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KIDNEY AND LIVER TRANSPLANTATION IN HUMAN IMMUNODEFICIENCY VIRUS-INFECTED PATIENTS: A PILOT SAFETY AND EFFICACY STUDY¹

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Background. Human immunodeficiency virus (HIV)-infected patients have historically been excluded from consideration for transplantation out of concern for the effects of immunosuppression on the progression of HIV disease. Improvements in HIV-related morbidity and mortality with the use of highly active antiretroviral therapy (HAART) have prompted a reevaluation of transplantation as a treatment option for HIV-infected patients with end-stage kidney and liver disease.

Methods. Eligible patients met standard transplant criteria. They had undetectable plasma HIV-1 RNA levels (viral load) for 3 months (kidney) or were predicted to achieve viral load suppression posttrans-

plantation if unable to tolerate HAART (liver); a CD4+ T-cell count of more than 200 cells/ μ L (kidney) or more than 100 cells/ μ L (liver) for 6 months; and no history of opportunistic infections and neoplasm. Standard immunosuppression included prednisone, mycophenolate mofetil (CellCept, Roche Pharmaceuticals, Basel, Switzerland), and cyclosporine (Neoral, Novartis, East Hanover, NJ).

Results. Fourteen patients received transplants (10 kidney transplants, mean follow-up 480 days; four liver transplants, mean follow-up 380 days). All of the kidney transplant recipients (100%) are alive and with functioning grafts, and three of four liver transplant patients (75%) are alive and well with functioning grafts (all liver transplant patients with normal liver function tests). The one death occurred 445 days posttransplantation in a liver recipient coinfecting with hepatitis C virus, who died as the result of its rapid reoccurrence. Rejection occurred in 5 of 10 kidney transplant recipients but did not occur in any of the four liver transplant recipients. HIV viral loads have remained undetectable in all patients maintained with HAART. CD4 counts have remained stable in patients not treated for rejection. Patients receiving protease inhibitors require 25% of the dose of cyclosporine compared with patients receiving nonnucleoside reverse transcriptase inhibitors.

Conclusions. There has been no evidence of significant HIV progression and no adverse effect of HIV on allograft function. Rejection is a concern in kidney transplant recipients, as is the possible poor outcome in hepatitis C virus-coinfecting liver transplant recipients. Preliminary data are encouraging and indicate that transplantation should be a treatment option for individuals with well-controlled HIV disease.

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Human immunodeficiency virus (HIV)-infected patients have historically been excluded from consideration for transplantation out of concern that the required immunosuppression would further deplete an already compromised immune system and accelerate HIV progression. The hesitation to perform transplantation in HIV-infected patients was compounded by additional concerns that HIV-associated morbidity and mortality were too high to justify the use of a scarce donor organ. Improvements in HIV-related morbidity and mortality with the use of highly active antiretroviral therapy (HAART) (1–3) have prompted a reevaluation of transplantation as a treatment option for HIV-infected patients with end-stage liver disease (ESLD) and end-stage kidney disease.

HIV-infected patients are living longer and demonstrating fewer HIV-related causes of morbidity since the advent of HAART therapy in 1996. A consequence of the increasing longevity, however, is that HIV-infected patients are now developing ESLD and end-stage kidney disease. ESLD is emerging as a major cause of morbidity and mortality in the HAART era. Because of the common routes of transmission, people with HIV are commonly coinfecting with hepatitis C virus (HCV) and hepatitis B virus (HBV). Estimates for the incidence of coinfection with HCV have ranged between 22% and 33% (4, 5) and approximately 9% for HBV (5). Similarly, end-stage renal disease (ESRD) is an increasing problem in patients with HIV, and it is estimated that between 4% to 7% demonstrate ESRD (6). HIV-associated nephropathy is the most common cause of ESRD in HIV-infected people, although renal insufficiency has also been attributed to increased risks of hemolytic-uremic syndrome, immunoglobulin (Ig)A nephropathy, and membranous glomerulonephritis. Among African Americans aged 20 to 64 years, HIV-associated nephropathy is the third leading cause of ESRD and accounts for 10% of all new cases each year (7, 8).

