ORIGINAL ARTICLE

Outcomes of Kidney Transplantation in HIV-Infected Recipients

Peter G. Stock, M.D., Ph.D., Burc Barin, M.S., Barbara Murphy, M.D., Douglas Hanto, M.D., Ph.D., Jorge M. Diego, M.D., Jimmy Light, M.D., Charles Davis, M.D., Emily Blumberg, M.D., David Simon, M.D., Ph.D., Aruna Subramanian, M.D., J. Michael Millis, M.D., G. Marshall Lyon, M.D., Kenneth Brayman, M.D., Doug Slakey, M.D., Ron Shapiro, M.D., Joseph Melancon, M.D., Jeffrey M. Jacobson, M.D., Valentina Stosor, M.D., Jean L. Olson, M.D., Donald M. Stablein, Ph.D., and Michelle E. Roland, M.D.

ABSTRACT

BACKGROUND

The outcomes of kidney transplantation and immunosuppression in people infected with human immunodeficiency virus (HIV) are incompletely understood.

METHODS

We undertook a prospective, nonrandomized trial of kidney transplantation in HIV-infected candidates who had CD4+ T-cell counts of at least 200 per cubic millimeter and undetectable plasma HIV type 1 (HIV-1) RNA levels while being treated with a stable antiretroviral regimen. Post-transplantation management was provided in accordance with study protocols that defined prophylaxis against opportunistic infection, indications for biopsy, and acceptable approaches to immunosuppression, management of rejection, and antiretroviral therapy.

RESULTS

Between November 2003 and June 2009, a total of 150 patients underwent kidney transplantation; survivors were followed for a median period of 1.7 years. Patient survival rates (±SD) at 1 year and 3 years were 94.6±2.0% and 88.2±3.8%, respectively, and the corresponding mean graft-survival rates were 90.4% and 73.7%. In general, these rates fall somewhere between those reported in the national database for older kidney-transplant recipients (≥65 years) and those reported for all kidney-transplant recipients. A multivariate proportional-hazards analysis showed that the risk of graft loss was increased among patients treated for rejection (hazard ratio, 2.8; 95% confidence interval [CI], 1.2 to 6.6; P=0.02) and those receiving antithymocyte globulin induction therapy (hazard ratio, 2.5; 95% CI, 1.1 to 5.6; P=0.03); living-donor transplants were protective (hazard ratio, 0.2; 95% CI, 0.04 to 0.8; P=0.02). A higher-than-expected rejection rate was observed, with 1-year and 3-year estimates of 31% (95% CI, 24 to 40) and 41% (95% CI, 32 to 52), respectively. HIV infection remained well controlled, with stable CD4+ T-cell counts and few HIV-associated complications.

CONCLUSIONS

In this cohort of carefully selected HIV-infected patients, both patient- and graft-survival rates were high at 1 and 3 years, with no increases in complications associated with HIV infection. The unexpectedly high rejection rates are of serious concern and indicate the need for better immunotherapy. (Funded by the National Institute of Allergy and Infectious Diseases; ClinicalTrials.gov number, NCT00074386.)

From the University of California, San Francisco, San Francisco (P.G.S., J.L.O., M.E.R.); EMMES Corporation, Rockville, MD (B.B., D.M.S.); Mount Sinai School of Medicine, New York (B.M.); Beth Israel Deaconess Medical Center, Boston (D.H.); University of Miami School of Medicine, Miami (J.M.D.); Washington Hospital Center (J.L.) and Georgetown University (J.M.) — both in Washington, DC; the University of Maryland (C.D.) and Johns Hopkins University School of Medicine (A.S.) — both in Baltimore; the University of Pennsylvania (E.B.) and Drexel University College of Medicine (J.M.J.) — both in Philadelphia; Rush University Medical Center (D.S.), the University of Chicago (J.M.M.), and Northwestern University (V.S.) — all in Chicago; Emory University, Atlanta (G.M.L.); the University of Virginia, Charlottesville (K.B.); Tulane Medical Center, New Orleans (D.S.); and the University of Pittsburgh, Pittsburgh (R.S.). Address reprint requests to Dr. Stock at the University of California, San Francisco, 505 Parnassus Ave., M-884, Box 0116, San Francisco, CA 94143-0116, or at peter.stock@ucsfmedctr.org.

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An increasing number of persons living with human immunodeficiency virus (HIV) infection who have end-stage renal disease (ESRD) are seeking renal transplantation. Despite the efficacy of highly active antiretroviral therapy (HAART) in reducing the risk of HIV-related renal disease, the incidence of ESRD continues to increase among patients with HIV infection.[1-5] In the United States and Europe, nearly 1% of patients with ESRD are infected with HIV, and HIV-associated nephropathy is the third most common cause of ESRD among blacks in the United States who are between 20 and 64 years of age.[6-9] We conducted a multicenter, prospective trial to examine the safety and efficacy of transplantation in this population.

METHODS

In this nonrandomized trial, 150 HIV-infected kidney-transplant recipients were followed for up to 3 years at 19 U.S. transplantation centers. The research protocol was approved and monitored by the institutional review boards at all participating centers, and each patient provided written informed consent.

PATIENTS

Patients had CD4+ T-cell counts of at least 200 cells per cubic millimeter and undetectable plasma HIV type 1 (HIV-1) RNA levels (<50 copies per milliliter) on ultrasensitive polymerase-chain-reaction assay (Amplicor HIV-1 Monitor, Roche) or <75 copies per milliliter on viral-load assay (bDNA Versant 3.0, Bayer) while receiving stable HAART in the 16 weeks before transplantation. Patients also met standard, center-specific transplant criteria (for details, see the Supplementary Appendix, available with the full text of this article at NEJM.org). Patients with previously treated opportunistic complications, with the exception of progressive multifocal leukoencephalopathy, chronic intestinal cryptosporidiosis, primary central nervous system lymphoma, and visceral Kaposi's sarcoma, were eligible.

