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Survival of Liver Transplant Patients Coinfected with HIV and HCV Is Adversely Impacted by Recurrent Hepatitis C

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Although liver transplantation (LTx) in HIV-positive patients receiving highly active antiretroviral therapy (HAART) has been successful, some have reported poorer outcomes in patients coinfected with hepatitis C virus (HCV). Here we discuss the impact of recurrent HCV on 27 HIV-positive patients who underwent LTx. HIV infection was well controlled post-transplantation. Survival in HIV-positive/HCV-positive patients was shorter compared to a cohort of HIV-negative/HCV-positive patients matched in age, model for end-stage liver disease (MELD) score, and time of transplant, with cumulative 1-, 3- and 5-year patient survival of 66.7%, 55.6% and 33.3% versus 75.7%, 71.6% and 71.6%, respectively, although not significantly ($p = 0.07$), and there was a higher likelihood of developing cirrhosis or dying from an HCV-related complication in coinfected subjects (RR = 2.6, 95%CI, 1.06–6.35; $p = 0.03$). Risk factors for poor survival included African-American race ($p = 0.02$), MELD score >20 ($p = 0.05$), HAART intolerance postLTx ($p = 0.01$), and postLTx HCV RNA >30 000 000 IU/mL ($p = 0.00$). Recurrent HCV in 18 patients was associated with eight deaths, including three from fibrosing cholestatic hepatitis. Among surviving coinfected recipients, five are alive at least 3 years after LTx, and of 15 patients treated with interferon-α /ribavirin, six (40%) are HCV RNA negative, including four with sustained virological response. Hepatitis C is a major cause of graft loss and patient mortality in coinfected patients undergoing LTx.

Key words: HAART, interferon-α , ribavirin

Abbreviations: LTx, liver transplantation; HAART, highly active antiretroviral therapy; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HBV, hepatitis B virus; CMV, cytomegalovirus; HAI, histological activity index; HCC, hepatocellular carcinoma; BR, biochemical response; VR, virological response; SVR, sustained virological response

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Introduction

The introduction in 1996 of highly active antiretroviral therapy (HAART) for the treatment of human immunodeficiency virus (HIV) infection has significantly improved the survival of patients as well as decreased the incidence of opportunistic infections (1). An anticipated consequence of these benefits, however, has been a significant increase in the number of patients presenting with end-stage liver disease, mainly from chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections (2–4). The presence of HIV infection has been considered as a contraindication to liver transplantation (LTx) not only because of psychosocial reasons but also due to historically poorer outcomes prior to HAART (5). The success of HAART, however, has increasingly led some centers to perform LTx in HIV-positive patients (6), mainly through a multicenter study sponsored by the National Institutes of Health (http://www.clinicaltrials.gov/ct/show/NCT00074386) and in large centers in Europe.

Several series have demonstrated comparable patient and graft survival after LTx between HIV-negative recipients and HIV patients with HBV cirrhosis, drug-induced liver failure and fulminant liver failure (7–11). However, some have reported poor outcomes in the transplantation of coinfected HIV and HCV patients (9,11,12). In particular, in the early experience at King's College, none of their LTx recipients survived over 2 years, with the majority dying as a result of recurrent hepatitis C (9). Others have also reported severe HCV recurrence and fibrosing cholestatic hepatitis leading to graft failure and early patient death (12–14). These studies, however, all had relatively short follow-ups. The current study is an extension of our earlier reports, one in collaboration with the University of Miami (7,15), on coinfected HIV/HCV patients who underwent LTx under coverage of HAART, and it provides a more detailed account with a longer follow-up on the impact of recurrent hepatitis C on the outcomes of LTx in these patients.

Patients and Methods

Evaluation of HIV positive patients for LTx

HIV-positive patients with end-stage liver disease were evaluated for LTx using the same criteria for HIV-negative subjects. Due to the presence of severe portal hypertension and splenomegaly, patients with CD4 counts as low as 100/mm^3 were not precluded from being placed in the liver transplant list. In addition, patients who were viremic as a consequence of discontinuing their HAART medications because of liver failure and/or intolerable side effects were considered for listing provided they had a previous documented treatment response to HAART or if they could be predicted by resistance testing to have a regimen that would suppress HIV posttransplantation. Patients with an active opportunistic infection or a history of progressive multifocal leukoencephalopathy were not considered for transplantation. Prior to LTx, two patients in this series had a history of *Pneumocystis carinii* pneumonia that resolved after treatment and another patient had a history of mycobacterium avium complex infection that cleared after therapy.

HIV-negative, HCV-positive control patients

Between January 1, 1997 and December 31, 2005, 1485 HIV-negative adult subjects underwent LTx at the University of Pittsburgh Medical Center, 487 of whom were transplanted for HCV-associated cirrhosis for the first time. Of these, 61 who received induction immunosuppression with Alemtuzumab (16) or rabbit antithymocyte globulin (17) were excluded from further analysis, as these subjects were part of a study on spaced weaning of immunosuppression and were found to have worse outcomes from recurrent hepatitis C. Of the 426 remaining HIV-negative and HCV-positive subjects who did not receive any pretransplant induction antibody therapy, a control group was randomly selected 2:1, HIV-negative controls to HIV-positive subjects, matched for age (within 4 ± 4 years), time of transplant (within 1 ± 0.4 years), severity of disease at the time of transplant (MELD [model for end stage liver disease] score within 1 ± 1.5 points), and the presence or absence of respiratory failure or renal failure requiring hemodialysis prior to transplantation. Baseline immunosuppression in control patients consisted of tacrolimus and steroids.

HAART and immunosuppression

For the treatment of HIV, HAART medications were resumed once patients' liver function tests (LFTs) normalized posttransplant (i.e. total bilirubin <2 mg/dL). The HAART regimen used pre-LTx, either a nucleoside reverse transcriptase inhibitor (NRTI) plus a protease inhibitor (PI) or an NRTI plus a nonNRTI (nevirapine was avoided due to severe potential hepatotoxicity posttransplant), was reinstituted posttransplant. HAART intolerance was defined as the permanent discontinuation of antiretroviral drugs because of toxicity. Immunosuppression consisted of tacrolimus and steroids and no induction therapy was utilized. Solumedrol was administered in the operating room followed by a standard steroid taper and prednisone. Steroids were weaned beginning 1 month postoperatively. Rapamune or mycophenolate mofetil were utilized for patients with renal insufficiency or as additional immunosuppression for those who had acute cellular rejection (ACR).