Given the increasing incidence of ESLD and end-stage kidney disease in HIV-infected people, the Liver and Kidney Transplant Services at the University of California, San Francisco, initiated a pilot safety and efficacy trial of solid-organ transplantation in HIV-infected patients. Despite historical reports of poor outcomes and exacerbation of HIV disease after transplantation (9–15), the timing for a pilot trial was based on several advances in the medical management of both HIV and transplant recipients. First, the ability

to suppress viral load and progression of HIV in the HAART era justifies a reexamination of the safety and efficacy of transplantation in HIV-infected patients. Second, there have been substantial advances in immunosuppressive regimens and the ability to provide prophylaxis to suppress opportunistic infections problematic in both HIV and immunosuppressed transplant recipients. In fact, immunosuppressive agents once believed to be strictly contraindicated in HIV-infected patients have been documented to have antiretroviral (ARV) qualities (16–21). This pilot safety and efficacy trial determines the impact of immunosuppression on the progression of HIV disease, determines the impact of HIV on allograft function and survival, and describes the pharmacologic interactions between ARV and immunosuppressive agents.

METHODS

To be considered for this trial, all liver and kidney transplant recipients had to meet the same standard criteria for transplantation as did HIV-negative candidates. Additional inclusion criteria included the following: undetectable HIV viral load for 3 months; CD4 T-cell counts greater than 200/mL for kidney recipients or greater than 100/mL for liver recipients; no history of opportunistic infections; and tolerating a stable ARV regimen for 3 months before transplant. The institutional review board approved exceptions to the requirement for undetectable HIV viral load, and stable ARV regimens were made if potential liver recipients had discontinued ARV therapy secondary to hepatotoxicity and if the HIV clinician could predict full virologic suppression posttransplant. On the basis of the ARV and HIV-1 RNA (viral load) history, in addition to any available drug resistance tests, the clinician can predict ARV drug resistance, cross-resistance, and response to future therapy. Exclusion criteria included the following: acquired immune deficiency syndrome (AIDS)-defining opportunistic infection; history of cancer or opportunistic neoplasm (except for treated basal cell carcinoma or in situ anogenital cancer), and HCV positivity in kidney patients with findings of cirrhosis on liver biopsy.

HAART regimens varied depending on the agents that patients were receiving at the time of referral. ARV administration was guided by physicians with expertise in HIV management and consisted of combinations of protease inhibitors (PIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and nucleoside analogs to optimize suppression of HIV-1 RNA. The various combinations of HAART for each patient are listed in Tables 1 and 2. Immunosuppressive regimens were guided by transplant physicians and sur-

TABLE 1. Kidney transplant recipients-demographics

ID	Sex	Age	Race	Indication	Donor	Pre-Tx CD4	Latest CD4	ARVs	Rejections	Cr	Survival days ^a
2	M	45	AA	HTN	LR	366	429	3TC, ABC, NFV	2	2.5	855
4	M	53	AA	HTN/HIVAN	CAD	334	396	3TC, ABC, NVP	1	1.4	727
5	M	38	C	Diabetes	HR	407	975	3TC, ABC, NFV(→NFP)	0	1.5	773
6	F	44	AA	HTN/HIVAN	HR	422	812	3TC, ddI (→ABC), NVP	0	1.4	774
8	M	49	C	HTN/HIVAN	HR	583	142	3TC, ddI, NFV, IDV → 3TC, D4T, NFV, EFV	1 ^b	2.5	607
10	M	45	C	Diabetes	LR	480	184	3TC, ABC, NVP	1 ^b	1.3	381
16	M	44	C	IgA/Neph	LR	578	471	3TC, ABC, NVP	0	1.5	284
17	M	38	C	Inter Neph	LR	377	282	3TC, ABC, NVP, DDI	0	1.3	241
23	M	53	AA	HIVAN	CAD	356	66	LOR/r, D4T, NVP	1 ^b	1.5	70
24	M	40	C	HIVAN	HR	332	440	LOP/r, DDI, 3TC, D4T	0 ^b	1.1	91

^a Survival days as of 8/22/02.

