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HIV-Infected Kidney Graft Recipients Managed With an Early Corticosteroid Withdrawal Protocol: Clinical Outcomes and Messenger RNA Profiles¹

Thangamani Muthukumar^{2,3,4}, Cheguevara Afaneh^{2,5}, Ruchuang Ding³, Demetra Tsapepas⁶, Michelle Lubetzky³, Samantha Jacobs⁷, John Lee³, Vijay Sharma^{3,8}, Jun Lee^{3,4,8}, Darshana Dadhania^{3,4}, Choli Hartono^{3,4,8}, Jennifer McDermott⁶, Meredith Aull⁵, David Leiser⁵, Sandip Kapur⁵, David Serur^{3,4,8}, and Manikkam Suthanthiran^{3,4}

³Division of Nephrology and Hypertension, Department of Medicine, New York Presbyterian-Weill Cornell Medical Center, New York, NY

⁴ Department of Transplantation Medicine, New York Presbyterian-Weill Cornell Medical Center, New York, NY

⁵ Division of Transplant Surgery, Department of Surgery, New York Presbyterian-Weill Cornell Medical Center, New York, NY

⁶Department of Pharmacy, New York Presbyterian Hospital, New York, NY

⁷Division of Infectious Diseases, Department of Medicine, New York Presbyterian-Weill Cornell Medical Center, New York, NY

⁸The Rogosin Institute, New York, NY

Abstract

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Address correspondence to: Thangamani Muthukumar, M.D. Division of Nephrology and Hypertension, Department of Transplantation Medicine 525 East 68th Street, Box 3, New York, NY 10065 Phone: 1-212-746-4430, Fax: 1-212-746-6894 muthu@med.cornell.edu.

²Contributed equally to this work

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Background—The outcome of HIV-infected kidney transplant recipients managed with an early corticosteroid withdrawal protocol is not known.

Methods—Eleven consecutive HIV-infected patients with undetectable plasma HIV RNA and $>200/\text{mm}^3$ CD4+ T-cells underwent deceased (n=8) or living donor (n=3) kidney transplantation at our center. All were managed with an early corticosteroid withdrawal protocol; 9 of 11 received anti-thymocyte globulin and 2 received basiliximab induction. We analyzed patient and graft outcomes, acute rejection (AR) rate, HIV progression, BKV replication, infections and urinary cell mRNA profiles.

Results—The median follow-up was 44.5 months (range: 26-73). The incidence of AR was 9% at one year and patient and allograft survival rates were 100% and 91%, respectively. Estimated glomerular filtration rate at one year (mean $\pm$ SD) was 78 ± 39 ml/min/1.73m². Plasma HIV RNA was undetectable at 24 months and none had BKV replication. Six of the 11 kidney recipients developed eight infections requiring hospitalization. Urinary cell levels of mRNA for complement components and complement regulatory proteins, cell lineage specific proteins CD3, CD4, CD8, CTLA4, Foxp3, chemokine IP-10, cytotoxic perforin and granzyme B and BKV-VP1 mRNA were not different ($P>0.05$) between HIV-infected patients and HIV-negative recipients (n=22) with stable graft function and normal biopsy results.

Conclusion—An early steroid withdrawal regimen with anti-thymocyte globulin induction was associated with excellent graft and patient outcomes in HIV-infected recipients of kidney allografts. Their urinary cell mRNA profiles are indistinguishable from those of HIV negative patients with stable graft function and normal biopsy results.

Keywords

Kidney transplantation; HIV; Gene expression; Tacrolimus

INTRODUCTION

Highly active anti retroviral therapy (HAART) has had a dramatic positive impact on the survival of HIV-infected individuals (1). However, the prevalence of kidney disease among individuals infected with HIV is increasing (2, 3), and the survival of HIV-infected individuals with end-stage renal disease and managed with dialysis therapy is lower than that of matched HIV-negative individuals (4). With respect to renal transplantation, the understandable reluctance to use immunosuppressive therapy in patients with HIV and the striking disparity between organ supply and demand have functioned to restrain organ transplantation in this patient population. Fortunately, thoughtful re-considerations of the risks involved (reviewed in [5]) have resulted in a welcome foray in to providing kidney or liver allografts to HIV-infected patients (6-9). Indeed, the evolving literature support the strategy of renal transplantation in carefully selected HIV-infected recipients (Table 1).

