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This research is supported by a grant from the University of California Universitywide AIDS Research Program (Award #TP99-SF-001). This project is named the "Migden HIV Transplant Initiative" to honor Assemblywoman Carole Migden's contribution to obtaining the UARP-administered funds.



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Solid Organ Transplantation in HIV Disease

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INTRODUCTION

- People with HIV infection have usually been excluded from consideration for transplantation because of concerns about the potential adverse effects of immunosuppressive drugs on HIV disease progression and reluctance to allocate a scarce resource to those with a poor prognosis.
- Improvements in the treatment and survival of people with HIV have resulted in the need for individual Transplant Centers and third party payers to re-evaluate this policy.

SPECIFIC AIMS

- To evaluate the impact of kidney and liver transplantation, and post-transplant immunosuppression, on HIV disease progression and markers of immune function and activity.
- To evaluate the impact of HIV infection on graft function and survival.
- To describe the pharmacokinetic interactions between immunosuppressive agents and the hepatically metabolized antiretroviral (ARV) agents.

METHODS

CLINICAL

Inclusion Criteria

1. Meet standard criteria for placement on transplant waiting list
2. Kidney: CD4+ T-cell count \geq 200/mm³ x 6 months
Liver: CD4+ T-cell count \geq 100/mm³ x 6 months
3. HIV-1 RNA < 50 copies/mL x three months
4. On stable ARV regimen x 3 months prior to entry or with a persistently undetectable HIV-1 RNA level without the use of ARVs.
5. Kidney candidates with HCV infection: liver biopsy pathology non-cirrhotic.

Exclusion Criteria

1. History of:
 - a. AIDS-defining opportunistic infection or neoplasm except drug-susceptible Candida esophagitis.
 - b. Neoplasm except *in situ* anogenital carcinoma, adequately treated basal or squamous cell carcinoma of the skin, solid tumors treated with curative therapy and disease free for more than 5 years.
2. Cirrhosis on liver biopsy in kidney candidates with hepatitis-C co-infection.

IMMUNOLOGY STUDIES

1. PBMC phenotyping to assess lymphocyte composition (e.g. naive vs memory) and state of cell activation
2. CFC: intracellular cytokine expression following stimulation of lymphocytes with staphylococcal enterotoxin B and CMV

PHARMACOLOGY STUDIES

1. Cyclosporine (CsA) levels at each clinical visit
2. 12 hour pharmacokinetic evaluation of immunosuppressant, PI, and NNRTI concentrations using HPLC/MS assays pre-transplant, then at Weeks 1 and 4, month 6, and Years 1, 2 and 5 post-transplant *and* whenever there is a change in ARVs, a significant change in immunosuppressants, or the development of an opportunistic infection.

RESULTS

PATIENT CHARACTERISTICS

ID	Sex	Age	Race	Indication	Donor ¹	Pre-Tx CD4	Latest CD4	ARVs	Rejections	Days since Tx ²
1/3	M	15	L	HCV	L - HR	910	323	3TC, D4T, ddl, NFV (intermittent)	0	315
2	M	45	AA	HTN	K - LR	366	112	3TC, ABC, NFV	2	292
4	M	53	AA	HTN/HIVAN	K - CAD	348	387	3TC, ABC, NVP	1	162
5	M	38	C	Diabetes	K - HR	478	567	3TC, ABC, NFV	0	209
6	F	44	AA	HTN/HIVAN	K - HR	561	571	3TC, ddl (-> ABC), NVP	0	208
7	M	49	C	HTN/HIVAN	K - CAD	375	448	3TC, ddl, NFV, IDV	0	40

¹ LR = living related; CAD = cadaveric; HR = high risk cadaveric
² Survival days: as of 1/23/00

