

# Survival of Human Immunodeficiency Virus–Infected Liver Transplant Recipients

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(See the editorial by Fishman on pages 1405–11.)

Human immunodeficiency virus (HIV) infection has been considered an absolute contraindication to solid-organ transplantation. With immune function restoration possible with highly active antiretroviral therapy (HAART), we evaluated 24 HIV-positive subjects with end-stage liver disease who were undergoing orthotopic liver transplantation (OLT) after the availability of HAART. The cumulative survival among HIV-positive recipients was similar to that among age- and race-comparable HIV-negative recipients ( $P = .365$ , by log-rank test). At 12, 24, and 36 months after OLT, survival was, respectively, 87.1%, 72.8%, and 72.8% among HIV-positive patients, versus 86.6%, 81.6%, and 77.9% among HIV-negative patients. Survival was poorer among subjects with post-OLT antiretroviral intolerance ( $P = .044$ ), a post-OLT CD4<sup>+</sup> cell count of <200 cells/ $\mu$ L ( $P = .005$ ), a post-OLT HIV load of >400 copies/mL ( $P = .016$ ), and hepatitis C virus infection ( $P = .023$ ). These findings suggest that survival of HIV-positive liver transplant recipients does not differ from that of HIV-negative liver transplant recipients, and they suggest that HIV infection should no longer be a contraindication to OLT. Further prospective studies are warranted.

Despite advances in highly-active antiretroviral therapy (HAART), which suppresses HIV replication, enhances immune function, slows disease progression, and reduces mortality [1–3], some individuals with HIV infection are surviving such infection to die of end-stage liver disease (ESLD), especially those with coinfection with hepatitis C virus (HCV) or hepatitis B virus (HBV) [4]. In the United States, as many as 30% of individuals with HIV infection are coinfecting with HCV [5], although, in some groups (e.g., individuals with hemophilia),  $\geq 80\%$  are coinfecting with HCV [4]. Moreover, the risk of ESLD among hemophiliacs who are HIV positive is nearly 4-fold greater than that among hemophiliacs who are HIV negative [4], and liver disease

has become the second leading cause of death in this group, after HIV infection [4, 6].

Although the mechanism by which HIV increases progression to ESLD is not known, HIV up-regulates cytokines, which may increase liver fibrosis and lead to liver disease progression [7]. Treatment with HAART may contribute to hepatotoxicity, yet, in some studies, HAART appears to protect against liver disease progression [4]. Because the increasing duration of HIV infection is an independent marker for liver disease progression, it is likely that ESLD will continue to be a growing problem among a significant number of coinfecting individuals [4].

Historically, HIV infection has been considered an absolute contraindication to transplantation [8] because of the high mortality rate of opportunistic infection associated with HIV infection and antirejection immunosuppression [9, 10]. However, the improvement in both immune system function and survival among individuals with HIV infection, which was made possible by the introduction of HAART in 1996 [1–3], led us to hypothesize that the use of postoperative

Received 10 April 2003; accepted 30 July 2003; electronically published 12 November 2003.

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The Journal of Infectious Diseases 2003;188:1412–20

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HAART therapy for HIV-positive subjects with ESLD who are undergoing orthotopic liver transplantation (OLT) would result in survival comparable to that seen among HIV-negative liver transplant recipients. We therefore prospectively evaluated the outcome of OLT performed, after the availability of HAART, for 24 HIV-positive subjects with ESLD.

## SUBJECTS AND METHODS

**Subjects.** Twenty-four subjects with HIV infection and ESLD who fulfilled standard listing criteria for liver transplantation underwent OLT at 5 institutions (10 subjects underwent OLT at the University of Pittsburgh [Pittsburgh, PA]; 6 at the University of Miami [Miami, FL]; 4 at the University of California, San Francisco [San Francisco, CA]; 3 at King's College [London, United Kingdom]; and 1 at the University of Minnesota [Minneapolis, MN]) between 1997 and 2001, after the 1996 introduction and licensure of HAART. Although active opportunistic infection was considered a contraindication for transplantation surgery, past opportunistic infection was not considered a contraindication, nor was any level of CD4<sup>+</sup> cell count or HIV load. All but 2 of the 24 subjects received preoperative antiretroviral therapy, and all but 1 subject received postoperative antiretroviral therapy. Institutional review board approval was obtained for the research protocols at each institution.

**Methods.** Liver transplantation was performed by standard orthotopic placement of the donor allograft liver into the recipient [11]. Twenty-three subjects received a cadaveric liver, and 1 subject received a liver from a living donor. The latter subject experienced early graft failure resulting from a "small-for-size" mismatch; this led to a second transplantation with a cadaveric liver. Although all donors were HIV negative, some were HCV positive; however, their organs were used only in HCV-positive recipients, which is a safe and common practice in transplantation. Survival was measured from the time of the first transplantation. The method of reconstruction was institution specific and generally included anastomosis of the allograft portal vein to the recipient portal vein and anastomosis of the allograft hepatic artery to the recipient hepatic artery, with bile duct reconstruction or roux-en-Y choledochojejunostomy [11]. Packed RBCs, fresh frozen plasma, platelets, and clotting factor were transfused as needed during and after the procedure.

