

Orthotopic Liver Transplantation in Patients With Human Immunodeficiency Virus and End-Stage Liver Disease

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Patients with human immunodeficiency virus (HIV) most often have hepatitis C virus (HCV) or hepatitis B (HBV) virus coinfection, or both, as a cause of their liver disease. Recent survival statistics show that patients infected with HIV treated with highly active antiretroviral therapy (HAART) can expect a significant prolongation of life by interfering with the natural progression of HIV to acquired immune deficiency syndrome (AIDS). Therefore, HIV-positive patients experiencing complications of liver failure are at greater immediate risk of dying from their end-stage liver disease (ESLD) rather than their HIV. Many transplant centers still consider HIV infection as a contraindication for orthotopic liver transplantation (OLT). At our two institutions, we believe that patients with HIV suffering from ESLD should be considered for OLT. This study evaluates the survival of patients undergoing OLT with HIV under HAART therapy. OLT was performed in 16 patients with HIV suffering from ESLD as a result of chronic HCV, chronic HBV, or fulminant hepatic failure (FHF). Collected data include patient demographics, patient and graft survival, pre-OLT assessments, and postoperative complications (including opportunistic infections). Ten patients at Pittsburgh and 6 patients at Miami received OLT. Of the 16 patients who received OLT, 14 remain alive to date. Thirteen of 16 patients are more than 12 months post-OLT, whereas the last patient is currently 6 months post-OLT. Five patients at Miami and 9 of 10 patients at Pittsburgh received HAART therapy before OLT, although 2 of the Pittsburgh patients had their HAART therapy discontinued before OLT because of significant liver dysfunction. The pre-OLT viral loads were undetectable in 13 of 16 patients. The cluster determinant (CD)4 count was less than 200 in 6 patients and greater than 100 in 2 patients before OLT. In all patients, CD4 counts increased above 200 in the post-OLT period. Tacrolimus toxicity associated with the pharmacologic inhibition of cytochrome p450 metabolism caused by protease inhibitors occurred in 6 patients after OLT. Six patients (38%) experienced acute cellular rejection immediately after OLT. Our experience suggests that OLT is effective in selected HIV-positive patients suffering from ESLD. Patient and graft survival was similar to non-HIV-positive patients suffering from the same indications for OLT. Acute cellular rejection was no less frequent than seen in non-HIV-positive patients. Given the complex pharmacologic interactions between the protease inhibitors and tacrolimus, careful monitoring, and attention is required to prevent toxicity or underdosing. (*Liver Transpl* 2003;9:239-247.)

Orthotopic liver transplantation (OLT) has advanced markedly since its introduction in 1964. One-year survival rates, 30% in the 1970s under azathioprine immunosuppression, are now well above 80%. The improved survival rates are the result of advances in patient selection, posttransplant management, immunosuppression, and antiviral prophylaxis. This has led to reevaluation of the original contraindications to surgery and broadening the spectrum of patients who should be considered for OLT.

Until recently, one concurrent illness considered by many to be an absolute contraindication for OLT is the presence of human immunodeficiency virus (HIV). However, the introduction of highly active antiretroviral therapy (HAART) has resulted in a dramatic improvement in the survival of patients infected with HIV.^{1,2} Thus, the prevalence of HIV patients coinfecting with hepatitis C virus (HCV), hepatitis B virus (HBV), or both, who present with end-stage liver disease (ESLD) is increasing.³⁻⁵ HIV coinfecting patients tend to suffer from an aggressive HCV course, thus resulting in liver failure at a faster rate when compared with individuals without coinfection.⁶ In addition, almost all of the antiretroviral agents used for the treatment of HIV are metabolized in the liver. Patients with hepatic metabolic impairment cannot use these agents, resulting in increased mortality associated with acquired immune deficiency syndrome (AIDS).^{1,7}

The success with HAART regimens has uncovered a dilemma, namely patients with HIV dying secondary to

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ESLD. In fact, associated liver failure in coinfecting HIV positive patients is one of the leading causes of death in men between the ages of 25 and 44 years.^{8,9} Whereas OLT is considered a standard therapeutic modality for the treatment of nearly all ESLD, patients with HIV generally have been excluded despite the improvement in survival since the implementation of the HAART regimen. This exclusion is a result of the pre-HAART fears of disease progression and the scarcity of organs. It is possible that death in many of these patients may be prevented if OLT could be shown to have a similar utility to non-HIV OLT recipients.