CLINICAL EVENTS

HIV Issues

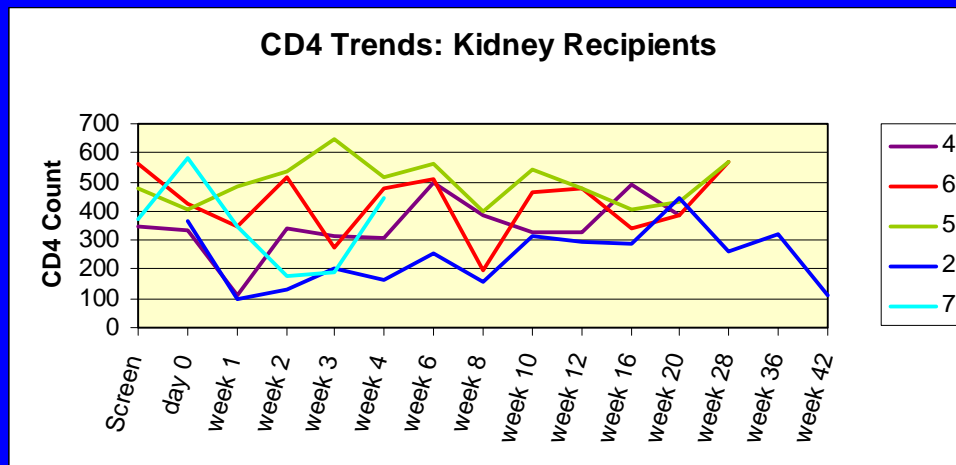
- No opportunistic infections or neoplasms
- 1 episode of reversible genital HSV recurrence
- 1 case of peripheral neuropathy
- Anal dysplasia detected at baseline in 1 subject (high grade) and mild anal atypia due to HPV infection developed at week 4 in a second subject with a normal baseline exam (week 28 results pending)
- Pt with baseline high grade lesion elected no pre-transplant therapy. At week 4, clinical exam unchanged, cytology normal, no biopsies obtained

Transplant Issues

- Liver patient required re-transplantation (small for size graft lesion) at week 7 and treatment of HCV. Received kidney also.
- 2 episodes of reversible kidney rejection + 1 episode currently being treated
- Reversible DM in one patient on prednisone and tacrolimus (prograph)
- 1 case of delayed graft function (2 weeks)

Markers of HIV Disease Progression: CD4+ T-cell Counts and HIV-1 RNA Load

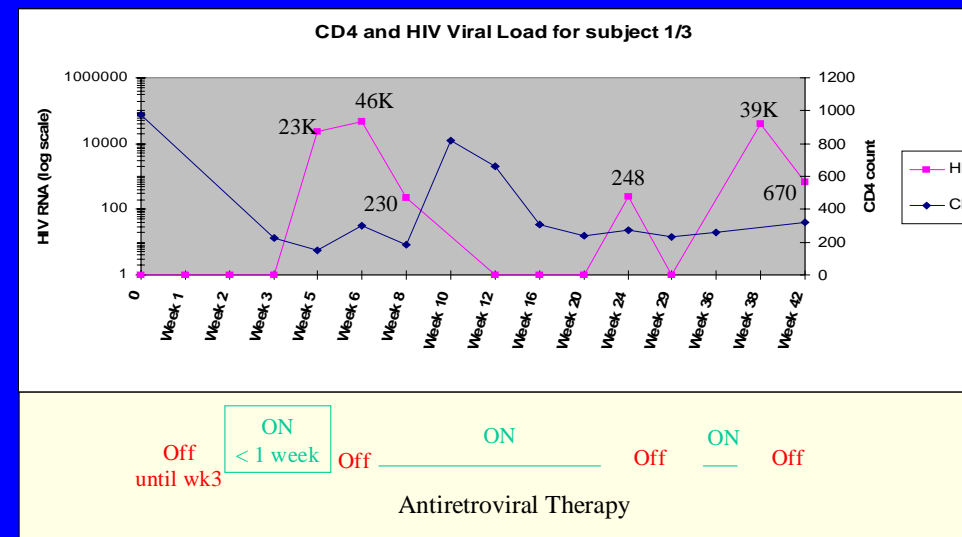
- CD4 + T-cell counts fell a mean of 144 and 39 cells/mm³ at weeks 1 and 4 respectively, and then rose a mean of 11 and 67 cells/mm³ at weeks 12 and 28 respectively.



