Surgical Complications in 275 Human Immunodeficiency Virus (HIV) Infected Liver and/or Kidney Transplant Recipients

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Abstract

Background—This report examines the surgical safety and complications (SC) among 125 liver (L) and 150 kidney (K) HIV+ transplant (TX) recipients in a prospective non-randomized US multicenter trial.

Methods—Subjects required CD4+ T-cell count > 200/100 cells/mm3 (K/L) & undetectable plasma HIV-1 RNA (VL) (K) or expected post-transplant suppression (L). Impact of SCs (N≥7) was evaluated using proportional hazards (PH) models. Baseline morbidity predictors for SCs (N≥7) were assessed in univariate PH models.

Results—At median 2.7 [interquartile range (IQR) 1.9, 4.1] & 2.3 [1.0, 3.7] years post- TX, 3-month & 1-year graft survival were [K] 96% (CI 91%, 98%) & 91% (85%, 94%) & [L] 91% (85%, 95%) & 77% (69%, 84%). 14K and 28L graft losses occurred in the first year; 6K and 11L were in the first 3 months. 26(17%) K and 43 (34%) L experienced 29 and 62 SCs, respectively. In the liver multivariate model, re-exploration was marginally associated (HR: 2.8; 95% CI: 1.0-8.4;
p=0.06) with increased risk of graft loss, while higher MELD pre-transplant (HR: 1.07 per point increase; 95% CI: 1.01-1.14; p=0.02), and detectable viral load pre-TX (HR: 3.6; 95% CI: 0.9-14.6; p=0.07) was associated with an increased risk of wound infections/dehiscence.

Conclusions—The rates and outcomes of surgical complications are similar to what has been observed in the non-HIV setting in carefully selected HIV-infected liver and kidney TX recipients.

Introduction

Infection with HIV has excluded many patients from consideration for solid organ transplantation due to concerns about potential opportunistic and non-opportunistic infections and associated complications due to chronic immune deficiency. With the advent of effective anti-retroviral therapy, patients are no longer dying as frequently from progression of HIV \(^1,2\). However, a significant number of HIV infected patients are progressing to end stage renal and liver disease as a result of co-morbidities associated with HIV infection. Many transplant centers consider infection with HIV a contraindication for solid organ transplantation, however there is mounting evidence that solid organ transplantation is safe in patients infected with HIV \(^3-8\), and control of these patients’ HIV infection can be maintained adequately with antiretroviral therapy despite standard post-transplantation immunosuppressive regimens \(^3\). This report focuses on the surgical complications observed in the US multicenter trial examining the safety and efficacy of liver and kidney transplants in the HIV infected recipients.

Methods

In this nonrandomized prospective trial, 125 liver and 150 kidney HIV-infected transplant recipients were followed for a median of 2.3 [IQR 1.0, 3.7] and 2.7 [IQR 1.9, 4.1] years respectively at 21 U.S. transplantation centers (all cases had at least 1 year of follow up, except 8 liver recipients with 110 to 352 days of follow-up). The research protocol was approved and monitored by the institutional review boards at all participating centers, and each patient provided written informed consent.

Inclusion requirements included; 1. CD4+ T-cell (CD4) counts > 200 cells per cubic millimeter and undetectable plasma HIV-1 RNA levels (<50 copies per milliliter) for kidney transplant recipients; 2) CD4 counts >100 cells per cubic millimeter and undetectable or likely suppressible (in the event of hepatotoxicity to anti-retroviral drugs) HIV RNA plasma levels for liver transplant recipients; and 3) absence or history of treated opportunistic infections with the exception of chronic cryptosporidiosis, multifocal leukoencephalopathy, and visceral Kaposi’s sarcoma.