We retrospectively analyzed a group of patients infected with HIV from the University of Miami (UM) and the University of Pittsburgh (UPMC) transplant centers with ESLD that received OLT in the HAART era. The purpose of this analysis is to describe the management strategies, survival, and drug interactions when HIV infected patients with liver failure undergo OLT.

Methods

Patient Selection

All patients with HIV and ESLD who underwent OLT at UM and UPMC liver transplant centers between September, 1997, and December, 2001, were reviewed. The information was obtained in a standardized manner with an extraction form. Consent for OLT and follow-up treatment was obtained in every patient and review of clinical data was approved by the institutional review boards (IRBs).

Immunosuppression and HAART Therapy

The standard treatment post-OLT for non-HIV patients included tacrolimus, administered to maintain a 12-hour trough level of 8 to 12 ng/mL, corticosteroids tapered to discontinuation by week 12, a proton pump inhibitor for acid suppression, and sulfamethoxazole/trimethoprim prophylaxis against *Pneumocystis carinii*. The HIV OLT population received the same treatment except for adjusted serum levels of tacrolimus when protease inhibitors (PIs) were initiated; target levels for 24 hours was 5 to 7 ng/mL. Prophylaxis for cytomegalovirus (CMV) and herpes simplex virus (HSV) was performed in standard fashion with ganciclovir, acyclovir, or both.

HAART therapy was individualized based on known response and resistance patterns. In all OLT patients in this series, HAART consisted of a PIs with one or two nucleoside reverse transcriptase inhibitors. These were started when liver functions returned close to normal and when oral intake was satisfactorily resumed, usually by the second posttransplant week.

Assessment

The data collected included pretransplant labs: complete blood count (CBC) with differential; pre-OLT HIV, HCV, and HBV viral loads; and history of opportunistic infections. Posttransplant data collection included monthly HIV and CD4 counts, HCV RNA polymerase chain reaction (PCR) and/or HBV DNA, liver chemistries, immune suppression doses, and all clinically relevant events, such as rejection and infectious complications.

Results

Patient Characteristics

A total of 16 patients with ESLD received OLT, 6 at UM (cases 1 through 6) and 10 at UPMC (cases 7 through 16) (Table 1). Eleven patients had ESLD secondary to HCV infection (1 with concomitant HCC), 3 with ESLD secondary to chronic HBV infection, and 2 patients with fulminant hepatic failure (FHF). The etiology of FHF in 1 patient was presumably because of toxicity of nucleoside analogs used for HIV therapy and the other with acute HBV. All patients were listed for OLT as outlined by United Network of Organ Sharing (UNOS). All patients were listed and transplanted using the status designation that existed before implementation of model for end-stage liver disease (MELD) in March, 2002: status 1, acute liver failure; status 2A, chronic liver disease with expected survival of less than 7 days; status 2B, chronic liver disease with expected survival of more than 7 days.

Patient Summaries: UM

The first HIV-positive OLT recipient at UM suffering from cirrhosis secondary to chronic HBV occurred in March of 1999. The HAART regimen consisted of nevirapine, lamivudine, and abacavir sulfate and was continued postoperatively. His posttransplant course was complicated by HSV-zoster at month 4, treated with acyclovir. The infection was believed the result of overimmunosuppression and his tacrolimus was lowered. He subsequently experienced an episode of acute cellular rejection (ACR) that responded to steroid pulses. His HIV status has remained stable, HIV viral load undetectable, and the CD4 count returned to greater than 1,000. The HBV has remained DNA-negative since OLT while treated with lamivudine.