^b Treated with antibody therapy.

ARV, antiretrovirals; LR, living related; CAD, cadaveric; HR, high-risk cadaver; HIVAN, human immunodeficiency virus-associated nephropathy; Ig, immunoglobulin; HTN, hypertension.

TABLE 2. Liver transplant recipients-demographics

ID	Sex	Age	Race	Indication	Donor ^a	Pre-Tx CD4	Latest CD4	ARVs ^a	Rejections	Survival days
1/3	M	15	L	HCV	LR → CAD	973	200	3TC, D4T, ddl, NFV (intermittent)	0	day 445
14	M	48	C	HBV	LR	439	305	3TC, D4T, ddl, SQV, DLV, NVP → CBV, NFV, NVP	0	491
15	M	54	A	HBV	CAD	175	330	3TC, ABV, NVP, IDV	0	399
19	M	41	C	FUL/HAV	CAD	209	992	3TC, DDI, EFV, →3TC, DDI, NVP	0	249

^a Survival days as of 8/22/02.

HBV, hepatitis B virus; HCV, hepatitis C virus; HAV, hepatitis A virus.

geons with expertise in immunosuppressive protocols. Antibody induction therapy was not used in liver or kidney recipients. The preferred maintenance immunosuppression included cyclosporine A (CsA) to maintain trough levels between 150 and 200 ng/mL, mycophenolate mofetil (MMF) 2 to 3 g per day, and steroids. CsA and MMF were chosen because of literature supporting the ARV qualities of these agents (16–21). The standard practices for liver or kidney transplants were used in the treatment of rejection episodes. Mild rejection was treated with bolus steroids and a switch in maintenance immunosuppression from CsA to tacrolimus. Vascular (type II) rejection was treated with the polyclonal anti-T-cell agent Thymoglobulin, bolus steroids, and a switch in maintenance immunosuppression from CsA to tacrolimus. Standard prophylaxis for *Pneumocystis*, cytomegalovirus (CMV), and fungal infections were used according to standard transplant protocols.

Outcome measures included the following: survival, graft function, incidence of opportunistic infections, changes in CD4 counts, HIV viral load, anogenital human papilloma virus (HPV) disease progression, pharmacokinetic (PK) analysis of PIs, NNRTIs, and immunosuppressive drugs. Subjects were evaluated at the University of California, San Francisco, General Clinical Research Center with 12- or 24-hr PK studies pretransplant and at weeks 2, 12, 28, and 52.

RESULTS

Ten patients received kidney transplants and four patients received liver transplants according to this protocol. The patient demographics are included in Tables 1 and 2. Four of the kidney transplants were from living donors, and six were from cadaveric donors. Of the six cadaveric renal transplants, four were from high-risk donors. These donors were serologically negative for HIV or viral hepatitis but had engaged in high-risk activity as defined by the Centers for Disease Control and Prevention.

Four liver transplants were performed. Two of the four patients received a living-related orthotopic liver transplantation because of the difficulty in obtaining cadaveric livers before physical deterioration precluding transplantation. One of the living donor liver transplants (left lobe) required retransplantation with a cadaveric liver and kidney 28 days posttransplantation secondary to poor liver function related to a small-for-size graft. All cadaveric liver transplants were from low-risk cadaveric donors and were allocated according to standard United Network for Organ Sharing procedures.

Effect of HIV Infection on Patient and Graft Survival

Patient and graft survival in the 10 patients who underwent renal transplant were 100% (>1 year posttransplant for most patients) (Table 1). Biopsy-proven rejection occurred in 5 of 10 renal transplant patients (50%), and three of five patients required polyclonal anti-T-cell therapy (Thymoglobulin 6 mg/kg total dose) to treat type II (vascular) rejection.