INTERVENTIONS

Kidneys from both deceased and living donors were used. Initial immunosuppressive therapy included glucocorticoids, cyclosporine or tacrolimus, and mycophenolate mofetil. Sirolimus was used in patients with calcineurin-inhibitor–associated nephrotoxicity. Antibody induction therapy with an interleukin-2–receptor blocker, antithymocyte globulin, or both was permitted. These decisions were made at the discretion of the treating provider (Table 1).

There were no absolute HAART restrictions (see the Supplementary Appendix). In most cases, patients continued their pretransplantation antiretroviral regimen. Doses of renally administered drugs depended on the level of kidney function, with frequent adjustments in the early post-transplantation period and during periods of graft dysfunction. Potential nephrotoxicity of antiretroviral agents and agents used to prevent opportunistic infection was considered, and medications were changed as indicated.

Prophylaxis against opportunistic infection included lifelong therapy to prevent *Pneumocystis jiroveci* pneumonia, fluconazole for antifungal prophylaxis, and valganciclovir or ganciclovir to prevent cytomegalovirus infection (depending on the infection status of both the recipient and the donor). Macrolide prophylaxis against *Mycobacterium avium* complex was required when the CD4+ T-cell count dropped below 75 cells per cubic millimeter. Patients with prior opportunistic infections continued to receive secondary prophylaxis on the basis of the CD4+ T-cell count, according to national guidelines, and for 1 month after transplantation or rejection therapy.[10]

To be eligible for kidney transplantation alone, patients with hepatitis B virus and hepatitis C virus (HCV) coinfection had to undergo a liver biopsy that showed no cirrhosis (defined as stage 2 fibrosis or higher). Patients with hepatitis B coinfection had to have undetectable hepatitis B virus surface antigen while receiving stable antiviral therapy. Patients coinfected with HCV were advised about the potential immunostimulatory effects of post-transplantation interferon therapy and could elect pretransplantation interferon treatment.

MEASUREMENTS AND OUTCOMES

Patients were evaluated before transplantation and then 13 times during the first year after transplantation, every 3 months during post-transplantation years 2 and 3, and every 6 months during years 4 and 5. At baseline, data on demographic characteristics, medical history, donor type, and donor–recipient immunologic measures were collected. Data on the use of immunosuppressant and antiretroviral medications, trough immunosuppressant levels, plasma HIV-1 RNA levels, and CD4+ T-cell counts were collected longitudinally.

Patient survival and graft survival were the primary outcomes. Secondary outcomes included opportunistic complications, changes in the CD4+ T-cell count, and detectable plasma HIV-1 RNA levels. Allograft biopsies were performed for clinical indications, and rejection was defined according to the Banff classification. Rejection episodes required biopsy confirmation. Approximately 80%

Table 1. Baseline Characteristics of Allograft Donors and of 150 HIV-Infected Kidney-Transplant Recipients and Post-Transplantation Characteristics.*

Characteristic	Value
Donor at baseline	
Age — yr	
Median	41
Interquartile range	27–49
Six-antigen–matched kidney — no. (%)	21 (14)
Deceased — no. (%)	102 (68)
Expanded criteria — no. (%)†	18 (18)
High infectious risk — no. (%)	31 (30)
Recipient at baseline	
Age — yr	
Median	46
Interquartile range	40–51
Male sex — no. (%)	117/150 (78)
Race or ethnic group — no. (%)‡	
White	42/150 (28)
Black	103/150 (69)
Other	5/150 (3)
Cause of disease — no. (%)§	
Hypertension	38/150 (25)
HIV-associated nephropathy	36/150 (24)
Diabetic nephropathy or glomerulosclerosis	13/150 (9)
Focal glomerulosclerosis	9/150 (6)
Unknown or other cause	54/150 (36)
Prior opportunistic complication — no. (%)¶	36/150 (24)
CD4+ count — per mm^3‖	
Median	524
Interquartile range	385–672
Viral hepatitis — no. (%)	
Hepatitis C RNA detectable	28/150 (19)
Hepatitis B surface antigen–positive	5/150 (3)
HAART regimen — no. (%)**	
Protease-inhibitor–based	63/150 (42)
NNRTI-based	59/150 (39)
Protease-inhibitor–based and NNRTI-based	15/150 (10)
Nucleoside analogues only	5/150 (3)
Raltegravir-based	6/150 (4)
None	2/150 (1)

Table 1. (Continued.)

Characteristic	Value
Recipient after transplantation	
Immunosuppression at 1 wk — no. (%)	
Tacrolimus	99/150 (66)
Cyclosporine	33/150 (22)
Mycophenolate mofetil	131/150 (87)
Basiliximab or daclizumab induction	76/150 (51)
Antithymocyte globulin induction	48/150 (32)
Cyclosporine trough level — ng/ml	
At 1 mo	
Median	176
Interquartile range	118–246
At 1 yr	
Median	127
Interquartile range	106–142
Tacrolimus trough level — ng/ml	
At 1 mo	
Median	9.1
Interquartile range	6.0–11.9
At 1 yr	
Median	7.2
Interquartile range	5.5–9.1

* HAART denotes highly active antiretroviral therapy, and NNRTI nonnucleoside reverse-transcriptase inhibitor.
† These criteria indicate that the donor organ is at higher risk for graft loss due to organ quality.
‡ Race was self-reported.
§ Biopsy confirmation was available for 21% of the patients: 78% of those with focal glomerulosclerosis and less than 30% of those with other diagnoses.
¶ The most common opportunistic complications before transplantation were *Pneumocystis jiroveci* pneumonia, cytomegalovirus-associated retinitis, *Mycobacterium avium* complex, and Kaposi's sarcoma.
‖ The pretransplantation CD4+ count was obtained within 16 weeks before transplantation.
** The protease inhibitor–based regimen, NNRTI-based regimen, protease-inhibitor–based and NNRTI-based regimen, and nucleoside analogues–only combinations included at least two nucleoside analogues (except for eight that included a single nucleoside analogue) and did not include raltegravir or maraviroc. Of the six raltegravir-based combinations, two included maraviroc and a protease-inhibitor–based regimen, and the rest included an NNRTI-based regimen in addition to raltegravir.

of the biopsy specimens were reviewed by a central pathologist. The last follow-up date for each outcome was the last visit before July 8, 2009. For the outcome of graft survival, we used the date of the patient's return to dialysis or death.

