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Safety and success of kidney transplantation and concomitant immunosuppression in HIV-positive patients

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Safety and success of kidney transplantation and concomitant immunosuppression in HIV-positive patients.

Background. Human immunodeficiency virus–associated nephropathy (HIVAN) has become the third leading cause of end-stage renal disease (ESRD) in African Americans, and is expected to grow exponentially. Highly active antiretroviral therapy (HAART) has significantly prolonged the survival of patients with HIV infection. Despite the growing number of HIV-positive dialysis patients with prolonged life expectancy, kidney transplantation with immunosuppression has been declined because it is considered a waste of scarce donor kidneys due to potential increases in morbidity and mortality.

Methods. The institutional review board of Drexel University College of Medicine and Hahnemann University Hospital approved this prospective study. The aim was to find out safety and success of kidney transplantation, and the effect of immunosuppression on HIV infection. Forty HIV-positive dialysis patients received kidney transplantation between February 2001 and January 2004. Patient inclusion criteria were maintenance of HAART, plasma HIV-1 RNA of <400 copies/mL, absolute CD4 counts of 200 cells/μL or more. Immunosuppression was basiliximab induction and maintenance with cyclosporine, sirolimus, and steroids. HAART was continued post-transplant. Acute rejections were diagnosed by biopsy and treated with methylprednisolone. Surveillance biopsies were completed at 1, 6, 12, and 24 months, and evaluated for subclinical acute rejection, chronic allograft nephropathy, and HIVAN.

Results. One- and 2-year actuarial patient survival was 85% and 82%, respectively, and graft survival was 75% and 71%, respectively. Plasma HIV-1 RNA remained undetectable, and CD4 counts remained in excess of 400 cells per μL with no evidence of AIDS for up to 2 years.

Conclusion. One- and 2-year graft survival is comparable to other high-risk populations receiving kidney transplantation. One- and 2-year patient survival is higher than HIV patients maintained on dialysis. Immunosuppression does not adversely affect HIV recipients maintained on HAART in the short term.

Key words: kidney transplant, HIV positive status, immunosuppression.

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Before the highly active antiretroviral therapy (HAART) era, HIV was one of the top 10 causes of death among adults younger than 44 years old [1]. HAART has significantly reduced the mortality, and prolonged the life expectancy of HIV-positive patients, and 5% to 10% of HAART-maintained patients develop HIV-associated nephropathy (HIVAN) and end-stage renal disease (ESRD). HIVAN has become the third leading cause of ESRD among young African Americans in the United States [2, 3]. Until recently, chronic dialysis was the only form of treatment available for these patients. Kidney transplantation was not considered an option for fear of increased morbidity and mortality due to therapeutic immunosuppression. The allocation of cadaver kidneys to these patients was also considered improper due to expected inferior patient graft survival [4, 5]. This study was initiated to determine the safety and success of kidney transplantation as an alternative to dialysis and to improve the quality of life in HIV-positive ESRD patients, and to evaluate the effect of chronic immunosuppression on the HIV status.

METHODS

Patient selection and institutional approval

The institutional review board of Drexel University College of Medicine and Hahnemann University Hospital (Tenet facility) approved a protocol for kidney transplantation in HIV-positive dialysis patients in February 2001. Forty HIV patients with ESRD were transplanted between February 2001 and January 2004. The first 10 patients were transplanted under the IRB-approved protocol, and the remaining 30 patients were transplanted as standard of care following the same protocol. Selection criteria required that patients be adherent to dialysis treatment and HAART, have plasma HIV-1 RNA <400 copies/mL, and absolute CD4 count of ≥200 cells/μL of blood, were able to sign informed consent, and recommended by their treating nephrologists, dialysis social worker, and infectious disease specialist. All patients

were evaluated according to standard pretransplant criteria [6, 7]. This study was entirely funded by the clinical revenue of the authors from the transplant program, and no external funding was obtained.