All patients who received Thymoglobulin demonstrated sustained decreases in CD4 counts to less than 100/mL with slow recovery. Of note, one patient developed *Staphylococcus aureus* endocarditis after treatment with Thymoglobulin and was successfully treated with a 6-week course of antibiotics. Another patient requiring anti-T-cell therapy for vascular rejection developed *Pseudomonas aeruginosa* pneumonia and sepsis 2 weeks after therapy, which was successfully treated with a 2-week course of antibiotic therapy. Attempts at treating rejection with conversion of maintenance calcineurin inhibitor (CI) to tacrolimus were complicated by the development of diabetes mellitus and drug toxicity. Diabetes resolved after conversion back to CsA-based CI therapy with the addition of sirolimus. Other significant adverse events in the renal transplant recipients included two cases of *S. aureus* wound infections and one case of *Influenza B* pneumonia requiring hospitalization and antibiotic therapy. Despite the high incidence of rejection, all renal transplant recipients demonstrate good function as outlined in Table 1.

The first living donor liver transplant in an HIV-positive recipient was performed in a 15-year-old boy with severe liver insufficiency secondary to HCV, which was acquired through a transfusion (treatment for leukemia) when he was 2 years of age. He received a left lobe from his mother but required retransplantation with a cadaveric liver and kidney 28 days after the first transplant secondary to a small-for-size graft and renal insufficiency secondary to membranoproliferative glomerulonephritis related to his HCV. Although he recovered after transplantation and demonstrated good initial function of both the kidney and liver, he developed a rapid and severe recurrence of HCV. His viral loads remained greater than 120 million copies despite therapy with interferon and ribavirin, and repeat biopsies demonstrated fibrosing cholestatic hepatitis. He maintained low HIV viral loads despite stopping HAART therapy for prolonged periods of time secondary to the rapidly progressive liver disease. He developed CMV esophagitis associated with rapid deterioration in his liver function, and he died 64 weeks posttransplantation secondary to recurrent HCV. A second right lobe living donor liver transplant was performed in a 40-year-old man who demonstrated ESLD secondary to HBV. This patient was receiving adefovir therapy secondary to his lamivudine resistance, a common problem in patients receiving HAART therapy. He is doing well with normal liver function more than 1 year posttransplant. He continues on monthly hepatitis B Ig (HBIG) prophylaxis and adefovir, and his HIV and HBV viral load remain undetectable. Another patient with ESLD secondary to lamivudine-sensitive HBV underwent an orthotopic liver transplant and also continues to do well with normal liver function. His HBV and HIV viral load

remain undetectable and monthly HBIg infusions continue. He did, however, develop lamivudine resistance 36 weeks after transplant, and tenofovir was started at that time. A fourth patient underwent emergency liver transplantation for fulminant liver failure secondary to hepatitis A. Although this patient was not receiving ARVs at the time of transplant with an HIV viral load of 69,182 copies, he underwent emergency transplantation and was placed on HAART therapy posttransplant. He demonstrates normal liver function, and his HIV viral load became undetectable 8 weeks after beginning HAART. His HIV viral load remains undetectable at 44 weeks posttransplant.

Effect of Immunosuppression on HIV Progression

HIV viral load has remained undetectable in all patients maintained on HAART. The child with severe recurrence of HCV discontinued ARVs for 9 months secondary to the hepatotoxicity of HAART compounded by HCV. His viral load fluctuated between undetectable and 9,600 copies. His CD4 counts fluctuated between 214 and 444. A few weeks before his death, he developed CMV esophagitis when his viral load was 9,600 and his CD4 count decreased to 200/mL.