The second HIV-positive OLT recipient also had chronic HBV and underwent transplantation in February, 2000. He was maintained on the following HBV therapy and HAART regimen: lamivudine, zidovudine, and nevirapine. He developed a biopsy-proven ACR 4 days after OLT that required muromonab-CD3 ther-

Table 1. Demographic Information and Etiology of Liver Disease

Case	Gender	Ethnicity	Age (y)	Comorbid	OLT Date	Outcome
1*	Male	Caucasian	40	HBV	March 1999	Alive
2*#	Male	Caucasian	50	HBV	Feb 2000	Alive
3*	Male	Haitian	51	FHF/HBV	August 2000	Alive
4*	Female	Caucasian	47	HBV/HCV	Sept 2000	Alive
5*#	Male	Caucasian	51	HBV/HCV	Oct 2000	Alive
6*	Female	African American	48	HCV/CR	May 2001	Alive
7†	Male	Caucasian	43	HCV/Hem	Sept 1997	Alive
8†	Male	Caucasian	48	HCV	Dec 1998	Alive
9†#	Male	Caucasian	43	HCV/Hem	Jan 1999	Deceased (12 days)
10†#&	Male	Caucasian	44	HCV/Hem	Mar 1999	Deceased (570 days)
11†#	Female	African American	42	FHF	May 2000	Alive
12†	Male	Caucasian	53	HCV	Oct 2000	Alive
13†#	Male	Caucasian	34	HCV/Hem	Jan 2001	Alive
14†	Male	Caucasian	50	HCV	Oct 2001	Alive
15†	Male	Caucasian	55	HCV/HCC	Nov 2001	Alive
16†	Male	Caucasian	67	FHF/HBV	Dec 2001	Alive

NOTE. Footnote symbol denotes site of transplantation.
 *Miami
 †Pittsburgh
 #Patient experienced acute rejection
 &patient experienced chronic rejection
 \$OKT-3
 Abbreviations: HCV, chronic hepatitis C virus; HBV, chronic hepatitis B virus-HbsAg-positive; HBc, hepatitis B core antibody-positive; Hem, hemophilia; FHF, fulminant hepatic failure.

apy. The HIV viral load has remained undetectable, and the CD4 count has returned to more than 400. Approximately 20 months after transplant, he developed an HBV lamivudine mutant that was treated with tenofovir and is currently HBV DNA-negative.

The third OLT HIV-positive recipient was a Haitian man who presented to the emergency room with fulminant HBV requiring OLT in August, 2000. This patient was naive to antiretroviral medications at the time of presentation. He was started on lamivudine for the treatment of HBV and after OLT on zidovudine and nelfinavir mesylate for HIV. His post-OLT course has been complicated by an unexpected drug interaction with ritonavir that resulted in toxic levels of tacrolimus. The patient was given a standard posttransplant dose of 3 mg of tacrolimus that resulted in a level of 50 ng/mL. At 12 weeks, he developed biopsy-proven ACR, managed with steroid therapy. He has remained HBV DNA-negative since transplantation. The HIV status required HAART management adjustment from lamivudine, zidovudine, and nelfinavir mesylate to lamivudine, zidovudine, and efavirenz at week 48, because his HIV viral load reached 6,000 copies/mL particles. The viral load has since become undetectable with the HAART regimen adjustments.

The fourth HIV-positive OLT candidate underwent transplantation in September, 2000, secondary to HCV-related cirrhosis. Her HAART regimen included zidovudine, lamivudine, and nevirapine. The postoperative medical course was complicated by a ritonavir interaction and subsequent tacrolimus toxicity. The tacrolimus was decreased to 0.25 mg every fourth day. Lopinavir was used to replace ritonavir as a result of clinical hepatitis with abnormal transaminases two times greater than normal. Two months later, a liver biopsy specimen showed marked steatosis, and lopinavir was replaced with amprenavir. Her HAART regimen required several adjustments and is currently zidovudine, lamivudine, abacavir, and tenofovir. The HCV recurrence was seen at week 8 with positive RNA PCR test results of 15 million copies/mL and an elevation of her liver chemistries 1.5 times normal. Liver histology revealed moderate inflammation, and the patient was placed on pegylated interferon alfa 2b with ribavirin therapy. Histology at after 12 months of interferon and ribavirin therapy revealed a slight reduction in inflammation but stage 2 fibrosis (stage 1, portal fibrosis; stage 2, few bridges; stage 3, many bridges; stage 4, cirrhosis).