Immunosuppression protocols

Immunosuppression consisted of basiliximab induction and maintenance cyclosporine, sirolimus, and prednisone. Basiliximab, 20mg, was infused on the day of transplant and on postoperative day 4. Cyclosporine, modified, and sirolimus were initiated orally on day 1. Cyclosporine doses were adjusted to obtain trough blood levels of 150 to 200 ng/mL of whole blood. Sirolimus doses were adjusted to a goal trough level of 5 to 10 ng/mL. Cyclosporine and sirolimus levels were measured by monoclonal antibody method and high-performance liquid chromatography-mass spectrometry (HPLC-MS) method, respectively [8, 9]. Steroids were given as 250 mg of intravenous methylprednisolone on the day of transplantation, 125 mg on day 1, and converted to 30 mg of oral prednisone tapered by 5 mg weekly and maintained at 5 mg/day.

Surveillance biopsy

All recipients underwent surveillance biopsies at 1, 6, 12, and 24 months after transplantation. Renal tissue was stained with hematoxylin and eosin, trichrome, and Jones silver stain. Biopsies were scored for acute and chronic allograft nephropathy according to Banff 1997 criteria [10]. Biopsies were assessed for HIVAN, infection, and recurrent/de novo disease [11]. Subclinical acute rejection (SCAR) was defined as clinically stable kidney function with pathologic signs of acute rejection in protocol biopsy [abstract; Kumar MSA et al, *Transplantation* 74:487, 2002].

Diagnosis and treatment of acute rejection and subclinical acute rejection

Acute rejection was diagnosed by persistent elevation of serum creatinine by 15% or more above baseline and confirmed by biopsy. Acute and subclinical rejections were treated with intravenous methylprednisolone, 250 mg daily for 3 days. Lymphocyte depleting antibodies were not used for treatment of rejection. Steroid-resistant antibody-mediated rejections were treated with intravenous immune globulin and/or 1 dose of 375 mg/m^2 of rituximab.

Infection prophylaxis

Infection prophylaxis was ganciclovir or valgancyclovir for cytomegalovirus, trimethoprim/sulfamethoxazole or dapsone for *Pneumocystis carinii*, and nystatin for oral and esophageal thrush for 200 days after transplantation.

Table 1. Recipient and donor characteristics

Recipient and donor characteristics	Number of patients
Number of recipients	40
Male gender	37
African American race	39
Mean age ± SD	46 ± 6
Mean body mass index	25.4 ± 2.2
Pretransplant diabetes mellitus	2
Cause of end-stage renal disease	
Hypertension	18
HIVAN	10
HIVAN and hypertension	3
Unknown cause	3
Type 1 diabetes mellitus	1
Adult polycystic kidney disease	1
Mesangioproliferative glomerulonephritis	1
Donor source	
Cadaver donor	36
Living donor	4
Cadaver donor characteristics	
History of drug abuse	8
Alternative lifestyle	3
Expanded criteria donors	8
Common cadaver donor pool	17

Post-transplant monitoring and HAART therapy

A multidisciplinary transplant team performed outpatient surveillance. Post-transplant monitoring included serial measurements of serum creatinine, calculated creatinine clearance, liver function tests, and complete blood counts every month. Urine was tested for proteinuria and infection every 2 months. All patients continued their HAART regimens. Post-transplant monitoring of HIV status included monthly measurement of plasma HIV-1 RNA copies and absolute CD4 lymphocyte count. Persistent increases in viral copies were investigated for HIV drug resistance, and treated by a change in the HAART regimen [12].

Statistical methods

Computerized SPSS system (Chicago, IL, USA) was used for statistical analysis, and actuarial patient and graft survival by Kaplan-Meier estimate.

RESULTS

Between February 2001 and January 2004 40 HIV-positive dialysis patients received kidney transplants. Recipient and donor characteristics are listed in Table 1.

Patient and graft survival

All recipients completed 6 months after transplantation; 35 (87%) patients completed 12 months, and 15 patients (37%) 24 months or more post-transplantation. The median and mean follow-up was 19.2 months and 20.4 months, respectively. One- and 2-year actuarial patient survival was 85% and 82%, respectively, and graft

Table 2. Cause of patient death

Cause of death	Post-transplant day	Number of patients
Pulmonary embolism	2	1
Anaphylactic reaction to drug	6	1
Intractable gastrointestinal bleeding	107	1
Sepsis		
Chest infection	37	1
Necrotizing fasciitis	238	1
Infection of the lymphocele	285	1
Myocardial infarction	545	1

