

Solid Organ Transplantation in HIV Positive Patients:
A Briefing Book

Multi-Site Trial Planning Meeting

Hotel Sofitel, 1914 Connecticut Street NW
Washington, D.C.
August 12-14, 2000

Hosted by:

AIDS Research Institute, University of California, San Francisco

Dr. Thomas J. Coates, Director, ARI

Dr. Peter Stock, PI, UCSF HIV Transplantation Project

Dr. Michelle Roland, Co-PI, UCSF HIV Transplantation Project

National Institute of Allergy and Infectious Diseases, National Institutes of Health

Dr. William Duncan, Associate Director, Therapeutics Research Program, Division of AIDS

Dr. Kerr, Genetics and Transplantation Branch Division of Allergy, Immunology and
Transplantation

The Emmes Corporation

Dr. Donald Stablein, President

Sunday August 13

Overview Presentations

9:15 AM - Noon

A. Review of UCSF Protocol

9:15 – 9:45 AM

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.*

Review of Current Protocols for Kidney and Liver

- Common inclusion/exclusion criteria
- Kidney vs. liver: differences in eligibility
 - CD4, viral load, antiretroviral use
- Medication regimens
 - antiretrovirals, immunosuppressives, prophylaxis (transplant and HIV)
- Clinical and laboratory follow-up
- Special studies and donor issues

Common Eligibility Criteria

- No history of opportunistic infection or neoplasm
 - except fluconazole sensitive candida esophagitis
- No h/o aspergillus, TB, cocci, resistant fungal infections, specific neoplasia, recent flu or RSV
- No age limitations (peds ok)
- Monitoring (including biopsies) and treatment of HCV co-infection

Eligibility Criteria Differences

Kidney

- CD4 \geq 200
- VL < 50
- Stable ARV regimen

Liver

- CD4 \geq 100
- VL < 50 on stable ARV regimen *or*
- Detectable viral load off ARVs but ability to predict full suppression post-tx

Medication Regimens

- **Immunosuppressive Protocols**
 - Cyclosporine-based therapy
 - Prednisone
 - Anti-metabolites: MMF or imuran
 - Standard rejection therapy
- **Antiviral therapy**
 - Optimize suppression of HIV-1 RNA
 - Minimize development of resistance
 - Avoid AZT, D4T (MMF interactions)
- **Prophylaxis**
 - pneumocystis, cytomegalovirus, fungal infections
 - MAC, TB
 - HCV: interferon and ribavirin
 - HBV: HBIG and lamivudine

Clinical Follow-Up Schedule

- 5 year follow-up
- Min. 6 GCRC visits (12-24-hour) at Week 1, 4, 6 months, and 1, 2 and 5 years + + +
- --> weekly (x 4)
- --> every other week (x 4)
- --> monthly (x 2)
- --> every 8 weeks (x 4)
- --> every 12 weeks for the next two years
- --> every 6 months for the final two years

Current Sub-Study Elements

- Immunology Studies
 - HIV
 - Transplant
- Virology Studies
 - HIV
 - HCV, HBV
 - HPV
 - HHV8
- Pharmacology Studies

Immunology Studies: HIV

- **Immunophenotyping**
 - (T and B cells, naïve vs memory, activation state)
- **LPA**
 - (PTH and recall antigens)
- **Cytokine flow cytometry (CFC)**
 - (to CMV and staph enterotoxin B)
- **NK cell function**
- **Soluble activation markers**
 - neopterin, beta-2-microglobulin
- **CAF** (CD8 mediated antiviral response)
- **CMV, EBV and HHV6 ELISAs**
- **Thymus CT**

Immunology Studies: Transplant

- LPA against alloantigen (donor)
- Donor reactivity
 - (MLC, CML and CFC)
- Chimerism studies

Virology Studies HIV, HCV, HBV

- Plasma and tissue HIV-1 RNA quant (bDNA)
- Plasma and tissue HCV RNA quant. (bDNA)
- HCV genotype and quasispecies
- Plasma and tissue HBV DNA quantification (bDNA and PCR)

Virology Studies: HHV8 and HPV

- HHV8: Ab, cell associated and plasma viral load, cellular immunology, saliva
- HPV: cytology and biopsy with colposcopy

Pharmacology Studies

- Trough CSA and prograph levels
- ? MMF levels
- Full pK of protease inhibitor and NNRTI
 - HPLC assays
- Urine tox for illegal and prescription drugs

Donors

- Living related
- Cadaveric
- High Risk

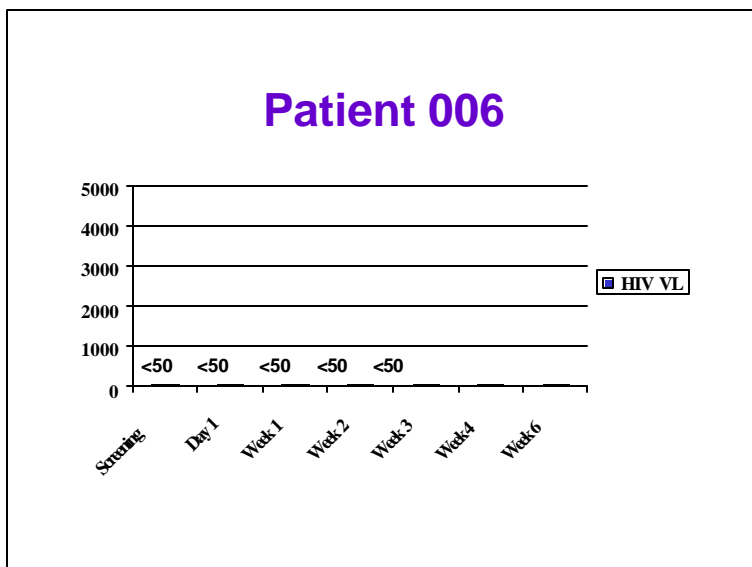
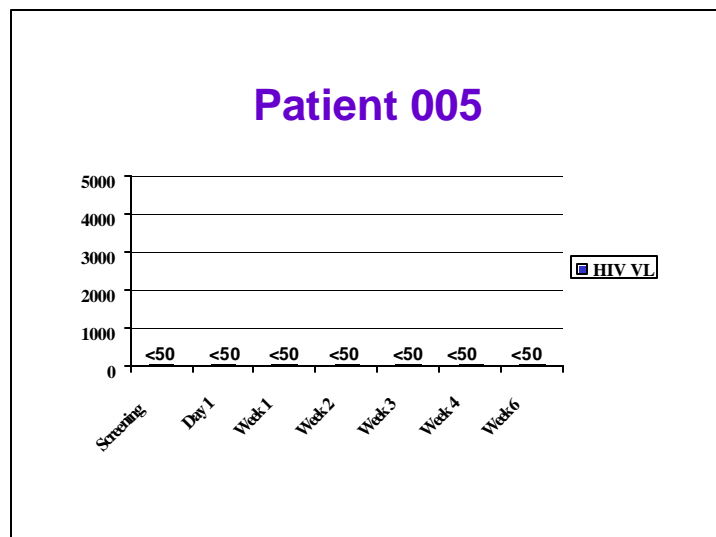
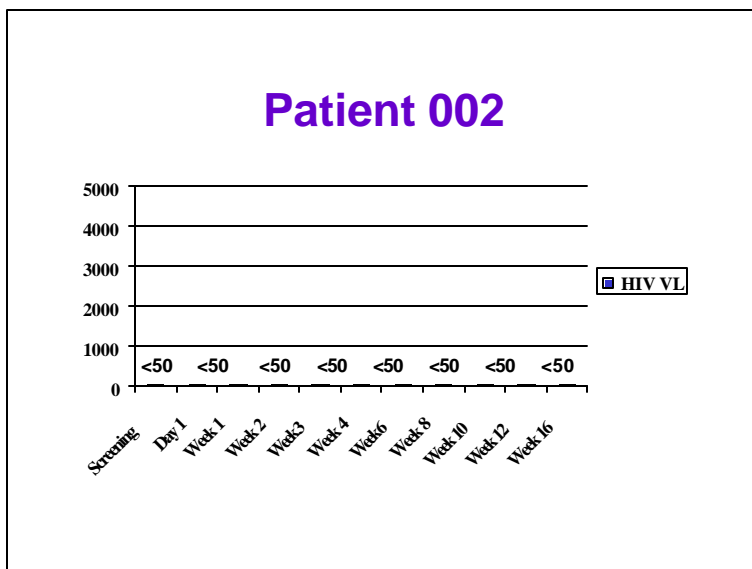
Sunday August 13