Monitoring of HIV and cytomegalovirus after LTx

CD4 counts and HIV viral titers were obtained at 4–12 week intervals posttransplantation. The presence of cytomegalovirus (CMV) in peripheral blood was monitored by weekly serum testing of the CMV matrix protein pp65 antigen in the first 3 months and bimonthly in months 4–6 after transplantation. No CMV prophylaxis is administered after LTx as our center has for many years (18) preemptively treated asymptomatic CMV antigenemia until it becomes undetectable with intravenous ganciclovir (10 mg/kg/day) or oral valganciclovir (900 mg twice a day) adjusted for renal function. CMV disease (defined as symptomatic CMV infection or evidence of CMV in tissues) was treated regardless of CMV antigenemia status.

Diagnosis and treatment of rejection episodes and recurrent hepatitis C

Liver biopsies were obtained when clinically indicated (e.g. rise in serum aminotransferases) and 1 year after transplantation. ACR was treated with 1 g of i.v. solumedrol with or without a steroid recycle and by maintaining tacrolimus trough levels around 8–15 ng/mL. Recurrent hepatitis C was graded and staged using Ishak's modified histological activity index (HAI) and staging (19). Quantitative HCV RNA was obtained every 3–6 months during treatment and/or biannually after the first year posttransplant, and LFTs were checked frequently. In some patients, HCV RNA could not be obtained routinely, e.g. in subjects who resided at a distance from our center. Patients were evaluated for HCV treatment on an individualized basis by surgeons and hepatologists. Our policy was to treat patients who had elevated LFTs and histological evidence of recurrent hepatitis C; those who had progression of fibrosis and/or those with excessive HCV viral loads (e.g. $>$20–30 000 000) were especially aggressively treated. Some patients, however, were being followed up by their local gastroenterologist and the initiation of treatment in these subjects was difficult and unsuccessful at times. Prior to 2001, the antiHCV regimen included interferon-α-2b (Intron-A; Schering-Plough, Kenilworth, NJ) 1–3 million units subcutaneously three times a week and ribavirin (Rebetol; Schering-Plough) 400–1200 mg p.o. daily. From 2001 and thereafter, the combination of PEG-Intron (pegylated interferon alfa-2b; Schering-Plough) 1.0 μg/kg/week SQ or Pegasys (Peginterferon alfa-2a; Roche, Nutley, NJ) 90–180 μg/week SQ and ribavirin (same doses as above) was utilized. Our goal was to reach the maximum dose of each medication in every patient. The duration of treatment was a minimum of 48 weeks, though longer courses of therapy were implemented at times under the discretion of the surgeon or hepatologist. Biochemical response (BR) to treatment was defined as normalization of serum aminotransferases, and virological response (VR) was defined as clearance of HCV RNA from serum. Patients with a VR of more than 6 months after cessation of therapy were regarded as having a sustained virological response (SVR).

Statistical analysis

Patient survival analysis was performed using the Kaplan-Meier method and groups were compared using the log-rank test and Cox regression analysis. Categorical variables were compared using Fisher's exact test while continuous variables were compared using Student's *t*-test or Mann-Whitney U test. Statistical significance was defined as a p-value of <0.05. All analyses were performed using SPSS 13.0 statistical software (SPSS Inc., Chicago, IL).

Results

Between September 1997 and August 2005, 33 liver transplants in 31 HIV positive patients were performed at the Thomas E. Starzl Transplantation Institute. Twenty-seven of the patients were HCV RNA-positive and these patients comprise the current study group. Of the four patients excluded in this analysis, three had hepatitis B cirrhosis and the other patient had drug-induced fulminant hepatic failure. Two subjects in this series (patients 24 and 25) were enrolled in the NIH-sponsored multicenter study in solid organ transplantation in HIV patients, and the remainder of the patients was part of a study approved by the Institutional Review Board of the University of Pittsburgh on

Table 1: Characteristics of HIV and HCV coinfected patients who underwent liver transplantation

					HIV viral load[1]/CD4 count			
						PostLTx with HAART		
Patient	Age/sex race	OLT date	Survival, months[2]	Status/clinical outcome	PreLTx	Year 0–1	Year 2–3	Year 4–5
1	38/M/W	Sep 97	57.3	Deceased (invasive aspergillosis); HCV cirrhosis	UD/168	UD/245	UD/332	UD/478
2	44/M/W	Dec 98	81.7	Alive; HCV cirrhosis	UD/263	UD/224	**1250**/298	UD/343
3	43/M/W	Jan 99	2 weeks	Deceased (MOF)	**175 559**[3]/250	–	–	–
4	42/M/W	Mar 99	19.8	Deceased (chronic rejection and HCV)	**21 040**[3]/168	**1886**/132	–	–
5	52/M/W	Oct 00	59.4	Alive with recurrent HCV	UD/218	UD/328	UD/308	UD/343
6	33/M/W	Jan 01	56.6	Alive with recurrent HCV	UD/506	UD/300	UD/405	UD/448
7	48/M/W	Oct 01	48.9	Deceased (fungal sepsis, MOF); recurrent HCV	UD[3]/76	UD/114	UD/264	–
8	54/M/W	Nov 01	12.0	Deceased (recurrent HCC)	UD/447	UD/131	–	–
9	50/F/B	Mar 02	1 week	Deceased (PNF, retransplant, MOF)	**84 477**[3] / 270	–	–	–
10	49/F/W	May 02	39.8	Alive with recurrent HCV	**9416**[3]/231	UD/257	UD/316	–
11	48/M/W	Jun 02	38.7	Alive with recurrent HCV	**2167**[3]/210	UD/172	UD/258	–
12	33/M/W	Jul 02	6.0	Deceased (sepsis)	UD/98	–	–	–
13	42/M/W	Sept 02	14.1	Deceased (recurrent HCV cirrhosis)	UD/227	UD/130	–	–
14	55/M/W	Nov 02	1.3	Deceased (sepsis, MOF)	946/456	–	–	–
15	59/M/B	Apr 03	9.0	Deceased (cholestatic hepatitis C)	**183 088**[3]/408	UD/175	–	–
16	59/M/B	Jul 03	11.5	Deceased (sepsis, MOF); recurrent HCV	UD/1051	UD/314	–	–
17	34/M/W	Aug 03	24.5	Alive with recurrent HCV	UD/228	UD/207	UD/642	–
18	42/M/W	Sep 03	13.5	Deceased (cholestatic hepatitis C)	UD/802	UD/255	–	–
19	34/M/W	Oct 03	22.9	Alive; spontaneous clearance of HCV	UD/765	UD/355	UD/355	–
20	52/M/W	Oct 03	22.4	Alive with recurrent HCV	UD/263	UD/696	UD/678	–
21	40/M/B	Nov 03	4.3	Deceased (sudden cardiac death); recurrent HCV	**33 030**/345	UD/325	–	–
22	35/M/W	Dec 03	21.1	Alive with recurrent HCV	UD/194	UD/247	UD/215	–
23	44/M/W	Jan 04	19.6	Alive with recurrent HCV	UD/379	UD/158	–	–
24	46/M/W	Mar 04	17.7	Alive spontaneous clearance of HCV	**740**/303	UD/335	–	–
25	52/M/B	Mar 04 Oct 04	17.7	Alive; retransplanted for cholestatic HCV	UD/302	UD/120	–	–
26	42/M/W	Jun 04	15.2	Alive with recurrent HCV	UD/672	UD/212	–	–
27	46/M/W	Jun 05	2.3	Deceased (biliary sepsis)	UD/333	–	–	–