Table 3. Cause of graft loss

Cause of graft loss	Days of graft loss	Number of grafts lost
Patient deaths from Table 2	2, 6, 37, 107, 238, 285 and 545	7
Acute vascular rejection	12	1
Bleeding at the transplant site	15	1
Hemolytic uremic syndrome	55	1
Steven Johnson syndrome due to Dapsone	152	1

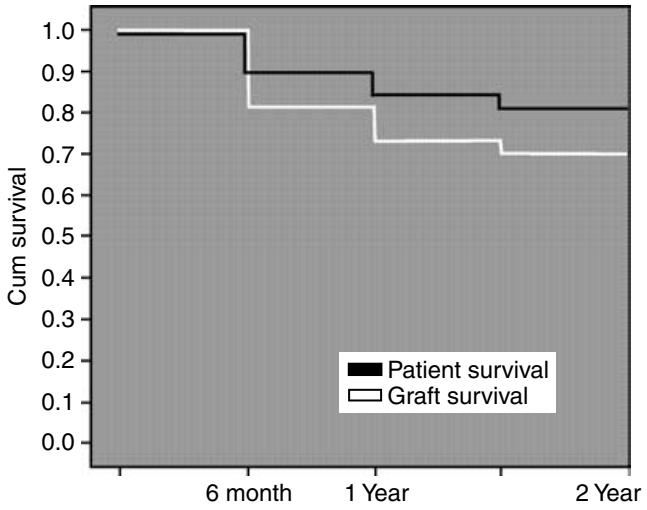

Fig. 1. Two-year actuarial patient and graft survival.

survival was 75% and 71%, respectively. Seven patients died between 2 days and 18 months after transplantation. The causes of death and graft loss are shown in Tables 2 and 3, respectively.

Renal function

The mean serum creatinine at 1 year and 2 years was 2.0 and 2.2 mg/dL, respectively, and calculated creatinine clearance was 55 and 40 mL/min, respectively (Fig. 1).

Acute rejection

Acute rejection was diagnosed in 9 (22%) recipients and treated with methylprednisolone; 2 with combined cell- and antibody-mediated rejection also received intravenous immune globulin and rituximab. Acute rejection was reversed or controlled in 8 recipients, and 1 required transplant nephrectomy for irreversible vascular rejection. Three recipients developed acute rejections due to subtherapeutic levels of cyclosporine caused by drug interactions with HAART therapy, and 2 due to noncompliance.

Results of protocol biopsies

Protocol biopsies were completed as per protocol. SCAR was diagnosed in 10 (29%) patients. SCAR was treated with pulse doses of intravenous methylprednisolone. In 6- to 24-month protocol biopsies, chronic allograft nephropathy was mild in 11, moderate in 15, severe in 2, and absent in 6. Two patients expired before the 6-month biopsy period. HIVAN was diagnosed in 3 patients in 12-month protocol biopsies. Two patients have proteinuria of more than 1500 mg/day, and 1 patient remains asymptomatic. The diagnosis of HIVAN was based on collapsing glomerulonephritis and other characteristics described previously [13, 14]. The similarity of pathologic features between transplant kidney biopsy and native kidney pathology in these patients was also considered in making a diagnosis of HIVAN in transplant kidney. Acute cyclosporine nephrotoxicity was seen in 7 recipient biopsies and was treated by dose reduction.

Post-transplant complications

Six patients remained free of complications without hospitalization. Table 2 shows complications, their treatment, and outcome.

HIV status in the post-transplant period

Plasma HIV-1 RNA remains undetectable in 30 recipients. In 4 patients who returned to dialysis, HIV remains under control with continuation of HAART. The remaining 6 patients who expired had undetectable HIV-1 RNA in the blood, and CD4 counts remained greater than 400 cells/μL of blood until the time of their death. Four recipients developed acute pancreatitis, 2 due to didanosine therapy. These patients experienced temporary elevation of plasma HIV-1 RNA for approximately 3 weeks after temporary cessation of didanosine; after resumption of modified HAART, plasma HIV-1 RNA promptly returned to undetectable levels. Three recipients showed elevation of plasma HIV-1 RNA from undetectable to a range of 1570 to 70,000 copies/mL due to drug resistance confirmed by resistance studies. HAART modifications resulted in undetectable plasma HIV-1 RNA. Absolute CD4 lymphocyte counts fluctuated, but in most recipients trended upward. Figure 3 shows the mean CD4 counts at

