

Preliminary Experience With Renal Transplantation in HIV+ Recipients: Low Acute Rejection and Infection Rates

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Background. Only four centers have reported their results with renal transplantation in human immunodeficiency virus (HIV)+ recipients on highly active antiretroviral therapy, and acute rejection (AR) rates have consistently ranged from 43% to 67%.

Methods. We examined the outcomes of eight adult HIV+ primary renal allograft recipients with median 15 (range 8–47) months follow-up with multiple other high-risk factors, including African American ethnicity, hepatitis C virus (HCV) positivity, long waiting times, prior sensitization, paucity of live donors, and delayed graft function. Our immunosuppressive protocol consisted of an anti-interleukin-2 receptor antibody for induction, and mycophenolate mofetil, cyclosporin A, and prednisone for maintenance. Initial and 3- to 6-month cyclosporin A trough level targets were 250 to 300 and 225 to 275 ng/mL, respectively, and mycophenolate mofetil dose was adjusted according to 2 to 4 week surveillance and subsequent as needed mycophenolic acid predose concentrations during the first 6 months.

Results. Patient and graft survival were 100% and 88%, respectively, with an AR rate of 13% and excellent renal function. No patients developed new-onset diabetes, opportunistic or other serious infections, malignancy, or progression of hepatitis C virus-related liver disease. Excellent suppression of HIV replication with maintenance of CD4 counts was noted in all cases.

Conclusions. Our findings suggest that HIV+ patients on highly active antiretroviral therapy can undergo successful renal transplantation with a low incidence of both AR and AIDS-associated and non-AIDS associated infections, despite associated risk factors for poorer outcome. Our encouraging but preliminary results with this protocol will need to be verified in larger numbers of HIV+ renal allograft recipients with longer follow-up.

Keywords: Human immunodeficiency virus, Renal transplantation, Acute rejection.

(*Transplantation* 2008;86: 269–274)

Human immunodeficiency virus (HIV) positivity is still considered an absolute contraindication to renal transplantation in most transplant centers, and to our knowledge, only four programs have reported their single-center results to date (1–5). Although the initial experience of Stock et al. (1) in 10 kidney transplant patients receiving cyclosporin A (CSA)/mycophenolate mofetil (MMF)/prednisone maintenance therapy without induction was favorable with regard to patient and graft survival, control of HIV replication, and lack of AIDS-defining infections, acute rejection (AR) occurred in half the patients, with 60% of these requiring anti-lymphocyte antibody treatment. In addition, two patients developed wound infections, and there were three cases of significant bacterial or viral infection.

Based on this 2003 report, we began performing renal transplants in HIV+ candidates at our center in early 2004. We hypothesized that the incidence of AR could be significantly reduced while maintaining an acceptable infection rate, even in a cohort of patients at higher risk for poorer outcomes based on multiple immunologic and nonimmunologic factors, by introducing three modifications of the University of California, San Francisco regimen: (a) adding an anti-interleukin (IL)-2 receptor antibody for induction; (b) increasing CSA target trough levels; and (c) monitoring predose mycophenolic acid (MPA) concentrations from 2 to 4 weeks to 6 months posttransplant. The purpose of this report is to review our preliminary experience with this protocol in eight patients, with a focus on the endpoints of patient and graft survival; AR; renal function; and cytomegalovirus (CMV) and other infections.

METHODS

This is a retrospective study of adult HIV+ primary renal allograft recipients transplanted at our center between February 2004 and April 2007 and followed through December 2007. Approval was obtained from the Wayne State University Human Investigation Committee. Inclusion criteria were: (1) CD4 counts more than 200 cells/mm³ and ultrasensitive viral load (USVL) less than 50 RNA copies/mL for more than or equal to 6 months and (2) no history of significant AIDS-associated opportunistic infections or neoplasms, both while on highly active antiretroviral therapy (HAART).

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Received 31 January 2008. Revision requested 17 February 2008.

Accepted 23 March 2008.

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ISSN 0041-1337/08/8602-269

DOI: 10.1097/TP.0b013e318177884e

Transplant candidates who were also positive for hepatitis C virus (HCV) IgG antibody by a screening solid-phase enzyme immunoassay test underwent confirmatory quantitative polymerase chain reaction RNA testing. If the virus was detectable, the patient was categorized as HCV+ and underwent liver biopsy. If cirrhosis was not present, the patient was cleared for renal transplantation. Only HCV+ recipients were eligible to receive a kidney from a HCV+ donor, but no attempt was made to match viral subtypes. All deceased-donor kidneys were preserved using cold storage before transplantation, with none undergoing pulsatile perfusion.