[1]Copies/mL.
[2]From the time of transplant to March 1, 2006 or patient death.
[3]Off HAART at the time of transplant.
Dashed line (–) indicates that the patient has expired or has not reached the time point.
UD = undetectable (<400 copies/mL); LTx = liver transplantation.

the safety and efficacy of LTx in HIV patients (IRB 980704). Three patients in this series had hepatocellular carcinoma (HCC) (patients 8, 19 and 25). One patient (patient 23) was a live donor recipient. The mean follow-up for all patients was 26.6 ± 5.1 months, and 13 of 27 (48%) subjects are currently alive (Table 1).

Impact of HIV status on patient outcome after LTx

To determine the impact of HIV infection on the survival of HCV-infected patients after LTx, we compared the outcomes of HIV-positive, HCV-positive patients to a contemporaneous, matched cohort of HIV-negative, HCV-positive subjects. There were no differences between the two groups with respect to patient and donor characteristics known to adversely affect HCV recurrence outcomes and posttransplant survival of hepatitis C patients (20) (Table 2). HIV-positive, HCV-positive patients had lower survival compared to HIV-negative, HCV-positive patients (cumulative 1-, 3- and 5-year patient survival of 66.7%, 55.6% and 33.3%, respectively, vs. 75.7%, 71.6% and 71.6%) (Figure 1A). This difference trended toward but did not reach statistical significance. Graft survival was similarly worse in HIV-positive subjects (1-, 3- and 5-year graft survival of 63%, 51.9% and 31.1%, respectively) compared to HIV-negative patients (68.2%, 64.1% and 64.1%) (Figure 1B), although the difference also did not reach statistical significance ($p = 0.21$). Some studies have shown that in the nontransplant setting, coinfected HIV-positive, HCV-positive patients have faster progression of fibrosis and cirrhosis compared to HIV-negative, HCV-positive patients (21,22). We found that after LTx, coinfected patients were more likely to develop an HCV-related complication (i.e. either the occurrence of an HCV-related death or the development of stage 4 or 5 cirrhosis over time) compared to the HIV-negative cohort (RR = 2.6, 95% CI, 1.06–6.35; $p = 0.03$) (Figure 2). There was no difference in the number of patients who had a VR to HCV treatment when both groups were compared (not shown).

Table 2: Characteristics of HCV-infected, HIV-positive and HIV-negative LTx patients

Characteristic	HIV-positive (n = 27)	HIV-negative (n = 54)	p-value
Age (years)	45.3 ± 7.7	47.2 ± 6.0	0.23
MELD score	19.0 ± 7.9	19.2 ± 8.0	0.92
Donor age (years)	41.2 ± 14.5	42.8 ± 16.3	0.65
HCV-positive donor	9 (33%)	8 (15%)	0.08
Cold ischemia time	668 ± 176	671 ± 228	0.94
Genotype			
1	16 (59%)	30 (55%)	1.00
2	2 (7%)	3 (6%)	1.00
3	1 (4%)	3 (6%)	1.00
not available	8 (30%)	18 (33%)	1.00
No. of patients with CMV antigenemia	14 (52%)	17 (31%)	0.09
No. of patients with ACR	10 (37%)[1]	28 (52%)	0.80
No. of patients retransplanted	2 (7.4%)	6 (11.1%)	0.71
Recurrent HCV	1	0	
Primary nonfunction	1	6	
Received HCV treatment	15 (56%)	25 (46%)	0.49
VR	6 (40%)	7 (28%)	0.50

[1]Five HIV+ patients did not have a liver biopsy.
Values are presented as mean ± standard deviation.
LTx = Liver transplantation; MELD = Model for End-stage Liver Disease; CMV = cytomegalovirus; ACR = acute cellular rejection.

Clinical course of HCV and HIV infections

Tables 1 and 3 chronicle the HIV and HCV clinical courses of the patients after LTx. The first subject transplanted in this series was diagnosed with recurrent HCV cirrhosis at his first biopsy 21 months posttransplant. He was treated initially with interferon-α-2b/ribavirin but was a nonvirologic responder and was subsequently placed on PEG-Intron/ribavirin. He died 57 months posttransplant from disseminated aspergillosis. His HIV infection was well controlled with HAART throughout his entire posttransplant course. Patient 2 is more than 7 years posttransplant and was diagnosed with HCV recurrence (stage 2–3 fibrosis) 5 months after LTx. He had an SVR after a prolonged course of interferon-α-2b/ribavirin therapy; however, his latest biopsy 45 months posttransplant showed cirrhosis and he is currently being evaluated for retransplantation. His HIV has been in good control with HAART, although he occasionally has had a low HIV viral load posttransplant alternating with undetectable titers. Patient 3 was a UNOS status 2A patient who was in renal and respiratory failure at the time of transplant. He died after 2 weeks from multiorgan failure. Patient 4 was transplanted in March 1999 and developed acute and then chronic rejection 19 months posttransplant when his primary care physician discontinued a PI without notifying our center, resulting in undetectable tacrolimus levels for several weeks. He had recurrent hepatitis C (stage 3 fibrosis) along with the chronic rejection and he died from allograft failure.