Table 4. Post-transplant complications

Complication	Number of patients	Treatment	Outcome
Surgical complications	2	Surgical correction	Resolved
Urine leak			
Hematoma	2	Surgical drainage	Resolved
Lymphocele	3	Percutaneous drainage by intervention radiology in 2 and open surgical drainage in 1	Death due to sepsis in recipients with percutaneous drainage (2); lymphocele resolved in 1
Gastrointestinal bleeding	1	Blood transfusion	Death
Bleeding at transplant site	1	Transplant nephrectomy	Graft loss
Nonsurgical complications			
Pulmonary embolism	1	Anticoagulation	Death
Congestive heart failure	2	Medical management	Resolved
Insulin dependent diabetes mellitus	6	Insulin therapy	Controlled
Anaphylactic reaction to IVIG therapy	1	Supportive treatment	Death due to respiratory failure
Infectious complications			
Wound infection	1	Antibiotic therapy	Resolved
Chest infection due to *Pseudomonas aeroginosa* in 1 and *Staphylococcus aureus* in 1	2	Diagnosis by bronchioalveolar lavage and lung biopsyAntibiotic therapy	Resolved (1); death (1)
Sepsis	3	Antibiotic therapy	Resolved
Urinary tract infection	12[a]	Antibiotic therapy	Resolved
HAART-related complications			
Acute pancreatitis	4	Temporary withdrawal and change of HAART regimen	Resolved
HIV drug resistance	3	Phenotype study and change in HAART regimen	Controlled
Immunologic complications			
Acute rejection	9	Steroid therapy	Controlled (8); graft loss (1)
Hemolytic uremic syndrome	2	Discontinuation of cyclosporine	Graft loss (2)
Drug allergy	1	Discontinuation of dapsone	Graft loss

[a]Nine admissions due to urinary tract infection.

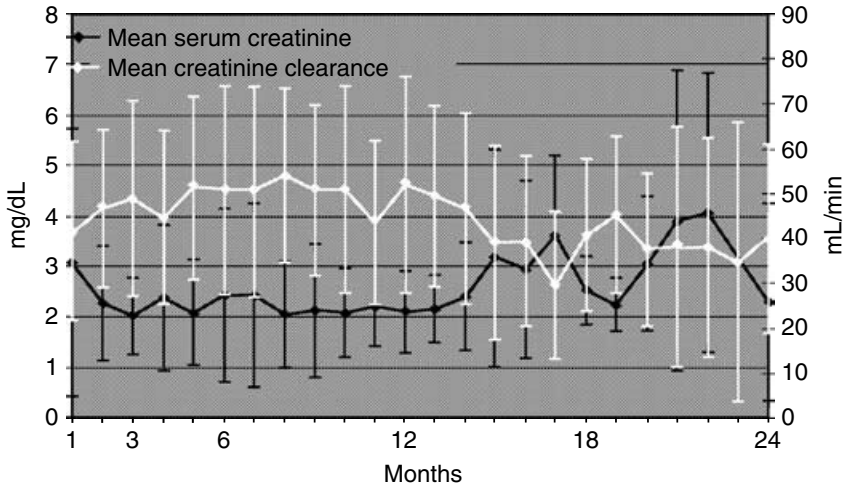

Fig. 2. Mean serum creatinine levels and creatinine clearances for 2 years' post-transplant.

monthly intervals. Opportunistic infections were not observed in these 40 recipients.