All patients received induction therapy with basiliximab (20 mg on postoperative days 0 and 4) or daclizumab (1.5 mg/kg on days 0 and 7). Patients were started on MMF 2 g/day postoperatively. Twelve-hour serum trough levels for MPA (High-Performance Liquid Chromatography, ARUP Laboratories, Salt Lake City, UT) were obtained routinely at 2 to 4 weeks, and thereafter as clinically indicated, with an attempt to maintain levels within the target range of 1.3 to 3.5 mg/L as permitted by gastrointestinal side effects or leukopenia. Methylprednisolone 250 mg intravenous (IV) was given intraoperatively, followed by doses of 125, 100, and 100 mg on subsequent days. All patients were maintained on oral prednisone, with tapering to 20 mg by 1 week, 10 mg at 1 month, and 5 mg at 6 weeks. CSA was started within 24 to 48 hr after surgery, with an intention to maintain target 12-hr whole-blood trough levels (Fluorescence Polarization Immunoassay, Abbott Diagnostics, Abbott Park, IL) 250 to 300 ng/mL during the first 3 months; 225 to 275 ng/mL from 3 to 6 months; 150 to 225 ng/mL from 6 to 12 months; 100 to 150 ng/mL from 1 to 2 years; and 75 to 125 ng/mL thereafter. This immunosuppressive regimen differs from that used by our center in HIV- recipients, in whom Thymoglobulin is used for induction, and tacrolimus or sirolimus+MMF±prednisone for maintenance (6). All patients were maintained on the same HAART regimen as that used pretransplant, with drug doses adjusted for renal function as appropriate. Monitoring of CD4 counts and USVL was performed every 3 months. Delayed graft function (DGF) was defined as the need for hemodialysis during the first week posttransplant.

Antimicrobial prophylaxis was initiated within the first 24 to 48 hr after surgery. All patients received trimethoprim/sulfamethoxazole one single-strength daily for 6 months and nystatin 5 mL four times per day for 1 month. Cytomegalovirus prophylaxis was administered depending on the patient's risk-stratified profile. High-risk recipients with CMV- serostatus who received an organ from a CMV+ donor received valganciclovir 900 mg/day for 3 months, while all CMV+ patients received 450 mg/day for the same period, with dose adjustment according to renal function.

An unexplained rise in serum creatinine was followed by ultrasound examination of the renal transplant and biopsy as indicated. The biopsy specimens were evaluated by light, immunofluorescence, and electron microscopy. All episodes of AR were confirmed by biopsy and graded according to the Banff 97 schema. Antibody-mediated rejection was diagnosed by positive staining of peritubular capillaries for C4d and detection of donor specific antibody in recipient serum. Borderline or grade I rejection episodes were treated with methylprednisolone 500 mg IV for 3 days, followed by a steroid taper. Steroid-resistant grade I, and grade II rejections

were treated with 5 to 7 daily doses of Thymoglobulin with target absolute CD3 counts less than or equal to 10.

Graft loss was defined as return to dialysis or death with a functioning graft. New-onset diabetes mellitus was diagnosed in non-diabetic recipients with FBG more than 125 mg/dL on at least two occasions over a 1-month period, or by the need for hypoglycemic agents for more than 1 month. The presence of pp65 antigenemia or quantitative polymerase chain reaction more than 250 copies/mL was considered diagnostic of CMV infection in the presence of suggestive clinical symptoms, signs, and laboratory studies. Data are reported as counts or median with range, as appropriate.

RESULTS

Follow-up of the eight patients ranged from 8 to 47 months, with a median of 15 months. Patient characteristics are given in Table 1, notable for a high percentage of African American (AA) recipients, prolonged time on dialysis, a majority coinfecting with HCV, a paucity of live donors, and a high fraction of sensitized recipients. The causes of end-stage renal disease were hypertension in four patients, and diabetes, pyelonephritis, focal segmental glomerulosclerosis, and HIV-associated nephropathy in one patient each. Donor demographics were: median age 33 (17–43); 100% male; 88% non-AA; 25% HCV+; and 0% extended criteria or donation after cardiac death donors. DGF occurred in three patients (38%).