Kidneys or livers from both deceased and living donors were utilized. Maintenance immunosuppression included corticosteroids, cyclosporine or tacrolimus, and mycophenolate mofetil. In patients with calcineurin inhibitor nephrotoxicity, sirolimus was used. Induction therapy with antibody preparations including interleukin-2-receptor blockers, antithymocyte globulin, or both was permitted at the discretion of the treating physicians for kidney transplant recipients. There were no absolute restrictions in anti-retroviral therapy, and most candidates were maintained on the anti-retroviral therapy that was effective in controlling HIV at the time of referral. Doses of drugs requiring renal clearance were based on the patient’s kidney function. Potential nephrotoxicity of antiretroviral agents as well as antimicrobials used to treat opportunistic infections was considered and these medications were changed as indicated.

Standard post-transplantation prophylaxis for opportunistic infections included lifelong therapy to prevent *Pneumocystis jiroveci*, fungus (1 month), and cytomegalovirus (CMV) (3
months) infections. Prophylaxis against *Mycobacterium avium* complex with macrolide antibiotics was required when the CD4+ T-cell count dropped below 75 cells per cubic millimeter. Liver transplant recipients coinfected with Hepatitis B virus received Hepatitis B immune globulin and antiviral (HBV) therapy following transplantation. Hepatitis C virus infected liver recipients were treated for recurrent disease with interferon and ribavirin when they developed cholestatic hepatitis or evidence of fibrosis on liver biopsy.

Patients were evaluated before transplantation and 13 times during the first year after transplantation. During years 2 and 3 post transplantation patients were evaluated every 3 months, then every 6 months in years 4 and 5. Data collected included demographic characteristics, medical history, immunosuppressant and antiretroviral medications, immunosuppressant levels, HIV-1 RNA levels, CD4+ T-cell counts, Hepatitis C virus infection, MELD score, body mass index (BMI), and donor history. Measured outcomes included patient and graft survival, and surgical complications following transplantation. All analysis was conducted with follow up data as of November 14th, 2010.

For surgical complications with a sample size of 7 or more, proportional hazards models were fit to determine whether each complication as a time-varying covariate was associated with death or graft loss. All surgical complications from the univariate graft loss analysis with P<0.10 were evaluated in a multivariate model adjusted for other potential risk factors for graft loss including pre-transplant CD4 count, viral load at enrollment, Hepatitis C virus infection, dual Liver/Kidney transplant, pre-transplant BMI, donor age, initial calcineurin inhibitor (CNI) use (Tacrolimus vs. Cyclosporin A).

Univariate proportional hazards models were fit to examine the impact of baseline predictors on each surgical complication with sample size of 7 or more. The baseline factors evaluated included: age, sex, race, CD4 pre-transplant nadir/level at study enrollment/most recent pre-transplant (per 50 cells/μL), viral load at enrollment and pre-transplant, HCV infection status, dual liver/kidney transplant, MELD score pre-transplant, BMI at enrollment or pre-transplant, initial thymoglobulin therapy, opportunistic infection history, donor source/age/HCV infection status/marginal status, extended criteria donor (ECD). A search of the PubMed database for keywords HIV infection, kidney transplantation, liver transplantation, and surgical complications yielded relevant journal articles citing rates of surgical complications in non-HIV infected transplant recipients.

**Results**

**Patient and Graft Survival**

Of the 150 transplanted kidney subjects, 37 experienced graft failure and/or death, and of the 125 transplanted liver subjects, 46 experienced liver graft failure and/or death. Of the 37 kidney graft losses, 6 occurred within the first 3 months and 14 overall in the first year. Of the 46 liver graft losses, 11 occurred within the first 3 months and 28 overall in the first year. Three-month, one-year and three-year Kaplan-Meier estimates for patient and graft survival are shown in Table 1.