HAART and immunosuppressive regimens

All recipients continued HAART combined with immunosuppression. The majority of recipients received protease inhibitor (PI) or non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens. Immunosuppression for all patients consisted of basiliximab, cyclosporine, sirolimus, and prednisone. Due to the drug interaction profile of the various HAART regimens with immunosuppression, the daily requirement of cyclosporine and sirolimus varied dramatically among recipients. Recipients receiving PI-based HAART regimens required much lower cyclosporine and sirolimus doses than convention dictates, with many requiring once daily to once weekly dosing to maintain target trough levels. The mean daily cyclosporine dose in these recipients was 65 $\pm$ 40 mg/day. In comparison, the mean

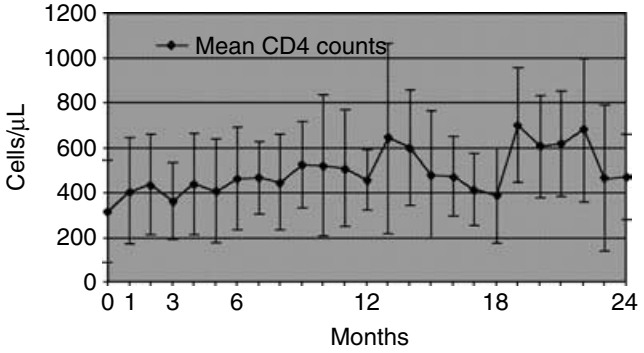

Fig. 3. Measurement of HIV status as measured by absolute CD4 counts in the peripheral blood.

daily cyclosporine dose in recipients using NNRTI-based regimens was 313 ± 208 mg/day, and 186 ± 78 mg/day for those taking only nucleoside reverse transcriptase inhibitors (NRTI). Similarly, the mean daily dose of sirolimus ranged from 0.1 mg to 1.0 mg with dosing as little as once a week. Figure 3 shows mean cyclosporine dose and levels.

DISCUSSION

This study was carried out in HIV-positive patients with ESRD who were stable and compliant with HAART and dialysis. HIV patients on dialysis who were not compliant and had higher plasma HIV-1 copies in blood were excluded from the study. The introduction of HAART for the treatment of HIV infection has significantly decreased the mortality, and extended the life span of HIV-positive patients. Increased life span has resulted in these patients developing long-term complications of HIV infection, including ESRD. HIV patients may develop ESRD secondary to preexisting conditions such as diabetes and hypertension, or the primary cause may be HIVAN [10, 15]. HIVAN is seen more frequently in male African American patients with a history of intravenous drug abuse, and progresses rapidly to ESRD, requiring renal replacement therapy [16, 17]. HIVAN may be treated by steroid therapy with a low success rate that postpones the inevitable ESRD by only a few months. Chronic dialysis treatment was the only option available for these patients until 2001. HIV infection was considered a contraindication for kidney transplantation because of the expected increased in morbidity and mortality from surgery and immunosuppression based on pre-HAART experience [5]. Expected inferior survival led many to believe it morally and ethically inappropriate to allocate kidneys to these patients for fear of wasting scarce resources [4, 5, 18]. A survey conducted by our program showed that in the Philadelphia region, 2% to 5% of dialysis patients were HIV-positive and were maintained on HAART (unpublished data). Further analysis of our survey showed that many of these patients were intolerant to dialysis, and were seeking kidney transplantation, but were denied the opportunity by all transplant programs in Philadelphia. Many of these young HIV-positive patients compliant with HAART and dialysis treatment were referred to Hahnemann University Hospital transplant program for kidney transplantation in 1999 and 2000. These patients had improved their lifestyle by strict adherence to recommended medical treatment and modifying their personal and social behaviors. We initiated an IRB-approved protocol for kidney transplantation in HIV-positive patients in February 2001 to offer these patients an alternative treatment to chronic dialysis therapy, and to improve their quality of life. Patient selection criteria were rigorous to protect their interests, and to minimize the potential aggravation of HIV disease.

Earlier reports of transplantation in HIV patients are sporadic and include smaller series of patients, and the follow-up was 1 year or less [19, 20, abstract; Kumar MSA et al, *Am J Transplant* 2 (Suppl 3):174, 2002]. In this series, 39 patients were African American and 1 was Caucasian. Male gender was predominant (91%). This represents the prevalence of HIV disease in metropolitan areas of the United States of America. Before transplantation, all patients were compliant with medical treatment, and their HIV infection was controlled, as shown by their plasma HIV-1 RNA copies and CD4 counts. Our results demonstrate that HIV-positive patients maintained on HAART are capable of mounting an immune response, as evidenced by a rejection rate of 25%. This indicates that allograft reactivity is preserved in these patients, and without immunosuppression they will reject an allograft. There are no data available regarding the long-term effects of combining immunosuppression and HAART. Our data extend up to 2 years and show that the combination of HAART and low-dose immunosuppression utilized is not associated with serious adverse effects. For these reasons, we continue to utilize low doses of immunosuppression with HAART. This could explain higher rates of acute rejections in these patients compared to non-HIV patients.