B. Review of UCSF and Pittsburgh patient experience:

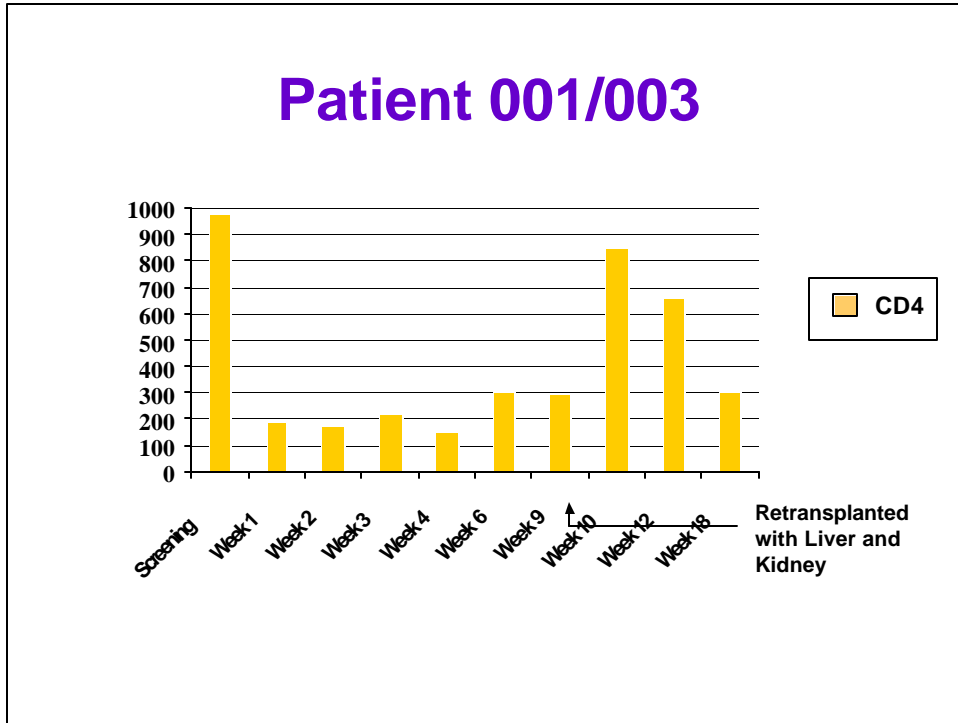
9:45 – 10:15

- transplant, immunology, HIV and pharmacology issues

UCSF patients:



Adolescent male, HIV and HCV co-infected:



Pittsburgh experience:

The first series of patients who were positive for HIV at the time of transplantation and patients who acquired HIV (presumably from the donor) was reported by the University of Pittsburgh. In a retrospective serologic survey of organ donors and transplant recipients, seven of the 18 HIV+ transplant recipients had antibodies to HIV-1 before transplantation; while the other 11 HIV+ recipients seroconverted at a mean of 96 days after transplantation. Nine (50%) of the 18 HIV-1 seropositive transplant recipients died a mean of 6 months after transplant surgery, and 9 (50%) were still alive a mean of 43 months after transplantation. Of the 15 liver transplant patients, 7 were alive at a mean of 2.75 years. In more recent followup (12.75 years), only 2 liver transplant patients remained alive, both on anti-HIV therapy.

The purpose of this presentation is to examine the impact of organ transplantation the progression of HIV and immune deficiency; patient and graft survival; and the interaction of antiretroviral therapy and antirejection regimens.

Since the advent of HAART therapy, 5 patients with ESLD have received OLTX at the University of Pittsburgh. Four had ESLD secondary to HCV infection, while one patient developed acute liver failure, presumably due to toxicity of the nucleoside analogs used for HIV therapy. OLTX was performed between September 1997 and May 2000. One patient with not only advanced HIV infection but also with advanced liver failure, manifest by ventilator dependency and renal failure, died 12 days following OLTX from bacterial infection (not related to HIV). Four other patients have survived between 4 and 24 months. In all cases, OLTX reversed the stigmata of acute and chronic liver failure, including ascites, encephalopathy, muscle wasting, fatigue, hypersplenism and jaundice. While HCV recurrence requiring ribavirin and interferon therapy was required in three patients, all patients have excellent liver function, while being monitored at our center.

PI use was associated with significant cytochrome P450 3A interference. Tacrolimus dosing was markedly reduced to minimize levels of tacrolimus and resultant toxicity. The average dose of tacrolimus was 1 mg/week. However, in one case, the local physician treating HIV, elected to take the patient off of HAART therapy (“drug-free holiday”). The elimination of the PI caused drastic reduction in tacrolimus levels precipitating moderate acute rejection. This highlights the critical nature of the complex pharmacologic interactions and the need for the transplant service and the HIV virologists to communicate before making adjustments in medications.

HIV loads remained undetectable in all patients during the entire followup period, remaining on HAART with protease inhibitor (PI). No patient has developed opportunistic infections (one patient had an elevated CMV pp65 level, but had no disease). Total CD4 counts, which were all <200 cells/mm³ prior to OLTX, improved to >200 cells/mm³ following OLTX.

Two patients with ESRD received KTX at the University of Pittsburgh. Both had cadaveric kidney transplantation with good function. As with the OLTX patients, HIV loads remained undetectable in both patients during the followup, using a variation of HAART therapy, based on NNRTI. No patient has developed opportunistic infection, and all CD4 counts remained >200 cells/mm³ during the post-KTX period.