STATISTICAL ANALYSIS

Estimated rates of patient survival, graft survival, and graft rejection over a period of 3 years were calculated with the Kaplan–Meier method, and 95% confidence intervals were estimated by means of Greenwood's formula. Survival estimates were compared with the U.S. Scientific Registry of Transplant Recipients (SRTR) results. Study results were compared with SRTR data for all kidney-transplant recipients and also for kidney-transplant recipients 65 years of age or older (who are offered transplantation selectively because they are at increased risk for graft loss or death). One-year patient-survival and graft-survival rates were prospectively monitored with a closed sequential probability ratio test, with error rates of 0.05; for trial continuation, results had to be within 12% of the results for recipients 65 years of age or older in the national database. The log-rank test was used to compare survival esti-

mates between patients with and those without HCV infection, patients who did and those who did not receive antithymocyte globulin induction therapy within 1 week after transplantation, and patients with a diagnosis of HIV-associated nephropathy versus those with all other causes of ESRD. Multivariate proportional-hazards modeling was performed.

At years 1 and 3, changes from baseline in CD4+ T-cell counts and changes in the estimated glomerular filtration rate (GFR) (measured with the use of the abbreviated Modification of Diet in Renal Disease equation) from the value at 3 months were analyzed with the use of the Wilcoxon signed-rank test. The rank-sum test was used to compare the estimated GFR in patients with and those without rejection. Negative binomial regression was used to compare the number of serious infections per follow-up year in two subgroups: patients with HCV infection and those who received antithymocyte globulin induction therapy during the first week after transplantation.

A two-sided P value of less than 0.05 was considered to indicate statistical significance. Statistical analyses were performed with the use of SAS software, version 9.2 (SAS Institute) (see the Supplementary Appendix).

RESULTS

PATIENT AND DONOR CHARACTERISTICS

We enrolled 150 patients in the study from November 2003 through June 2009. Survivors were followed for a median of 1.7 years (interquartile range [IQR], 0.7 to 3.0). One patient withdrew consent at 6 months. At the time of analysis, 53 patients had completed at least 3 years of follow-up. Recipient and donor characteristics, pretransplantation HAART regimens, and initial induction and maintenance immunosuppressive regimens are presented in Table 1. Antiretroviral therapy was withheld immediately after transplantation in 54 patients (36%). HAART was restarted within a week after transplantation in 46 patients and between 1 and 3 weeks after transplantation in the remaining 8 patients.

PATIENT AND GRAFT SURVIVAL

Patient survival rates (±SD) at 1 year and 3 years were 94.6±2.0% and 88.2±3.8%, respectively (Fig. 1). The 1-year and 3-year graft-survival rates were 90.4% and 73.7%, respectively. Patient- and graft-survival rates were generally between those reported in the SRTR database for older kidney-transplant recipients (≥65 years) and for all kidney-transplant recipients during a similar time frame (Table 2 and Fig. 1).

A total of 11 patients died: 3 from cardiac causes, 2 each from sepsis and pulmonary infection, 2 from renal-cell carcinoma in the native kidneys, and 2 from unknown causes. The graft was still functioning at the time of death in 8 patients. An additional 13 grafts failed owing to chronic rejection or chronic allograft nephropathy (5 grafts), vascular thrombosis (3 grafts), acute rejection (3 grafts), technical reasons (1 graft), and nonadherence to medical therapy (1 graft).

Univariate proportional-hazards models showed that an increased risk of graft loss was potentially associated with treated rejection (hazard ratio, 3.0; 95% confidence interval [CI], 1.3 to 7.1; P=0.01), antithymocyte globulin induction (hazard ratio, 2.1; 95% CI, 0.9 to 4.6; P=0.08), and delayed graft function (hazard ratio, 2.1; 95% CI, 1.0 to 4.8; P=0.07); the use of a graft from a living donor was protective (hazard ratio, 0.2; 95% CI, 0.04 to 0.70; P=0.02). In the multivariate proportional-hazards model, an increased risk of graft loss was associated with treated rejection (hazard ratio, 2.8; 95% CI, 1.2 to 6.6; P=0.02), and antithymocyte globulin induction (hazard ratio, 2.5; 95% CI, 1.1 to 5.6; P=0.03). The use of a graft from a living donor was protective (hazard ratio, 0.2; 95% CI, 0.04 to 0.80; P=0.02).