Overall patient and graft survival at the conclusion of the follow-up period were 100% and 88%, respectively, with median serum creatinine at 6 and 12 months of 1.5 (1.0–2.3; n=8) and 1.2 (1.2–1.4; n=5) mg/dL, respectively. There was only one case of BK virus nephropathy, one episode of CMV infection, and one episode of AR during the entire follow-up period, all occurring sequentially in the single patient who ultimately lost his graft at 11 months posttransplant. This patient underwent renal transplant biopsy for elevated serum creatinine at 5-months posttransplant, revealing BK nephropathy. Despite CSA and MMF dose reduction, the patient developed CMV infection 2 weeks later, at which time his CD4 count was 684 cells/mm³. Finally, his subsequent course was complicated by development of community-

TABLE 1. Demographics of HIV+ renal allograft recipients (n=8)

Recipient age	48 (36–62)
AA	7 (88%)
Male	5 (63%)
Years ESRD	7.2 (0.6–12.1)
HCV+	5 (63%)
Live donor	1 (13%)
Diabetes	2 (25%)
Cold ischemic time (hr) ^a	10.0 (7.4–15.0)
Peak PRA ≥10%	4 (50%)
HLA mismatches	4.5 (2–6)

^a Deceased-donor recipients.

AA, African American; ESRD, end-stage renal disease; HCV, hepatitis C virus; PRA, panel reactive antibody; HLA, human leukocyte antigen.

TABLE 2. Daily cyclosporin A dosing (mg) in HIV+ renal allograft recipients at various time points posttransplant according to composition of highly active antiretroviral therapy regimen

Patient	NRTIs	NNRTI	PI	3 mo	6 mo	12 mo	24 mo	36 mo
1	X		X	50/50 ^a	175 q 72 hr ^b	175 q 72 hr	175 q 72 hr	175 q 72 hr
2	X	X		100/75	75/75	100/75	75/50	100/75
3	X		X	25 q 24 hr	25 q 48 hr	25 q 48 hr		
4	X		X	75 q 48 hr	125 q 48 hr			
5	X	X		150/125	150/125	125/100		
6	X			200/200	200/175	175/100		
7	X		X	25 q 24 hr	25 q 48 hr			
8	X		X	75/50	75/50			

^a 50/50 = 50 mg at 0900 and 50 mg at 2100 (twice daily).

^b 175 q72 hr = 175 mg every 72 hr (every third day).

NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

acquired pneumonia and grade IIB AR at 8 and 9 months, respectively.

Three other patients developed bacterial urinary tract infections that promptly responded to appropriate antibiotic therapy. No patients developed new-onset diabetes mellitus, opportunistic or serious infections, malignancy, or progression of HCV-related liver disease. In all patients, USVL remained less than 50 RNA copies/mL and CD4 counts more than 200 cells/mm³ at all time points posttransplant.

All recipients were maintained on at least two nucleoside reverse transcriptase inhibitors, three in combination with a ritonavir-boosted protease inhibitor (PI), two in combination with a non-boosted PI, and two in combination with nevirapine (a nonnucleoside reverse transcriptase inhibitor). Table 2 gives the daily CSA dosing requirements for each patient at various time points posttransplant according to composition of HAART regimen, ranging from every 12 to 72 hr administration. Those on a PI had extremely low CSA requirements throughout the follow-up period, with four of the five patients receiving a single dose every other day or every third day. As a result of this profound drug interaction, we were forced to adopt new target 24-, 48-, and 72-hr trough level targets for these patients. These were initially set at 200, 175, and 150 ng/mL, respectively, during the first 6-months posttransplant, and then reduced over time in parallel with the 12-hr trough targets given in the Methods section. In contrast, the remaining three patients who did not receive a PI demonstrated more modestly, but still significantly, reduced CSA dose requirements when compared with those generally observed in HIV- recipients, ranging from 1.0 to 2.8 mg/kg every 12 hr (Table 2).