Major challenges exist in the management of HIV-infected organ graft recipients. A consistent finding across studies, perhaps counterintuitive, is the high incidence of acute rejection in the HIV-infected recipients (6, 9-11). Whether HIV related perturbations to the immune system, the difficulties in maintaining therapeutic concentrations of calcineurin inhibitors in the context of drugs administered to control HIV replication and/or the general reluctance to use lymphocyte-depleting induction agents contribute to the high rates of acute rejection as compared to the 12% reported in the US Scientific Registry of Transplant Recipients (SRTR) (12), remain unresolved.

We examined the efficacy of a novel corticosteroid sparing regimen (novel for HIV-infected recipients) comprised of anti-thymocyte globulin as the primary induction agent, intravenous

methylprednisolone during post-operative days 0-4 only, and maintenance therapy with tacrolimus, mycophenolate mofetil and no prednisone. This regimen initiated at our center in November 2001 originally for low-risk living related donor renal allografts has been found to be associated with a low acute rejection rate (13). Because of this low incidence of acute rejection and because induction with anti-thymocyte globulin is associated with a lower acute rejection rate compared to induction with monoclonal antibodies directed at CD25 (14,15), we considered it reasonable to investigate the safety and efficacy of anti-thymocyte globulin induction and early steroid withdrawal protocol in HIV-infected recipients of kidney allografts. Our approach was also informed by considerations that steroid sparing regimens may help reduce adverse cardiovascular outcomes (16). The salutatory impact on cardiovascular outcomes is significant since cardiovascular diseases have emerged as a major cause of mortality and morbidity in HIV infected patients (17) and HAART increases risk of myocardial infarction (18).

Generalized immune activation is a key feature of HIV infection that continues despite sustained antiretroviral therapy (19, 20). To begin to resolve the immune consequences of an anti-thymocyte induction and early corticosteroid withdrawal protocol in HIV-infected recipients, we performed urinary cell mRNA profiling and measured levels of mRNA encoding proteins implicated in innate immunity and adaptive immunity. We and others have shown that renal allograft rejection can be defined noninvasively by measurement of urinary cell mRNA levels of a panel of mechanistically related genes (21-30). Importantly, in a prospective multicenter trial comprised of 485 renal allograft recipients, we also found that urinary cell mRNA profiles of allograft recipients distinguish those who develop acute rejection from those with stable allograft function and whose clinical status does not require clinically indicated (for-cause) biopsies during the first 12-months of transplantation (31).

Herein, we report the excellent clinical outcomes, albeit short-term, observed with an early corticosteroids withdrawal protocol, and demonstrate that urinary cell mRNA profiles of HIV-infected recipients are indistinguishable from the profiles found in HIV-negative recipients with stable graft function and normal biopsy results.

RESULTS

Kidney Allograft Recipients

Between May 2006 and May 2010, 11 consecutive HIV-infected patients received kidney allografts at our institution (Table 2). All patients were being managed with hemodialysis therapy prior to transplantation and were continued on their HAART after transplantation with HAART resumed on the same day of transplant in 6 recipients, on post-transplant day 1 in 3 recipients and on post transplant day 2 in two recipients. Survivors (10 of 11 patients) were followed for a median duration of 44.5 months (range: 26-73). At the time of data analysis all 10 patients had completed 2 years and 7 patients had completed 3 years of follow-up.