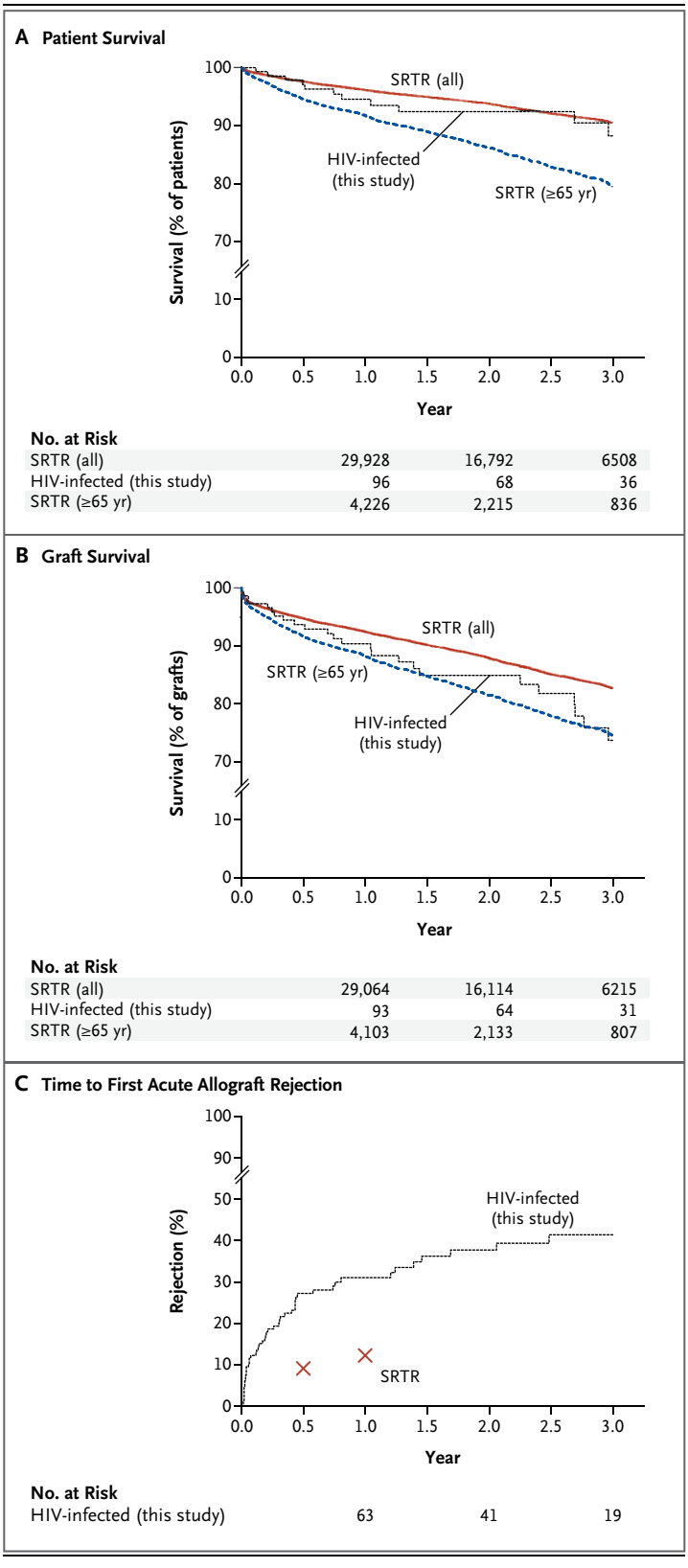
Figure 2 shows the patient- and graft-survival curves according to whether the patient was infected with HCV. The risks of death and of graft loss were marginally higher for patients who received antithymocyte globulin induction therapy than for those who did not (P=0.06 and P=0.07, respectively, by the log-rank test). When patients with a baseline diagnosis of HIV-associated nephropathy were compared with those who had ESRD from other causes, there were no significant differences in the 1-year patient survival rates (96.8% and 93.9%, respectively; P=0.63 by the log-rank test) or in the 1-year graft survival rates (87.3% and 91.3%, respectively; P=0.24 by the log-rank test).

ALLOGRAFT REJECTION

Among the kidney-allograft recipients, 49 (33%) had 67 acute rejection episodes. The cumulative incidence of rejection was 31% (95% CI, 24 to 40)

Figure 1. Kaplan–Meier Estimates of Patient and Graft Survival and First Acute Kidney-Allograft Rejection.

Rates of patient survival (Panel A) and graft survival (Panel B) were generally within those rates reported in the national Scientific Registry of Transplant Recipients (SRTR) for older kidney-transplant recipients (≥65 years) and for all kidney-transplant recipients in the United States during a similar time frame. The rate of graft survival was calculated on the basis of graft failure from any cause. The 1-year and 3-year cumulative incidences of graft rejection in the study recipients were 31% (95% confidence interval [CI], 24 to 40) and 41% (95% CI, 32 to 52), respectively. The 1-year SRTR rejection rate was estimated to be 12.3% (95% CI, 11.9 to 12.7) (Panel C).



at 1 year and 41% (95% CI, 32 to 52) at 3 years. The 1-year SRTR rejection rate was 12.3% (95% CI, 11.9 to 12.7) (Fig. 1). Figure 2 shows the time to a first acute rejection episode according to HCV infection status. There were 42 acute cellular rejection episodes (63%), 4 acute vascular rejection episodes (6%), 7 acute cellular and vascular rejection episodes combined (10%), and 4 chronic and acute rejection episodes (6%). There were 23 rejection diagnoses in patients taking cyclosporine (34%) and 38 in those taking tacrolimus (57%); 32 rejection episodes (48%) responded to glucocorticoid therapy.

For cyclosporine, the median trough level at 1 month was 171 ng per milliliter (IQR, 129 to 209) for patients who entered the study during the first half of the enrollment period and 234 ng per milliliter (IQR, 93 to 358) for those who entered during the second half. For tacrolimus, the corresponding median trough levels at 1 month were 8.6 ng per milliliter (IQR, 6.0 to 12.5) and 9.4 ng per milliliter (IQR, 6.0 to 11.8). Because HAART inhibits the cytochrome P-450 system, 28% of the patients (15% of the cyclosporine group and 31% of the tacrolimus group) received less frequent doses of these drugs (i.e., every other day or every third day).