The fifth HIV-positive patient received his OLT in

October, 2000 for cirrhosis related to chronic HCV. The HAART regimen has been maintained with efavirenz, lamivudine, and zidovudine. The HCV after OLT recurred based on histology and PCR detection at week 12. He was started on pegylated interferon alfa 2b and ribavirin with resultant marked decrease in the HCV PCR to 300,000 IU/mL from 2 million IU/mL and improved inflammation score. His HIV status, including viral load, has been undetectable, and his CD4 count has reached 350. Liver biopsy at 24 months showed mild inflammation and stage 2 fibrosis.

The sixth HIV-positive case at UM was a woman requiring repeat OLT because of chronic rejection. The first transplant was performed for HCV cirrhosis. Her HAART regimen is maintained with efavirenz, lamivudine, and zidovudine. She became HIV-positive after her first OLT, developing graft failure 28 months later. She underwent retransplantation in May, 2001. Her HCV status remained undetectable for 1 year before repeat OLT and since retransplantation. Her HIV viral load is undetectable and the CD4 count greater than 400. Of the cases noted above from UM, none of the recipients have suffered from opportunistic infections, whereas two have developed HCV recurrence requiring pegylated interferon alfa 2b and ribavirin therapy.

Patient Summaries: UPMC

The first case seen at the UPMC was a 43-year-old HIV-positive man with hemophilia suffering from HCV-related cirrhosis in September, 1997. His HIV viral load was undetectable, with a CD4 count of 660/mL at the time of OLT. He developed asymptomatic CMV viremia (pp65) and was treated with intravenous gancyclovir, then switched to oral gancyclovir. He was maintained on lamivudine, nelfinavir mesylate, and stavudine. He developed recurrent HCV on biopsy 21 months later and was treated with interferon alfa and ribavirin with normalization of his liver function tests. His HIV viral load has remained undetectable with a CD4 cell count of 280.

The second HIV-positive OLT recipient was a 48-year-old man with chronic HCV-related cirrhosis in December, 1998. He had an unremarkable post-OLT course except for recurrent HCV and was started on interferon alfa 2b and ribavirin on the sixth posttransplant month. He has received combination therapy, interferon alfa 2b, and ribavirin, and his HCV RNA converted to negative by 6 months and remains serologically negative for HCV while off antiviral therapy. His HAART regimen consists of lamivudine, nelfinavir mesylate, and stavudine and his most recent CD4 cell count is 199.

The third OLT recipient was a 43-year-old HIV-positive man with hemophilia suffering from HCV-related cirrhosis and was status 2A (ventilator and hemodialysis) at the time of transplantation. He was not on HAART at the time of OLT (January, 1999) because of liver failure, with an HIV viral load of 16,000/mL. Postoperatively, he developed ACR that required muromonab-CD3 therapy and progressed to sepsis with multiorgan system failure, dying 12 days after OLT.

The fourth case was a 44-year-old HIV-positive man with hemophilia and chronic HCV-related cirrhosis who underwent OLT in March, 1999. His HAART regimen consisted of Nelfinavir mesylate and lamivudine and zidovudine and his HIV viral load remained undetectable after the first year. The local physician discontinued the Nelfinavir mesylate without adjustment in his tacrolimus dose. He subsequently developed ACR, progressing on to chronic rejection. Treatment for rejection was complicated by HCV recurrence. He developed renal failure, requiring dialysis, and died 19 months after OLT.