Transplant and HCV Issues

- Living donor and preservation injury
- 1 wound infection
- High risk donor and informed consent
- Recurrent HCV infection and re-transplantation
- HCV management

HIV/Immunology Issues

- Liver patient: not able to tolerate po meds for several weeks
- Patient off antiretroviral therapy for 4 weeks prior to return of HIV viremia
- No opportunistic infections
- Challenge to diagnose and appropriately attribute symptoms that are common in both settings, eg odynophagia, rash/folliculitis, peripheral neuropathy. Need to create clinical guidelines across disciplines.
- Initial CD4 declines in all patients (some to under 200 cells/mL), with return to or near baseline

Pharmacology Issues

- Complicated dosing schedules. Transplant nurses and pharmacists require training re HIV drug dosing issues.
- Need/desire to avoid MMF antagonistic interactions – adjust antiretrovirals as soon as possible pre-transplant to avoid AZT and D4T.
- Kidney patients may need dose adjustments post-transplant – anticipate and plan
- Mycophenolate levels below “therapeutic” in patients with presumed toxicity (bone marrow) – how to use these levels?
- Indinavir levels unexpectedly low in week 1 pK evaluation - ? metabolism, absorption. Resulted in change in therapy to new protease inhibitor..
- Variable indinavir levels in one set reevaluated with different sample preparation techniques
- Good nelfinavir levels in 2 patients
- NNRTI assays being developed; delay in nevirapine analyses

Sunday August 13

C. Review of statistical and data management issues 10:30 - 11:30

Statistical Method -

Once a month, for the duration of the study, a test will be performed to compare the null hypothesis that one-year graft survival is greater than or equal to 75%, against an alternative hypothesis that graft survival is less than 75%. The sequential testing procedure to be used is an extension of the Sequential Probability Ratio Test (SPRT). A brief description of the test follows: the test is fully described in the technical appendix.

To develop this test and investigate the operating characteristics, we must select a point θ_1 in the alternative region where a desired power is attained. The probability that the null hypothesis is rejected should be equal to a pre-assigned value α when the null hypothesis is true and the probability of accepting the null hypothesis should not exceed a pre-assigned value β whenever $\theta = \theta_1$. The particular restrictions imposed for this study are $\alpha = \beta \approx 0.10$ and $\theta_1 = (60\% \text{ 1 year graft survival})$. The extended SPRT test can be represented graphically. At each monthly interim analysis, the total time on study is plotted against the total number of observed graft failures. The trial will be stopped if a total of 75 patients are put on trial or the test statistic falls below the continuation region defined by a line with a slope of 2.57 and intercept of -8.14. If the trial is stopped because the test statistic crosses the bound, the null hypothesis will be rejected in favor of the alternative.

In standard kidney transplants, the hazard rate of graft failure is relatively constant during the first year on study. Thus the test assumes an exponential distribution for the time til graft failure, but censors data at the one-year time point. Only graft failures that occur before the patient has been followed for one year on study are counted. Total time on study is computed as time from entry to graft failure, or one year, whichever comes first, summed over all individuals on study.

The usual measures of performance of a SPRT are the error probabilities α and β of rejecting H_0 when $\theta = \theta_0$ and of accepting H_0 when $\theta = \theta_1$, respectively, and the expected sample size $E(N | \theta_i)$. The operating characteristics of the test to be used in this protocol are shown in Table 1 below. These operating characteristics were determined in a simulation study of 100,000 replications that assumed exponential time to graft failure and uniform accrual at the rate of 75 individuals over a three-year period.

Table 1 - Operating Characteristics of Sequential Testing Procedure from a simulation study with 100,000 replications

True 6 Month Survival	85%	80%	75%	70%	65%	60%	55%
Probability Reject Null	0.00	0.02	0.10	0.32	0.64	0.88	0.98
Mean Month Stopped	48	47	45	39	30	22	17
Mean # graft failures	11	15	18	18	17	14	11
Mean # Patients Enrolled	75	74	71	65	54	43	34

The procedure rejects the null hypothesis in favor of the alternative 10% of the time when the true survival rate is 75%, and 88% if the time when the true survival rate is 60%. This corresponds to a type I error rate $\alpha=0.10$ and a type II error rate of $\beta=0.12$. When the true one-year graft survival rate is 55%, the procedure is almost certain (98%) to reject the null hypothesis in favor of the alternative. In this situation, on average, the study will be halted 17 months after opening, when 11 graft failures have been observed in 34 patients.

While the motivation for this testing procedure is largely heuristic rather than theoretical, the simulation results validate the approach. When the true graft survival rate at one year was 75%, the test crossed the boundary in 10,315 of 100,000 replications, for an estimated type I error rate of 0.10. When the true graft survival rate at one year was 60%, the test failed to cross the boundary in 12,083 of 100,000 replications, for an estimated type II error rate of 0.12. The test is almost certain (98%) to reject the null hypothesis when the true graft survival rate at one year is 55%.

Sunday August 13

D. Review of funding issues and mechanisms

11:30 - noon

- Cooperative Clinical Trial in Adult Transplantation

The Cooperative Clinical Trial in Adult Transplantation was established in 1991 to expedite the evaluation of new treatment modalities to prevent kidney graft rejection. The effort was recompleted in 1995 and awards were made to three principal institutions. The cooperative program now includes 40 Transplant Centers throughout the U.S.

Poor long-term graft survival rates and the side effects of immunosuppression are still major obstacles in renal transplantation. Because many of the new immunosuppressive agents are being tested in a limited number of centers, the NIAID launched this cooperative research effort to provide the mechanism for establishing and coordinating multi-center clinical trials to evaluate the efficacy of new immunosuppressive protocols and agents. This is particularly important for testing the ability to successfully transplant HIV+ recipients and include pharmacokinetic, infectious disease and mechanistic studies as an integral part of the trials.

The NIAID will support the data collection and analyses of the trials of kidney transplantation in HIV+ recipients and support data coordinators at each kidney transplant site based on the number of transplants performed.

- UCSF ARI is engaged in active fundraising to support the data management of the liver portion of this multi-site study.
- Funding for the sub-studies is to be identified.
- R01 Prep

Sunday August 13

Specific Topic Discussions

1:00 – 5:00 PM

A. Eligibility Criteria: Kidney vs. Liver

1:00 – 1:45 PM

** Areas of further discussion and negotiation have been identified*

Key Kidney Transplant Inclusion Criteria:

1. * Current CD4+ T-cell count $\geq 200/\text{mm}^3$ * times ≥ 6 months.
2. HIV-1 RNA ≤ 50 for three months (Amplicor Monitor Ultrasensitive PCR or bDNA Quantiplex version 3.0)*. (Intermittent elevations to ≤ 1000 copies/mL, if not persistent on more than two sequential measures and followed by undetectable levels, are permitted.)
3. On a stable ARV regimen for ≥ 3 months prior to entry.
4. Ability of the study clinicians to predict successful ongoing HIV-1 suppression with the current ARV regimen, given the medication history and results of genotypic or phenotypic resistance testing if available. It is preferred, but not required, the study clinicians be able to construct a subsequent ARV regimen that is likely to result in successful ongoing HIV-1 suppression, given the medication history and results of genotypic or phenotypic resistance testing if available, should the current regimen result in persistent detectable plasma HIV-1 RNA.
5. If the patient also has HCV infection, must be willing to undergo frequent monitoring, including liver biopsies and treatment of HCV as recommended by the study clinicians.
6. Able to provide informed consent. In the case of a minor, parental or legally responsible person will be asked to provide informed consent.

*After eligibility is determined, patients will be asked to have CD4+ T-cell and HIV-1 RNA (Quantiplex or Amplicor, Ultrasensitive) assays performed every two months by their primary care provider and faxed to the study site. Eligibility at the time of organ availability will be determined based on the most recent CD4+ T-cell count and viral load result, not more than 8 weeks prior to transplant.