Within the first 24–48 h after transplantation, antirejection immunosuppression was begun with tacrolimus (FK506) or cyclosporine and with  $\geq 1$  of the following: mycophenolate mofetil, prednisone, and OKT3 monoclonal antibody. Antiretroviral therapy was begun within the first 3 postoperative weeks, after extubation, resumption of oral intake, and correction of liver-function test results toward the range considered to be

**Table 1. Baseline demographic and clinical characteristics of 24 human immunodeficiency virus (HIV)-positive subjects at liver transplantation.**

Characteristic	Value
Age, median (range), years	46 (15–66)
Race	
White	21 (87.5)
Black	2 (8.3)
Asian	1 (4.2)
Sex	
Male	20 (83.3)
Female	4 (16.7)
Cause of end-stage liver disease	
Hepatitis C virus infection	15 <sup>a</sup> (62.5)
Hepatitis B virus infection <sup>b</sup>	7 (29.2)
Fulminant hepatic failure <sup>c</sup>	3 (13.0)
HIV risk group	
Homosexual	7 (29.2)
Heterosexual	5 (20.8)
Hemophilic	5 (20.8)
Bisexual	3 (12.5)
Injection drug user	3 <sup>d</sup> (12.5)
Transfusion recipient	2 (8.3)
Unknown	1 (4.2)
Preoperative laboratory value, <sup>e</sup> median (range)	
Alanine aminotransferase, <sup>f</sup> U/mL	82 (25–648)
Total bilirubin, mg/dL	3.2 (0.7–27.0)
Creatinine, mg/dL	0.9 (0.5–2.2)
International normalized ratio	1.5 (0.6–3.6)
MELD score <sup>g</sup>	15 (7–33)
Platelet count, no. $\times 10^3$ platelets/ $\mu$ L	73 (28–185)
CD4 <sup>+</sup> cell count, <sup>h</sup> cells/ $\mu$ L	188 (76–973)
HIV RNA PCR load, <sup>i</sup> copies/mL	<400 (<400–179,000)
Preoperative antiretroviral therapy	
Ever received	
Protease inhibitor	13 <sup>j</sup> (54.2)
NNRTI	8 (34.8)
NRTI only	3 (12.5)
None	2 (8.3)
Intolerance	4 (16.7)

**NOTE.** Data are no. (%) of subjects, unless otherwise indicated. HBsAg, hepatitis B surface antigen; MELD, Model for End-Stage Liver Disease; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; PCR, polymerase chain reaction.

<sup>a</sup> Eight subjects also had past concomitant hepatitis B virus infection and are currently HBsAg negative.

<sup>b</sup> Four subjects (57.1%) had hepatitis B infection and were HBsAg positive.

<sup>c</sup> One case of fulminant hepatic failure was due to hepatitis B virus infection (HBsAg positive).

<sup>d</sup> One subject each also belonged to the bisexual and heterosexual risk groups.

<sup>e</sup> Obtained within 1–2 days of orthotopic liver transplantation.

<sup>f</sup> Not determined for 3 subjects

<sup>g</sup> MELD score =  $10 \times [0.378 \ln(\text{total bilirubin, mg/dL}) + 1.120 \ln(\text{international normalized ratio}) + 0.957 \ln(\text{creatinine, mg/dL}) + 0.643]$ .

<sup>h</sup> Twelve patients (50.0%) had a CD4<sup>+</sup> cell count of <200 cells/ $\mu$ L.

<sup>i</sup> Six patients (25.0%) had an HIV RNA PCR load of >400 copies/mL.

<sup>j</sup> Two subjects who were receiving PIs were also receiving NNRTIs.

**Table 2. Characteristics of human immunodeficiency virus (HIV)-positive subjects after orthotopic liver transplantation (OLT).**

Characteristic	No. (%) of subjects
Received ART	
With protease inhibitors	14 (58.3)
With nonnucleoside reverse-transcriptase inhibitors	5 (20.8)
With nucleoside reverse-transcriptase inhibitors	4 (16.7)
Did not receive ART	1 (4.2)
Had ART intolerance	6 (25.0)
Hepatitis C	14 (58.3)
Recurrence	7 (50.0)
Treated	4 (57.1)
Not treated	3 (42.8)
Received interferon and/or ribavirin	7 (50.0)
At recurrence	4 (57.1)
Empirically at OLT	3 (42.8)
Received antirejection therapy	
Tacrolimus	20 (83.3)
Cyclosporine	4 (16.7)
Experienced transplant rejection	12 (50.0)
Acute	10 (83.3)
Chronic	2 (16.7)
CD4 <sup>+</sup> cell count of <200 cells/ $\mu$ L <sup>a</sup>	4 (18.2)
HIV RNA PCR load of >400 copies/mL <sup>b</sup>	2 (8.3)
Cause of death	6 (25.0)
End-stage liver disease	5 (83.3)
Due to drug hepatotoxicity and ART intolerance	3 (60.0)
Complicated by recurrent HCV infection	3 (60.0)
Complicated by rejection	2 (40.0)
Complicated by pancreatitis and sepsis	1 (20.0)
Complicated by renal failure	1 (20.0)
Complicated by CNS bleed	1 (20.0)
Opportunistic fungal infection	1 (16.7)

**NOTE.** Postoperative laboratory values shown are those obtained at last follow-up (see the last sentence of the first paragraph of the Results section). ART, antiretroviral therapy; HCV, hepatitis C virus.