Although CD4 counts decreased immediately posttransplant in most patients, they rebounded within several weeks of transplantation. The exception to stable CD4 counts occurred in all patients treated with the polyclonal antilymphocyte agent Thymoglobulin. CD4 counts decreased below 220 cells/mL in all patients treated for vascular rejection with Thymoglobulin and have been slow in rebounding (Tables 1 and 2). There have been no AIDS-defining opportunistic infections, although most of the severe infections described in the previous section occurred after the treatment for type II rejection with polyclonal anti-T-cell antibody.

The progression of HPV and associated anal intraepithelial neoplasia (AIN) were monitored secondary to the high risk of this lesion in HIV-positive men and women, and its association with anal cancer (22, 23). The mean follow-up of the subjects was 439 days. Among the 12 HIV-positive transplant recipients examined to date, nine entered the study with abnormal cytology or histologic abnormalities (75%). Follow-up data are available in nine of the patients, and progression to a higher grade of AIN was noted in four of nine patients (44%). At baseline, 75% were positive for anal HPV. Follow-up samples were available on the subjects with negative results at baseline, and all demonstrated detectable HPV posttransplant. Among 19 samples that showed at least one detectable HPV type, 14 (74%) showed multiple HPV types, a risk factor for progression to AIN 2 or 3.

Preliminary Data: Pharmacokinetic Interactions Between Immunosuppressive and Antiretroviral Medications

The immunosuppressive agents and some of the ARVs affect similar cellular transport systems and metabolizing enzymes of the cytochrome p450 pathway. Formal PK assays have been performed on nelfinavir (PI), nevirapine (NNRTI), and CsA. As outlined in Figure 1, the area under the curves (AUCs) of nelfinavir are increased in the early posttransplant period but return to baseline levels by 52 weeks. The levels of nevirapine are relatively unaffected. The AUCs of both agents remain within the therapeutic range and, therefore, did not require alteration. Significant increases on CsA

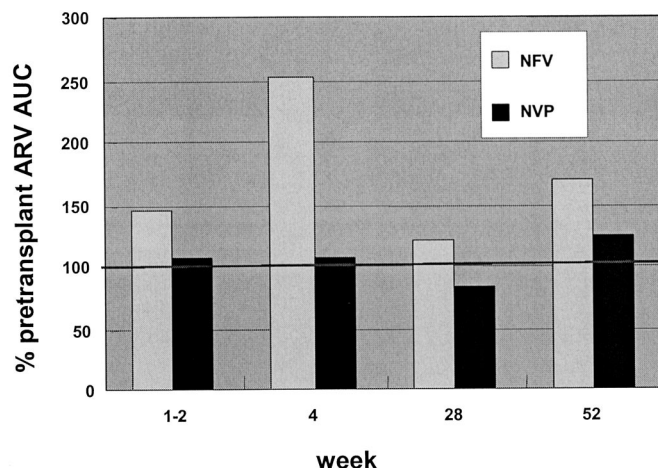


FIGURE 1. Change in antiretroviral (ARV) area under the curve (AUC) as a percentage of the pretransplant ARV AUC. NVP, nevirapine; NFV, nelfinavir. AUC in ng*mL/hr.

AUC dose occurred as a result of exposure to the nelfinavir (PI) but not nevirapine (NNRTI)(Fig. 2). Patients required approximately 25% of the standard dose of CsA (Neoral, Novartis, East Hanover, NJ) to achieve target plasma levels when compared with non-HIV-infected transplant recipients.

DISCUSSION

Despite logical concerns that further immunosuppression in an HIV-positive patient would lead to rapid progression of HIV disease, progression of HIV has not been a significant issue in the early analysis of this pilot trial. HIV viral load remained undetectable in all patients maintained with HAART therapy. CD4 counts remained stable in all patients, with the exception of patients treated for moderate to severe rejection with aggressive T-cell-depleting agents. It is important to note that the most severe infections noted in this trial occurred after treatment with Thymoglobulin, and that these agents must be used with trepidation.