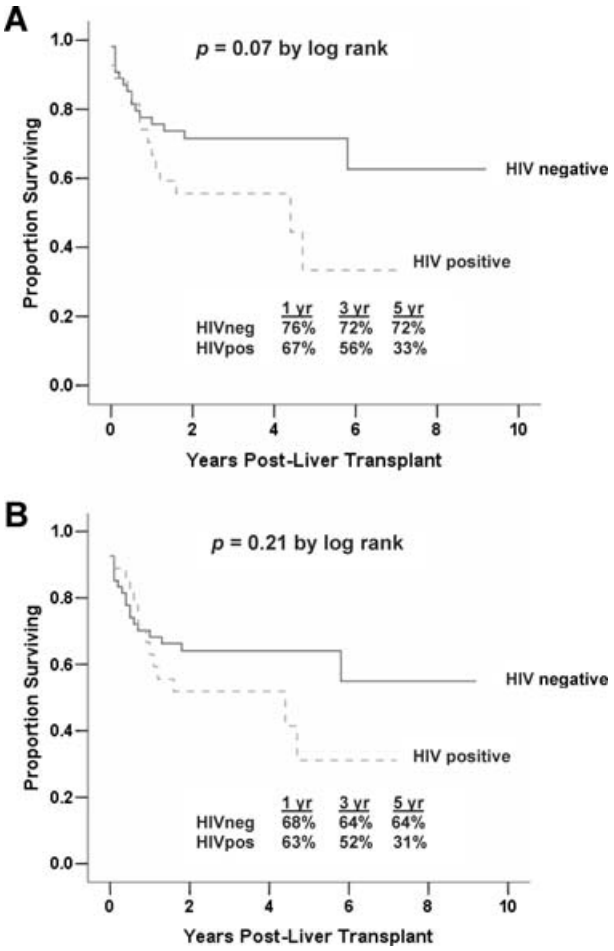

Figure 1: Kaplan-Meier analysis of the cumulative 1-, 3- and 5-year patient (A) and graft (B) survival of HIV-positive/HCV-positive (dashed line) and HIV-negative/HCV-positive (solid line) patients after liver transplantation. There was a trend toward shorter patient and graft survival in HIV-positive subjects.

Prior to LTx, he had a detectable HIV RNA level because of HAART intolerance but he rapidly became HIV RNA negative upon reinstitution of HAART posttransplantation. He became viremic just prior to his death when HAART was discontinued due to the graft dysfunction. Patient 5 has more than 5 years of follow-up postLTx. He has had stable, stage 1 fibrosis with a relatively low HCV RNA titer and, hence, has not had any HCV treatment. He has been HIV viral load negative during the entire posttransplant period. Patient 6 is also more than 5 years posttransplant. He has not undergone treatment for recurrent hepatitis C because of stable stage 0–1 fibrosis. He was recently found to have markedly elevated HCV RNA levels, but his local gastroenterologist has been reluctant to start treatment because of his stable HCV course. His HIV infection has been well controlled throughout his posttransplant course. Patient 7 was transplanted in October

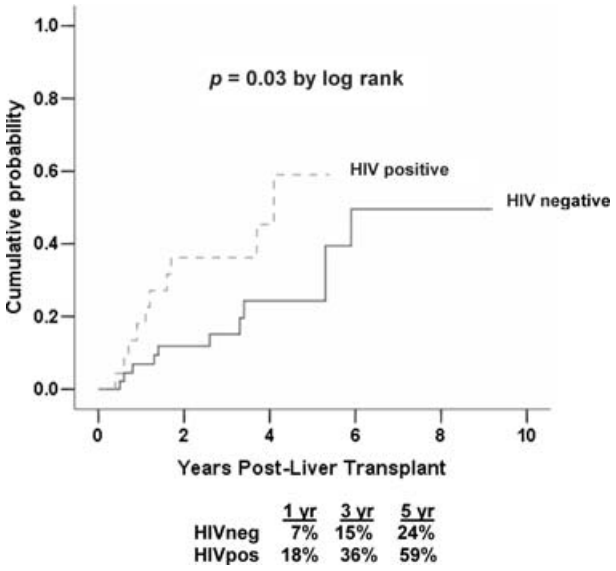

Figure 2: Cumulative probability of developing an HCV-related complication over time in HIV-positive/HCV-positive (dashed line) and HIV-negative/HCV-positive (solid line) patients after liver transplantation. HIV-positive patients had a higher likelihood of developing cirrhosis or dying of an HCV-related complication compared to HIV-negative subjects (RR = 2.6, 95% CI, 1.06–6.35; p = 0.03)