Patient and Kidney Allograft Survival

All patients were alive at one year post-transplantation. One male patient died 17 months after the kidney transplant procedure. He was 60 years old with a history of diabetes mellitus type II and hypertension and was found dead at his home. The patient was seen at our post-transplant clinic one month prior to his death and he had no specific complaints and his kidney graft function was stable and the serum creatinine level of 1.09 mg/dL at the last clinic visit. The cause of death was thought to be due to cardiovascular event. The 3-year Kaplan-Meier patient survival estimate was 90% (95% confidence interval [CI]: 72% to 100%) (Figure 1A). One-year allograft survival was 91% (95% CI: 74% to 100%) with one

of the 11 patients not recovering renal function after transplant (primary nonfunction) and returning to dialysis. Another patient had allograft failure 24 months after transplant following an episode of acute rejection at 16 months post-transplantation. The 3-years death-censored allograft survival was 81% (95% CI: 58% to 100%) (Figure 1B).

Acute Rejection

One of eleven patients experienced a mixed acute rejection (Banff acute antibody-mediated rejection, grade II and acute T-cell mediated rejection, grade IB) at 3-weeks post transplantation and another patient developed a mixed acute rejection (Banff acute antibody-mediated rejection, grade II and acute T-cell mediated rejection grade IA) at 16 months post-transplantation. The incidence of acute rejection at 1 year post-transplant was 9% (95% CI: 0% to 26%). The 3-year Kaplan-Meier estimate of acute rejection was 18% (95% CI: 0% to 41%) (Figure 1C).

The two acute rejection episodes were treated with pulse methylprednisolone, intravenous immunoglobulin and plasmapheresis and both grafts failed despite anti-rejection therapy. The first patient with mixed acute rejection at 3-weeks post transplantation never recovered allograft function and the second patient with mixed acute rejection at 16 months after transplant responded to treatment initially but his allograft failed eventually and was returned to dialysis 8 months after the incident rejection episode.

Tacrolimus Dosing

All patients received tacrolimus and all were receiving protease inhibitors (PI, n=7) or non-nucleoside reverse transcriptase inhibitors (NNRTI, n=10). At 1-year following transplant, only 4 of 10 HIV-positive kidney recipients were on the standard twice-daily tacrolimus regimen to maintain therapeutic tacrolimus trough levels. One patient required a daily dose, one needed alternate day dosing and in the remaining 4 patients, tacrolimus dosing needed to be spaced once every 5-7 days to maintain tacrolimus trough levels. The mean ($\pm$ SD) tacrolimus drug trough levels were 9.3 ± 3.7 , 9.0 ± 3.5 , 7.8 ± 1.9 , 6.9 ± 2.9 and 5.8 ± 1.9 ng/ml, respectively at 1, 3, 6, 9 and 12 months post transplantation (Figure 1D).

Tacrolimus Pharmacokinetic Studies

We performed pharmacokinetic profiling of tacrolimus on two kidney transplant recipients who were on PI based HAART regimen. Patient-1 was on atazanavir and Patient-2 was on tipranavir and ritonavir. The first patient required 0.5 mg of tacrolimus every 36 hours while the second patient required 1.5 mg every 12 hours to achieve therapeutic level (Supplementary digital content [SDC] Figure 1). While both the patients were on PI based HAART regimen they differed in tacrolimus dose requirement and dosing frequency to maintain tacrolimus therapeutic levels suggesting that tacrolimus-HAART interactions are difficult to predict even within the same category of HAART medicines.

Allograft Function

The mean ($\pm$ SD) glomerular filtration rate (GFR), estimated using the 4-parameter MDRD formula, was 31 ± 13 , 57 ± 22 , 56 ± 21 , 57 ± 20 and 66 ± 23 ml/min/1.73m², respectively at 1, 3, 6, 9 and 12 months post transplantation (Figure 1E).

HIV Progression

All 11 HIV-positive recipients had undetectable HIV mRNA in their plasma 20 months (median, range: 5-73) prior to transplantation. Two recipients had detectable viral copies after transplant; 13394 and 297 copies at 14 and 15 months respectively after transplant. Both of them had undetectable HIV mRNA at their last follow up. All 10 survivors had

undetectable HIV mRNA in their plasma at a median follow up of 43 months (range: 26-73) after transplant.