Key Kidney Transplant Exclusion Criteria:

1. Any history of any AIDS-defining OI or neoplasm except drug susceptible Candida esophagitis.
2. History of disease caused by aspergillus or aspergillus colonization.
3. History of pulmonary or extrapulmonary tuberculosis.
4. History of pulmonary coccidiomycosis.
5. History of documented resistant fungal infection (krussii, glabrata, candida).
6. History of documented influenza or RSV in the past 30 days.
7. History of any 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 ≥ 5 years.
8. New criteria pending IRB approval: no use of IL-2 or GM-CSF within 6 months prior to transplant

UCSF Protocol: LIVER

Key Liver Transplant Inclusion Criteria (that are different from Kidney):

1. *Current CD4+ T-cell count $\geq 100/\text{mm}^3$ * times ≥ 6 months.
2. HIV-1 RNA ≤ 50 for ≥ 3 months (Amplicor Monitor Ultrasensitive PCR or bDNA Quantiplex version 3.0)*. (Intermittent elevations to ≤ 1000 copies/mL, if not persistent on more than two sequential measures and followed by undetectable levels, are permitted.) This criteria may be waved at the discretion of the study HIV clinician if the patient has been unable to tolerate ARV medications secondary to liver dysfunction and the patient meets all other eligibility criteria, including #3.
3. Willing to agree to start or re-start ARV therapy in the immediate post-operative period if not currently on ARVs secondary to intolerance caused by liver dysfunction. If ARV therapy was not interrupted secondary to intolerance, patient must be willing to continue such therapy, or modify ARV therapy, at the direction of the study HIV clinician in conjunction with the primary care provider.

No Key Liver Transplant Exclusion Criteria are different from Kidney

Sunday August 13

<p style="text-align: center;"><u>DISCUSSION POINTS</u> Eligibility Criteria: Kidney vs. Liver</p>
--

Common Issues:

- *Philosophical question*: proof of principle in those we are least likely to harm based on relatively preserved immune function vs. access in those most likely to die from end stage organ disease
- *Options*: allow sites to have different criteria vs. transplantation off study
- *Question*: Are there statistical implications, additional questions that could be answered?

1. Stratified CD4 criteria

- Consider no lower CD4 criteria for liver at some sites?
- Consider higher CD4 criteria at some sites?
- Challenges: patient referral consistency

2. Flexible HIV viral load criteria for liver

- Challenge: do all sites have sufficient HIV clinician input with antiretroviral resistance expertise to accomplish the goal of only transplanting those with high likelihood of full suppression post-transplant? How does the study HIV clinician work with the primary HIV provider?
- Options: allow sites to have different criteria vs transplantation off study?
- Consider no VL criteria (ok to not be able to fully suppress HIV) for liver at some sites?
- Challenges: patient referral consistency

3. Opportunistic infection/neoplasm

- Options: allow sites to have different criteria vs transplantation off study?
- Consider no OI criteria for liver at some sites?
- Challenges: patient referral consistency

Sunday August 13

B. Specific Issues in the Co-infected Patient: HCV and HBV 1:45 – 2:00

Background

UCSF Protocol: METHODS – STUDY PROCEDURES

Patients will also be screened at baseline and followed every 6 months for the following markers of past or present infection: hepatitis B surface antigen (HBSAg) and quantitative hepatitis B DNA if surface antigen positive, hepatitis B surface antibody (HBSAb), hepatitis B core antibody (HepBcoreAb), hepatitis C antibody (HCV Ab) and quantitative hepatitis C RNA level and quasispecies determination if antibody positive.

All episodes of potential rejection, marked by increases in transaminases, will require liver biopsy for confirmation prior to the institution of rejection therapy. All tissue will also be evaluated for HIV load and other viruses as indicated by the patient's clinical history. Liver transplant patients who test positive for hepatitis C virus at post-transplant will have a liver biopsy performed at Month 4, every 12 weeks in Years 2 and 3 and every 6 months in Years 4 and 5.

<p style="text-align: center;"><u>DISCUSSION POINTS</u> Specific Issues in the Co-infected Patient</p>
--

1. HCV

- Kidney recipients must have full evaluation: U/S, liver biopsy
- Considerations for interferon/ribavirin therapy
- Liver patients: may have very poor outcome. Need stopping rules defined.

2. HBV

- Kidney recipients must have full evaluation: U/S, liver biopsy
- Considerations for specific therapy: 3TC, adefovir/tenofovir
- In those on 3TC for HIV, should genotype for HBV resistance be obtained?
- Liver patients: common peri-transplant treatment protocol

3. HIV, HBV, and HCV Co-Infection

Sunday August 13

C. Medication Regimens

2:00 – 3:00 PM

Background

UCSF Protocol: METHODS – STUDY PROCEDURES

The *immunosuppressive protocols* will consist of cyclosporine-based therapy and prednisone. Cyclosporine doses will be altered to obtain levels standard for either liver or kidney transplants. The immunosuppressive regimens will be guided by transplant physicians and surgeons with expertise in the immunosuppressive protocols. Anti-metabolites (imuran or mycophenolate mofetil) may be added to the regimens as deemed necessary for treatment of rejection. Further treatment of rejection episodes will be according to standard practices for liver or kidney transplants. Modification of dosages and drugs will be made for toxicity as per usual protocols for transplant recipients.

Antiviral therapy will consist of combinations of PIs, NNRTIs, and nucleoside analogues to optimize suppression of HIV-1 RNA. ARV therapy choices will be guided by study physicians with expertise in HIV management in consultation with the primary care provider.

Standard *prophylaxis* for pneumocystis, cytomegalovirus (CMV), and fungal infections will be utilized as per standard transplant protocols. Additional HIV-related prophylaxis will be directed as needed by the HIV physicians. Prophylaxis against recurrent hepatitis C will be provided with interferon and ribavirin. Prophylaxis against recurrent hepatitis B will be provided with monthly hepatitis B immune globulin (HBIG) and daily lamivudine.

Background – Cyclosporine and Its Effect on HIV

A Controlled Trial of Cyclosporine (CsA) in HIV Infection

L. H. CALABRESE*1, M. M. LEDERMAN1, N. PAREKH2, J. SPRITZLER2, R. COOMBS3, F. AWEEKA4, L. FOX5, and the ACTG 334 team. 1Cleveland, OH; 2Boston, MA; 3Seattle, WA; 4San Francisco, CA; and 5Bethesda, MD

HIV infection is characterized by a state of persistent immune activation that may result in adverse effects to the host and enhance viral immunopathogenesis. We have performed a multi-center randomized placebo-controlled trial of an inhibitor of T cell activation - CsA in patients with HIV disease to assess the safety of low dose immunosuppression and the effects of CsA on HIV induced immune activation, immune function and HIV replication.

Methods: 28 patients with CD4+ cells >500 cells/ul and HIV-RNA >600 copies/ml were randomized to CsA (4 mg/kg, Neoral®) or placebo for 12 weeks. Patients were either on no anti-retrovirals (n=) or stable dual nucleoside therapy (n=). The primary end point was state of immune activation as assessed by plasma IL2 receptor (sIL2R) levels, secondary endpoints included additional markers of immune activation, quantitative virology, and assays of immune function.