Graft function, as measured by serum creatinine, remains around 2 mg/dL in most of these patients. This may be explained by the use of marginal kidneys, the synergistic nephrotoxicity of cyclosporine and sirolimus, and drug interactions with HAART [21]. In the Philadelphia region, 30% of cadaver kidneys are harvested from marginal donors according to UNOS criteria [22]. Kidney biopsies in recipients with higher serum creatinines did not show any structural changes to explain poor function. In these patients, reduction of cyclosporine and sirolimus improved the kidney function, indicating that this combination of HAART and immunosuppression may be nephrotoxic. HAART doses were not reduced for fear of increased viremia.

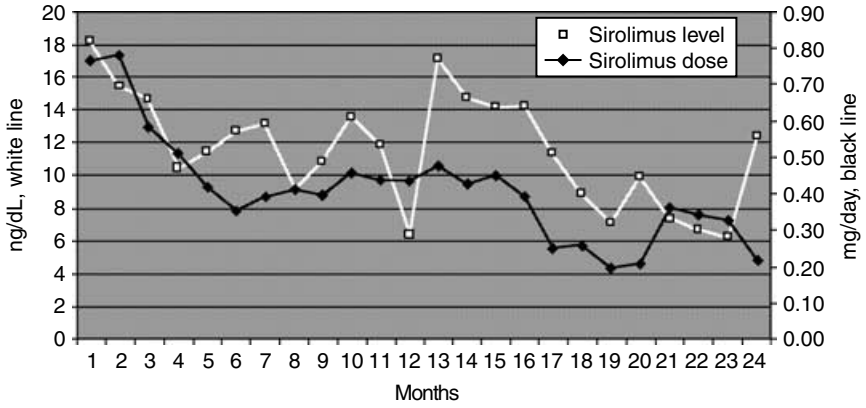

Fig. 4. Mean sirolimus doses and trough blood levels up to 2 years.

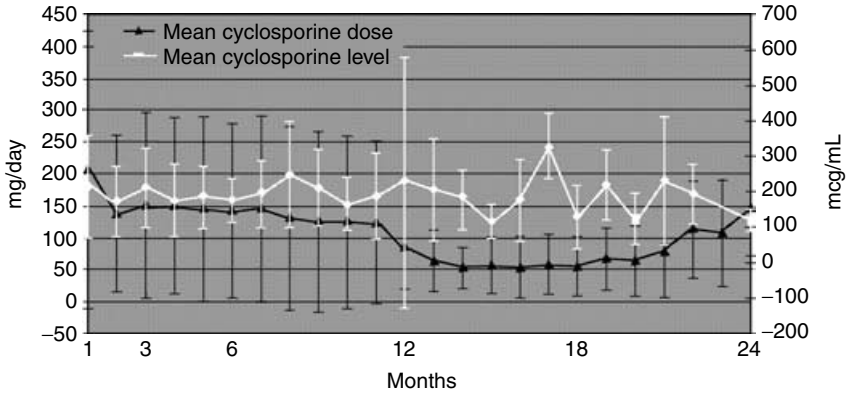

Fig. 5. Mean cyclosporine dose and trough blood levels up to 2 years.

Six recipients (15%) died within 1 year, and 1 in the second year. The causes of death were unrelated to HIV infection in 4 patients (1 each due to pulmonary embolism, myocardial infarction, anaphylactic reaction, and post surgical bleeding). The remaining 3 patients died of bacterial infection, which could be the result of added immunosuppression with HIV-positive status. Infection of lymphocele and severe sepsis occurred in 2 recipients with percutaneus drainage. Since the death of 2 recipients with overwhelming infections, our policy is to surgically drain the lymphoceles in HIV patients. We believe that at least 2 recipients with chest infection died because of delay in seeking treatment for 48 hours or longer. Most of these deaths occurred in the first 15 patients, and since that time frequent outpatient surveillance and intense patient education to seek early treatment has decreased the death rate. The plasma HIV-1 RNA copies in all patients at the time of death remained undetectable, and CD4 counts were greater than 400.