<sup>a</sup> The denominator used in the calculation of the percentage is 22, because the post-OLT CD4<sup>+</sup> cell count was not determined for 2 subjects. The median post-OLT CD4<sup>+</sup> cell count was 281 cells/ $\mu$ L (range, 87–1084 cells/ $\mu$ L).

<sup>b</sup> The median post-OLT HIV RNA PCR load was <400 copies/ $\mu$ L (range, <400–9600 copies/mL).

normal. “Antiretroviral intolerance” was defined as the permanent discontinuation of antiretroviral drugs because of toxicity; antiretroviral intolerance occurred in 4 subjects during the pretransplantation period and in 6 subjects during the post-transplantation period. The 4 subjects who discontinued receiving antiretroviral drugs because of toxicity in the *pretransplantation* period did not receive any antiretroviral drugs up to the time of transplantation. The 6 subjects who discontinued antiretroviral drugs *postoperatively* still were not receiving drugs at the time of death or last contact. Interferon therapy with or without ribavirin was given empirically to subjects with chronic HCV infection, either within the first 4 weeks after transplan-

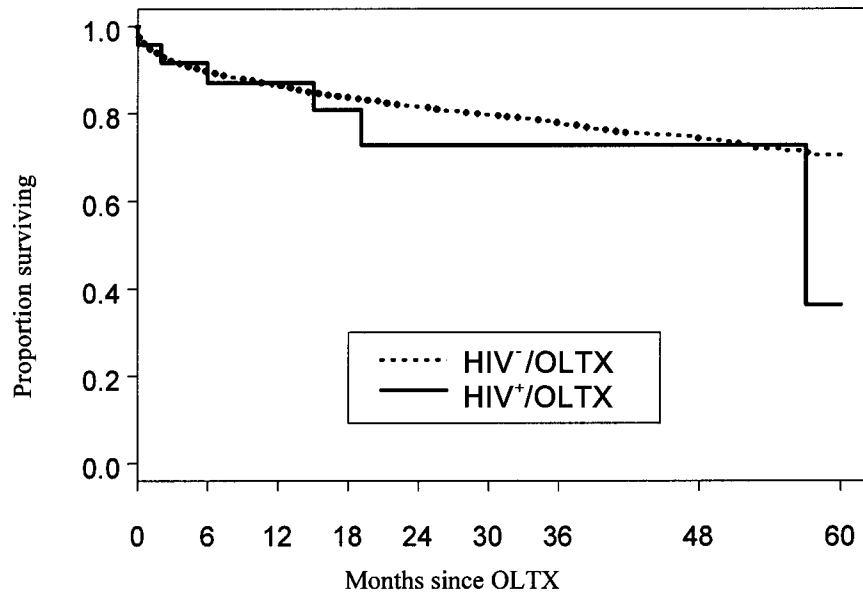
tation or after biopsy evidence of HCV infection recurrence, on the basis of institutional preference.

**United Network of Organ Sharing (UNOS) data.** To compare survival after liver transplantation among HIV-positive transplant recipients with that among HIV-negative liver transplant recipients, we obtained, from the UNOS Scientific Registry for Liver Transplantation, data on 54,994 individuals who had undergone liver transplantation in the United States since 1987 [12]. To make the 2 groups of transplant recipients comparable, the UNOS data were restricted to first liver transplantations performed from 1 January 1997 through 13 December 2001, which reduced the size of the UNOS cohort to 19,478 individuals. Only UNOS liver transplant recipients who were known to be HIV-antibody negative were included, which further reduced the size of the UNOS cohort to 13,574 individuals. The age range and race of the UNOS cohort were restricted to those of the HIV-positive cohort, and they were further restricted to individuals with known follow-up, which reduced the size of the UNOS cohort to 11,453 individuals. The cause of ESLD in the UNOS cohort was restricted to HCV infection, HBV infection, or fulminant hepatic failure, which further reduced the size of the UNOS cohort available for comparison, to 5225 individuals.