**Surgical Complications**

**Kidney Recipients**—26 (17%) kidney recipients experienced 29 surgical complications within the first year post-transplant. The surgical complications were 7 re-explorations, 3 perioperative cardiac complications, 6 wound infections/dehiscence, 3 vascular (venous/arterial) thromboses resulting in graft loss, 5 ureteral leak/strictures, 3 lymphoceles and 2 incisional hernias (Table 2). Of the 29 surgical complications, 22 occurred in month 1, 4 in month 2 or 3, and 3 beyond month 3.
Among the 26 kidney recipients with surgical complications, 3 subjects lost their graft due to vascular thrombosis (days 1, 7, 12), and 2 subjects had graft loss (on days 91 and 97) after experiencing wound infection/dehiscence (days 33 and 20, respectively) and ureteral leak (days 46 and 20, respectively). (The first subject later died due to pulmonary infection on day 179.) The other subjects are currently doing well except for 2 subjects who lost their graft on days 879 and 1218 due to acute rejection and acute myocardial infarction, respectively.

Liver Recipients—43 (34%) liver recipients experienced 62 surgical complications within the first year post-transplant. The surgical complications were 14 re-explorations, 4 perioperative cardiac complications, 9 wound infections/dehiscence, 6 hepatic artery thromboses, 2 portal vein thromboses, 7 biliary leaks, 15 biliary strictures (first 3 months) and 5 incisional hernias (Table 2). Of the 62 surgical complications, 45 occurred in month 1, 12 in month 2 or 3, and 5 beyond month 3.

Association of Surgical Complications with Graft Loss and Death—In univariate models, re-exploration in liver recipients was significantly associated with increased risk of death [HR: 2.8; 95% CI: 1.2-6.5; p=0.01] (Table 3). Re-exploration in liver recipients was significantly associated with increased risk of graft loss [HR: 2.3; 95% CI: 1.0-5.1; p=0.046]; biliary leak was marginally associated with increased risk [HR: 2.6; 95% CI: 0.9-7.4; p=0.07] (Table 4). In the multivariate analysis adjusted for other potential risk factors, re-exploration was marginally associated [HR: 2.8; 95% CI: 1.0-8.4; p=0.06] with increased risk of graft loss; biliary leak lost its marginal significance [HR: 1.6; 95% CI: 0.4-6.3; p=0.48]. Of the 6 liver recipients with hepatic artery thrombosis, 4 lost their graft. No other significant associations were identified (Table 3 and 4).

Impact of Baseline Morbidity Predictors on Surgical Complications—In univariate proportional hazards models, higher MELD pre-transplant [HR: 1.07 per point increase; 95% CI: 1.01-1.14; p=0.02] was significantly associated with increased risk of wound infection/dehiscence in liver recipients; detectable VL pre-TX was marginally associated with increased risk [HR:3.6; 95% CI: 0.9-14.6; p=0.07]. No other associations were identified.

Discussion and Conclusions

Discussion

There is mounting evidence to support the safety and effectiveness of solid organ transplantation in HIV infected recipients. This report from the largest prospective multicenter trial shows the rate of surgical complications in this patient population is similar to published data in non-HIV infected kidney and liver recipients (Table 2). Also, follow-up data for patient and graft survival rates of both populations are similar to earlier data previously published. The similar rates of surgical complications observed in this patient population strengthen the assertion that solid organ transplantation is safe in HIV-infected recipients, and combined with the follow-up data on patient and graft survival, makes a strong argument for inclusion of those patients on lists for kidney and liver transplantation. Notably, the rates of wound complications including infection and dehiscence are equal to or less than published rates in non-HIV infected patients, providing further evidence that co-morbidities of HIV infection and concurrent treatment with immunosuppression therapy do not significantly increase the incidence of these complications.