Three patients demonstrated initial surveillance and subsequent predose MPA levels in the therapeutic range, and did not require initial increases in MMF dose (Fig. 1A). In contrast, five patients had initial levels less than 1.5 mg/L, four of which were less than or equal to 0.7 mg/L, and in one case, undetectable (<0.5 mg/L). An attempt was made to increase the MMF dose to 2.5 to 3 g/day in these five patients as gastrointestinal tolerance would allow (Fig. 1B-F). Despite maximally-tolerated dose increases, MPA concentrations remained less than or equal to 1.6 mg/L in four patients during the first 6-months posttransplant.

DISCUSSION

Although clearly limited by a small number of patients without long-term follow-up, the results of our pilot study suggest that appropriately-selected HIV+ patients on HAART can undergo successful renal transplantation using anti-IL-2 receptor antibody induction and CSA-based triple therapy with a low incidence of AR and bacterial or viral infection, despite the presence of multiple other high-risk factors for poorer outcome. In comparison with the initial single-center report by Stock et al. (1) including 40% live donors and 40% AAs with follow-up ranging from 3 to 29 (mean 16) months, we were able to replicate the excellent patient and graft survival noted by the USCF group while maintaining excellent renal function and simultaneously decreasing the incidence of both AR and significant non-AIDS-associated bacterial infections. Indeed, our only case of AR occurred beyond 6-months posttransplant as a result of lowering the immunosuppressive burden in a patient with prior viral (BK and CMV) infection. In agreement with others (1, 3, 7, 8), we noted significantly decreased CSA dosage requirements in HIV+ kidney transplant patients maintained on a PI and modestly reduced CSA dose requirements when maintained on nucleoside reverse transcriptase inhibitors± nevirapine as part of their HAART regimen.

Since 2003, only four other single-center reports (including a second from USCF) have appeared regarding outcomes in HIV+ renal transplant recipients, all noting a significantly higher incidence of AR than that observed in our study (Table 3). In addition, only four compilations of multicenter data have reported on the incidence of AR in HIV+ renal allograft recipients in the HAART era. Roland (9) noted a rejection rate of 38% among 26 kidney transplant patients (including 54% AAs) enrolled in a pilot multicenter transplant study with median follow-up 9 months, but the fraction receiving induction therapy was not specified. Mazuecos et al. (10) examined the outcomes of 10 unsensitized, deceased-donor cases (10% AA, 60% HCV+) performed at five Spanish renal transplant centers with median follow-up 11 months. Four patients received induction therapy (three with anti-CD25 antibody and one with Thymoglobulin) and all were maintained on tacrolimus, MMF, and prednisone therapy.