Infections

Six of the 11 kidney recipients with a functioning allograft (55%) had eight episodes of infection requiring hospitalization. The 6 patients were diagnosed with: bacterial pyelonephritis (n=2 patients), *Clostridium difficile* diarrhea (n=1), pneumonia (n=1), lung abscess (n=1) and cervical spine osteomyelitis (n=1). Five of the 6 patients had their infections within the first year of transplantation. The patient who developed the lung abscess was also diagnosed with pulmonary tuberculosis five months later, and the patient with *Clostridium difficile* diarrhea developed gram-negative bacteremia 12 months later. An additional patient developed pneumonia 26 months after the transplant procedure and while on dialysis. All patients who developed infections requiring hospitalization were successfully treated.

Other Complications

Two kidney recipients had three cancers (one patient with anal cancer and Kaposi sarcoma and another patient with prostate cancer) prior to the kidney transplant procedure and were cleared by their oncologists for kidney transplantation. The patient with anal cancer and Kaposi sarcoma developed a new squamous cell carcinoma of the scalp at 3 months post transplantation. Another patient with no prior cancer history developed penile squamous intraepithelial cancer 28 months after transplantation. Both patients were treated successfully and are alive 23 and 10 months, respectively, following therapy.

Cardiovascular Risk Factors

We examined whether factors that have been associated with cardiovascular disease changed significantly following transplantation. Longitudinal measurement of cardiovascular risk factors showed no significant changes compared to pre-transplant values. Supplementary Table ST1 provides longitudinal data of the parameters analyzed and show that there were no changes in the weight of the recipients ($P=0.97$, Repeated Measures ANOVA), systolic ($p=0.24$) or diastolic ($P=0.82$) blood pressure, lipid profile or in the number of blood pressure or lipid lowering medications. Importantly, there were no cases of new onset diabetes mellitus after transplantation (NODAT) and in fact a marginal improvement in blood glucose levels, compared to pre-transplant levels, was observed ($113 \pm$ mg/dl vs. $97 \pm$ mg/dl, $P=0.09$).

Levels of mRNA in Urinary Cells

We obtained about 50 ml urine from the 9 HIV-infected kidney graft recipients and from 22 HIV-negative kidney graft transplant recipients for urinary cell mRNA profiling. We designed oligonucleotide primers and fluorogenic probes (SDC Table 2) for the absolute quantification of levels of mRNA and measured urinary cell levels of 17 mRNAs encoding proteins implicated in innate and/or adaptive immunity.

Unsupervised hierarchical clustering analysis of the absolute levels of 17 mRNAs quantified in the HIV-infected recipients and HIV-negative recipients showed no clustering of kidney graft recipients into those who were infected with HIV or not (Figure 2).

Urinary cell levels of mRNA for Toll like receptor [TLR]-4 (CD284) ($P=0.12$), complement component 3 (C3) ($P=0.20$), C5 ($P=0.37$), properdin ($P=0.06$) and complement regulatory proteins CD46 ($P=0.40$) or CD55 ($P=0.06$) were not significantly different between the HIV-infected and HIV-negative kidney graft recipients (Figure 3). Urinary cell levels of mRNA for the cell surface proteins CD4 ($P=0.35$), CD8 ($P=0.31$), and CD3 ($P=0.84$), T cell

co-inhibitory receptor CTLA4 ($P=0.62$), CD25 ($P=0.12$), regulatory T cell specification factor, Foxp3 ($P=0.81$), B cell CD20 ($P=0.11$), chemokine IP-10 ($P=0.37$), and the cytotoxic attack molecules perforin ($P=0.53$), or granzyme B ($P=0.17$) were also not significantly different between the two groups (Figure 3).

We have reported that BKV replication can be ascertained by measurement of BKV VP-1 mRNA in urinary cells (32). We examined whether BKV replication, an index of over-immunosuppression, is more frequent in HIV-infected recipients than the HIV-negative recipients. BKV VP1 mRNA was not detected in the urinary cells from either the HIV-infected recipients or the HIV-negative recipients.