A higher tacrolimus trough level was associated with a decreased risk of a first acute allograft rejection in the unadjusted model (hazard ratio, 0.90; 95% CI, 0.81 to 1.00; P=0.04). In the multivariate proportional-hazards model, the only variables associated with an increased risk of graft rejection were the use of a kidney from a deceased donor (hazard ratio, 2.3; 95% CI, 1.1 to 4.8; P=0.03) and cyclosporine use (hazard ratio, 2.1;

Table 2. Rates of Patient Survival and Graft Survival at 1 Year and 3 Years among HIV-Infected Kidney-Transplant Recipients (Study Patients) and Patients in the SRTR Database.*

Population	Patient Survival		Graft Survival	
	At 1 Year	At 3 Years	At 1 Year	At 3 Years
	percent (95 percent confidence interval)			
Study patients	94.6 (88.9–97.4)	88.2 (78.3–93.8)	90.4 (83.9–94.3)	73.7 (61.9–82.4)
SRTR patients				
Age ≥65 yr	91.8 (91.1–92.4)	79.5 (78.0–80.9)	88.3 (87.5–89.1)	74.4 (72.9–75.9)
Overall	96.2 (96.0–96.4)	90.6 (90.2–91.0)	92.5 (92.3–92.8)	82.8 (82.3–83.3)

* SRTR denotes Scientific Registry of Transplant Recipients.

95% CI, 1.1 to 3.9; P=0.02). A higher post-transplantation CD4+ T-cell count was marginally protective (hazard ratio per increase of 50 cells per cubic millimeter, 0.9; 95% CI, 0.9 to 1.0; P=0.07).

ALLOGRAFT FUNCTION

Delayed graft function, defined as the need for dialysis during the first week after transplantation, occurred in 15% of patients with transplants from living donors and in 46% of patients with transplants from deceased donors. The median change in the estimated GFR at years 1 and 3, as compared with the value 3 months after transplantation, was 0.0 ml per minute per 1.73 m² of body-surface area (IQR, –12.1 to 8.4; P=0.23) and –11.8 ml per minute (IQR, –26.8 to 7.2; P=0.04), respectively. Patients with rejection episodes had a significantly lower median estimated GFR than did those without such episodes at 1 year (51.8 vs. 60.5 ml per minute, P=0.05) and at 3 years (38.8 vs. 64.0 ml per minute, P=0.01).

PROGRESSION OF HIV DISEASE

There were two cases of newly diagnosed cutaneous Kaposi's sarcoma and one case each of candidal esophagitis, presumptive *P. jiroveci* pneumonia, and cryptosporidiosis. Two patients had biopsy-proven, newly diagnosed HIV-associated nephropathy in the absence of detectable virus. One of the two patients, a white recipient of a kidney from a white, related living donor, had a CD4+ T-cell count of 770 per cubic millimeter at the time of diagnosis, and the patient has continued to have excellent kidney function. The other patient was a black recipient of a kidney from a black deceased donor. At the time of diagnosis, his CD4+ T-cell count was 0, but it increased to 274 cells per cubic millimeter by 9 months. Unfortunately, kidney function continued to deteriorate in this patient.

The median change in the CD4+ T-cell count from baseline to 1 year after transplantation was significantly greater in patients who received early induction therapy with antithymocyte globulin than in those who did not (–238 vs. –135 cells per cubic millimeter, P<0.001) (Fig. 3). The corresponding median changes from baseline to 3 years after transplantation were –57 cells per cubic millimeter (IQR, –237 to 61; P=0.31) and –52 cells per cubic millimeter (IQR, –258 to 34; P=0.05), respectively. Of the 48 patients (32%) who had a detectable plasma HIV-1 RNA level at any time after transplantation, 29 had a detectable level on a single occasion; the HIV-1 RNA level was subsequently undetectable in 26 of these patients and was detectable at the time of graft loss in the other 3. Among the remaining 19 patients, there were 36 episodes of transient viremia (median peak HIV-1 RNA level, 604 copies per milliliter [IQR, 153 to 3270]). Only 1 patient had a detectable plasma HIV-1 RNA at year 3.

INFECTIONS AND HOSPITALIZATIONS

Of the 150 kidney recipients, 57 (38%) had a total of 140 reported infections that required hospitalization. Of these infections, 69% were bacterial, 9% fungal, 6% viral, and 1% protozoal. Culture was not performed or was negative for the remaining 15%. The most common organisms isolated were *Escherichia coli* (in 21 patients), enterococcus (in 17), *Staphylococcus aureus* (in 12), *S. epidermidis* (in 11), and klebsiella (in 8). The three most common sites of infection were the genitourinary tract (in 26% of cases), the respiratory tract (in 20%), and the