The fifth HIV-positive OLT recipient was a 43-year-old woman suffering from HAART regimen drug hepatotoxicity and presenting with FHF. She underwent OLT in May, 2000. Her postoperative course was complicated by ACR that was treated with steroids and sirolimus therapy. She also experienced hepatic artery stenosis, which was treated by surgical reconstruction. The HAART regimen consisted of lamivudine and zidovudine and nelfinavir mesylate, and her HIV viral load is currently undetectable, with a CD4 cell count of 311.

The sixth OLT case was a 54-year-old HIV-positive man with cirrhosis secondary to chronic HCV who was transplanted in October, 2000. His postoperative course has been unremarkable. The HAART regimen consists of lamivudine, indinavir sulfate, and zalcitabine, with HIV viral load undetectable and a 1-year CD4 count of 328. His HCV is detectable at low levels, but he has no evidence of hepatitis on biopsy and is not on anti-HCV treatment.

The seventh case at UPMC was a 35-year-old HIV-positive man suffering from hemophilia, chronic HCV, and cirrhosis. Postoperatively he became CMV-viremic, although asymptomatic, and was treated with intravenous gancyclovir for 5 weeks and converted to oral cytovene therapy. His postoperative course has been unremarkable. The HAART regimen consists of lamivudine and zidovudine and nelfinavir mesylate, maintaining an undetectable HIV viral load and a CD4

count of 396. He has normal liver function tests without clinical HCV recurrence.

The eighth HIV-positive OLT recipient was a 50-year-old man suffering from chronic HCV with cirrhosis who underwent transplantation in October, 2001. He developed an asymptomatic CMV reactivation, requiring intravenous gancyclovir with conversion to oral cytovene. His HAART regimen consists of lamivudine and zidovudine and amprenavir, and his HIV viral load remains undetectable. He developed mild HCV recurrence and is undergoing treatment with pegylated interferon and ribivirin with normal liver function tests.

The ninth case of HIV-positive OLT was performed for a 55-year-old man suffering from ESLD secondary to chronic HBV and hepatocellular carcinoma (HCC); he underwent transplantation in November, 2001. His postoperative course has been complicated by HCC recurrence; however, his HIV remains undetectable on a HAART regimen consisting of lamivudine, stavudine, and nelfinavir mesylate. The HBV-DNA is currently nondetectable. His HBV maintenance therapy is with lamivudine and hepatitis B immune globulin (HBIG).

The tenth HIV-positive OLT at UPMC was for a 67-year-old man suffering from chronic HBV and cirrhosis. He had documented YMDD mutation to lamivudine but was suppressed on adefovir dipivoxil before OLT. He was not on antiretroviral medications before OLT, had a HIV viral load of 24,000 copies/mL and a CD4 count of 176. He was transplanted in December, 2001. His postoperative course has been unremarkable, and he is tolerating his HAART regimen of adefovir dipivoxil, lamivudine, and zidovudine and nelfinavir mesylate. He is currently maintained on HBIG and adefovir dipivoxil.

Two patients (cases 3 [UM] and 10 [UPMC]) with FHF were listed and transplanted as UNOS status 1, 1 patient with advanced liver failure requiring ventilator and dialysis support was listed as UNOS status 2A, and the remainder underwent transplantation as UNOS status 2B. The patient listed as a status 2A (UPMC case 3) did not improve with transplantation and died soon thereafter. Overall, 2 patients (cases 3 and 4 [UPMC]) have died, of sepsis and HCV recurrence with chronic rejection, respectively.

Drug Interactions

Protease inhibitors (PI) have been associated with significant cytochrome P450 3A interference.¹⁰ Therefore, tacrolimus dosing was reduced markedly to minimize levels of tacrolimus and resultant toxicity. For example, the average dose of tacrolimus was 1 to 3

mg/wk in HIV-positive OLT patients on PI. This contrasts with OLT patients not on PI, for whom dosing is approximately 0.1 mg/kg/d (7 mg/d). In one case in particular (case 9), the local physician discontinued the patient's PI without consulting the OLT team. The elimination of the PI from the HAART regimen resulted in a drastic reduction in tacrolimus levels, precipitating acute rejection. In another case, PI was started without adjustment in the tacrolimus, resulting in toxic levels (greater than 30 ng/mL) for 3 weeks. ACR developed in 4 of 13 patients (31%) in the early post-OLT period. All rejections in this period were controlled and easily reversed. The incidence of acute rejection was similar to that seen in the non-HIV OLT patients.