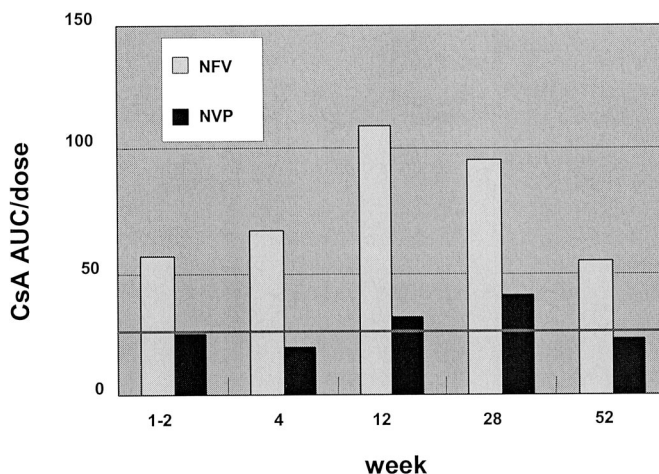


FIGURE 2. Cyclosporine (CsA) AUC dose ratios ("exposure"). CsA, cyclosporine. AUC in ng*mL/hr; dose in milligrams.

Although rejection was not an issue for the liver transplants, an unexpectedly high incidence of rejection was noted in the kidney transplant recipients. The rejection incidence of 50% is at least twofold the rate seen in HIV-negative patients undergoing transplantation with similar immunosuppressive protocols. The high rejection rates indicates that it is not the absence of an immune system but rather the presence of a dysregulated immune system in the patients with HIV. Patients with HIV are known to have a skewed T-cell repertoire, and it could be speculated that alloreactive clones may be present and responsible for the high rejection rates. In light of the high rejections, the use of CsA and MMF without induction therapy has been questioned. CsA and MMF were chosen on the basis of their known ARV qualities (15–21) and were believed to be adequate immunosuppression in these theoretically immunosuppressed patients. The initial hope was also to avoid antibody therapy, on the basis of historical data of poor outcome and progression of HIV to AIDS when OKT3 was used to treat rejection. By using CsA, we were able to switch to tacrolimus (Prograf, Fujisawa, Deerfield, IL) in the presence of acute rejection, along with a re-cycle of prednisone. On the basis of the initial high rejection rates in the kidney transplant recipients, we induced with an interleukin-2 receptor inhibitor. It has also been speculated that the high incidence of rejection could be related to suboptimal immunosuppression. There is no question that it was difficult to maintain stable levels of CsA secondary to interactions with the HAART therapy. However, it should be noted that at least three of the rejection episodes occurred during the first few days after transplantation, indicating that the rejection occurred rapidly and was unrelated to inadequate levels of maintenance immunosuppression.

For the liver transplant recipients, recurrent disease, rather than rejection, was the significant problem. The one patient who underwent transplantation as the result of HCV experienced an extremely aggressive recurrence of the hepatitis, with some of the highest viral loads seen in our post-transplant patients. The transplant group at King's College (London, U.K.) reported similar poor outcomes in patients undergoing transplantation for HIV and HCV coinfection. These patients experienced a rapid recurrence of HCV and died secondary to recurrent disease in the absence of HIV (24). This contrasts with recently reported data from the University of Pittsburgh group, who had relatively good results in six of nine HIV- and HCV-coinfected patients who underwent liver transplant (25). As with HIV-negative patients with HCV infection, better prophylaxis against recurrent disease will be required for better outcomes in this group. In contrast, the two HIV-positive patients undergoing liver transplantation for HBV have done well. Recurrent disease has been well controlled with monthly HBIG infusions, lamivudine and adefovir, and lamivudine and tenofovir.