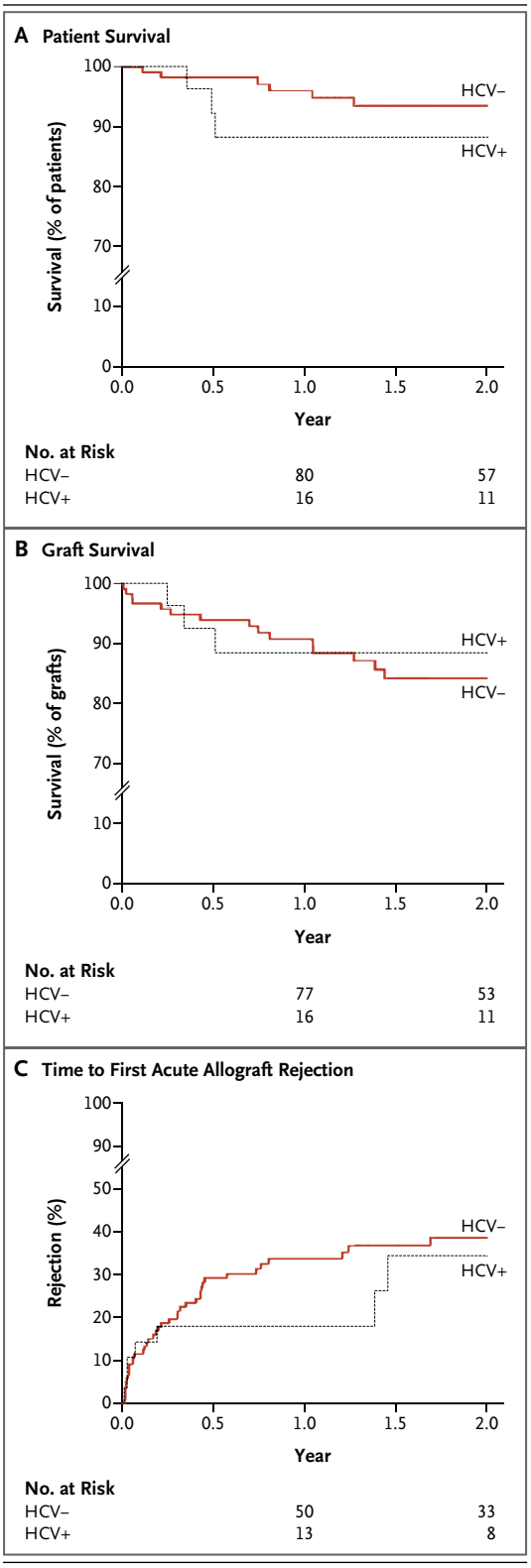


Figure 2. Kaplan–Meier Estimates of Patient and Graft Survival and First Acute Kidney-Allograft Rejection According to Presence or Absence of Hepatitis C Virus (HCV) Infection.

Panel A shows the rate of patient survival, Panel B the rate of graft survival, and Panel C the rate of rejection according to HCV status. Seven deaths occurred among 122 HCV-negative patients (6%) and 4 among 28 HCV-positive patients (14%). Among HCV-positive recipients, the 1-year product-limit estimates for patient survival and graft survival were 88.3% (95% CI, 67.9 to 96.1) and 88.6% (95% CI, 68.6 to 96.2), respectively. Among HCV-negative recipients, the corresponding estimates were 96.1% (95% CI, 90.0 to 98.5) and 90.9% (95% CI, 83.7 to 95.0). The hazard of death was marginally higher in the HCV-positive patients than in the HCV-negative patients (P=0.09 by the log-rank test) (Panel A). Time-to-event curves for graft loss (Panel B) and for graft rejection (Panel C) did not differ significantly between HCV-positive and HCV-negative patients (P=0.91 and P=0.36, respectively, by the log-rank test).

blood (in 19%). About 60% of the serious infections occurred within the first 6 months after transplantation.

Patients who tested positive for HCV infection had a higher average rate of serious infections per follow-up year than did those who tested negative (0.8 vs. 0.5, P=0.02). The patients who received antithymocyte globulin therapy in the first week had about twice as many serious infections per follow-up year as patients who did not receive such therapy (0.9 vs. 0.4, P=0.002). Five cases of polyomavirus nephropathy were reported. In addition, 212 hospitalizations were reported for reasons other than infection, about half of which were for the purpose of biopsy and diagnosis of rejection.

NEOPLASMS

Nine neoplasms were reported. In addition to the two cases of renal-cell carcinoma and two cases of Kaposi's sarcoma, there were two cases of oral squamous-cell carcinoma and one case each of squamous-cell skin cancer, basal-cell skin cancer, and cancer of the thyroid gland.

DISCUSSION

The early results of this prospective trial show that kidney transplantation is highly feasible in HIV-infected recipients. Inferences are limited by the relatively small number of patients, the short interim follow-up period, the multiple subgroups of patients, and the variations in post-transplantation antiretroviral and immunosuppressive therapies. Nonetheless, the diversity of the patient