DISCUSSION

We show in our single center study of HIV-infected kidney graft recipients that an early corticosteroid withdrawal immunosuppression regimen is associated with excellent patient and kidney graft survival rates, and that the acute rejection rate is numerically lower than that reported in studies of HIV-infected recipients managed with immunosuppressive regimens that have included maintenance corticosteroids therapy.

Rationale for and Outcomes with the Early Corticosteroid Withdrawal Protocol

The prolonged use of corticosteroids in kidney graft recipients is associated with a plethora of complications including hypertension, new-onset diabetes and hypercholesterolemia (33, 34). On the other hand, early corticosteroid withdrawal has been found beneficial over the long term in HIV negative recipients (35, 36). As HIV infected persons are living longer (1, 37), avoidance or minimization of steroids may be beneficial in HIV-infected recipients

In the multicenter trial of 150 HIV-infected kidney recipients, all treated with a steroid based triple drug immunosuppression regimen, Stock et al. (9) observed 90% kidney allograft survival and 95% patient survival at one year (Table 1). Touzot et al. reported 98% graft survival and 100% patient survival in 27 patients who received their kidney grafts in 5-transplant centers in Paris (38) and Mazuecos et al. reported 85% graft survival and 100% patient survival in 20 patients who received their renal transplants in multiple centers in Spain (39). Our 1-year allograft graft survival rate of 91% and patient survival rate of 100%, accomplished with an early corticosteroid withdrawal regimen, compares favorably with the earlier reports. Because of the small sample size of the current study ($N=11$ HIV-infected recipients) and the resultant wide confidence intervals of the outcome measures reported here, the high efficacy observed in this first investigation of early corticosteroid withdrawal regimen must be interpreted with due caution.

Low incidence of Acute Rejection

The one year incidence of acute rejection in our HIV-infected kidney recipients was 9%. In the multicenter trial (9), the incidence of acute rejection at one year was 31%. Patient selection and the tacrolimus trough levels at one month were similar between the multicenter cohort and our study. However, all our kidney recipients received antibody induction therapy as compared with 83% in the multicenter trial. Also, all our patients received tacrolimus, only 66% of the patients in the multicenter trial received tacrolimus and 12% were not on calcineurin-inhibitor based regimen. In the study by Touzat et al. all 27 HIV-infected kidney recipients received induction therapy and the incidence of acute rejection was 15% at 1-year (38). It is tempting to hypothesize that the universal use of induction therapy and tacrolimus-based immunosuppression contributed to the reduced incidence of acute rejection in our study. In this regard, the early corticosteroid withdrawal regimen used in this study was associated with a 6.7% incidence of acute rejection in 634 HIV negative

kidney recipients treated at our center (13). In a recent study, the 1-year incidence of acute rejection was 13% with antithymocyte globulin and 20% with basiliximab (40).

Tacrolimus-HAART interaction

Drugs belonging to the PI or NNRTI group of HAART are substrates for CYP3A4 enzyme that metabolizes tacrolimus and can induce, inhibit or have a mixed effect on the enzyme (41). Our tacrolimus pharmacokinetic profiles of the two HIV-infected kidney graft recipients suggest that tacrolimus-HAART interactions are difficult to predict even within the same category of HAART medicines. Close monitoring of drug levels and individualization of drug dosages may be of considerable importance.

Non-immunological complications

Infection and malignancy are dreaded post-transplant complications. We did not observe progression of HIV in our kidney recipients and the lack of detection of HIV viral copies at 24 months post-transplantation in our study mimics the finding from the multicenter trial (9). The incidence of infection in our study was not different from that in the INTAC study of kidney recipients without HIV infection who all received antibody induction and managed with or without an early steroid withdrawal protocol (40).

One of the HIV-infected recipients developed a new squamous cell carcinoma of the scalp at 3 months post transplantation and another developed penile squamous intraepithelial cancer 28 months after transplantation. Malignancy was successfully managed and both patients are alive currently, one 23 months and the other 10 months post-therapy.