One- and 2-year patient survival in our transplant series was 85% and 82%, respectively, compared to the reported 58% and 41% survival of HIV patients on dialysis [23]. The United States Renal Data System reported a 1-year death rate of 32.7% in HIV patients maintained on dialysis [22].

In this series, 97% were African American, and 50% received marginal kidneys; both characteristics are independent risk factors for lower graft survival [24]. Non-HIV African American kidney recipients have 1- and 2-year graft survival of 85% and 78%, respectively [24, 25]. The graft survival in this series of HIV-positive transplant recipients is comparable to the UNOS data on non-HIV African American recipients.

The immunosuppressive agents selected for this protocol were chosen to minimize the aggravation of HIV infection and the potential side effects of combining HAART and immunosuppression. Basiliximab is a nonlymphocyte-depleting induction agent with minimal side effects [26]. Cyclosporine was chosen because it has demonstrated some in vitro antiretroviral activity [27]. Sirolimus, an effective adjunct, is typically given once a day, and was chosen to decrease the pill burden, and to obtain compliance with the combined regimen with fewer gastrointestinal side effects. Steroids have traditionally been integral to immunosuppression. Clinical acute rejection in this series is higher than in non-HIV patients, and this may be due to low levels of immunosuppression used to avoid infectious. Cytochrome P450-3A4 drug interactions between HAART and immunosuppressives posed a challenge in dosing cyclosporine and sirolimus. Earlier reports in liver recipients showed that ritonavir is a very potent inhibitor of CYP450-3A4, and interferes with tacrolimus metabolism [28]. In our series, 9 patients received ritonavir-based HAART, and

7 of these experienced acute cyclosporine nephrotoxicity confirmed by biopsy despite low cyclosporine levels, implying that ritonavir potentiates cyclosporine nephrotoxicity regardless of trough level. In patients experiencing toxicity, doses were decreased with resolution of side effects. Eleven patients treated with efavirenz, a mixed inducer and inhibitor of CYP450-3A4, had subtherapeutic cyclosporine and sirolimus levels, and 3 of these patients developed acute rejection [29]. One patient treated with efavirenz was unable to achieve therapeutic cyclosporine levels despite increased cyclosporine dose and addition of a CYP450-3A4 inhibitor, ketoconazole; this patient developed vascular rejection and required transplant nephrectomy. Cyclosporine is known to affect the blood levels of antiretroviral drugs metabolized via the hepatic microenzyme systems [30]. Evaluation of antiretroviral levels was not a part of this study, and further investigation of these interactions is warranted.

The monitoring of combined immunosuppression and HAART due to major drug interactions is challenging and requires diligent surveillance and the coordinated care of transplant professionals, pharmacists, and HIV specialists. Further investigation to elucidate the complicated drug interaction profile and combined toxicity of imunosuppressives and HAART is a pressing need. Longer-term studies of patient and graft outcomes, the effect of prolonged immunosuppression on HIV therapy, and the benefit to patients and society of transplantation in HIV-positive patients are required**.** Although barriers to transplantation in relatively healthy HIV-positive patients remain, moral and ethical arguments have been made to refute them [31]. This study provides medical evidence that kidney transplantation in select HIV-positive patients maintained on effective HAART is safe and provides significantly higher 1- and 2-year patient survival compared to dialysis treatment in select group of HIV patients. One- and 2-year actuarial graft survival in HIV recipients is equivalent to other high-risk groups. HAART remains effective in controlling HIV infection over 2 years of follow-up after kidney transplantation and immunosuppression with basiliximab induction and low-dose 3-drug maintenance. None of the patients developed AIDS or opportunistic infections with the immunosuppression regimen used in our center. These patients tolerated combined immunosuppression and HAART medications. The economics of transplantation and dialysis in HIV patients with ESRD need to be estimated and applied to clinical practice. Based on our experiences we conclude that positive HIV status should not be considered a contraindication for kidney transplantation in select patients.

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