2001. He had one episode of ACR 10 days after transplant that resolved with steroids. He was diagnosed with HCV recurrence 3 months after transplantation and achieved an SVR after two courses of HCV treatment. His HIV was well controlled although he developed HIV viremia 18 months posttransplant when his HAART was temporarily held due to graft dysfunction secondary to concurrent recurrent hepatitis C and mild ACR. He became HIV RNA negative again upon reinstitution of HAART. He died 50 months after LTx from multiorgan failure and candida sepsis after presenting acutely with peritonitis and undergoing a negative exploratory laparotomy for possible intestinal ischemia. Patient 8 was a coinfected patient who expired 1 year posttransplant from recurrent HCC. He never had a clinical indication to perform a liver biopsy posttransplant and his HIV was well controlled with HAART. Patient 9 was transplanted in March 2002. She had primary nonfunction and died after 1 week from multiorgan failure after a second LTx. Patient 10 is now 45 months posttransplant. She began therapy with PEG-Intron/ribavirin 5 months after transplantation (stage 2 fibrosis) and had an SVR after a full course of treatment. She had a detectable HIV viral load prior to transplant that rapidly became negative once HAART was restarted after her transplant. Patient 11 underwent LTx in June 2002. He had a biopsy showing HCV recurrence after 5 months and had a full course of HCV treatment. Although he was a nonvirologic responder, his biopsies have remained stable at stage 0 fibrosis over the past 3 years. Similar to the previous patient, he had a detectable HIV viral load prior to his transplant that became undetectable posttransplant upon reinstitution of HAART. Patient 12 died of sepsis 6 months after a combined liver/kidney transplant, with both grafts functioning at the time of death. He had repeated bouts of highly resistant pseudomonas pneumonia posttransplant. This patient had an early liver biopsy that showed preservation injury. His HIV infection was well controlled with HAART posttransplantation. Patient 13 was the first subject to develop cholestatic HCV recurrence posttransplant. His HCV RNA titer peaked at over 85 000 000 IU/mL 2 months after LTx, prompting initiation of PEG-Intron/ribavirin therapy. He had rapid progression to cirrhosis and died after 14 months. He was HIV RNA negative during the entire posttransplant period. Patient 14 had an LTx in November 2002 and died from sepsis and multiorgan failure after 39 days. Postoperatively, he had severe sepsis from bacterial and fungal infections requiring multiple, high-dose pressors. His liver functions never normalized and he was never restarted on HAART. Patient 15 was another subject who developed early and aggressive cholestatic recurrent hepatitis C. His HCV RNA level peaked at over 50 000 000 IU/mL 3 months posttransplant prior to HCV treatment, and biopsies showed moderate hepatitis. He did not respond to interferon-α-2b/ribavirin and died 9 months after transplantation. His HIV infection was under good control with HAART. Patient 16 underwent LTx in July 2003. He had two episodes of ACR at 2 weeks and 2 months posttransplant that were successfully treated with steroid boluses. His HCV RNA levels subsequently reached over 63 000 000 IU/mL and Pegasys/ribavirin treatment was initiated 9 months after transplantation. Although he had extremely high HCV titers, he never developed a clinical picture of fibrosing cholestatic hepatitis. He eventually died of pneumonia, sepsis and multiorgan failure 11 months after LTx. His HAART medications were restarted 3 months posttransplant and he had a negative HIV viral load at last check. Patient 17 is now 30 months post-LTx. Liver biopsies have shown HCV recurrence (stage 3 fibrosis) but he is refusing treatment. His HIV has been well controlled with HAART. Patient 18 had a LTx in September 2003. He also developed cholestatic hepatitis C recurrence with biopsies showing rapid progression to stage 4–5/6 fibrosis 10 months posttransplant. Despite aggressive treatment with Pegasys/ribavirin, he expired 13.5 months after his transplant. His HAART medications were restarted 1 week after his transplant with good control of the HIV. Patient 19 underwent LTx in October 2003. He became HCV RNA-negative posttransplant without any HCV treatment and his latest biopsy showed no evidence of recurrent hepatitis C. His HIV infection was well controlled with HAART. Patient 20 is now 22 months postLTx. He had a mild ACR during the first week that resolved with a bolus of steroids and he was diagnosed with recurrent hepatitis C (stage 0 fibrosis) 5 months posttransplant. Pegasys/ribavirin therapy was initiated thereafter and he became HCV RNA negative. His HIV has been well controlled with HAART. Of note, he was diagnosed 19 months after transplantation

with hepatic artery thrombosis with collateral flow to the liver and he had one biloma percutaneously drained. He remains on HCV treatment and he currently has normal LFTs without any further infectious or biliary complications. Patient 21 underwent LTx in November 2003. He received a bolus of steroids 2 weeks posttransplant for an ACR. He had a liver biopsy that demonstrated HCV recurrence (stage 2 fibrosis) after 2 months and was on HCV treatment when he had sudden cardiac death. He was never on HAART prior to his transplant but he rapidly developed negative HIV RNA titers when he was started on HAART postLTx. Patient 22 was transplanted in December 2003 and had a biopsy that demonstrated HCV recurrence 3 months later. He was treated initially with a full course of PEG-Intron/ribavirin but was a nonvirological responder. However, he achieved a VR after being switched to Pegasys/ribavirin. His HIV RNA titers have been negative with HAART. Patient 23 underwent LTx in January 2004. He had two episodes of mild ACR treated successfully with steroid boluses. He had no biopsies that showed recurrent hepatitis C, but because he had an HCV genotype (2a) that was more responsive to treatment, his local physician treated him with Pegasys/ribavirin for 6 months. His HIV infection has been well controlled with HAART. Patient 24 is now 17 months posttransplant and was another patient who became HCV RNA-negative after LTx without any HCV treatment. Thus far, he has had no clinical indications for a liver biopsy. His HIV RNA titers have been negative

Table 3: Characteristics of HCV infection

		HCV RNA level postLTx[1]				
Patient	**G'type**	**6 months**	**1 year**	**3 year**	**5 year**	**Liver biopsy**
Patients with no biopsy evidence of recurrent HCV						
3[2]	NA	Exp				No biopsy done—early death
8[2]	3a	483	Exp			No biopsy done—died from recurrent HCC prior to 1 year biopsy
9[2]	1a	Exp				No biopsy done—early death
12[2]	NA	ND	Exp			Preservation injury (2 weeks)
14[2]	NA	Exp				No biopsy done—early death
19	NA	NEG[3]	NEG	–	–	Indeterminate for ACR (1 month); steatohepatitis (20 months)
23	2a	9,167	1119			ACR (1–2 weeks); indeterminate for ACR (3 weeks)
24	NA	NEG[3]	NEG	–	–	No biopsy done—1 year biopsy pending
27[2]	1a	Exp				Centrizonal dropout (10 days); indeterminate for ACR (3 weeks); cholangitis/no ACR or HCV (8 weeks)

		6 months	**1 year**	**2–3 year**	**4–5 year**	**0–1 year**	**1–2 year**	**2–3 year**	**3–4 year**	**4–5 year**
Patients with biopsy-proven recurrent HCV										
1[2]	1a	1500	ND	2000	491	ND	stage 4	ND	stage 6	Exp
2	NA	1580	VR	SVR	SVR	stage 2–3	ND	ND	stage 5	Pending
4[2]	NA	890	ND	Exp		stage 0	stage 1	Exp		
5	1b	19.2	24.2	6.4	352	stage 0	Stage 1	ND	stage 1	stage 1
6	1b	ND	633	3330	75 400	stage 0	stage 0	ND	ND	stage 1
7[2]	1b	17.9	24.4	VR	SVR	stage 2	stage 3	stage 3	ND	Exp
10	1a	360	367	SVR	–	stage 0	stage 2	ND	ND	–
11	1a	8,500	6440	2368	–	stage 0	stage 0	ND	stage 0	–
13[2]	1a	30,100	3067	Exp		stage 2 (3 months); stage 5 (10 months); Exp (14 months)				
15[2]	1a	50 000	Exp			stage 1	Exp			
16[2]	1a	63 735	Exp			stage 1–2	Exp			
17	1a	17 722	4301	Pending		stage 3	stage 3	Pending		
18[2]	NA	728	109	Exp		stage 2–3 (5 months); stage 4–5 (10 months); Exp (13.5 months)				
20	1a	23 038	1.0	VR	–	stage 0	ND	Pending		
21[2]	1a	7378	Exp			stage 2	Exp			
22	1a	1564	169	VR	–	stage 1	stage 3	Pending		
25[4]	1b	142 744				stage 1				
25		3463	5687	–	–	stage 0–1	Pending			
26	2b	405	SVR	–	–	stage 2	stage 2	–	–	–

[1]x 1000 I.U.
[2]Deceased.
[3]Spontaneous clearance of HCV (see text).
[4]Retransplanted after 4 months.
Dashed line (–) indicates that the patient has not reached the time point.
G'type = genotype; NA = not available; ND = not done; Exp = expired prior to or at the time point; ACR = acute cellular rejection; VR = virologic clearance (while on HCV treatment); SVR = sustained virologic response.

