

## Research Team

Peter G. Stock, MD PhD  
Asst. Professor of Surgery (PI)

Michelle E. Roland, MD  
Asst. Professor of  
Medicine (Co-PI)

Nancy L. Ascher, MD PhD  
Professor and Chair of Surgery

Leslie Z. Benet, PhD  
Biopharmaceutical Sciences  
and Pharmaceutical Chemistry

Jay A. Levy, MD  
Professor of Medicine

Jeffrey N. Martin, MD MPH  
Asst. Professor of Epidemiology  
and Biostatistics and Medicine

Joseph M. McCune, MD PhD  
Assoc. Professor, and Assoc.  
Investigator, Gladstone Institute

Lynda A. Frassetto, MD  
Asst. Clinical Professor

Advances in antiretroviral therapy have resulted in decreasing AIDS mortality rates. As HIV-positive people are living longer, there are increasing numbers of deaths from end-stage organ disease, rather than AIDS-associated opportunistic infections.

People with HIV infection have often been excluded from consideration for solid organ transplantation. Given the significant improvements in prognosis for people with HIV and AIDS, it is now time to provide adequate safety and efficacy data so that transplant centers and health insurers can re-evaluate this policy.

With funding from the State of California, UCSF has embarked on a pilot study—The Migden HIV Transplant Initiative—to collect data on HIV-positive transplant recipients. The initial impetus for the research came from Survive AIDS (formerly ACT UP Golden Gate), a community-based AIDS advocacy organization in San Francisco. UCSF researchers, working with community representatives, designed the research program that is now underway.

## Background

People with HIV disease are at risk for kidney and liver diseases, just like people who do not have HIV. Increasing numbers of patients with end-stage liver and kidney disease are seeking transplantation. Yet people with HIV infection have usually been considered ineligible for organ transplantation for two important reasons. First, prior to the recent developments in antiretroviral treatment, people with HIV infection had a shortened lifespan as a result of their underlying immunodeficiency. Due to the severe shortage of organs, transplant centers have made allocation decisions based in part on the likelihood of survival in the recipient. Second, the immunosuppressive drugs required post-transplant to prevent organ rejection may accelerate the progression of HIV-induced immune depletion, causing rapid disease progression, morbidity, and mortality.

Highly active antiretroviral therapy (HAART) has changed the natural history of HIV infection

in the developed world. People are living longer, healthier lives. Excluding people with HIV infection from consideration for organ transplantation based on the single criterion of length of survival can no longer be considered legitimate policy.

In spite of tremendous advances in the treatment of HIV disease, and the growing morbidity and mortality associated with end-stage organ failure among HIV-infected people, serious questions remain about the safety and efficacy of organ transplantation in people with HIV infection. It remains unclear to what extent HAART will restore immune function and allow transplant recipients to tolerate immunosuppression without an adverse impact on survival.

Immunosuppression is required after organ transplant, and HAART is recommended to suppress HIV replication. It is unknown how and to what extent the anti-rejection therapies will interact with antiretroviral (ARV) medications. Describing the interaction of HAART and immunosuppressive agents in HIV-positive transplant recipients will provide data crucial to improving the management of anti-rejection immunosuppression in the setting of HIV.

The UCSF study will begin to provide answers to these important questions. The study has been funded by \$2 million in State of California allocations administered through the University of California Office of the President, Universitywide AIDS Research Program (UARP).

## Experience with Organ Transplantation in People with HIV

Although some initial reports demonstrated worse outcomes following solid organ transplantation in HIV-positive recipients, there have also been reports suggesting that HIV infection does not have adverse effects on graft (transplanted organ) survival. In fact, there have been two reports of HIV-positive patients undergoing liver or renal transplantation who demonstrated normal graft function for at least eight years following the transplant.