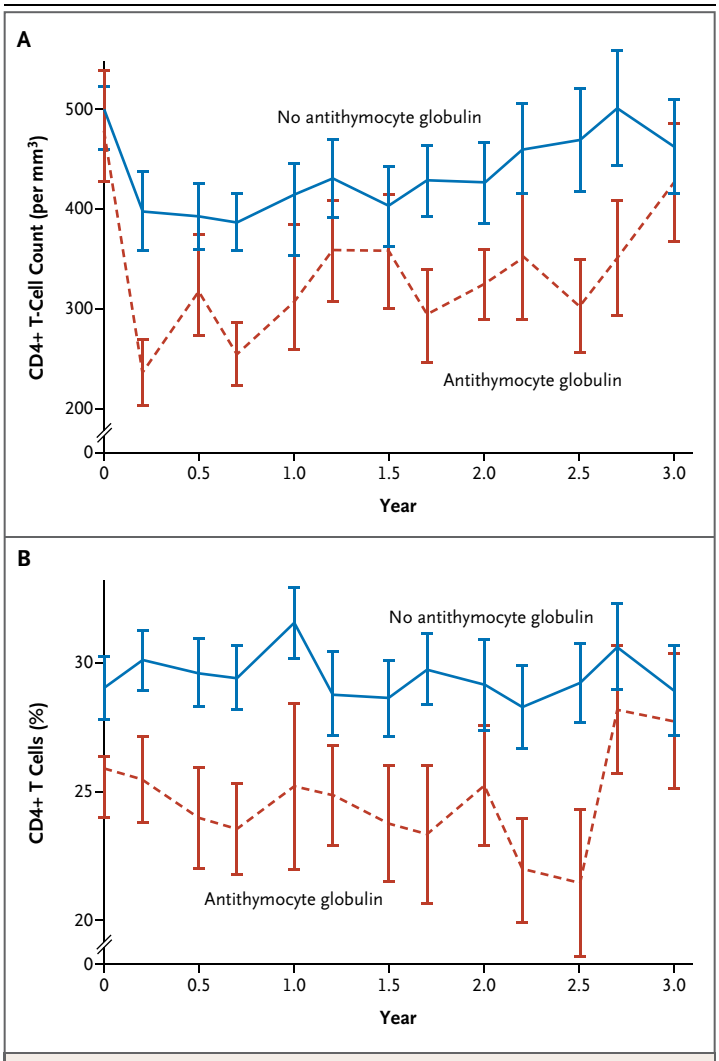


Figure 3. Changes in CD4+ T-Cell Count and Percentage of CD4+ T Cells after Transplantation, According to Antithymocyte Globulin Induction Status.

The mean (±SE) CD4+ T-cell counts and the mean (±SE) percentages of CD4+ T cells are plotted over time in Panels A and B, respectively. At year 0.2, the mean changes from baseline in numbers and percentages of CD4+ T cells were significantly greater in patients who received antithymocyte globulin induction therapy early than in those who did not ($P=0.004$ and $P=0.048$, respectively). After the initial drop, there was an increase in the CD4+ T-cell count ($P<0.001$), but the percentage of CD4+ T cells did not change significantly over time ($P=0.66$).

population and of the strategies for post-transplantation management reflects the population of candidates for transplantation and allows for an evaluation of causal factors associated with key outcomes. The rates of patient survival and graft survival at 3 years were generally between the reported rates in the national database for older kidney-transplant recipients (≥65 years of age) and for all kidney-transplant recipients. We believe that these favorable results were influenced by careful patient selection, adherence to clinical management protocols (available at www.hivtransplant.com), and close coordination among the multidisciplinary teams (including surgeons, nephrologists, nurse coordinators, pharmacologists, social workers, HIV experts, and referring primary care providers and nephrologists).

The greatest clinical challenge in this study was achieving therapeutic and nontoxic levels of the immunosuppressive drugs administered, owing to the complicated pharmacokinetic interactions of these agents with some antiretroviral agents. Nontherapeutic exposure to immunosuppressive agents may have contributed to the higher incidence of rejection. Although the 1-month trough levels of tacrolimus and cyclosporine were consistent with those in kidney-transplant recipients who do not have HIV infection, nearly one third of the HIV-infected recipients were receiving alternative dosing regimens, so their total exposure may have been considerably different. By avoiding the use of antiretroviral agents that affect cytochrome P-450-3A–metabolizing enzymes, we may achieve more therapeutic levels of calcineurin inhibitors and reduce the high incidence of allograft rejection.[11-13] The use of integrase inhibitor–based regimens may help us reach these goals.[14]

Since rejection rates were significantly increased with cyclosporine-based maintenance therapy, tacrolimus may be the calcineurin inhibitor of choice. Nonetheless, for patients coinfected with HCV, cyclosporine may be optimal on the basis of its in vitro efficacy against this virus.[15,16] Antithymocyte globulin induction therapy should be restricted to patients at very high immunologic risk for rejection.

The main finding of concern in this study, as well as in our pilot study,[17] was the unexpectedly higher rejection rates (by a factor of 2 to 3) in the HIV-infected kidney recipients, as compared with recipients who did not have HIV infection. About half these episodes were glucocorticoid-resistant, which is characteristic of aggressive rejection. Aggressive acute rejection within 6 months after transplantation suggests an inherently enhanced response to donor antigens. The subsequent gradual and steady increase in rejection despite low CD4+ T-cell counts may represent a memory response. Multiple explanations for this type of response can be hypothesized. First, HIV contains human leukocyte antigen molecules of the host, and their transmission to another host

may induce allosensitization.[18,19] Second, the homeostatic expansion of T cells in HIV infection is often coupled with the acquisition of memory phenotype, which in turn is associated with increased responsiveness of the T cell and nonspecific enhancement of alloimmunity.[20,21] Third, prior infections can lead to the generation of memory alloreactive T cells as a result of cross-reactivity.[22-29] All these potential mechanisms are being addressed in ongoing studies.

There was no evidence of accelerated HIV disease progression, despite the initial decline in the CD4+ T-cell count. HIV viremia was not precipitated by immunosuppression and, despite challenging drug interactions, continued to be well controlled. The two patients with newly diagnosed Kaposi's sarcoma were successfully treated with sirolimus, which has been reported to control human herpesvirus 8 infection.[30] Other newly diagnosed neoplasms were observed at rates consistent with kidney transplantation[31]; no cases of post-transplantation lymphoproliferative disease were seen. There was a trend toward reduced rates of survival among patients with HCV coinfection, which may be related to an increased risk of other serious infections.

In summary, kidney transplantation appears to be a feasible renal-replacement therapy in carefully selected HIV-infected patients. HIV infection has continued to be well controlled in patients with previously well-controlled HIV infection who are receiving stable antiretroviral therapy. Improved strategies for minimizing rejection and managing complex drug interactions are needed, and better control of infections in patients coinfected with HCV should continue to be explored.