Our comparison of the rates of surgical complications in HIV infected transplant recipients to those rates published for non-HIV infected recipients suggests that solid organ transplantation is safe in this carefully selected group. However, the comparison group of non-HIV infected recipients may have different baseline morbidity factors than the HIV infection.
infected group, given that the HIV infected recipients were carefully selected for transplantation. Since the HIV infected recipients may have less comorbidity than the comparison group and we have no matched control group, we cannot conclude that the lower rates of some complications in the HIV infected group indicate that transplantation is in fact safer in this group. We can conclude, however, that in this group of HIV infected recipients, the rates of common surgical complications were not higher than those expected for non-HIV infected recipients, suggesting that HIV infection alone should not be a contraindication for solid organ transplantation.

For kidney transplant recipients, no surgical complications were significantly associated with graft loss. For liver transplant recipients, only re-exploration was associated with increased risk of graft loss with a hazard ratio of 2.8 in the multivariate model (95% CI: 1.0-8.4; p=0.06). All other surgical complications measured were not significantly associated with graft loss. Despite the theoretic concerns that the immunodeficient state associated with HIV would compromise the ability to tolerate a surgical complication, this cohort of selected HIV positive transplant recipients were not adversely effected by the immunosuppressive requirements for transplantation. Although hepatic artery thrombosis, of which there were 6 occurrences in this cohort, did not reach statistical significance due to the small number of events, four (66%) of those patients lost their graft. This is consistent with the severity and poor prognosis associated with this complication. It could be speculated that the slightly higher rate of hepatic artery thrombosis observed in the study cohort, as compared to the historic rates observed in the HIV uninfected liver recipients, could be associated with a hypercoaguable state. However, a higher frequency of renal artery thrombosis was not observed in the cohort of HIV infected kidney transplant recipients.

The only baseline factor significantly associated with any of the observed surgical complications was higher MELD score pre-transplant, which was significantly associated with an increased risk of wound infection or dehiscence (HR:1.07; p=0.02) in liver transplant recipients. This is consistent with the deconditioned state associated with higher MELD scores. Notably, detectable HIV viral load pre-transplant was marginally associated with increased risk of wound infection/dehiscence, but did not reach statistical significance (HR:3.64; p=0.07). In this study, the association identified with increased risk of wound infection is of unknown relevance due to the small sample size, and was of borderline significance (p=0.07). The inability to suppress viral load to undetectable levels may be a surrogate marker for impaired physiologic response contributing to wound infection/complications. As this is a potentially modifiable selection criteria, this should be further evaluated in future analyses. These findings should alleviate fears that co-morbidities associated with HIV infection will lead to excessive rates of surgical complications in HIV-infected patients undergoing liver or kidney transplant.

In conclusion, this study lends further evidence that solid organ transplantation in selected HIV-infected patients is both safe and effective. The rates of common post-transplantation surgical complications are similar to those observed in the non-HIV infected population. Furthermore, the HIV positive recipients were generally able to tolerate treatment for these complications without compromising graft survival. Increasing awareness that HIV infection is no longer an absolute contraindication for kidney or liver transplantation, and continued multicenter research on the safety and efficacy of transplantation in this population will lead to better treatment of end-stage kidney and liver disease among HIV+ patients.
Acknowledgments

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References


### Table 1

Three-month, one-year and three-year Kaplan-Meier estimates for patient and graft survival.

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Patient Survival</th>
<th>Graft Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Kidney</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-month</td>
<td>99% (CI 95,100)</td>
<td>96% (CI 91,98)</td>
</tr>
<tr>
<td>1-year</td>
<td>95% (CI 90,98)</td>
<td>91% (CI 85,94)</td>
</tr>
<tr>
<td>3-year</td>
<td>91% (CI 85,95)</td>
<td>76% (CI 67,83)</td>
</tr>
<tr>
<td><strong>Liver</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-month</td>
<td>94% (CI 89,97)</td>
<td>91% (CI 85,95)</td>
</tr>
<tr>
<td>1-year</td>
<td>80% (CI 72,86)</td>
<td>77% (CI 69,84)</td>
</tr>
<tr>
<td>3-year</td>
<td>67% (CI 57,75)</td>
<td>62% (CI 52,71)</td>
</tr>
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</table>
Surgical complication rates in HIV+ liver transplant and kidney transplant recipients compared to published rates in non-HIV infected patients