**Statistical analysis.** Data are presented as frequencies and percentages, for categorical data, and as means, medians, 25th and 75th percentiles, and ranges, for continuous data. Time-to-event distributions were estimated using the product-limit estimate [13]. Subjects who were not known to have died were censored at their last contact date. Because of the small sample size and the small number of deaths, a log-rank test based on a permutation method was used to derive exact *P* values when survival rates of the subgroups of the HIV-positive recipients were compared (StatXact 5.0; Cytel Software). This log-rank test was also used to compare survival rates of HIV-positive and HIV-negative liver transplant recipients. The association of death with continuous covariates (e.g., age and alanine aminotransferase level) was examined using exact simple Poisson regression models (LogXact 4.1; Cytel Software). For both categorical and continuous variables, the estimates of the relative risks of death, reflecting the prospective nature of the study, were calculated with 95% confidence intervals and *P* values. A relative risk of greater (less) than 1 implies that the risk of death increases (decreases) as the value of the categorical or continuous variable increases. Statistical significance was defined as *P* < .05.

## RESULTS

The majority of HIV-positive subjects were white (21 [87.5%] of 24 subjects) and male (20 [83.3%] of 24 subjects). Among 24 subjects, the cause of ESLD was HCV infection in 15 subjects



	0 months	12 months	24 months	36 months	48 months	60 months
<b>HIV<sup>+</sup>/OLT</b>						
Survival	1.000	0.871	0.728	0.728	0.728	0.364
Standard error	-	0.070	0.110	0.110	0.110	0.263
No. at risk	24	15	6	3	2	1
<b>HIV<sup>-</sup>/OLT</b>						
Survival	1.000	0.866	0.816	0.779	0.743	0.706
Standard error	-	0.005	0.006	0.007	0.009	0.015
No. at risk	5225	3341	2099	1117	451	90

**Figure 1.** Cumulative survival after orthotopic liver transplantation (OLT) among human immunodeficiency virus (HIV)-positive (HIV<sup>+</sup>) liver transplant recipients (*solid line*). The proportions of subjects surviving at 12, 24, and 36 months after OLT were 87.1%, 72.8%, and 72.8%, respectively. This finding did not differ from the cumulative survival among the cohort of United Network of Organ Sharing (UNOS) HIV-negative (HIV<sup>-</sup>) liver transplant recipients (*dotted line*), who were comparable to HIV<sup>+</sup> transplant recipients with regard to age, race, and time of transplantation ( $P = .365$ ): survival at 12, 24, and 36 months in the UNOS HIV-negative cohort was 86.6%, 81.6%, and 77.9%, respectively.

(62.5%), HBV infection in 7 subjects (29.2%), and fulminant hepatic failure in 3 subjects (13%), in association with nevirapine-induced acute hepatic necrosis, acute hepatitis A infection, and acute hepatitis B infection (table 1). After OLT, 14 transplant recipients received a regimen including protease inhibitors (PIs), 5 received a regimen including nonnucleoside reverse-transcriptase inhibitors (NNRTIs), and 4 received a regimen including only nucleoside reverse-transcriptase inhibitors (NRTIs). One recipient died within 1 month and received no postoperative regimen. Median follow-up was 17.0 months. The posttransplantation values used in the analyses were the last available results.

The median pretransplantation CD4<sup>+</sup> lymphocyte count and the HIV load (values were those obtained closest in time to

OLT) are shown in table 1. At the time of the last follow-up after transplantation for each subject, the median CD4<sup>+</sup> cell count was 281 cells/ $\mu$ L (range, 87–1084 cells/ $\mu$ L), and the median HIV load was <400 copies/mL (range, <400 to 9600 copies/mL) (table 2). Six subjects (26.1%) experienced postoperative antiretroviral intolerance. Of these subjects, 4 (66.7%) died (table 2); all 4 had hepatitis C and developed antiretroviral intolerance, 2 in association with interferon and/or ribavirin therapy received for recurrence of hepatitis C. Antiretroviral intolerance in the 2 subjects who survived (neither of whom was hepatitis C positive) was associated with early post-OLT liver dysfunction, which subsequently resolved. By contrast, among the 4 subjects who died, antiretroviral intolerance that preceded death by 0–10 months was associated with recurrence

of hepatitis C treated with interferon and/or ribavirin: in 1 of the 4 subjects who died, superimposed parenteral antifungal therapy was also required for invasive aspergillosis.

Posttransplantation survival in the HIV-positive cohort was not significantly different from that in the HIV-negative UNOS cohort ( $P = .365$ ) (figure 1). The cumulative 12-month survival among HIV-positive subjects after liver transplantation was 87.1% (figure 1), compared with 86.6% among HIV-negative liver transplant recipients who were of comparable age and race and who had a comparable date of transplantation (table 3). The probability of survival among HIV-positive recipients at 24 and 36 months after liver transplantation was 72.8% at each time point, compared with survival probabilities of 81.6% and 77.9%, respectively, for HIV-negative UNOS transplant recipients.

Survival was significantly poorer among transplant recipients with post-OLT<sub>X</sub> antiretroviral intolerance ( $P = .044$ ) (table 4) but not among transplant recipients with pre-OLT<sub>X</sub> antiretroviral intolerance ( $P = .239$ ). Although these data suggest an association between poorer survival and post-OLT<sub>X</sub> antiretroviral intolerance, the sample size of this cohort is inadequate to allow us to examine whether antiretroviral intolerance is an independent risk factor for death in the HIV-positive OLT<sub>X</sub> cohort or to determine the explanation for this finding.