Table 4: Effect of various characteristics on the survival of 27 coinfected patients who underwent LTx

Covariates	Patients (%)	Kaplan-Meier estimates (%)	95% CI	p[1]
Race				0.02
White	22 (81)	50.3	34–67	
African American	5 (19)	9.7	3–17	
MELD score				0.05
≥ 20	11 (41)	26.0	10–41	
< 20	16 (59)	56.4	37–76	
CD4 count pre-LTx				0.6
>200	22 (81)	51.0	34–68	
≤200	5 (19)	37.4	16–58	
CD4 count post-LTx[2]				0.23
>200	13 (48)	58.6	39–78	
≤200	11 (41)	32.0	19–45	
HAART intolerance pre LTx				0.23
Yes	7 (26)	23.4	8–39	
No	20 (74)	49.0	32–66	
HAART intolerance post LTx[3]				0.01
Yes	6 (22)	26.5	9–44	
No	17 (63)	69.3	53–85	
HIV RNA pre-LTx				0.13
>400	10 (37)	21.8	9–34	
≤400	17 (63)	51.4	34–69	
HIV RNA post-LTx[2]				0.41
>400	1 (4)	19.8	19.8	
≤400	23 (85)	51.5	36–67	
HCV RNA post-LTx [3]				0.00
≤ 30 000 000 IU/mL	19 (70)	61.2	45–77	
> 30 000 000 IU/mL	4 (15)	9.7	6–14	
Acute cellular rejection				0.25
Yes	11 (41)	28.0	15–41	
No	16 (59)	52.3	33–72	

[1]By log-rank test.
[2]Patients who died early with missing data (patients 3, 9 and 14) were excluded.
[3]In addition to patients 3, 9 and 14, patient 27 was also excluded due to missing data.
MELD = model for end-stage liver disease; LTx = liver transplantation; HAART = highly active antiretroviral therapy.

with HAART. Patient 25 underwent his first LTx in March 2004. He developed cholestatic recurrent hepatitis C with cirrhosis despite early treatment with interferon-α-2b/ribavirin and was retransplanted after 7 months. He is currently on Pegasys/ribavirin therapy. He has been HIV RNA-negative throughout his whole posttransplant course. Patient 26 was a live donor recipient with over 15 months of follow-up. He was treated with Pegasys/ribavirin for 28 weeks to which he had a VR and was switched to PEG-Intron/ribavirin by his local hepatologist for unclear reasons. He is currently off treatment and has an SVR. His HIV infection has been well controlled with HAART. Patient 27 had a liver transplant in June 2005 and died after 2 months from septic complications following a bile leak which required a biliary reconstruction. This patient also had had a massive myocardial infarction requiring intraaortic balloon pump support immediately after his transplant.

HIV infection, HAART and immunosuppression

HIV status was monitored by HIV viral load, CD4 counts and the occurrence of opportunistic infections. Prior to LTx, CD4 counts ranged from 76 to 1051/mm^3, and HIV viral loads were detectable in nine patients, six of whom were off antiretroviral therapy at the time (Table 1). Analysis of key variables revealed that a CD4 count of ≤200, HIV viremia (HIV RNA level >400 copies/mL), and HAART intolerance prior to transplantation had no effect on patient survival after LTx (p = 0.6, 0.13 and 0.23, respectively) (Table 4).

Posttransplantation, HAART medications were restarted at a median of 30 days (range, 5–121 days). Patients were restarted on their pretransplant regimen—18 patients were placed on a PI -containing regimen while seven patients were started on a nucleoside or nonnucleoside-containing regimen (not shown). Six patients required cessation of their HAART because of aspergillosis in one patient or severe liver dysfunction secondary to recurrent hepatitis C in the other subjects. All of these patients had HAART intolerance (i.e. permanent discontinuation of HAART) with the exception of patient 7 whose regimen was restarted after LFTs normalized with HCV treatment. HAART intolerance

Table 5: Coinfected patients who received HCV treatment after LTx

Patient	Treatment	Time from LTx to treatment (months)	Status/duration of treatment (weeks)	Time from treatment to VR (weeks)	BR	VR	HCV stage	
							Before treatment	After treatment
1[1]	IFN/RIB	25	OFF, 99		Yes	No	stage 4	stage 6
	PEG/RIB	50	ON, 28		Yes	No	stage 6	Died
2	IFN/RIB	5	OFF, 131	21	Yes	SVR	stage 2	stage 5
7	Pegasys/RIB	11	OFF, 112	37	Yes	SVR	stage 2	stage 3
10	PEG/RIB	3	OFF, 112	77	Yes	SVR	stage 2	Pending
11	PEG/RIB	20	OFF, 55		Yes	No	stage 0	stage 0
13[1]	PEG/RIB	1.5	OFF, 36		No	No	stage 0	stage 5
15[1]	IFN/RIB	2	OFF, 26		No	No	stage 0	stage 1
	PEG/RIB	20	OFF, 3		No	No	stage 1	Died
16[1]	Pegasys/RIB	7	OFF, 16		Yes	No	stage 1	Died
18[1]	Pegasys/RIB	6	OFF, 19		No	No	stage 2–3	stage 4
20	Pegasys/RIB	9	ON, 62	23	Yes	Yes	stage 0	Pending
21[1]	PEG/RIB	2.8	ON, 6		No	No	stage 0	Died
22	PEG/RIB	3.5	OFF, 57		Yes	No	stage 1	stage 3
	Pegasys/RIB	18	ON, 39	18	Yes	Yes	stage 3	Pending
23	Pegasys/RIB	34	OFF, 20–27[2]		Yes	No	No biopsy	Pending
25	PEG/RIB	1.5	OFF, 18		No	No	stage 3	Retransplant
	Pegasys/RIB	8	ON, 36		No	No	stage 1	Pending
26	Pegasys/RIB	6	OFF, 28	5	Yes	Yes	stage 2	Switch to PEG
	PEG/RIB	12.6	OFF, 16		Yes	SVR	None	Pending

[1]Expired.