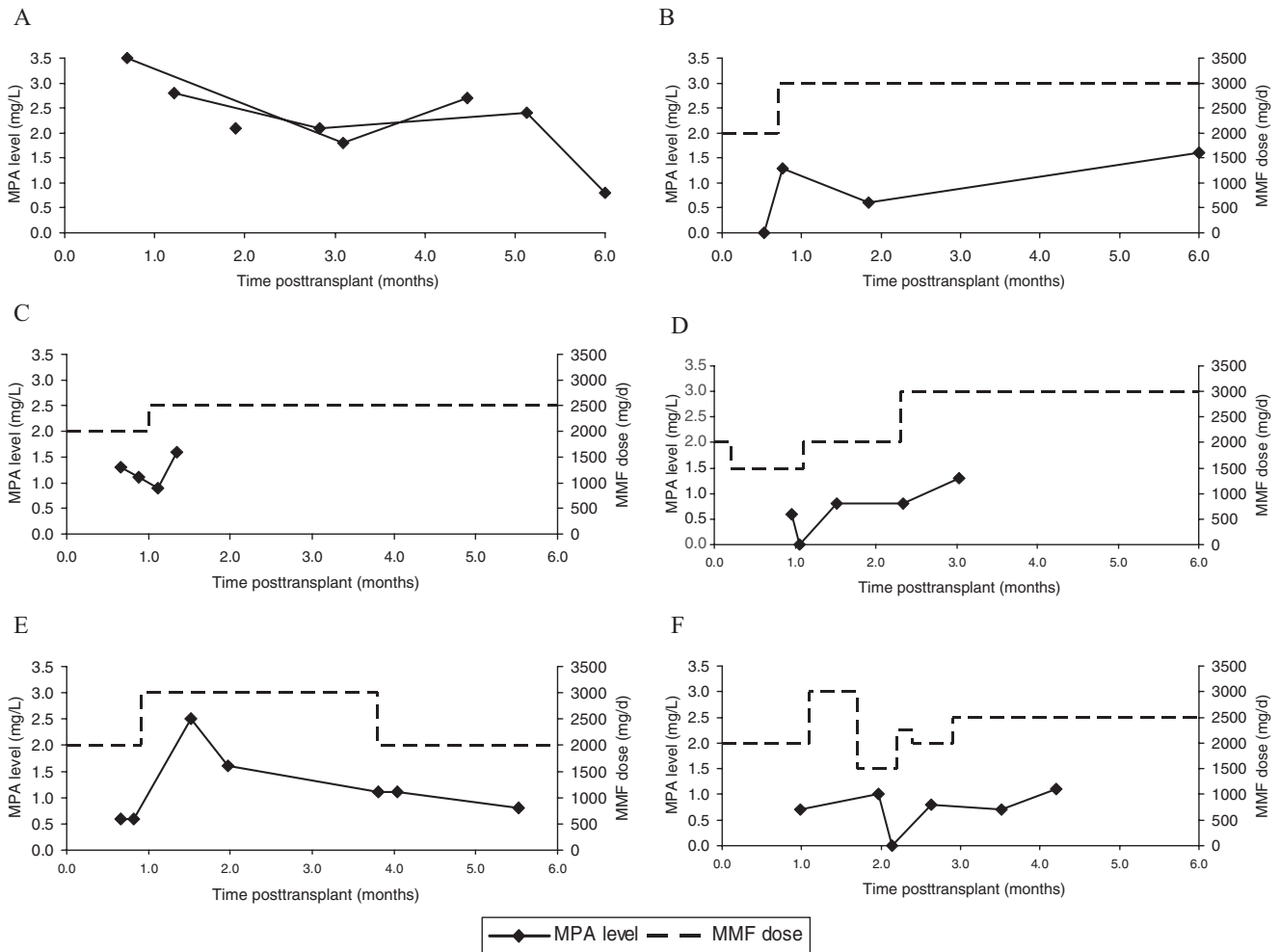


FIGURE 1. (A) Predose MPA concentrations in three patients who did not require MMF dose increases during the first 6-months posttransplant; (B–F) Predose MPA concentrations and MMF dosing in five patients with subtherapeutic initial MPA levels in whom an attempt was made to increase the MMF dose to 2.5 to 3 g/day as gastrointestinal tolerance would allow during the first 6-months posttransplant. MPA concentrations less than the lower limit of detectability of the assay, 0.5 mg/L, were plotted as zero.

TABLE 3. Summary of single-center studies of HIV+ renal allograft recipients transplanted in the highly active antiretroviral therapy era

Center	N	AA (%)	LD (%)	Induction	Maintenance	Target CSA level (ng/mL)	MMF dose (g/d)	AR (%)	Follow-up (mo)	Reference
UCSF	10	40	40	None	CSA/MMF/Pred	150–200	2–3	50	3–29	1
Pittsburgh	4	50	0	None	TCL-based	N/A	NS	75	39–69	2
	3	33	100	Alemtuzumab	TCL	N/A	N/A	0	5–11	2
Drexel	40	97	10	BSX	CSA/SRL/Pred	150–200	N/A	48 ^a	19 (median)	3
UCSF	20	50	40	BSX (55%)	CSA/MMF/Pred	150–200	2–3	36	4–56	4
				None (45%)	CSA/MMF/Pred	150–200	2–3	67		
Barcelona	3	33	0	Thymoglobulin	SRL/MMF/Pred ^b	N/A	2→1.5→1 ^c	67	18–30	5
Wayne State	8	88	13	BSX or DCZ	CSA/MMF/Pred	250–300 ^d	2 ^e	13	8–47	N/A

^a Clinical AR and subclinical AR occurred in 23% and 25% of patients, respectively, all of which were treated with pulse steroids.

^b One patient received TCL/MMF/Pred.

^c MMF dose was reduced from 2 g/day to 1.5 g/day at day 14 and further reduced to 1 g/day at day 30.

^d From 0 to 3 months; 225 to 275 ng/mL from 3 to 6 months.

^e With monitoring predose MPA concentrations.