Postoperative Care and HIV Status

In all survivors, OLT reversed the symptoms of acute and chronic liver failure, including ascites, encephalopathy, muscle wasting, fatigue, hypersplenism and jaundice. One patient, case 2 (UM), developed lamivudine resistance, requiring additional treatment. Several recipients suffered from ACR, requiring steroid therapy, two of which necessitated muromonab (CD3) cluster therapy.

HIV loads remained undetectable in all but 1 patient during the entire follow-up period, and all are maintained on HAART therapy. Adjustments in the HAART regimen resulted in undetectable viral loads at follow up in the patient with recurrent HIV viremia. Total CD4 counts, which were all < 200 cells/mm³ before OLT, improved to > 200 cells/mm³ after OLT and are listed in Table 2.

Survival and HCV Recurrence

The 1-year survival in both groups of patients is 94% (15 of 16), 100% (6 of 6) at UM and 90% (9 of 10) at UPMC. One OLT recipient at UPMC died on day 570 as a result of noncompliance and resultant chronic rejection with recurrent HCV. Overall, HCV recurrence as diagnosed clinically and histologically occurred in 66% (2 of 3) of UM cases and 100% (7 of 7) of UPMC recipients. Assessment of long-term survival at 3 years or greater is not possible because of the small patient number; however, at 2 years, the actuarial survival is 80%, well within the expected survival for non-HIV-positive OLT patients according to UNOS statistics.

Discussion

Overall, there are an estimated 300,000 HIV persons coinfecting with viral hepatitis B or C, or both, in the

Table 2. Results of CD4 Counts and HIV Viral Loads, Pre- and Post-OLT

Case	Pre-OLT	CD4 (mo)				Pre-OLT	Viral Load (mo)			
		1	3	6	12		1	3	6	12
1*	500	NA	NA	742	1084	< 400	ND	ND	ND	ND
2*	435	72	210	332	399	< 100	ND	ND	ND	ND
3*	99	32	108	185	240	NA	6444	ND	912	ND
4*	200	458	452	470	500	ND	ND	ND	ND	ND
5*	149	176	214	350	400	ND	ND	ND	ND	ND
6*	400	250	300	503	600	ND	ND	ND	ND	ND
7†	660	62	123	256	384	ND	ND	ND	ND	ND
8†	380	235	99	357	256	ND	ND	ND	ND	ND
9†	528	deceased				16,000	deceased			
10†	168	107	97	102	132	115,776	62	ND	3556	ND
11†	103	196	201	370	433	ND	ND	ND	ND	ND
12†	218	437	347	266	328	ND	1764	ND	ND	ND
13†	506	468	663	396	432	ND	ND	ND	ND	ND
14†	76	102	194	195	114	ND	ND	ND	ND	ND
15†	318	405	471	224	—	ND	ND	ND	ND	—
16†	176	112	253	—	—	24,000	110	161	—	—

NOTE. Footnote symbol denotes transplantation site.
Abbreviations: ND, not detectable; NA, not done.
*Miami
†Pittsburgh

United States, representing a significant proportion of persons with HIV infection.^{11,12} With the advent of HAART, a decline in morbidity and mortality in patients with HIV infection have been observed over the past few years.¹³ As a result of this new treatment, mortality attributable to other underlying diseases such as viral hepatitis infection has increased, resulting in an increased prevalence of HIV patients with ESLD.¹⁴

OLT is now an accepted therapy for a wide variety of irreversible diseases of the liver. At present, more than 4,000 liver transplantations are performed in the United States each year. Chronic HCV is the leading reason within the United States for OLT. Patients with HIV infection generally have been excluded from solid-organ transplantation.^{15,16} Because solid-organ transplantation is not considered for this subset of patients, death related to ESLD is imminent.¹⁷ The primary concern is the potential side effects of immunosuppression after OLT and the effect it may have on HIV disease progression.¹⁸⁻²⁴ The conceptual conflict lies in the iatrogenic immunosuppression of an already immunosuppressed individual (i.e., an HIV-positive patient). Early reports, before the advent of HAART, suggested that the course of HIV infection is accelerated in transplant patients, either because of the effect of immunosuppression on, or the role of alloantigenic stimulation in, HIV replication.^{22,25}