Lack of deterioration of cardiovascular risk profile

Longitudinal measurement of cardiovascular risk factors showed no significant changes compared to pre-transplant values and there were no cases of NODAT. These observations are consistent with the recent meta-analysis showing reductions in the risk of hypertension, new-onset diabetes, and hypercholesterolemia with steroid avoidance or withdrawal after kidney transplantation (34). Since we did not have a control group maintained on corticosteroids, we are not able to attribute the lack of deterioration in cardiovascular risk factors and the 0% incidence of NODAT to early steroid withdrawal.

Urinary cell mRNA profiles suggestive of lack of intraorgan inflammation

HIV infection, even with suppressive antiretroviral therapy, is characterized by chronic generalized immune activity (19,20). In this study, we demonstrate that the urinary cell profiles of HIV infected kidney transplant recipients are indistinguishable from that of HIV negative kidney graft recipients with stable graft function and normal biopsy results. Our findings that the mRNA levels of proteins implicated in innate and adaptive immunity are not significantly higher in the HIV-infected recipients compared to the HIV-negative recipients suggest that the state of the HIV-negative recipients managed with the early corticosteroid withdrawal regimen is not one of chronic immune activation. It also appears that the use of thymoglobulin induction is not associated with profound depletion of major T cell subsets and B cell populations in HIV negative recipients since the levels of mRNA for CD3, CD4, CD8, CD25 and CD20 were not lower in the HIV infected recipients compared to HIV negative recipients. A lack of profound immunosuppression in the study cohort is also suggested by the absence of BKV replication in urine. Our finding that urinary cell Foxp3 mRNA level is not lower in the HIV infected recipients compared to HIV negative recipients suggest that post-transplant immunosuppression did not completely deplete regulatory T cells.

Several limitations to our study must be acknowledged. Our study is comprised of 11 patients only and the observed promising outcome measures need confirmation with a larger sample size. Second, the evolution of immune alterations in this study cohort was not analyzable due to the cross sectional study design. Third, we did not perform surveillance biopsies to validate urinary cell mRNA profiling showing a lack of intragraft inflammation. These shortcomings however do not negate the supposition that an early corticosteroid withdrawal regimen for kidney transplantation in HIV infected individuals is safe, well-tolerated and associated with immunological profile indistinguishable from the profile observed in HIV-negative recipients with stable graft function and normal biopsy results.

METHODS

Patients

We reviewed charts to study the clinical course of 11 consecutive kidney transplant recipients infected with HIV who were managed with an early corticosteroid withdrawal immunosuppression protocol at our center. These recipients formed part of our Institutional Review Board approved early corticosteroid withdrawal immunosuppression protocol after kidney transplantation and urinary mRNA expression studies. Each individual provided a written informed consent for urinary cell mRNA expression profiling. The selection criteria used for transplanting patients infected with HIV, the details of medications and the data collected for the study are provided in SDC text.

Urinary Cell mRNA Expression Studies

We measured absolute levels of mRNAs encoding proteins implicated in innate and adaptive immunity. We isolated total RNA from the urinary cells and measured mRNA levels using preamplification enhanced real time PCR assays. Additional details are provided in SDC text and SDC Table 2.

Statistical Analyses

We used Kaplan-Meier analysis to estimate patient survival, death-censored allograft survival, time to development of first episode of acute rejection and infection requiring hospitalization. The levels of mRNA in the urinary cells for each sample were normalized by the levels of 18S rRNA in the same sample. The overall gene expression pattern was analyzed by unsupervised hierarchical clustering. mRNA levels between groups were compared using Mann-Whitney U test. We used GraphPad Prism v 5.03 (GraphPad Software Inc, USA) for statistical analyses.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Kaplan-Meier Survival Estimates, Tacrolimus trough levels and eGFR in HIV-infected Kidney Graft Recipients

Kaplan-Meier curves of patient survival (A), death-censored allograft survival (B), time from transplant to the development of first episode of acute rejection (C), and time from transplant to the development of first episode of infection requiring hospitalization (F) for the 11 HIV infected kidney graft recipients. Box plots show the 10th, 25th, 50th (median), 75th, and 90th percentiles of tacrolimus trough level (D) and eGFR (E) values. eGFR was calculated using the modified 4-variable MDRD equation.