There was a trend toward poorer survival among transplant recipients receiving regimens including NRTIs, compared with those receiving regimens including PIs or NNRTIs, although this was not statistically different ( $P = .091$ ) (table 4). On the basis of the last available posttransplantation values, survival was poorer among transplant recipients with a post-OLT<sub>X</sub> CD4<sup>+</sup> cell count of <200 cells/ $\mu$ L than among those with a post-OLT<sub>X</sub> CD4<sup>+</sup> cell count of  $\geq$ 200 cells/ $\mu$ L ( $P = .005$ ), and survival was also poorer among those with a post-OLT<sub>X</sub> HIV load of >400 copies/mL than among those with a post-OLT<sub>X</sub> HIV load of  $\leq$ 400 copies/mL ( $P = .016$ ), which suggests the importance that post-OLT<sub>X</sub> viral suppression and an increase in the CD4<sup>+</sup> cell count have for survival.

By contrast, a pre-OLT<sub>X</sub> CD4<sup>+</sup> cell count of <200 cells/ $\mu$ L (compared with  $\geq$ 200 cells/ $\mu$ L;  $P = .602$ ) and a pre-OLT<sub>X</sub> HIV load of >400 copies/mL (compared with  $\leq$ 400 copies/mL;  $P = .494$ ) were not significantly associated with survival. Post-OLT<sub>X</sub> survival was not associated with the type of antirejection therapy ( $P = .532$ ) (table 4) or the route of HIV infection (bloodborne vs. not bloodborne,  $P = .124$ ). Post-OLT<sub>X</sub> survival was better among subjects for whom sexual contact was the route of transmission of infection than among subjects for whom sexual contact was not the route of transmission ( $P = .042$ ); however, the sample size was too small to allow us to determine whether this finding was confounded by the frequency of hepatitis C in the latter group of subjects. Although

**Table 3. Comparison of characteristics of human immunodeficiency virus (HIV)-positive and HIV-negative liver transplant recipients who underwent transplantation during the period from 1 January 1997 through 13 December 2001.**

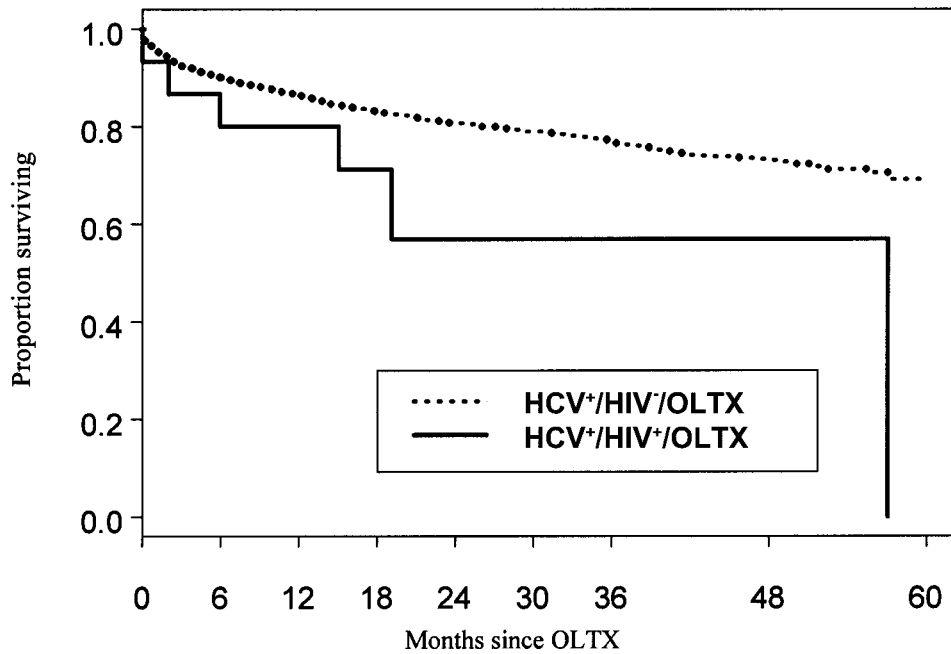
Characteristic	Liver transplant recipients	
	HIV-positive (n = 24)	HIV-negative UNOS cohort <sup>a</sup> (n = 5225)
Age		
Mean $\pm$ SD, years	44.3 $\pm$ 9.9	49.0 $\pm$ 9.0
Median, years	45.5	49.0
Range, years	15.0–66.0	15.0–66.0
Percentiles, 25th and 75th	40.0, 50.5	44.0, 54.0
Race		
White	21 (87.5)	4489 (85.9)
Black	2 (8.3)	492 (9.4)
Asian	1 (4.2)	244 (4.7)
Sex		
Male	20 (83.3)	3594 (68.8)
Female	4 (16.7)	1631 (31.2)
Cause of end-stage liver disease		
Hepatitis C virus infection	15 (62.5)	4062 (77.7)
Hepatitis B virus infection or FHF	9 (37.5)	1163 (22.3)

**NOTE.** Data are no. (%) of subjects, unless otherwise indicated. FHF, fulminant hepatic failure; UNOS, United Network of Organ Sharing.