Results: 26 patients were available for analysis with 2 lost to follow up. Overall, CsA therapy was safe with no serious adverse effects noted in the study group. Markers of immune activation including sIL2R, CD4-DR, CD8-DR, beta-2-microglobulin fell in the CsA group and either increased or remained unchanged in the placebo group but none of these achieved statistical significance. Total CD4 and CD8 lymphocyte numbers as well as CD38 and CD25 expression did not differ between the groups. Functional assays including DTH response and apoptosis were unchanged while lymphocyte proliferation to tetanus, PHA, streptokinase and Candida tended to fall in the CsA treated patients but these did not achieve significance. Virologic data are pending analysis.

Conclusions: 1. Therapy with low doses of the immunomodulator CsA appears safe in patients with non-advanced HIV disease. 2. At doses of 4 mg/kg CsA (Neoral) has no effect or only modest effects on immune activation or function. 3. These findings support the evaluation of CsA for use in HIV infected patients undergoing organ transplantation or with autoimmune diseases.

Key Words: cyclosporine, immune activation, immune-based therapy

***From the 6th Conference on Retroviruses and Opportunistic Infections, January and February, 1999.**

Background – Antiretroviral Issues

Antiretrovirals and Immunosuppressant Drug Interactions:

Although immunosuppression is required for graft maintenance and effective ARV therapies are required to suppress HIV replication, it is unknown how and to what extent the anti-rejection therapies will interact with the ARV medications. All viral aspartyl protease inhibitors that exhibit anti-HIV activity are metabolized by CYP3A4 and these same drugs also act as inhibitors and sometimes inducers of CYP3A4^{54, 55}. Since the immunosuppressants cyclosporine (CSA), tacrolimus and sirolimus, as well as the ARVs in use, are substrates, inhibitors, and/or inducers of CYP3A4, we expect to see significant drug interactions when these medications are given concomitantly. It is likely that the immunosuppressants will effect the plasma concentrations of the ARVs under study, but it also very likely that the presence of the PIs and NNRTI ARVs may act upon the metabolizing enzymes and transport pumps in such a way as to increase immunosuppressant levels as well. It is anticipated there will be an increase in cyclosporine concentrations, especially with concomitant oral administration of PIs. The development and validation of analytical methods for the specific and sensitive quantification of immunosuppressive drugs and ARV compounds are a prerequisite for the evaluation of the pharmacokinetic interactions between these drugs. Validated HPLC/MS methods for the determination of cyclosporine (CSA), tacrolimus, and sirolimus from biological specimens have been established in our laboratory^{56, 57, 58}, as has a method for the simultaneous determination of the PIs. Since organ transplantation in HIV-positive patients is in its nascent stage, describing the long-term pharmacokinetic profiles of concomitant immunosuppressive agents and ARVs in HIV-positive transplant recipients will provide crucial data that will improve the management of anti-rejection immunosuppression in the setting of HIV.

Abacavir-Mycophenolate Interactions:

1. Margolis, D., Heredia, A., Gaywee, J., Oldach, D., Drusano, G., & Redfield, R. (1999). **Abacavir and mycophenolic acid, an inhibitor of inosine monophosphate dehydrogenase, have profound and synergistic anti-HIV activity.** *Journal of Acquired Immune Deficiency Syndromes*, 21(5), 362-70.

ABSTRACT: The use of inhibitors of purine nucleoside metabolism has been advocated for the treatment of HIV-1 infection. Abacavir is the first clinically available guanosine analogue HIV-1 reverse transcriptase inhibitor, and the most potent nucleoside analogue yet developed. Mycophenolic acid (MA), a specific inhibitor of lymphocyte proliferation that is currently in use in organ transplantation, acts on inosine monophosphate dehydrogenase to block conversion of inosine monophosphate to guanosine monophosphate. We found abacavir and MA inhibited HIV-1 replication in stimulated peripheral blood mononuclear cells (PBMCs) and in monocyte-derived macrophages (MDMs). Inhibition was potent and synergistic to an extent not previously observed with other antiretroviral combinations. MA was effective at concentrations (0.25 microM) far below those used for immunosuppression in organ transplantation. An HIV strain encoding the M184V mutation was susceptible to the combination of MA and abacavir. However, the combination of MA and zidovudine (ZDV) or stavudine (d4T) was antagonistic. Although the translation of these observations must be carefully evaluated in clinical trials, the judicious combination of antiretrovirals and inhibitors of nucleoside metabolism may emerge as an important strategy in the treatment of HIV infection.

2. Heredia, A., Margolis, D., Oldach, D., Hazen, R., Le, N., & Redfield, R. (1999). Abacavir in combination with the inosine monophosphate dehydrogenase (IMPDH)-inhibitor mycophenolic acid is active against multidrug-resistant HIV-1 [letter]. *Journal of Acquired Immune Deficiency Syndromes*, 22(4), 406-7.
3. Chapuis, A. G., Rizzardì, G. P., D'Agostino, C., Attinger, A., Knabenhans, C, et al. (2000). **Effects of mycophenolic acid on human immunodeficiency virus infection in vitro and in vivo.** *Nature Medicine*, 6(7): 762-68.

ABSTRACT: Mycophenolic acid, a selective inhibitor of the de novo synthesis of guanosine nucleotides in T and B lymphocytes, has been proposed to inhibit human immunodeficiency virus (HIV) replication in vitro by depleting the substrate (guanosine nucleotides) for reverse transcriptase. Here we show that mycophenolic acid induced apoptosis and cell death in a large proportion of activated CD4+ T cells, thus indicating that it may inhibit HIV infection in vitro by both virological mechanisms and immunological mechanisms (depletion of the pool of activated CD4+ T lymphocytes). Administration of mycophenolate mofetil, the ester derivative of mycophenolic acid, to HIV-infected subjects treated with anti-retroviral therapy and with undetectable viremia resulted in the reduction of the number of dividing CD4+ and CD8+ T cells and in the inhibition of virus isolation from purified CD4+ T-cell populations. Based on these results, the potential use of mycophenolate mofetil in the treatment of HIV infection deserves further investigation in controlled clinical trials.

Background

Antiretroviral Dosing in ESRD and Dialysis:

1. Jayasekara, D., Aweeka, F. T., Rodriguez, R., Kalayjian, R. C., Humphreys, M. H., & Gambertoglio, J. G. (1999). **Antiviral therapy for HIV patients with renal insufficiency.** *Journal of Acquired Immune Deficiency Syndromes*, 21(5), 384-95.

ABSTRACT: Patients with HIV infection and HIV-related opportunistic infections are treated extensively with a spectrum of drugs. Introduction of new antiretroviral drugs, such as protease inhibitors and nonnucleoside reverse transcriptase inhibitors in addition to nucleoside reverse transcriptase inhibitors, has created exciting dimensions in treatment strategies. Renal dysfunction is also common in HIV-infected patients. Because some drugs used in HIV are primarily excreted unchanged by the kidney, dose adjustments are necessary in patients with renal insufficiency. Drugs such as foscarnet, cidofovir and adefovir are directly nephrotoxic, whereas acyclovir can crystallize in the kidneys, and indinavir may cause nephrolithiasis. This paper reviews the impact of renal insufficiency on pharmacokinetics of antiviral drugs used in HIV disease and discusses dosage recommendations needed to avoid toxicity. Finally, we summarize the effects of dialysis on removal of these drugs.