Figure 2. Unsupervised Hierarchical Clustering analysis of urinary cell mRNA levels in HIV-infected recipients and HIV negative recipients

Urine was collected from the HIV-infected recipients at the time of their scheduled clinic visit and the median time for urine collection was 293 days post transplantation (range: 190-980) and their kidney graft function was stable at the time of urine collection. Urine from the HIV-negative recipients were collected at the time of surveillance biopsies (median: 44 days after transplant, range: 30-451); these patients were also managed with the early corticosteroid withdrawal regimen and all 22 patients had stable graft function and normal allograft biopsy findings.

Heat map depicts the unsupervised hierarchical clustering based on the absolute levels of the 17 mRNAs in the urinary cells of HIV-infected kidney graft recipients (N=9) and HIV-negative recipients with stable graft function and normal biopsy results (N=22). Absolute levels of 17 mRNAs were measured using preamplification enhanced, real time quantitative PCR assays.

Clustering analyses did not differentiate the HIV-infected recipients from HIV-negative recipients. The dendrogram represents the degree of relatedness of the expression patterns (right) in the urinary cells and the degree of similarity between individual samples (top). The color in each cell reflects the level of expression of the corresponding mRNA in the corresponding sample, relative to its median level of expression in the entire set of samples. Increasing intensities of red indicate that a specific mRNA has a higher expression in a given sample and the increasing intensities of green indicate that this mRNA has a lower expression.

Figure 3. Urinary Cell mRNA Levels in HIV-infected Kidney Graft Recipients and HIV-negative Kidney Graft Recipients

Boxplots show the 10th, 25th, 50th (median), 75th, and 90th percentiles of 18S rRNA-normalized, log transformed mRNAs measured in the urinary cells of HIV-infected kidney graft recipients (green, N=9) and HIV-negative kidney graft recipients (blue, N=22). Levels of mRNA were measured using preamplification enhanced real-time quantitative PCR assays and were not different between the two groups ($P > 0.05$, Mann-Whitney test).

Table 1
Characteristics and Outcomes of Kidney Transplant Recipients Infected with HIV

Characteristics		Published Reports ^a									
Author	Stock	Tan	Kumar	Carter	Roland	Gruber	Touzot	Stock	Mazuecos	Present Study	
Year published										-	
PMID	12883195	15591960	15780120	16539632	18093266	18645490	20840478	21083386	20858765	-	
Number of patients	10	7	40	20	18	8	27	150	20	11	
Males (%)	90	86	93	95	94	63	48	78	70	91	
Blacks (%)	40	43	98	50	44	88	74	69	10	82	
Age, years	45 (median)	46±9 (mean±SD)	46±6 (mean±SD)	40-57 (range)	44 (median)	36-62 (range)	45 (median)	46 (median)	46 (mean)	53 (median)	
Deceased donor (%)	60	57	90	60	56	88	93	68	100	73	
Antibody induction	none	Alem 43%	Basilixi 100%	Basilixi 55%	IL2R Ab 39%	IL2R Ab 100%	Basilixi 97% ATG 3%	IL2R Ab 51% ATG 32%	Basilixi 30% ATG 5%	ATG 82% Basilixi 18%	
Immunosuppression	CsA, MMF	Tac, Siro, MMF	CsA, Siro	CsA or Tac, Siro, MMF	CsA or Tac, Siro, MMF	CsA, MMF	CsA or Tac, MMF	CsA or Tac, MMF	CsA or Tac, MMF	Tac, MMF	
Steroid maintenance (%)	100	57	100	100	100	100	100	100	100	0	
Follow up, months	16.5 (median)	39 (median)	19.2 (median)	3.7-46.8 (range)	48 (median)	15 (median)	29 (mean)	20.4 (median)	40.4 (mean)	44.5 (median)	
Acute rejection in year-1 (%)	n/a	n/a	n/a	n/a	52	12.5	15	31	n/a	9	
Acute rejection total (%)	50	43	22	50	73 ^b	12.5	15	41 ^b	40	18	
Infections (% of patients)	50%	0% (OI)	45%	ATG 55% ^c No ATG 22%	6% (OI)	50%	n/a	38% ^c	30% (OI)	55% ^c	
Infections (total episodes)	5	0 (OI)	n/a	ATG 10 ^c No ATG 2	1 (OI)	6	32	140 ^c	14 (OI)	8 ^c	
Patient survival (1-year, %)	100	100	85	95	94	100	100	95	100	100	
Graft survival (1-year, %)	100	71 ^d	75	90	83	98	98	90	85	91	