The exact role of immunosuppression in patients with HIV is unknown. However, the existence of HIV replication pathways that are inhibited by cyclosporine and tacrolimus have led some to consider employing these agents in the treatment of HIV infection.²¹ The early studies involving patients with HIV included cyclosporine as the primary immunosuppressant. Others have shown that mycophenolate mofetil, an inhibitor of the purine metabolism pathway, also potentiates some antiretroviral nucleoside analogs.

The first series of HIV patients that received OLT were HIV-positive at the time of transplantation or acquired the virus perioperatively was reported on by UPMC.^{26,27} This report predated the HAART era and, for most of its patients, even predated the availability of lamivudine monotherapy. In a retrospective serologic survey of organ donors and transplant recipients, seven of the 18 HIV-positive transplant recipients had antibodies to HIV before transplantation, whereas the other 11 HIV-positive recipients seroconverted at a mean of 96 days after transplantation. Nine of the 18 HIV-positive seropositive transplant recipients died a mean of 6 months after transplant surgery, and 9 (50%) were still alive a mean of 43 months after transplantation. Of the 15 liver transplant patients, 7 were alive at a mean of 2.75 years. This study did not show any survival statistical difference between the HIV-positive

Table 3. Treatment Information for Coinfected OLT Recipients (Subjects # 2–4 had regimen changes)

Case	Disease	HAART	Anti-HBV/HCV	HBV/HCV Status	HIV Status
1*	HBV	NEV/LAM/ABC	LAM	ND	HIV ND
2*	HBV	NEV/COM	LAM	HBV BT (mo 22)	HIV ND
2*	HBV	NEV/COM/TEN	LAM/TEN	present HBV DNA (–)	HIV ND
3*	HBV	NEL/COM/ddI	LAM	ND	HIV ND
3*	HBV	NEL/TRI	LAM	ND	HIV ND
4*	HCV	COM/RIT/SAQ	INT/RIBA	HCV VL 500KIU/ML	HIV ND
4*	HCV	COM/LOP/r	INT/RIBA	HCV VL 500KIU/ML	HIV ND
4*	HCV	COM/AMP	INT/RIBA	HCV VL 500KIU/ML	HIV ND
4*	HCV	TRI/TEN	INT/RIBA	HCV VL 500KIU/ML	HIV ND
5*	HCV	EFA/COM	INT/RIBA	HCV VL 100KIU/ML	HIV ND
6*	HCV	EFA/COM	None	ND	HIV ND
7†	HCV	NEL/LAM/STA	INT/RIBA	HCV VL 100KIU/ML	HIV ND
8†	HCV	NEL/LAM/STA	INT/RIBA	ND	HIV ND
9†	HCV	None	None	deceased	deceased
10†	HCV	NEL/COM	INT/RIBA	deceased	deceased
11†	FHF	NEL/COM	None	ND	HIV ND
12†	HCV	IND/LAM/ddC	None	HCV VL 9KIU/NL	HIV ND
13†	HCV	NEL/COM	None	HCV VL 35KIU/ML	HIV ND
14†	HCV	AMP/COMB	INT/RIBA	HCV VL 850KIU/ML	HIV ND
15†	HBV	NEL/LAM/STA	LAM	ND	HIV ND
16†	HBV	NEL/ADE/COMB	ADE	ND	300

NOTE. Footnote symbol denotes site of transplantation.