3. GlaxoWellcome. (2000). *Administration and Safety of Eпивir in Patients with Renal Impairment*. Research Triangle Park, NC: GlaxoWellcome.
4. GlaxoWellcome. (2000). *Administration of Ziagen in Patients with Renal Impairment*. Research Triangle Park, NC: GlaxoWellcome.
5. GlaxoWellcome. (2000). *Pharmacokinetics of Agenerase in Adults and Pediatrics*. Research Triangle Park, NC: GlaxoWellcome.
6. GlaxoWellcome. (2000). *Use of Retrovir (Zidovudine) in Patients with End-Stage Renal Disease (ESRD) on Dialysis*. Research Triangle Park, NC: GlaxoWellcome.
7. GlaxoWellcome. (2000). *Potential Safety Concerns with the large amount of propylene glycol in AGENERASE (amprenavir) Oral Solution*. Research Triangle Park, NC: GlaxoWellcome Inc.
8. Merck. (2000). *CRIXIVAN (Indinavir sulfate) Dosing*. West Point, PA: Merck & Co., Inc. Study of 1 patient showing increased clearance rates with hemodialysis.

2. **Renal Dosing of Antiretrovirals (table).** (1999). Rodriguez, R. A., and Schoenfeld, P. A., Renal Manifestations of HIV Infection. In Cohen, P. T., Sande, M. A., and Volberding, P. A. (Eds.), *The AIDS Knowledge Base: A Textbook on HIV Disease from the University of California, San Francisco and the San Francisco General Hospital* (3rd ed.), New York: Lippincott, Williams & Wilkins.

ANTIRETROVIRAL DRUG	CREATININE CLEARANCE		
	Normal	10-50 ml/min	<10 ml/min
Nucleoside Reverse Transcriptase Inhibitors			
AZT Zidovudine Retrovir™	200 mg TID	100 mg TID	100 mg TID
D4T Stavudine Zerit™	40 mg BID	20-15mg BID/QD	No data
DDC Zalcitabine HIVID™	0.75 mg TID	0.75 mg QD	Avoid
DDI Didanosine Videx™	DDI (Tabs)	200 mg BID	150 mg QD
	DDI (Powder)		
	250 mg BID	167 mg QD	100 mg QD
3TC Lamivudine Epivir™	150 mg BID	50-100mg BID	50 mg QD (10 mg/cc--5cc po QD)
Protease Inhibitors			
Saquinavir Invirase™	600 mg TID	No adjustment necessary	
Ritonavir Norvir™	600 mg BID	No adjustment necessary	
Indinavir Crixivan™	800 mg TID	No data	No data
Nelfinavir Viracept™	750 mg TID	No data	No data
Non-Nucleoside Reverse Transcriptase Inhibitors			
Nevirapine Viramune™	200 mg daily x 14 days Then 200 mg BID	No data	No data
Delaviridine Rescriptor™	400 mg TID	No data	No data

The AIDS Knowledge Base can be found on the web at: <http://hivinsite.ucsf.edu/akb/>
The URL for this table is <http://hivinsite.ucsf.edu/akb/current/05renal/toctable1.html>

Background

Antiretroviral dosing in ESLD:

1. Veronese, L., Rautureau, J., Sadler, B. M., Gillotin, C., Petite, J. P., Pillegand, B., Delvaux, M., Masliah, C., Fosse, S., Lou, Y., & Stein, D. S. (2000). **Single-dose pharmacokinetics of amprenavir, a human immunodeficiency virus type 1 protease inhibitor, in subjects with normal or impaired hepatic function**. *Antimicrobial Agents and Chemotherapy*, 44(4), 821-6

ABSTRACT: Amprenavir (141W94) is extensively metabolized by P450 cytochromes, specifically, CYP3A4. Because hepatic insufficiency reduces P450-mediated metabolism, the concentrations in plasma of drugs metabolized through this pathway are often increased in subjects with liver disease. Following administration of a single, oral dose of 600 mg of amprenavir, pharmacokinetic parameters were determined for 10 subjects with severe cirrhosis, 10 subjects with moderate cirrhosis, and 10 healthy volunteers. Model-independent methods for determining the area under the plasma concentration-time curve (AUC) from time zero to infinity (AUC(0-infinity)) showed an increase in amprenavir AUC(0-infinity) of 2.5-fold in the group with moderate cirrhosis and 4.5-fold in the group with severe cirrhosis compared with that in the control group of healthy volunteers ($P < 0.05$). AUC(0-infinity) was linearly related to the severity of liver disease, as assessed by the Child-Pugh score. Of the laboratory data used to calculate the Child-Pugh score, only the mean total bilirubin concentration showed a significant relationship with AUC(0-infinity). The relationship between the total bilirubin concentration and the AUC(0-infinity) of amprenavir was well characterized by a simple E(max) model, suggesting that the total bilirubin concentration may be a useful parameter for predicting the amprenavir AUC in subjects with hepatic insufficiency. Finally, the sera of cirrhotic subjects showed significant decreases in the levels of alpha(1)-acid glycoprotein, the primary plasma binding protein for amprenavir. On the basis of the results of this study, for an exposure equivalent to a clinical dose of 1,200 mg twice daily in subjects without cirrhosis, subjects with Child-Pugh scores of 5 to 8 should receive a twice-daily 450-mg dose of amprenavir, and subjects with Child-Pugh scores of 9 to 15 should receive a twice-daily 300-mg dose of amprenavir.

2. GlaxoWellcome. (2000). **Potential Safety Concerns with the large amount of propylene glycol in AGENERASE (amprenavir) Oral Solution**. Research Triangle Park, NC: GlaxoWellcome Inc.

Sunday August 13

<p style="text-align: center;"><u>DISCUSSION POINTS</u> Medication Regimens</p>

1. Immunosuppressives – calcineurin inhibitors
 - Pros and cons of single vs. multiple regimens.
 - Statistical issues if stratified by site

2. Antiretrovirals – MMF interactions
 - Consideration of protocol-mandated exclusion of AZT and D4T in those on MMF

3. Prophylaxis – HIV and Transplant
 - Review protocol for any additions/changes
 - Additive bone marrow toxicities
 - MAC prophylaxis
 - INH for h/o positive PPD

4. PEP in the OR
 - Consider PEP regimen prior to OR based on patient antiviral history
 - National PEPLine 888/448 (HIV) – 4911 (see flier) to assess and manage exposures
 - Consider having dose of meds in OR

Sunday August 13

D.Labs/Studies - Define core and optional sub-studies

3:15 – 4:45

Background

UCSF Protocol: METHODS – STUDY PROCEDURES

Toxicity and Clinical Event Monitoring: A complete baseline history and physical exam will be performed to confirm eligibility in those subjects deemed eligible by past medical history. Follow-up clinical evaluations and physical examinations at each clinical visit (see 4A.) will focus on signs and symptoms suggestive of HIV disease progression. Clinical evaluation will concentrate on symptoms, review of systems, and examination findings of the oropharynx, respiratory, cardiac, gastrointestinal, skin, lymphatic, and nervous systems. CD4+ and CD8+ T-cell numbers, percents, and ratios and quantitative HIV-1 RNA by Ultrasensitive bDNA assays will be monitored at each outpatient and GCRC clinical visit. Standard baseline and follow-up laboratory tests will be performed at each outpatient and GCRC visit, including urinalysis, electrolytes, blood urea nitrogen (BUN), creatinine (Cr), complete blood count with platelets and differential (CBC-diff), liver function tests (bilirubin, SGOT/AST, SGPT/ALT, alkaline phosphatase), albumin, calcium, phosphorus. A chest x-ray (CXR) and fasting lipid panel will be obtained at baseline. CRX will be repeated at Week 4, 12, and each subsequent visit. Lipids will be monitored every 6 months.