[2]Exact duration unclear (treated by local physician).

IFN = interferon-α-2b (1–3 million units 3 times a week); PEG (PEG-Intron®) = pegylated interferon-α-2b (1.0 μg/kg); Pegasys® = 90–180 μg/week; RIB = ribavirin (800–1000 mg daily); BR = biochemical response; VR = virological response; SVR = sustained virological response.

posttransplant was associated with 100% mortality and adversely impacted survival ($p = 0.01$) (Table 4). All but two of the patients who were tested had a negative HIV viral load after transplantation, and all patients generally maintained CD4 counts of >200 postLTx (mean postLTx CD4 count for all patients, 256.2/mm^3). Neither HIV viremia nor a CD4 count of ≤200 after transplantation had a significant effect on patient survival after LTx ($p = 0.41$ and $p = 0.23$, respectively). With respect to the occurrence of opportunistic-type infections, one patient presented with sinus-invasive aspergillosis and died from CNS complications. This patient had a CD4 count of 333/mm^3 and an undetectable HIV viral load at the time. Fourteen patients (52%) presented with CMV antigenemia after their transplant, including one subject who had a concurrent positive CMV early antigen in a bronchoalveolar lavage specimen. All patients received treatment with either oral valganciclovir or IV ganciclovir with resolution of the CMV infection or disease.

Tacrolimus levels were maintained between 5 and 15 ng/mL after transplantation and steroids were weaned off at a median of 8 months after transplant. Six patients were placed on rapamune and four were started on mycophenolate mofetil. Eleven patients developed ACR and all episodes responded to steroid treatment with the exception of an early rejection in patient 3 that was treated with OKT3. The occurrence of rejection did not have a significant effect on survival ($p = 0.25$) (Table 4).

Clinical features and treatment of HCV recurrence

Recurrent HCV infection after LTx was diagnosed histologically and graded and scored by a transplant pathologist. Eighteen patients had biopsies that showed evidence of recurrent hepatitis C, five patients did not have liver biopsies, and four subjects had nine biopsies altogether that showed no evidence of HCV recurrence (Table 3). The mean time from transplantation to the first biopsy demonstrating recurrent hepatitis C was 5.6 ± 5.5 months (range, 1.3–21.3 months), and at the time of diagnosis, the mean total bilirubin, ALT, AST and GGTP were 1.8 mg/dL, 159 IU/L, 167 IU/L and 396 IU/L, respectively. The HCV genotypes in 19 patients whose results were available were: genotype 1–16 patients, genotype 2—two patients, and genotype 3—one patient. Eight of the 18 patients with biopsy-proven HCV recurrence have died, including three subjects who expired from cholestatic recurrence and allograft failure despite aggressive HCV treatment, two of whom also had rapid progression to cirrhosis. This clinical picture was associated with HCV viral loads of over 50 000 000 IU/mL prior to initiation of treatment. A fourth patient who developed fibrosing cholestatic hepatitis survived after retransplantation. Of the 10 patients with biopsy-proven recurrent

hepatitis C who remain alive, five have lived more than 3 years after LTx (Table 3). Analysis of several key variables revealed that patients with a MELD score of greater than 20 pretransplant ($p = 0.05$) and those with postLTx HCV RNA levels of greater than 30 million IU/mL had poorer survival after LTx ($p = 0.00$), as did African-American (AA) patients ($p = 0.02$) (Table 4). Three of four AA subjects who had HCV recurrence died and a fifth AA patient died after retransplantation for primary nonfunction. Earlier, we showed that HIV-positive patients had a higher likelihood than HIV-negative patients of developing a HCV-related complication over time (Figure 2). There were 10 coinfected subjects who developed cirrhosis or died from HCV-related causes and 14 coinfected patients who had a less aggressive course of HCV recurrence (three patients died early) (Table 1). We found no significant differences between the two groups when we compared donor age, steroid use for the treatment of rejections, use of HCV-positive livers and the incidence of CMV infections, factors that have been reported to exacerbate recurrent hepatitis C posttransplantation (not shown) (20).

Overall, 15 patients have undergone HCV treatment, and the median time to initiation of treatment was 6 months posttransplant (range, 1.5–34 months), with the majority of patients having stage 0–2 fibrosis at the time (Table 5). Seven patients have received a full course of therapy ranging from 54 to 131 weeks in duration. Five patients were converted from one form of interferon to another because of the absence of a VR to the first treatment regimen, and one patient had a VR after such a switch. Aside from six subjects who died while receiving HCV treatment, two patients did not finish a full course of treatment: Patient 23 was a nonvirological responder and patient 26 received a shorter course of therapy after achieving a VR (he was genotype 2b). Because the majority of patients was HCV genotype 1, we were not able to assess the impact of genotype on HCV recurrence or on HCV treatment responses. Interferon-α and ribavirin therapy was relatively well tolerated and the most common side effect was fatigue. Two patients (patients 7 and 20) required temporary cessation of both medications because of allograft dysfunction and their treatment was resumed once liver functions improved. Five patients also had their ribavirin temporarily held because of anemia. Three patients had to have a decrease in their interferon doses for leukopenia and/or thrombocytopenia while seven patients had their ribavirin doses lowered for anemia (not shown). Ten patients reached the maximum dose for interferon (see Methods section); the average dose for ribavirin was 800 mg/day and only two subjects were able to take the maximum dose of 1200 mg/day. Nine patients required GM-CSF for the prevention or treatment of leukopenia, and 12 received erythropoeitin for anemia.

Ten subjects (66%) had a BR to treatment (Table 5), and the average time for LFTs to normalize was 6–8 weeks after initiation of HCV treatment. Patients who did not have a BR had worse outcomes, with four out of five patients dying from HCV-related complications and the fifth patient requiring retransplantation for aggressive HCV recurrence. Six patients (40%) have had a VR, including four with SVR, and the median time of treatment to achieve a VR was 22 weeks (range 5–77 weeks). Histologically, two patients (patients 7 and 11) had stabilization of their fibrosis stage as demonstrated by serial biopsies posttreatment. Six patients are either still receiving treatment or are awaiting posttreatment biopsies. Three patients had progression of fibrosis despite treatment, including in one patient who had a SVR, and HCV treatment was wholly ineffective in four subjects who had cholestatic recurrent hepatitis C.