Graph 1: CD4+ T-cell Trends in 5 Kidney Transplant Recipients

- HIV-1 RNA levels remained undetectable in:
 - All patients when on ARV therapy
 - In 1 patient with delayed graft function whose ARVs were held for 2 weeks

- HIV-1 RNA rebound was not immediate and levels remained relatively low (maximum 45,741 copies/mL) in 1 liver transplant patient who required 4 ARV treatment interruptions



Graph 2: CD4 + T-cell Count and HIV-1 RNA Trends in Liver Recipient Requiring ARV Treatment Interruptions

2 Subjects with Hepatitis C Co-Infection

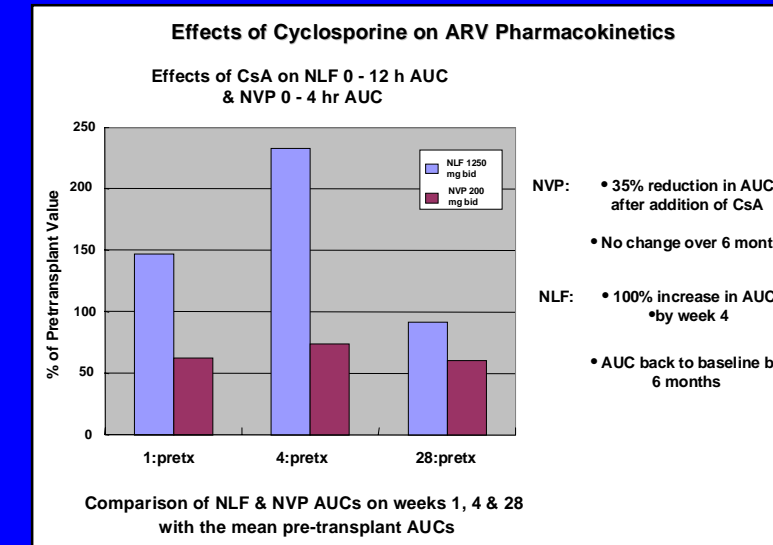
- Liver recipient had had poor response to pre-transplant INF/Ribavirin, initial rapid HCV RNA rebound post-transplant, with eventual reductions in HCV RNA post-transplant
- Kidney recipient with grade 1 pathology on liver biopsy pre-transplant elected no pre-transplant HCV therapy

IMMUNOLOGY

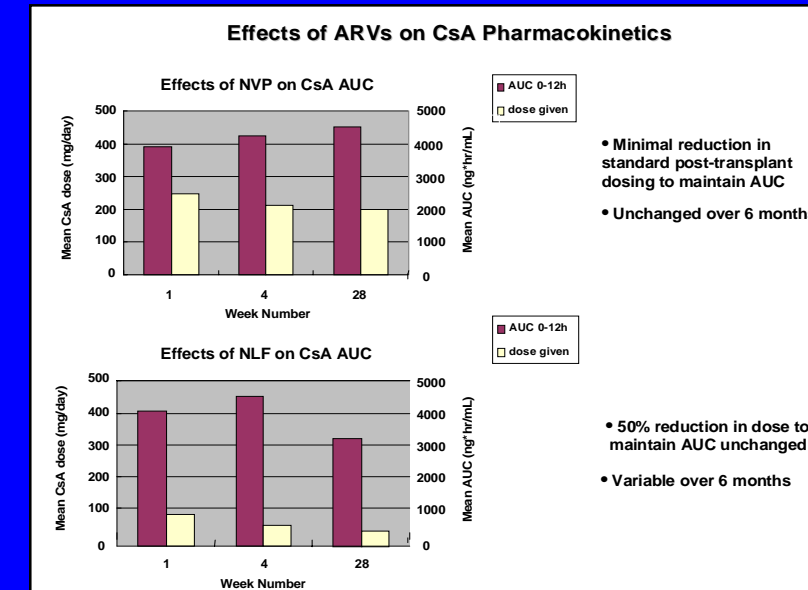
1. Patients were evaluated at varying time points after transplantation for changes in the composition, activation status, and antigen responsiveness of circulating peripheral blood lymphoid cells. Between baseline and 4 weeks post-transplant, no substantial changes were observed in the circulating percentages of:
 - CD4+CD3+ or CD8+CD3+ T cells
 - naïve (CD45RA+CD62L+) CD4+ or CD8+ T cells
 - memory/effector (CD45RA-CD62L+/-) CD4+ or CD8+ T cells
 - CD3-CD19+ B cells
 - CD3-CD56+ NK cells.
 - Amongst CD4+ or CD8+ T cells, no substantial changes were observed in the expression of the activation markers CD38 or HLA-DR.
2. No substantial changes were observed in the ability of circulating CD4+ T cells to produce TNFalpha or IFNgamma in response to stimulation by the superantigen SEB or to stimulation by cytomegalovirus (CMV) antigens, as measured using the cytokine flow cytometry assay.