Patients will also be screened at baseline and followed every 6 months for the following markers of past or present infection: syphilis by RPR/VDRL, toxoplasmosis titer, CMV antibody status, hepatitis B surface antigen (HBSAg) and quantitative hepatitis B DNA if surface antigen positive, hepatitis B surface antibody (HBSAb), hepatitis B core antibody (HepBcoreAb), hepatitis C antibody (HCV Ab) and quantitative hepatitis C RNA level and quasispecies determination if antibody positive, cervical PAP smear (women) and optional anal Pap smear, anoscopy and if necessary, anal biopsy (Baseline, Week 4 and every 6 months) for detection of human papilloma virus (HPV), blood and sputum cultures for *Mycobacterium avium* complex (MAC) if CD4 nadir <75, MRI of the head at baseline and as needed for evaluation of subsequent alterations in mental status, cerebrospinal fluid (CSF) for JC virus if MRI is suspicious for progressive multifocal leukoencephalopathy (PML), PPD, and the following markers of human herpes virus 8 (HHV8) infection: HHV-8 antibody, HHV-8 quantitative plasma viral load, HHV-8 cell-associated viral load, cellular immunologic studies related to HHV-8 and saliva HHV8 studies. CMV and hepatitis serologies and PPD will only be repeated in those patients with previous studies indicating no current or past infection to monitor development of new exposure or infection. All of these studies except the HHV8 related assays are considered standard of care in this setting.

All episodes of potential rejection, marked by increases in transaminases, will require liver biopsy for confirmation prior to the institution of rejection therapy. All tissue will also be evaluated for HIV load and other viruses as indicated by the patient's clinical history. Liver transplant patients who test positive for hepatitis C virus at post-transplant will have a liver biopsy performed at Month 4, every 12 weeks in Years 2 and 3 and every 6 months in Years 4 and 5.

Background

UCSF Protocol: METHODS – STUDY PROCEDURES

Immunology Studies: The immunologic consequences of solid organ transplantation and immunosuppression in HIV-1 seropositive recipients will be followed with the following tests pre-transplant, then at weeks 4, 28, 52 and years 2 and 5: 1) peripheral blood phenotyping to assess the composition of circulating subpopulations of lymphocytes (e.g. naive vs memory) and state of cell activation; 2) intracellular cytokine expression following stimulation of recipient lymphocytes with staphylococcal enterotoxin B and CMV; 3) lymphoproliferation assays to assess changes in response to alloantigen (against donor targets), phytohemagglutinin, and recall antigens (measles, tetanus, CMV); 4) natural killer (NK) cell function; 5) soluble markers of activation including serum beta-2 microglobulin and neopterin; 6) CD8+ cell suppressing activity (CAF); 7) donor reactivity; 8) chimerism studies; 9) chest computed tomography (CT) to assess thymic index will be obtained pre-transplant and at weeks 4 and 52 and year 2. All of these studies are considered to be research related and not standard of care in this setting.

Specific laboratory studies and UCSF Labs:

Dr. Mike McCune's laboratory will perform baseline and follow-up measurements of phenotypic and functional properties of circulating T, B and NK cells as well as thymic function. These parameters of immune function will be correlated with clinical assessments of HIV progression and allograft function to address the hypothesis that post-transplant immunosuppression will have either a beneficial effect on markers of immune activation or no significant adverse effect on these markers.

- NK, LPA, and immunophenotyping can be done at regional sites, using certified ACTG protocols (ACTG Immunology ATLS).
- CFCs currently need fresh cells
- Methods currently being developed (implementation possible this August) to allow central labs to perform CFC on viably cryopreserved PBMC or whole blood.
- Alternatively, local labs could process cells for shipping centrally with 50% yield

The laboratory of Dr. Jay Levy will examine the effect of immunosuppression on suppressing the CD8+ mediated antiviral response, with the hypothesis that transplant associated immunosuppression may potentially either compromise or enhance CD8+ T-cell mediated control of the HIV infection.

- Cells could be sent to a central lab at UCSF
- Levy labs need 20 million PBMC frozen at each time point.

The transplantation laboratory of Dr. Peter Stock will measure the alloimmune response against donor and third-party using the standard mixed lymphocyte culture (MLC), cell mediated lympholysis (CML) assays, as well as a more precise flow cytometry-based assay that provides a measurement of the frequency of alloreactive lymphocytes, with the hypothesis that HIV-infected recipients may have a reduced alloimmune response compared with HIV-negative controls.

The immunogenetics laboratory of Dr. Baxter-Lowe will analyze the presence of donor-derived cells in the peripheral blood of transplant recipients. This laboratory will study the hypothesis that HIV infection will significantly alter the dynamic interaction between the graft and the host that relate to circulating donor-derived cells.

HHV8 Background:

HHV-8 causes KS. KS is a common problem post-transplant among persons who are HHV-8-infected. (Interestingly, HHV-8 can also be transmitted via transplant). Having KS post-transplant is problematic. HHV-8 may also be causing problems other than KS post-transplant. The incidence of post-transplant KS among HHV-8-infected persons is relevant to our study of transplantation in HIV disease because HIV-infected gay men have the highest prevalence of HHV-8 in the US. Therefore it is natural for us to be concerned about what will be the effect of the dual influence of HIV-related and iatrogenic immunosuppression on the course of HHV-8 infection in HIV-infected persons who receive transplantation. Therefore, we propose to examine the dual influence of HIV-related and iatrogenic immunosuppression on the course of HHV-8 infection

Specific objectives: To determine:

- prevalence of HHV-8 infection among those receiving transplants
- incidence of KS post-transplant among those who are HHV-8-infected
- changes in HHV-8 virologic activity (salivary shedding, presence of cell-free and cell-associated virus in blood) post-transplant
- changes in host humoral and cellular immune response
- influence of prophylactic regimens for CMV disease on HHV-8 activity

HHV-8 and Organ Transplantation

- **Human herpesvirus 8 (HHV-8)**
 - aka Kaposi's sarcoma-associated herpesvirus (KSHV)
 - a gamma-herpesvirus, most closely related to EBV
 - found in all forms of KS
 - now consensus that it is the causative agent of KS
- **Transplant-associated KS**
 - incidence parallels local HHV-8 prevalence
 - highest (3 to 5%) in Southern Italy, Middle East
 - 10 - 30% incidence in HHV-8-seropositive tx recipients
 - diffuse cutaneous and visceral involvement common

HHV8 Background

Other Non-Malignant Post-transplant Manifestations of HHV-8

- **Case Reports from Italy**
Luppi et al. 2nd Intl Wkshp on HHV-8/KSHV, 1999
 - a) 35 yo s/p autologous stem cell tx
 - fever, rash, and hepatitis 17 days s/p tx
 - associated with development of HHV-8 viremia
 - other known causes excluded
 - b) 63 yo s/p autologous stem cell tx
 - neutropenia, thrombocytopenia, fever
 - HHV-8 viremia
 - HHV-8 present in stromal cells of aplastic marrow