<sup>a</sup> The UNOS HIV-negative transplant recipients who were used as a comparison group for this study underwent initial liver transplantation between 1 January 1997 and 13 December 2001; were 15–66 years of age; were of white, black, or Asian race; and had end-stage liver disease caused by hepatitis C virus infection, hepatitis B virus infection, or FHF only.

subjects in the study who acquired HIV infection through blood transfusion were younger at the time of transplantation (median age, 40 years) than were those who acquired HIV infection through sexual contact (median age, 47 years), the sample size was too small to allow us to determine whether poorer post-OLT<sub>X</sub> survival among younger subjects was confounded by the route of HIV infection or any other factor.

Survival was significantly poorer among the HIV-positive subjects with ESLD caused by HCV infection than among those without HCV infection (50.0% vs. 100.0%;  $P = .023$ ) (table 4). All 6 of the HIV-positive transplant recipients who died, including 3 hemophiliacs and 1 transfusion recipient, had received blood products in the past (table 4). Again, the small sample size precludes determination of whether poorer survival among HCV-positive subjects is the result of a confounding variable. It should be noted that, among those with ESLD due to HCV, the decrease in survival after 2 years (figure 2) was the result of a single, late death of an HCV-positive subject who developed a fatal opportunistic infection 57 months after OLT<sub>X</sub>. Of note, a comparison of survival in the HCV-positive UNOS HIV-negative cohort to that among HCV-positive HIV-positive transplant recipients revealed no significant difference ( $P = .058$ ), although the small sample size limits statistical power.



	0 months	12 months	24 months	36 months	48 months	60 months
<b>HCV+/HIV+/OLT</b>						
Survival	1.000	0.800	0.569	0.569	0.569	0.000
Standard error	-	0.103	0.162	0.162	0.162	0.000
No. at risk	15	9	4	3	1	0
<b>HCV+/HIV-/OLT</b>						
Survival	1.000	0.865	0.808	0.770	0.731	0.691
Standard error	-	0.006	0.007	0.008	0.011	0.018
No. at risk	4062	2560	1577	822	330	61

**Figure 2.** Cumulative survival after orthotopic liver transplantation (OLT) among hepatitis C virus–positive (HCV+) liver transplant recipients, comparing HIV-positive (HIV+) and United Network of Organ Sharing (UNOS) HIV-negative (HIV-) liver transplant recipients. The proportions of subjects surviving at 12, 24, and 36 months after OLT were 80.0%, 56.9%, and 56.9%, respectively, for the HCV+ HIV+ recipients (*solid line*). This did not differ from the cumulative survival among the UNOS HCV+ HIV- liver transplant recipients ( $P = .058$ ): survival at 12, 24, and 36 months after OLT among UNOS HCV+ HIV- transplant recipients was 86.5%, 80.8%, and 77.0%, respectively (*dotted line*). Note that the abrupt decrease in survival in the HIV+ HCV+ group is the result of the single, late death of a coinfecting subject who developed a fatal opportunistic infection 57 months after OLT.

**CONCLUSION**

The results of this study demonstrate that 1-year survival after liver transplantation is 87.1% among HIV-positive subjects, which is comparable to 1-year survival among age- and race-comparable HIV-negative liver transplant recipients in the United States during the same period. Although they are preliminary, these data suggest that HIV infection should no longer be considered an absolute contraindication for liver transplantation. Although the small sample size, short follow-up, and subsequent small number of deaths limit both the long-term projection of survival after liver transplantation and the elimination of confounders that might explain survival differences

among recipient subgroups, these findings warrant further large prospective studies of HIV-infected subjects undergoing liver transplantation.

The optimal antiretroviral regimen after organ transplantation is not known. Although survival was worse among subjects receiving a regimen including only NRTIs than among subjects receiving a regimen including PIs or NNRTIs, the differences were not statistically significant. A larger prospective study will be necessary to determine whether the latter regimens are superior in suppressing the HIV load and/or restoring sufficient immune function to improve survival after transplantation. It is not known whether the antirejection drugs tacrolimus and

**Table 4. Demographic and clinical characteristics of and survival among human immunodeficiency virus (HIV)-positive liver transplant recipients.**