*The objective of this pilot Phase I study is to begin collecting safety and efficacy data that will be valuable in guiding the management of increasing numbers of HIV-infected people confronted with end-stage liver and kidney disease in the face of well-controlled HIV disease.*

Retrospective reviews suggest that certain immunosuppressive regimens may decrease HIV disease progression. The long-term survival of HIV-positive transplant recipients without progression to AIDS is notable in that many of these patients were immunosuppressed with the drug cyclosporine. Cyclosporine inhibits proliferation of some T-cells, so it theoretically could interfere with the T-cells that serve as targets of HIV. The exact mechanism of a potential beneficial impact on HIV is unknown, but researchers have hypothesized that cyclosporine may decrease immune system over-activation, thought to be part of the pathogenic mechanism associated with HIV infection.

The historical data suggest that there is a sub-population of HIV-positive transplant recipients who tolerate immunosuppression and, in several cases, have demonstrated transplant survival comparable to that of HIV-negative transplant recipients. The prognosis for people with HIV infection continues to improve with the use of HAART; epidemiological data show a decreased incidence of opportunistic infections and hospitalizations associated with the use of HAART. It follows that the use of HAART in immunosuppressed, HIV-positive transplant recipients may further improve patient and graft survival following transplantation.

## Aims of the UCSF Study

The objective of this pilot Phase I study is to begin collecting safety and efficacy data that will be valuable in guiding the management of increasing numbers of HIV-infected people confronted with end-stage liver and kidney disease in the face of well-controlled HIV disease. The UCSF research team will collect data regarding HIV-infected transplant recipients so that the following specific aims can be addressed:

- Evaluation of the impact of kidney and liver transplantation, and post-transplant immunosuppression, on HIV disease progression and markers of immune function;
- Evaluation of the impact of HIV infection on graft function and survival; and
- Description of the pharmacokinetic (drug) interactions between immunosuppressive agents and antiretroviral agents, especially with regard to the liver-metabolized protease inhibitors and non-nucleoside reverse transcriptase inhibitors (NNRTIs).

## Inclusion Criteria

Eligibility criteria for the study include meeting standard listing criteria for placement on a transplant waiting list, no history of opportunistic infections (except esophageal candidiasis) or neoplasms,<sup>1</sup> and willingness to use PCP, herpes virus, and fungal prophylaxis as indicated. If the patient also has Hepatitis C (HCV) infection, he or she must be willing to undergo frequent monitoring, including liver biopsies, and treatment of HCV as recommended by the study clinicians. Males and females of any age are eligible for the study. Female subjects of childbearing age must have been tested for pregnancy within 14 days of screening. All subjects must practice barrier contraception.

CD4+ T-cell count criteria vary for potential kidney and liver recipients. Kidney transplant recipients must have a CD4+ T-cell count of at least 200; liver recipients must have a CD4+ T-cell count of at least 100. Kidney and liver recipients also need to have been on a stable ARV regimen for three months or longer prior to entry, with an undetectable viral load.

<sup>1</sup> This criteria will be changed after the first 20 transplant recipients nationally have survived for six months if one or fewer opportunistic infections develop. At that time, a prior history of opportunistic infections will no longer exclude patients from participation.

## Follow-Up Schedule

The total study period is five years. Following transplantation and a post-operative recovery period, this will be primarily an outpatient study. However, there will be a minimum of five inpatient, 14-hour General Clinical Research Clinic (GCRC) visits at week four, six months, and one, two, and five years post-transplant. These visits are for the pharmacokinetic studies that require multiple blood draws in order to determine how the immunosuppressive and ARV drugs interact. Additional GCRC visits will be required when ARV or immunosuppressive regimens are significantly altered, or if the patient develops an opportunistic infection or neoplasm. Patients will be evaluated daily during the initial hospitalization, then weekly (four times), every other week (four times), monthly (twice), every eight weeks (four times), and every 12 weeks for the next two years, then every six months for the final two years of follow-up.

## Special Studies

A series of specialized sub-studies are being performed to address specific research questions about solid organ transplantation in this patient population.