The PK interactions of the immunosuppressive and antiviral agents were pronounced, particularly when PIs were used in conjunction with the CIs and sirolimus. These interactions particularly affected the levels of CIs and sirolimus, with significant reduction in the dosing regimens required to avoid toxicity. Patients on NNRTI-based regimens have not required significant alteration in CsA dosing. Formal PK studies have not been performed to determine the interactions between HAART and tacrolimus or sirolimus. However,

the limited experience with these agents indicates that patients on PI ARV regimens require only 1 to 2 mg of sirolimus per week and 1 to 2 mg of tacrolimus per week to achieve therapeutic levels. Although the patients on regimens avoiding PIs were easier to manage in terms of achieving stable and therapeutic immunosuppressive levels, all HAART regimens achieving successful control of HIV should be used with fastidious attention to CI dosing and levels.

The early results from this pilot safety and efficacy study indicate that solid-organ transplantation is safe and effective in a select group of patients with stable HIV disease. Immunosuppression has not resulted in the progression of HIV disease. Early graft and patient survival is comparable to liver and kidney allograft survival in HIV-negative recipients. Long-term follow-up will focus on the continued ability to suppress HIV and viral hepatitis, and recurrent disease in the transplanted allograft. These data support the hypothesis that HIV should no longer be considered an absolute contraindication to solid-organ transplantation.

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DYSLIPIDEMIA IN RENAL TRANSPLANT RECIPIENTS TREATED WITH A SIROLIMUS AND CYCLOSPORINE-BASED IMMUNOSUPPRESSIVE REGIMEN: INCIDENCE, RISK FACTORS, PROGRESSION, AND PROGNOSIS¹

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Background. This retrospective study compared the incidence, severity, and predisposing factors for dyslipidemia among renal transplant patients treated for up to 6 years with a cyclosporine ± prednisone-based concentration-controlled regimen without (n=118) or with (n=280) ascending exposures to sirolimus.

Methods. The diagnosis of dyslipidemia was established when the serum cholesterol value (CHO) was more than 240 mg/dL or serum triglycerides (TG) were more than 200 mg/dL. Generalized estimating equations and mixed-modeling procedures were used for statistical analyses.

Results. Hypercholesterolemia was observed in 46% to 80% and hypertriglyceridemia in 43% to 78% of sirolimus-treated patients during the first 6 posttransplantation months. The mean peak serum lipid levels among patients in the sirolimus group (CHO=285.5 mg/dL; TG=322.4 mg/dL) were significantly higher than those in the nonsirolimus group (CHO=250.2 mg/dL and TG=267.6 mg/dL; both $P < 0.01$). The lipid

values, which were persistently elevated during the first posttransplantation year, decreased slowly thereafter but remained significantly higher than the pretransplantation levels beyond 4 years after transplantation. The two forms of hyperlipidemia tended to occur in parallel (Pearson's coefficient of correlation, $r=0.5$, $P < 0.001$), showing a positive predictive value of 0.67 and a negative predictive value of 0.65. However, there was no significant difference in the incidence of cardiovascular events within 4 years after transplantation among patients treated with versus without sirolimus.

Conclusion. The dyslipidemia associated with sirolimus therapy, albeit persistent, does not seem to represent a major risk factor for the early emergence of cardiovascular complications.

Dyslipidemia represents a compelling problem among renal transplant recipients who are known to be predisposed to cardiovascular complications, including cerebrovascular accidents, hypertension, and accelerated atherosclerosis (1–3). In addition to the significant risk factors of advanced age and male gender in the general population, transplant patients frequently display disorders that produce or exacerbate hyperlipidemia: namely, elevated pretransplantation lipid values, renal graft dysfunction, nephrotic syndrome, and hypertension. In addition, drug therapy with beta blockers, diuretics (1), cyclosporine (CsA) (1–3), and steroids (2,3) may produce hyperlipidemic effects. Recently, the potent, macrocyclic lactone immunosuppressant sirolimus, which interrupts cytokine signal transduction pathways in a variety of tissues, has been shown to contribute to dyslipidemia as a result of inhibited lipid clearance from the circulation (4). Other adverse reactions to this drug, including thrombocyto-

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