Characteristic	Survivors (n = 18)	Nonsurvivors (n = 6)	RR <sup>a</sup>	P <sup>b</sup>
Age, median (range), years	48 (33–66)	39 (15–43)	0.42 <sup>c</sup>	.026 <sup>c</sup>
Sex, no. of males:no. of females	15:3	5:1	0.86	.960
Race				
White	15 (83.3)	6 (100.0)	... <sup>d</sup>	.629
Black	2 (11.1)	0 (0)	...	
Asian	1 (5.6)	0 (0)	...	
HIV risk group				
Homosexual	7 (38.9)	0 (0)	0.00 <sup>e</sup>	.074
Heterosexual	4 (22.2)	1 (16.7)	0.80	.820
Hemophiliac	2 (11.1)	3 (50.0)	3.25	.111
Bisexual	3 (16.7)	0 (0)	0.00 <sup>e</sup>	.518
Injection drug user	3 (16.7)	0 (0)	0.00 <sup>e</sup>	.371
Transfusion recipient	1 (5.6)	1 (16.7)	2.20	.674
Unknown	0 (0)	1 (16.7)	... <sup>f</sup>	... <sup>f</sup>
Cause of end-stage liver disease				
Hepatitis C virus infection	9 (50.0)	6 (100.0)	... <sup>d</sup>	.023
Hepatitis B virus infection	9 (50.0)	1 (16.7)	0.21	.090
Fulminant hepatic failure	3 (16.7)	0 (0)	0.00 <sup>e</sup>	.414
Laboratory value at baseline, <sup>g</sup> median (range)				
Alanine aminotransferase, U/mL	82 (25–648)	69 (66–136)	0.96 <sup>h</sup>	.690
Total bilirubin, mg/dL	2.9 (0.7–27.0)	4.7 (1.5–16.4)	1.01 <sup>i</sup>	.730
Creatinine, mg/dL	0.8 (0.5–1.5)	1.0 (0.7–2.2)	1.12 <sup>j</sup>	.160
International normalized ratio	1.3 (0.6–3.6)	1.7 (1.4–2.6)	1.43 <sup>k</sup>	.511
MELD score, median (range)	15 (7–33)	21 (12–30)	1.95 <sup>l</sup>	.238
Platelets, no. × 10 <sup>3</sup> cells/μL	82 (28–185)	64 (52–146)	1.10 <sup>m</sup>	.412
Post-OLT <sub>X</sub> antiretroviral therapy				
With protease inhibitors	12 (66.7)	2 (33.3)	0.18	.131
With nonnucleoside reverse-transcriptase inhibitors	4 (11.1)	1 (16.1)	1.38	.818
With nucleoside reverse-transcriptase inhibitors	2 (11.8)	2 (33.3)	5.65	.091
Antiretroviral therapy intolerance				
Before OLT <sub>X</sub>	2 (11.1)	2 (33.3)	3.58	.239
After OLT <sub>X</sub>	2 (11.1)	4 (66.7)	7.27	.044
Acute post-OLT <sub>X</sub> rejection	7 (38.9)	3 (50.0)	2.89	.530
Antirejection therapy				
Tacrolimus	15 (83.3)	5 (83.3)	0.48	.532
Cyclosporine	3 (16.7)	1 (16.7)	...	
Pre-OLT <sub>X</sub> CD4 <sup>+</sup> cell count				
Median cells/μL	209	170	1.02 <sup>n</sup>	.338
<200 Cells/μL	8 (44.4)	4 (66.7)	1.69	.602
Post-OLT <sub>X</sub> CD4 <sup>+</sup> cell count				
Median cells/μL	311	135	0.81 <sup>n</sup>	.003
<200 Cells/μL	1 (5.9) <sup>o</sup>	3 (60.0)	21.53	.005
Pre-OLT <sub>X</sub> HIV RNA PCR load				
Median copies/mL	≤50	≥400	1.00	.589
>400 Copies/mL	4 (22.2)	2 (33.3)	2.15	.494
Post-OLT <sub>X</sub> HIV RNA PCR load				
Median copies/mL	≤50	≤50	1.02	.139
>400 Copies/mL	0 (0)	2 (33.3)	27.75	.016

**NOTE.** Data are no (%) of subjects, unless otherwise indicated. MELD, Model for End-Stage Liver Disease; OLT<sub>X</sub>, orthotopic liver transplantation; RR, relative risk.

- <sup>a</sup> Estimated from univariable Cox model, except where otherwise indicated.
- <sup>b</sup> By exact log-rank test, except where otherwise indicated.
- <sup>c</sup> Calculated for each 10-year increase in age and based on exact Poisson regression.
- <sup>d</sup> Cannot be estimated because there were no deaths in the comparison group.
- <sup>e</sup> Estimated RR is zero because there were no deaths in the group.
- <sup>f</sup> RR cannot be estimated because only 1 subject in this group died.
- <sup>g</sup> RR and P value are estimated from exact Poisson regression.
- <sup>h</sup> Calculated per 10-U/mL increase in the alanine aminotransferase level. Note that the alanine aminotransferase level was determined for all but 3 subjects (1 survivor and 2 nonsurvivors).
- <sup>i</sup> Calculated per 1 mg bilirubin per dL.
- <sup>j</sup> Calculated per 0.1-mg increase in creatinine per dL.
- <sup>k</sup> Calculated per 1.0-unit increase in the international normalized ratio.
- <sup>l</sup> Calculated per 10-unit increase in the MELD score.
- <sup>m</sup> Calculated per 10 × 10<sup>3</sup>-platelet increase per microliter.
- <sup>n</sup> Calculated per 10-cell increase in the CD4<sup>+</sup> cell count and per 100 copies/mL (for HIV load).
- <sup>o</sup> Denominator is 17, because the CD4<sup>+</sup> cell count was missing for 2 subjects.