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REFERENCES

1. Rao TK, Filippone EJ, Nicastri AD, et al. Associated focal and segmental glomerulosclerosis in the acquired immunodeficiency syndrome. N Engl J Med 1984; 310:669-73.
2. Pardo V, Aldana M, Colton RM, et al. Glomerular lesions in the acquired immunodeficiency syndrome. Ann Intern Med 1984;101:429-34.
3. Ross MJ, Klotman PE. Recent progress in HIV-associated nephropathy. J Am Soc Nephrol 2002;13:2997-3004.
4. Choi AI, Rodriguez RA, Bacchetti P, et al. Low rates of antiretroviral therapy among HIV-infected patients with chronic kidney disease. Clin Infect Dis 2007;45: 1633-9.
5. Fine DM, Perazella MA, Lucas GM, Atta MG. Renal disease in patients with HIV infection: epidemiology, pathogenesis and management. Drugs 2008;68:963-80.
6. Abbott KC, Trespalacios FC, Agodoa LY, Ahuja TS. HIVAN and medication use in chronic dialysis patients in the United States: analysis of the USRDS DMMS Wave 2 study. BMC Nephrol 2003;4:5.
7. Trullàs JC, Barril G, Cofan F, et al. Prevalence and clinical characteristics of HIV type 1-infected patients receiving dialysis in Spain: results of a Spanish survey in 2006: GESIDA 48/05 study. AIDS Res Hum Retroviruses 2008;24:1229-35.
8. Monahan M, Tanji N, Klotman PE. HIV-associated nephropathy: an urban epidemic. Semin Nephrol 2001;21:394-402.
9. Ahuja TS, Borucki M, Funtanilla M, Shahinian V, Hollander M, Rajaraman S. Is the prevalence of HIV-associated nephropathy decreasing? Am J Nephrol 1999;19:655-9.
10. 1999 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus. MMWR Recomm Rep 1999;48(RR-10):1-59, 61-6.
11. Frassetto L, Baluom M, Jacobsen W, et al. Cyclosporine pharmacokinetics and dosing modifications in human immunodeficiency virus-infected liver and kidney transplant recipients. Transplantation 2005;80:13-7.
12. Frassetto L, Thai T, Aggarwal AM, et al. Pharmacokinetic interactions between cyclosporine and protease inhibitors in HIV+ subjects. Drug Metab Pharmacokinet 2003;18:114-20.
13. Frassetto LA, Browne M, Cheng A, et al. Immunosuppressant pharmacokinetics and dosing modifications in HIV-1 infected liver and kidney transplant recipients. Am J Transplant 2007;7:2816-20.
14. Tricot L, Teicher E, Peytavin G, et al. Safety and efficacy of raltegravir in HIV-infected transplant patients cotreated with immunosuppressive drugs. Am J Transplant 2009;9:1946-52.
15. Firpi RJ, Zhu H, Morelli G, et al. Cyclosporine suppresses hepatitis C virus in vitro and increases the chance of a sustained virological response after liver transplantation. Liver Transpl 2006;12:51-7.
16. Watashi K, Hijikata M, Hosaka M, Yamaji M, Shimotohno K. Cyclosporin A suppresses replication of hepatitis C virus genome in cultured hepatocytes. Hepatology 2003;38:1282-8.
17. Roland MBB, Carlson L, Frassetto L, et al. HIV-infected liver and kidney transplant recipients: 1- and 3-year outcomes. In: Proceedings of the XVI International AIDS Conference, Toronto, August 13–18, 2006.
18. Langlois AJ, Weinhold KJ, Matthews TJ, Greenberg ML, Bolognesi DP. Detection of anti-human cell antibodies in sera from macaques immunized with whole inactivated virus. AIDS Res Hum Retroviruses 1992;8:1641-52.
19. Chan WL, Rodgers A, Hancock RD, et al. Protection in simian immunodeficiency virus-vaccinated monkeys correlates with anti-HLA class I antibody response. J Exp Med 1992;176:1203-7.
20. Tanchot C, Rosado MM, Agenes F, Freitas AA, Rocha B. Lymphocyte homeostasis. Semin Immunol 1997;9:331-7.
21. Wu Z, Bensinger SJ, Zhang J, et al. Homeostatic proliferation is a barrier to transplantation tolerance. Nat Med 2004; 10:87-92.
22. Adams AB, Williams MA, Jones TR, et al. Heterologous immunity provides a potent barrier to transplantation tolerance. J Clin Invest 2003;111:1887-95.
23. Brehm MA, Markees TG, Daniels KA, Greiner DL, Rossini AA, Welsh RM. Direct visualization of cross-reactive effector and memory allo-specific CD8 T cells generated in response to viral infections. J Immunol 2003;170:4077-86.

24. Welsh RM, Markees TG, Woda BA, et al. Virus-induced abrogation of transplantation tolerance induced by donor-specific transfusion and anti-CD154 antibody. J Virol 2000;74:2210-8.
25. Williams MA, Tan JT, Adams AB, et al. Characterization of virus-mediated inhibition of mixed chimerism and allospecific tolerance. J Immunol 2001;167:4987-95.
26. Williams MA, Onami TM, Adams AB, et al. Cutting edge: persistent viral infection prevents tolerance induction and escapes immune control following CD28/CD40 blockade-based regimen. J Immunol 2002;169:5387-91.
27. Yang H, Welsh RM. Induction of alloreactive cytotoxic T cells by acute virus infection of mice. J Immunol 1986;136:1186-93.
28. Yang HY, Dundon PL, Nahill SR, Welsh RM. Virus-induced polyclonal cytotoxic T lymphocyte stimulation. J Immunol 1989;142:1710-8.
29. Selin LK, Brehm MA, Naumov YN, et al. Memory of mice and men: CD8+ T-cell cross-reactivity and heterologous immunity. Immunol Rev 2006;211:164-81.
30. Stallone G, Schena A, Infante B, et al. Sirolimus for Kaposi's sarcoma in renal-transplant recipients. N Engl J Med 2005;352:1317-23.
31. Bosmans JL, Verpooten GA. Malignancy after kidney transplantation: still a challenge. Kidney Int 2007;71:1197-9.

Northern Flicker Peter Pak, M.D.