1. **Pharmacokinetics (pK):** Many of the immunosuppressive drugs, as well as all of the protease inhibitors and NNRTIs, are metabolized by the liver. An enzyme system called the p450 system is involved in this metabolism to varying degrees for the different drugs. The purpose of this sub-study is to gather data about the interactions between these individual drugs, and drug classes, which are currently somewhat predictable but not well defined. Some combinations will result in altered levels (increased or decreased) of one or more of the drugs in the blood. In addition to monitoring cyclosporine levels in the blood at clinical visits and between clinical visits as necessary by standard clinical practice, whole blood and/or plasma will be analyzed for immunosuppressant, protease inhibitor, and NNRTI concentrations over a 12-hour dosing period several times throughout the study. Urine toxicology screening for illegal and prescription drugs will be performed as well to evaluate any interactions with the ARV or immunosuppressant medications.

2. **Human Papilloma Virus (HPV):** HPV infection is associated with the development of cellular abnormalities (dysplasia) as well as cancer in the cervix, anus, and rectum. People with HIV infection, as well as people who have received transplants, are at an increased risk for the development of these cancers. Thus, prior to and following transplant, full examinations of the cervix, anus, and rectum will be performed using a special microscope called a colposcope. Biopsies will be taken from areas that appear abnormal on examination. Cervical and anal Pap smears will be performed to look for the presence of dysplastic or cancerous cells. A treatment algorithm will be followed prior to transplant in those who have abnormalities on exam, Pap smear, and/or biopsy. Those patients who cannot be treated prior to transplant will be monitored to observe the progression of the dysplasia, to try to determine if that progression occurs more rapidly in this cohort of immunosuppressed patients with HIV infection.

3. **Human Herpes Virus 8 (HHV8):** HHV8 is associated with the development of Kaposi's Sarcoma (KS) as well as several other neoplastic (cancerous) and non-neoplastic disorders. KS is seen both in people with HIV infection, and in the transplant population. Interactions between HIV and post-transplant immunosuppression affecting the acquisition and progression of HHV8-related clinical disease and laboratory markers will be monitored. These markers include HHV8 antibody, quantitative plasma viral load, cell-associated viral load, saliva studies, and cellular immunologic studies.

4. **Immunology:** The immunologic consequences of transplant and immunosuppression in HIV-positive patients will be followed with the following tests pre- and post-transplant: For HIV, peripheral blood phenotyping to assess the composition of circulating subpopulations of lymphocytes (e.g., naïve vs. memory) and the state of cell activation; intracellular cytokine expression following stimulation of recipient lymphocytes with staphylococcal enterotoxin B and CMV to assess cellular function; lymphoproliferation assays to assess cellular function by evaluation responses to alloantigen (against donor targets), phytohemagglutinin, and recall antigens (measles, tetanus, CMV); natural killer cell function; soluble markers of immune activation including serum beta-2 microglobulin and neopterin; CD8+ cell suppressing activity; chest computed tomography to assess thymic index; donor reactivity and chimerism studies for transplant.

## Future Research Directions

Current pilot funding will only enable UCSF to provide clinical and research evaluations for approximately 15 recipients of kidney or liver transplants. UCSF researchers are working with insurers to encourage them to cover clinical costs and thereby enable the study to involve as many interested and eligible individuals as possible. To further the goals of this pilot study, UCSF researchers have been working with clinicians and investigators from around the country to construct a multi-site study with a common protocol and a centralized data collection and analysis facility. In order to proceed with a multi-site study that would provide the numbers

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of patients necessary to conduct a properly controlled efficacy evaluation, the UCSF team and others will apply for a grant from the National Institutes of Health.