Discussion

Prior to the introduction of highly active antiretroviral therapy (HAART), LTx in HIV patients was associated with poor results, mainly due to opportunistic infections posttransplantation associated with immunosuppressive therapy superimposed on severe HIV immune deficiency (23,24). As a result of significant improvements in posttransplant management leading to improved liver transplant outcomes and the advent of HAART for HIV, patients may now survive up to 5 years or more following LTx (6–8). This is evident in the present series as well as at several other centers—HIV progression posttransplantation is well controlled with HAART as demonstrated by the maintenance of CD4 counts and the suppression of HIV replication. Although there was one case of a fatal opportunistic infection (aspergillosis) in this series, the presence of adequate CD4 counts and undetectable HIV viral load in the patient at the time suggests that this was a complication of transplant immunosuppression rather than an HIV-related opportunistic infection, as previously discussed (8). The incidence of CMV antigenemia was 52%, higher than infection rates in HIV-negative patients after LTx and similar to that of kidney-pancreas transplant recipients (25). Our approach of preemptive treatment of CMV infection (19) was highly successful in that only one subject developed CMV pneumonitis that responded readily to treatment, and no patient developed CMV disease after antigenemia was treated. Nevertheless, because CMV infection is a risk factor for severe recurrent hepatitis C (20), instituting CMV prophylaxis in these patients may offer some benefit.

In contrast to the relative ease of controlling HIV with HAART after LTx, control of recurrent HCV infection and liver damage in coinfected patients has been more difficult. (9,11,12). Our current experience does indicate that HCV recurrence is a significant cause of graft loss and patient mortality in these patients. This finding is not completely unexpected since progression of fibrosis and cirrhosis has been shown to be faster than expected in HIV/HCV positive patients in the nontransplant setting (21,22), recurrence of hepatitis C is nearly universal after LTx (26), and HCV infection is known to adversely affect patient and graft

survival after LTx in HCV-positive, HIV-negative patients (27,28). Though the differences did not reach statistical significance, there was a trend toward lower patient and graft survival in HIV subjects compared to a contemporaneous matched cohort of HIV-negative patients in our study. In addition, coinfected subjects were also more likely to develop cirrhosis over time or die of an HCV-related complication compared to HIV-negative patients. The impact of recurrent hepatitis C on coinfected patients was further evident in that HCV recurrence was a factor in 8 of 14 deaths, including three patients who died from allograft failure secondary to cholestatic recurrence and early cirrhosis. Cholestatic recurrent hepatitis C was associated with extremely high serum HCV RNA levels (>30 000 000 IU/mL) and had a mortality rate of 75% despite the initiation of early HCV treatment within 1–3 months posttransplant. Elucidating the host and viral immunologic mechanisms that permit uncurtailed HCV replication in these patients will be important. Because interferon-α and ribavirin therapy was ineffective against cholestatic HCV recurrence, we rescued the next patient who developed fibrosing cholestatic hepatitis with retransplantation, a controversial undertaking because of scarce organs and relatively poor patient survival (29,30). This incidence of cholestatic recurrent hepatitis C (15%) after LTx is higher than that reported in the HIV-negative population (31) and comparable to what has been reported in other smaller series of coinfected patients (14–25%) (12,14,32). At our center, we evaluate every recipient (regardless of the HIV status) who develops allograft failure from recurrent hepatitis C for retransplantation on a case-by-case basis, and our general approach is to preclude subjects who are in the ICU with multiple organ failure.

The optimal immunosuppressive regimen for these patients is not known. A link between immunosuppression and recurrence of hepatitis C has been postulated (33), and we have purposely avoided the use of induction therapy with monoclonal antibodies in these patients so as not to increase HCV recurrence (17) and to avoid immunodepletion of T cells (34). Dual immunosuppression with tacrolimus and steroids was utilized, and the latter were typically weaned off within 6 months postoperatively. ACRs were managed with steroids with no adverse effect on survival. Liver toxicity, particularly in patients with HBV or HCV coinfection, is a known side effect of HAART (35), and in patients with allograft dysfunction and jaundice, HAART medications were discontinued until liver functions recovered. HAART intolerance postLTx was associated with 100% mortality, a finding we previously showed (8).

In light of the poorer outcomes associated with LTx in coinfected patients, the question arises on whether it would be justified to use scarce organs to perform this life-saving procedure in this population. Although, considerable attention may be focused on the group of patients who developed aggressive hepatitis C recurrence, it is important to point out that a number of patients in this series have had clinical courses that have been relatively similar to what is reported for HIV-negative, HCV-positive LTx patients, the majority of whom develops histological evidence of chronic hepatitis, among whom approximately 8–44% develop cirrhosis from recurrent hepatitis C 5 years after LTx (21,28,36–38). The over 3 year survival in five of these subjects indicate that although some co-infected patients may develop a rapid course of recurrent hepatitis C after LTx, there is a subset of patients who experience a less aggressive clinical course of HCV infection, although there were no predictors of such outcomes. It is also noteworthy that the overall VR rate to interferon-α and ribavirin therapy in coinfected patients (40%) is similar to response rates reported in the nonHIV population (39–41). In addition, our observation was that coinfected patients as well as non-HIV patients tolerated HCV treatment. The optimal time to initiate HCV treatment in these patients is unclear, although our practice has been to delay interferon and ribavirin therapy until patients are tolerating HAART (8). In patients with biopsy-proven HCV recurrence, treatment should be started as soon as possible, particularly in patients with high HCV RNA titers and/or those with rapid progression of fibrosis. The use of prophylactic or preemptive HCV treatment (42) in coinfected patients has not been reported to our knowledge, but this approach may be worth utilizing to improve HCV outcomes.

In summary, recurrent hepatitis C is a major problem in coinfected patients, significantly affecting graft and patient survival. The determinants contributing to this poorer outcome remain to be elucidated, and improvements in HCV treatment may further improve LTx outcomes in this patient population. Prospective studies of larger size, longer duration and with routine histologic sampling will be needed to confirm or refute these findings in order to fully determine the benefit of LTx in these patients.

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