ND, not detectable; BT, breakthrough; ZDV, zidovudine; LAM, lamivudine; COM, coformulated zidovudine and lamivudine; ABC, abacavir; ddI, didanosine; STA, stavudine; TRI, coformulated zidovudine, lamivudine and abacavir; ADE, adefovir; TEN, tenofovir; EFA, efavirenz; ddC, Zalcitabine; VIR, nevirapine; NEL, nelfinavir; LOP, coformulated lopinavir with ritonavir; IND, indinavir; SAQ, saquinavir hard gel preparation; INT, pegylated interferon alfa 2-b; RIB, ribavirin.

*Miami

†Pittsburgh

and -negative patients. Although the HIV-positive patients did experience an increase in infectious complications, particularly those patients that required anti-lymphocyte antibody preparations during cyclosporine therapy. Similarly, when transplant patients with HIV and without HIV were compared, there was no statistical significance ($P = .69$) in regard to AIDS-free survival. Furthermore, HAART therapy was not available at that time; hence, there was no immune reconstitution in patients on therapy for HIV. In more recent follow-up (12.75 years), 2 liver transplant patients remained alive, both on anti-HIV therapy, instituted late after their OLT.

The European experience comes primarily from the King's College review of 5 patients, 3 transplants for chronic HCV cirrhosis. The rapid progression of HCV was a major concern because survival in this group of patients was between 6 and 25 months.²⁸ In abstract form at the Eighth Conference on Retroviruses and Opportunistic Infections in 2001, the King's group reported on 7 coinfecting patients, 4 with HCV recurrence, and an overall survival between 3 and 25 months.

There are other European reports of transplantation in coinfecting patients; however, they tend to predate the HAART regimen era.^{29,30}

It is important to recognize that not all patients with HIV and liver failure may be acceptable candidates for OLT. Patients with profound immunosuppression attributable to advanced AIDS or with a detectable viral load caused by HAART therapy from multiple drug resistance may not be good candidates for transplantation at this time. In addition, patients with advanced liver failure requiring life support such as dialysis or mechanical ventilation are high-risk candidates regardless of their HIV status. Of the 16 patients who underwent transplantation in this study, 2 died. One patient's death was related to sepsis from vancomycin-resistant enterococcal infection, unrelated to HIV, whereas the second patient's death was caused by chronic rejection and HCV recurrence. Overall, the 92% 1-year survival in this group of HAART regimen-treated HIV-positive patients is at least equal to that seen in the HIV-negative OLT patients.

HCV universally reoccurs after transplant and

results in cirrhosis in over 20% of cases within 5 years, regardless of HIV status. However, the exact time and percentage of HCV recurrence can be debated. Recurrence and disease progression resulting in allograft injury as reported was a major concern in the King's College group. Patient survival in this subset was decreased as a result of HCV recurrence. The HCV-positive OLT recipients in our report had a better survival rate than those in the King's group. In fact, 1 UPMC recipient is alive at more than 5 years, and 1 recipient at UM is currently without HCV recurrence at more than 20 months after OLT. However, the impact of HIV and HCV recurrence and disease progression in OLT recipients in this small subset with relatively short follow-up does not allow us to draw a definitive conclusion. The development of HBV resistance to lamivudine occurred in only 1 patient at UM. Tenofovir was combined with the lamivudine, and the patient became HNB DNA-negative 6 months later.

We have performed 16 liver transplantations in patients with ESLD and HIV. The results have been encouraging, with excellent patient survival. During the period that our patients received HAART therapy, nearly all maintained adequate CD4 counts greater than 200 cells/mm³ and undetectable or low HIV viral loads. Our results suggest that patients with HIV suffering from ESLD can benefit from and survive OLT.

This experience suggests that OLT is effective in selected HIV-positive patients. We propose that while further follow-up of these patients to assess long-term benefits and risks is needed, more liberal application of OLT in selected HIV candidates be considered. Nationally, most centers continue to exclude the HIV population from OLT as a possible life-saving measure without sufficient objective information to support these practices. Without an OLT, patients with HIV and significant liver disease will not survive. In addition, we should consider HIV-positive patients who have extenuating circumstances, with detectable HIV viral loads before OLT when they may not be able to tolerate potent antiretroviral medications in the presence of significant liver dysfunction.

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