## References

- Ahuja TS, Zingman B, Glicklich D. Long-term survival in an HIV-infected renal transplant recipient. *Amer J Nephrol*. 1997;17:480-2.
- Barry M, Gibbons S, Back D, Mulcahy F. Protease inhibitors in patients with HIV disease: clinically important pharmacokinetic considerations. *Clin Pharmacokinet*. 1997;32:139-143.
- Detels R, Munoz A, McFarlane G, et al. Effectiveness of potent ARV therapy on time to AIDS and death in men with known HIV infection duration. *JAMA*. 1998;280:1497-1503.
- Erice A, Rhame FS, Heussner RC, Dunn DL, Balfour HH, Jr. Human immunodeficiency virus infection in patients with solid-organ transplants: report of five cases and review. *Reviews of Infectious Diseases*. 1991;13:537-47.
- Eyster ME, Fried MW, Di Bisceglie AM, et al. Increasing hepatitis C virus RNA levels in hemophiliacs: relationship to human immunodeficiency virus infection and liver disease. *Blood*. 1994;84:1020-3.
- Eyster ME, Diamondstone LS, Lien LM, et al. The natural history of hepatitis C virus (HCV) infection in multitransfused hemophiliacs: effects of coinfection with human immunodeficiency virus (HIV). *J Acquir Immune Defic Syndr*. 1993;6:602-10.
- Fauci AS, Pantaleo G, Stanley S, Weissman D. Immunopathogenic mechanisms of HIV infection. *Ann Intern Med*. 1996;124:654-63.
- Huss R, Hoy CA, Ottinger H, Grosse-Wilde H, Deeg HJ. Cyclosporine-induced apoptosis in CD4+ T-lymphocytes and computer-simulated analysis: modeling a treatment scenario for HIV infection. *Research in Immunology*. 1995;146:101-8.
- Karpas A, Lowdell M, Jacobson SK, Hill F. Inhibition of human immunodeficiency virus and growth of infected T-cells by the immunosuppressive drugs cyclosporin A and FK 506. *Proceedings of the National Academy of Sciences of the United States of America*. 1992;89:8351-5.
- Palella F, Delany K, Moorman A. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. *New Engl J Med*. 1998;338:853-860.
- Ragni MV, Bontempo FA, Lewis JH. Organ transplantation in HIV-positive patients with hemophilia [letter] *New Engl J Med*. 1990;322:1886-7.
- Rodriguez R, Schoenfeld P. Renal manifestation of HIV infection. In: Cohen P, Volberding P, ed. *The AIDS Knowledge Base*. 1998 ed; 1998.
- Schoenfeld P, Mendelson M, Rodriguez R. Survival of ESRD patients with HIV infection. *J Am Soc Nephrol*. 1995;6:561.
- Schoenfeld P, Rodriguez R, Mendelson M. Patients with HIV infection and end-stage renal disease. *Adv Renal Replace Ther*. 1996;3:287-292.
- Schwarz A, Offermann G, Keller F, et al. The effect of cyclosporine on the progression of human immunodeficiency virus type 1 infection transmitted by transplantation: data on four cases and review of the literature. *Transplantation*. 1993;55:95-103.
- Thomas DL, Cannon RO, Shapiro CN. Hepatitis C, hepatitis B, and human immunodeficiency virus infections among non-intravenous drug using patients attending clinics for sexually transmitted diseases. *J Infect Dis*. 1994;169:990-5.
- Tzakis AG, Cooper MH, Dummer JS, Ragni M, Ward JW, Starzl TE. Transplantation in HIV+ patients. *Transplantation*. 1990;49:354-8.

## Materials Available

Further information on organ transplantation in people with HIV disease is available on the web at HIVInSite: <http://hivinsite.ucsf.edu>.

Information is also available by contacting:

*Study-related questions*  
Laurie Carlson  
Study Coordinator  
[CarlsonL@surgery.ucsf.edu](mailto:CarlsonL@surgery.ucsf.edu)  
415/502-8322

*Transplant-related questions*  
Peter Stock, MD  
Principal Investigator  
[stockp@surgery.ucsf.edu](mailto:stockp@surgery.ucsf.edu)  
415/353-1117

*HIV-related questions*  
Michelle Roland, MD  
Co-Principal Investigator  
[mroland@php.ucsf.edu](mailto:mroland@php.ucsf.edu)  
415/476-4082, x432

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