addition, potentially important variables, such as donor risk index, were not available.

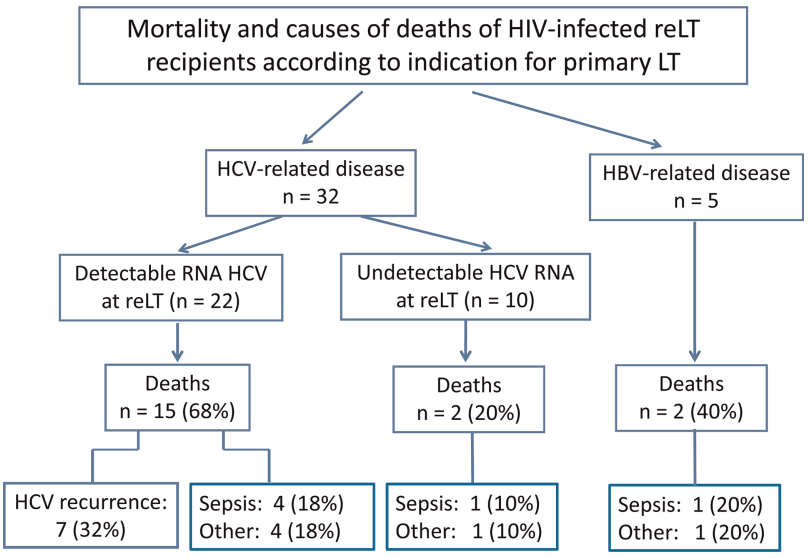

Figure 2: Mortality and causes of death in HIV-infected retransplanted patients classified according to the indication for primary LT and, in cases of HCV infection, to whether or not serum HCV RNA at reLT was detectable. HCV, hepatitis C virus; LT, liver transplantation; reLT, liver retransplantation.

Table 4: Characteristics and outcome of liver retransplantation in HIV-infected patients from the participating countries

Country	Spain	US	Italy	Germany	UK	Argentina	Portugal	Switzerland	Total
Number of primary LTs	270	125	118	30	24	10	13	10	600
Number of reLTs (%)	14 (5)	9 (7)	5 (4)	4 (13)	2 (8)	1 (10)	1 (8)	1 (10)	37 (6)
Year of reLT									
1997	0	0	0	1	0	0	0	0	1
2001	0	0	0	0	1	0	0	0	1
2004	3	1	0	0	0	0	0	0	4
2005	0	1	1	2	0	0	0	0	4
2006	0	1	0	0	0	0	0	0	1
2007	2	3	1	0	1	0	0	0	7
2008	2	1	1	0	0	1	0	0	5
2009	3	2	0	1	0	0	0	1	7
2010	2	0	2	0	0	0	1	0	5
2011	2	0	0	0	0	0	0	0	2
Reasons for reLT (%)									
Vascular complications	6	2	1	1	2	—	1	—	13 (35)
PNF	3	—	3	2	—	—	—	—	8 (22)
Rejection	4	3	—	—	—	—	—	—	7 (19)
HCV recurrence	1	3	—	1	—	—	—	—	5 (13%)
Other**	—	1	1	—	—	1	—	1	4 (11)
Follow-up (months)*	13 (3–46)	35 (6–49)	1 (1–63)	18 (2–144)	98 (62–133)	22	0	39	22 (2–57)
Mortality rate (%)	8 (57)	3 (33)	3 (60)	3 (75)	0	1 (100)	1 (100)	0	19 (51)
Cause of death (%)									
HCV recurrence	4	2	—	—	—	1	—	—	7 (37)
Infections	2	—	2	2	—	—	—	—	6 (32)
Miscellaneous**	2	1	1	1	—	—	1	—	6 (32)

Data are shown as counts except as indicated.
*Median and interquartile range.
**Stroke in two cases, and PNF, heart failure, rejection and massive perioperative bleeding in one case each.
HCV, hepatitis C virus; LT, liver transplantation; PNF, primary graft nonfunction; reLT, liver retransplantation; UK, United Kingdom; US, United States.

In summary, although reLT in HIV-infected patients has become accepted practice, it raises several concerns. First, primary LT in this group remains controversial owing to poorer survival—particularly in patients with HCV/HIV coinfection—than in non–HIV-infected patients. Second, survival is poorer in reLT than in primary LT, with the consequent reluctance of LT teams to use a scarce resource (ie, a donor liver) for reLT; therefore, it seems reasonable that reLT, which is often the only alternative to death, should be reserved for those patients who are most likely to benefit from it. Based on our results, reLT appears to be an acceptable option for HIV-infected patients with HBV or HCV coinfection but undetectable HCV RNA at reLT. The indication for reLT in HIV-infected patients with active HCV infection remains unresolved, although it should be reassessed prospectively in the era of new anti-HCV direct

Table 5: Patient survival rates following first liver retransplantation according to geographical area

			Survival (%)		
Area	Number of patients	Time period	1 year	3 years	5 years
US[1]	4617	1998–2009	68	60	54
Europe[2]	8704	1998–2013	72	64	59
Present study					
Whole cohort	37	1997–2011	56	51	51
Primary LT for HBV disease	5		80	80	80
Primary LT for HCV disease					
HCV RNA undetectable at reLT	10		80	80	80
HCV RNA detectable at reLT	22		39	30	30

[1]Based on Organ Procurement and Transplantation Network data as of May 8, 2015.
[2]Based on European Liver Transplant Registry data as of June 16, 2015.
HBV, hepatitis B virus; HCV, hepatitis C virus; LT, liver transplantation; reLT, liver retransplantation; US, United States.

antiviral agents. Prospective validation based on a much larger number of patients is needed to confirm these results.

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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*.

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Appendix

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