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraoperative death</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Re-exploration post-tx</td>
<td>7 (5%)</td>
<td>14 (11%)</td>
<td>11.5% 9</td>
<td></td>
</tr>
<tr>
<td>Perioperative cardiac complications</td>
<td>3 (2%)</td>
<td>4 (3%)</td>
<td>5.6% 10</td>
<td>4.5% 11</td>
</tr>
<tr>
<td>Wound infections/wound dehiscence</td>
<td>6 (4%)</td>
<td>9 (7%)</td>
<td>2.5% 12, 13</td>
<td>9% 14</td>
</tr>
<tr>
<td>Ureteral [K] / Biliary [L] leak</td>
<td>3 (2%)</td>
<td>7 (6%)</td>
<td>1.7% 15-17</td>
<td>1.25% 18, 19</td>
</tr>
<tr>
<td>Ureteral [K] / Biliary [L, first 3 months] stricture</td>
<td>2 (1%)</td>
<td>15 (12%)</td>
<td>1.6% 15-17</td>
<td>3-14% 20</td>
</tr>
<tr>
<td>Incisional Hernias</td>
<td>2 (1%)</td>
<td>5 (4%)</td>
<td>4% 13</td>
<td>5% 21</td>
</tr>
<tr>
<td>Lymphoceles [K]</td>
<td>3 (2%)</td>
<td>N/A</td>
<td>1.26% 22</td>
<td></td>
</tr>
<tr>
<td>Vascular Thrombosis Resulting in Graft Loss [K]</td>
<td>3 (2%)</td>
<td>N/A</td>
<td>0.3-6.1% 23</td>
<td></td>
</tr>
<tr>
<td>Hepatic Artery Thrombosis [L]</td>
<td>N/A</td>
<td>6* (5%)</td>
<td>2.8% 24</td>
<td></td>
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<tr>
<td>Portal Vein Thrombosis [L]</td>
<td>N/A</td>
<td>2 (2%)</td>
<td>0.3-2.2% 25</td>
<td></td>
</tr>
</tbody>
</table>

* Led to graft loss in 4 cases.
Table 3

Univariate Proportional Hazards Regression Models for Death

<table>
<thead>
<tr>
<th>Univariate Predictor</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Re-exploration (kidney) §</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Re-exploration (liver)</td>
<td>2.8 (1.2-6.5)</td>
<td>0.01</td>
</tr>
<tr>
<td>Wound infection / dehiscence (liver)</td>
<td>1.4 (0.5-3.9)</td>
<td>0.54</td>
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<tr>
<td>Biliary leak (liver)</td>
<td>1.8 (0.6-5.9)</td>
<td>0.33</td>
</tr>
<tr>
<td>Biliary stricture (liver)</td>
<td>1.7 (0.7-4.0)</td>
<td>0.24</td>
</tr>
</tbody>
</table>

§ Model did not converge
### Table 4

Univariate Proportional Hazards Regression Models for Graft Loss

<table>
<thead>
<tr>
<th>Univariate Predictor</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Re-exploration (kidney)</td>
<td>0.7 (0.1-4.9)</td>
<td>0.70</td>
</tr>
<tr>
<td>Re-exploration (liver)</td>
<td>2.3 (1.0-5.1)</td>
<td>0.046</td>
</tr>
<tr>
<td>Wound infection / dehiscence (liver)</td>
<td>1.2 (0.4-3.3)</td>
<td>0.75</td>
</tr>
<tr>
<td>Biliary leak (liver)</td>
<td>2.6 (0.9-7.4)</td>
<td>0.07</td>
</tr>
<tr>
<td>Biliary stricture (liver)</td>
<td>1.7 (0.8-3.9)</td>
<td>0.18</td>
</tr>
</tbody>
</table>