cyclosporine contribute to HIV suppression through their known inhibition of HIV growth and replication [14], reduction in HIV cell-to-cell transmission and infectivity [15, 16], and/or suppression of the growth of HIV-infected cells [17]. Future clinical trials and clinical experience will be necessary before specific recommendations can be made regarding optimal post-OLT<sub>X</sub> antiretroviral therapy.

A detectable preoperative HIV load of >400 copies/mL and a low CD4<sup>+</sup> cell count of <200 cells/ $\mu$ L constitute criteria by which some institutions exclude potential candidates for transplantation. Data from this study, however, suggest that pre-OLT<sub>X</sub> antiretroviral drug intolerance (e.g., that due to liver failure) does not adversely affect post-OLT<sub>X</sub> survival. Three subjects with pre-OLT<sub>X</sub> antiretroviral drug intolerance and a detectable HIV load demonstrated effective virus load suppression after postoperative resumption of HAART, despite previous antiretroviral-induced virus load suppression. By contrast, post-OLT<sub>X</sub> antiretroviral intolerance was associated with shorter survival. Because liver failure may prevent tolerance of antiretroviral treatment before OLT<sub>X</sub>, these data suggest that strict criteria related to pre-OLT<sub>X</sub> HIV load and CD4<sup>+</sup> cell count may be less important in the selection of transplant candidates than evidence of adequate HIV suppression and an increase in CD4<sup>+</sup> cells with antiretroviral therapy *before* the development of ESLD.

Although hepatitis C recurrence is a nearly universal complication among HCV-positive transplant recipients [17–22], there is no standard approach to prevention or treatment of HCV infection among HCV-positive subjects undergoing organ transplantation. In this study, 3 institutions prescribed interferon with or without ribavirin only after biopsy evidence of hepatitis C recurrence was obtained, whereas 2 institutions treated HCV infection empirically. The development of antiretroviral intolerance in some subjects after the post-OLT<sub>X</sub> initiation of antiviral treatment for HCV infection suggests that adverse drug interactions may contribute to shortened survival after transplantation. Moreover, given the poor prognosis associated with post-OLT<sub>X</sub> antiretroviral intolerance, these data suggest that consideration should be given to delaying HCV treatment until after there is clear evidence of post-OLT<sub>X</sub> HAART tolerance.

The shorter posttransplantation survival among HCV-infected transplant recipients, compared with posttransplantation survival among HCV-negative transplant patients, is well documented [23] and is not unique to HIV-positive transplant recipients. Our observation that post-OLT<sub>X</sub> survival among HIV-positive HCV-positive transplant recipients was *similar* to that among HIV-negative HCV-positive recipients argues against exclusion of HIV-positive transplantation candidates on the basis of their HCV status, and it further underscores the

need for HCV drug development, given the high rate of recurrence of HCV infection.

Late invasive fungal opportunistic infection developed in 2 subjects after OLT<sub>X</sub>, despite adequate HIV suppression and a CD4<sup>+</sup> cell count of >200 cells/ $\mu$ L with post-OLT<sub>X</sub> antiretroviral therapy. Such infection was fatal in one subject. Because the latter subject was HCV positive and was the longest-surviving patient in this cohort (survival time, 57 months), his death accounts for the abrupt decrease in survival among HCV-infected subjects after 48 months. It is known that fungal infections may occur in up to 40% of HIV-negative liver transplant recipients with associated high mortality, and, thus, the death of the longest-surviving patient was not an unanticipated event in the transplantation setting [24].

In summary, in contrast to the finding of past inferior survival observed among HIV-infected transplant recipients (few, if any, of whom received antiretroviral therapy and all of whom had opportunistic infections [10, 18–21]), the major finding of this study is that successful liver transplantation is possible for HIV-infected subjects and that, for HIV-infected subjects, post-OLT<sub>X</sub> survival with antiretroviral therapy is similar to that for HIV-negative subjects [25]. These data provide a scientific rationale to justify that HIV infection should no longer be considered an absolute contraindication to transplantation, which is consistent with recent transplantation arguments based on ethical considerations [26].

## Acknowledgments

We thank Dr. Kimberly Schlesinger and Ms. Suzanne Rohal of the University of Pittsburgh; Ms. Laurie Carlson and Rodney Rogers of the University of California, San Francisco; and Dr. P. Srinivasan of King's College, for help in assembling clinical data. We also thank Ms. Denise Tripp, for assistance in obtaining, for comparison analyses, data from the Organ Procurement and Transplantation Network, and Mrs. Karen Saban, for help in preparation of the manuscript.

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