AA, African American; LD, live donor; CSA, cyclosporin A; MMF, mycophenolate mofetil; AR, acute rejection; UCSF, University of California, San Francisco; Pred, prednisone; TCL, tacrolimus; N/A, not applicable; NS, not stated; BSX, basiliximab; SRL, sirolimus; DCZ, daclizumab.

Three patients developed steroid-sensitive AR and one antibody-mediated rejection requiring plasmapheresis, for an overall incidence of 40%. Qiu et al. (11) compared outcomes in 38 HIV+ patients with those of 38 HIV- patients receiving kidneys from the same deceased donor, and found an identical, low incidence of AR within the first year in both groups (11%). Finally, Roland et al. (12) recently reported 1- and 3-year outcomes from a nonrandomized trial involving 18 renal allograft recipients (44% AA, 44% live donor, 28% HCV+, 50% with DGF) at four transplant centers, with 39% receiving anti-IL-2 receptor antibody induction in combination with various maintenance regimens. Somewhat paradoxically, six of the seven patients receiving induction and 6 of the 11 patients not receiving induction developed AR (overall incidence 67%), although the panel reactive antibody of individual patients was not given. Importantly, 9 of the 12 patients with AR experienced their first episode within the first 6-months posttransplant.

We believe the low incidence of AR we observed when compared with that noted by the USCF and Drexel groups and recent multicenter study (3, 4, 12), even when an anti-IL-2 receptor antibody was also used for induction, is unlikely to simply be a reflection of our small number of patients. In the only two studies giving the precise timing of AR episodes (5, 12), virtually all occurred in the first 6 months, and all of our patients were followed for at least 8 months. Alternatively, we believe our ability to prevent AR within the first 6-months posttransplant may be explained by the use of higher CSA trough level targets and adjustment of MMF dose according to MPA trough concentrations (Table 3).

We found that surveillance predose MPA levels were low or undetectable in 50% and subtherapeutic in 63% of patients at 1-month posttransplant, which resulted in attempts to increase the dose and maintain it at maximally-tolerated levels over the next several months (Fig. 1). Interestingly, even with these dose increases, MPA concentrations that were only in the low therapeutic range could be attained in four of the five patients. It is now well-established that CSA decreases MPA exposure by inhibiting the enterohepatic recirculation of the drug (13, 14), and although we are unaware of any additional effects of antiretroviral medications on MMF pharmacokinetics, it may be that adequate MPA exposure is particularly critical in preventing AR in HIV+ recipients, especially given the frequent presence of other high-risk factors, such as AA ethnicity. Moreover, the absence of clear support in the literature for a substantial clinical benefit of therapeutic drug monitoring of MPA (15), along with the demonstration that MPA trough values are more variable and less predictive for the risk of AR than is the area under the curve and that predose concentrations poorly correlate with area under the curve (15-20), still do not negate the possibility that monitoring of MPA levels played a contributory role in preventing AR in our patients. Along these lines, several investigators have established trough level cutoffs below which the incidence of AR was felt to be significantly increased in adult renal transplant recipients on CSA in the early posttransplant period, ranging from 0.8 to 1.3 mg/L (17-19, 21). Without monitoring, most of our patients (and perhaps many of those in the prior studies mentioned) would have carried MPA levels below this threshold beyond the first posttransplant month, presumably increasing their risk for

AR. Finally, given the pronounced pharmacokinetic interactions between the antiretrovirals and calcineurin inhibitors, close monitoring on the part of the transplant center and total compliance on the part of the recipient are essential for a successful outcome, and these factors may also account for differences in the rate of AR in HIV+ patients at different programs. For example, we have previously demonstrated that HCV+ renal allograft recipients have similar patient, but decreased graft, survival when compared with their HCV- counterparts due primarily to increased graft loss secondary to noncompliance (22).

In summary, the results of our pilot study suggest that appropriately selected HIV+ patients on HAART can undergo successful renal transplantation with a low incidence of both AR and AIDS-associated and non-AIDS associated infections, despite the presence of multiple other high-risk factors. These encouraging but preliminary results, using IL-2 receptor inhibitor induction therapy in combination with increased CSA target trough levels and both surveillance and as-needed predose MPA concentration monitoring in the early posttransplant period, will need to be verified in larger numbers of HIV+ renal allograft recipients with longer follow-up.

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