^aWe searched PubMed, the MEDLINE (Medical Literature Analysis and Retrieval System Online) database maintained by the United States National Library of Medicine at the National Institutes of Health for manuscripts published in the English language between June 1981 and May 2012 for kidney transplants in individuals infected with HIV and who were treated with highly active anti retroviral therapy. Reports with five or more cases are shown in the table. Reports from analyses of registry data are not included.

^b3-years cumulative incidence.

^cinfections requiring hospitalization.

^d graft survival during the follow up period. PMID: PubMed identifier. Alem: Alemtuzumab. Basilixi: Basiliximab. ATG: Anti-thymocyte globulin. IL2R Ab: Interleukin-2 receptor antibody. Tac: Tacrolimus. Siro: Sirolimus. MMF: Mycophenolate mofetil. CsA: Cyclosporine. OI: Opportunistic infections

Table 2**Characteristics of HIV-infected Kidney Transplant Recipients**

Characteristic	Value
Donor	
Age, median (IQR)	35 (21-57)
Gender, male:female	8:3
Race	White: 2, Black: 6, Hispanic: 2
Deceased, no. (%)	8 (73)
Expanded criteria, no. (%)	4 (50)
Standard criteria, no. (%)	4 (50)
Donation after cardiac death, no. (%)	1 (25)
Recipient	
Age, years, median (IQR)	53 (47-58)
Gender, male:female	10:1
Race	Black: 9, Hispanic: 2
Body mass index, Kg/m ² , median (IQR)	24.8 (23.8-28.9)
Duration of HIV infection, months, median (IQR)	170 (112-206)
Cause of chronic kidney disease, no. (%)	
Unknown	5 (45)
HIV-associated nephropathy	3 (27)
Hypertension	2 (18)
Diabetes mellitus	1 (9)
Time on dialysis, months, median (IQR)	82 (41-100)
Hepatitis B virus, no. (%)	1 (9)
Hepatitis C virus, no. (%)	0 (0)
Prior opportunistic infections, no. (%)	0 (0)
Prior cancer ^a , no. (%)	
Anal cancer	1 (9)
Cutaneous Kaposi's sarcoma	1 (9)
Prostate cancer	1 (9)
CD4+ cells, per mm ³ , median (IQR)	496 (473-682)
HIV viral copies undetected, no. (%)	11 (100)
HAART regimen, no. (%)	
Protease inhibitor	7 (64)
Non-nucleoside reverse-transcriptase inhibitors	4 (36)
Nucleoside reverse-transcriptase inhibitors	10 (91)
Integrase inhibitors (Raltegravir)	3 (27)
Cold ischemia time, hours, median (IQR)	31 (27-35)
Human leukocyte antigen ABDR mismatches ^b , no. (%)	
0	3 (27)
3	1 (9)
4	1 (9)

Characteristic	Value
5	2 (18)
6	4 (36)
Induction therapy, no. (%):	
Antithymocyte globulin	9 (82)
Basiliximab	2 (18)
Delayed graft function, n (%)	7 (88)

IQR: Inter quartile range.

^aThere were three cancers in two individuals prior to transplant.

^bThere were three living related donor transplants; two were 2-haplo-identical (0 mismatch); one was 1-haplo-identical (3 mismatches).