PHARMACOLOGY

- 30% reduction in NVP AUC after addition of CsA was associated with free unbound drug levels within published IC95 values; no viral rebound has been observed
- Clinically significant elevations in NFV AUC at week 4 have resolved by 6 months. NFV induces metabolic enzymes over time; this enzyme induction appears to be overcoming the metabolic inhibitory effects of CsA that are the predominant factor early on.



Effects of CsA on NLF 0 - 12 h AUC & NVP 0 - 4 hr AUC



Effects of ARVs on CsA Pharmacokinetics

DISCUSSION

HAART-associated improvements in morbidity and mortality have brought a formal re-evaluation of traditional policies regarding transplantation in people with HIV to the forefront of the scientific and policy agenda.

Several observations from this preliminary prospective study of the impact of post-transplant immunosuppression in people with HIV disease are quite reassuring:

- There has been no evidence of impaired graft function in 4 of the 5 kidney recipients.
- There has been no significant HIV clinical, virologic nor immunologic disease progression.
- 5 episodes of ARV treatment interruption in 2 patients have resulted in minimal and delayed HIV rebound, suggesting that one or more of the immunosuppressive drugs (including mycophenolate and cyclosporine) may have antiviral activity (direct or immune mediated).
- PI and NNRTI levels have been affected but remain within adequate treatment ranges. Cyclosporine doses have been low in those on PIs and typical in those on NNRTIs. NVP does not affect standard dosing regimens for CsA; variable dose adjustments are required with NFV (starting at 50% reduction).

Areas of particular concern in the management of HIV-infected transplant recipients include:

- The need for a multi-disciplinary health care team to participate actively in patient monitoring and management, with excellent communication among team members. This is particularly important relative to medication changes.
- HCV: control of HCV infection is challenging in liver recipients, and the degree of HCV disease progression among HIV-infected kidney recipients is unknown.
- HPV: HVP-related cervical and anorectal disease, already accelerated in people with HIV infection, may be exacerbated by post-transplant immunosuppression.
- HHV8: HHV8-related disease, particularly KS, may be exacerbated or reactivated by post-transplant immunosuppression.

Next steps and additional research and policy questions include:

- These initial findings have prompted the creation of a multi-site study that will more definitively evaluate the safety and efficacy of organ transplantation in people with HIV in the context of a growing need and limited resources.
- Initial studies will evaluate healthier patients in an attempt to prove the hypothesis that post-transplant immunosuppression is safe in people with HIV infection. If proven, subsequent populations to be evaluated might include patients with:
 - previous opportunistic infections or neoplasms,
 - detectable HIV-1 RNA levels who are unable to tolerate ARV therapy, and
 - lower CD4 cell counts.
- Donors: "high risk" donors are currently being considered at many transplant centers. The safety of accepting HIV positive donors for HIV positive recipients is unknown, as the question of the existence and clinical impact of super-infection remains unanswered.