Seroprevalence of HHV-8

Group	Seroprevalence
U.S/Northern Europe	
HIV + homosexual men	40 to 65%
HIV – homosexual men	15 to 30%
Heterosexual men/women	1 to 7%
Southern Europe	
Overall adults	12 to 25%
Middle East	
Overall adults	40 to 60%
Africa	
Overall adults	35 to 65%

Study of HHV-8 Infection in HIV-infected Transplant Recipients

- **General objective**
 - Examine dual influence of HIV-related and iatrogenic immunosuppression on course of HHV-8 infection
- **Specific objectives**
 - To determine:
 - prevalence of HHV-8 among transplant recipients
 - incidence and determinants of post-transplant KS
 - pre and post-transplant changes in:
 - HHV-8 virologic activity (in blood and saliva)
 - host humoral and cellular immune response to HHV-8
 - influence of prophylaxis for CMV on HHV-8 activity

HHV8 Background

HHV-8-specific Measurements

- **Time points:** pre-tx, post-tx (1 wk, 1 mo, q 3 mo)
- **Samples:** blood and whole saliva
- **Storage:** plasma/saliva at -70°, cryopreserve PBMC's
- **Assays**
 - PCR of plasma, PBMC's, saliva
 - for portion of HHV-8 orf26
 - antibodies
 - to LANA and whole virus
 - cytotoxic T-lymphocyte response
 - to epitopes of orf73

HHV8: Per Jeff Martin.

- It is essential that one lab perform all lab work.
- No commercial assays for HHV8.
- Live cells not needed. Specimens could be batched and sent at intervals.
- All work can be done with frozen PBMCs, but should be high yield prep.
- Whole blood could be shipped overnight to a central repository for processing and storage.

HPV cervical and anal cytology: Per Joel Palefsky.

- Prefers that all samples be sent to UCSF – consistency is key
- If all samples are collected according to UCSF protocol and sent to UCSF, processed cells should make no difference.
- Proper anoscopic evaluation requires training – training can be done but it costs \$

Routine Safety Labs - Proposed

<i>Core</i>	<i>Optional</i>	<i>Central vs. Local</i>
Cyclosporine Levels		Local
Renal/Electrolytes		Local
LFTs		Local
Amylase		Local
Lipase		Local
E. CBC-diff		Local
PT/PTT		Local
CMV Ab		Local

HIV Safety Labs - Proposed

<i>Core</i>	<i>Optional</i>	<i>Central vs. Local</i>
CD4+/CD8+ T-cell		Local
HIV-1 RNA (bDNA/PCR)		Central?
RPR/VDRL		Local
Toxoplasmosis Quant.		Local
G6PD		Local
LDH		Local
Fasting Lipid Panel		Local
HepBSAg		Local
HepBSAb		Local
HepB core Ab		Local
HepB DNA		Local
MAC-blood		Local
MAC-sputum		Local
CSF JC virus		Local

HCV Labs - Proposed

<i>Core</i>	<i>Optional</i>	<i>Central vs. Local</i>
HCV Ab		Local
HCV RNA (HepC patients)		Central?
HCV Genotype		Central?
	HCV Quasispecies	Central?
Liver Biopsy		Local

HHV8 Labs - Proposed

<i>Core</i>	<i>Optional</i>	<i>Central vs. Local</i>
	HHV8 Ab	Central
	HHV8 Viral Load (cell-associated)	Central
	HHV8 Viral Load (plasma)	Central
	HHV8 Cellular Immunology	Central
	HHV8 Saliva	Central

Pharmacology/Pharmacokinetics - Proposed

<i>Core</i>	<i>Optional</i>	<i>Central vs. Local</i>
PI/NNRTI/CSA pK		Central

Immunology (HIV) Labs - Proposed

<i>Core</i>	<i>Optional</i>	<i>Central vs. Local</i>
	F. Phenotype	Regional ACTG ATL
	Cytokine Flow Cytometry	Regional ACTG ATL
	Lymphoproliferative Assays	Regional ACTG ATL
	Natural Killer Cells	Regional ACTG ATL
Soluble Activation Markers (neopterin, B2microglobulin)		Local
	CT Thymus	Regional ACTG ATL???
	HIV specific CTLs	Central
	CAF	Central
	CMV ELISA	Central
	EBV ELISA	Central
	HHV6 ELISA	Central

Immunology (Transplant) Labs - Proposed

<i>Core</i>	<i>Optional</i>	<i>Central vs. Local</i>
	Chimerism	Central?
	Donor alloreactivity	Central?

Sunday August 13

DISCUSSION POINTS

Labs/Studies - Define core and optional sub-studies

1. Clinical safety labs (HIV and Transplant)
 - Frequency of CD4 and viral load testing
 - Can/should viral load testing be centralized?
 - PT/PTT only routine in liver patients

2. Immunology (HIV and Transplant)
 - Local capabilities and interest
 - Funding for optional studies
 - Additional studies

3. Virology (HIV, HCV, HBV, HHV8, HPV)
 - HIV: frequent RNA monitoring
 - HCV and HBV: RNA/DNA may be available from Bayer
 - HHV8: Jeff Martin's research proposal; funding for sample prep/shipping?
 - HPV: interest in colposcopic cervical and anal evaluations and training needs

Sunday August 13

Baseline and Follow-up Schedules

4:45 – 5:00 PM

General Study Design. The total study period will be five years. Following transplantation and post-operative recovery (minimum one week), this will be an outpatient study with the exception of six or more inpatient 24-hour GCRC visits at Weeks 1 and 4, 6 months, and 1, 2 and 5 years post-transplant. Patients will be seen daily during the initial hospitalization, then weekly (x 4), every other week (x 4), monthly (x 2), every 8 weeks (x 4), every 12 weeks for the next two years (from the beginning of Year 2 through the end of Year 3), then every 6 months for the final two years of follow-up.

Table 2. HIV Transplantation Project Schedule of Events

Years:	0		Year 1															Years 2 and 3	Years 4 and 5	
Weeks:	Scr. 1	Scr. 2 ¹⁰	Day 0 ³	Q day ⁴	1	2	3	4	6	8	10	12	16	20	28	36	44	52	53-156	157-260
CLINICAL:																				
G. Physical Exam	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X ¹	X ²
Symptom Review	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X ¹	X ²
Medication Review	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X ¹	X ²
Vaccination Review (Pneumovax, Hepatitis A and B)	X																			
PPD ⁶	X		X												X			X	X ²	X ²
TB/MAC Prophylaxis Review	X		X																	
Pap Smear (Cervical/Rectal)	X							X							X			X	X ²	X ²
RADIOLOGY:																				
MRI head ⁵	X		X																	
CXR	X		X				X				X	X	X	X	X	X	X	X	X ¹	X ²
SAFETY LABS: (Clinical Lab)																				
Cyclosporine levels				X	X	X	X	X	X	X	X	X	X	X		X	X	X	X ¹	X ²
CMV Ab ⁶	X		X												X			X	X ²	X ²
Renal/Electrolytes	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X ¹	X ²
LFTs	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X ¹	X ²
Amylase	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X ¹	X ²
Lipase	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X ¹	X ²
CBC-diff	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X ¹	X ²
PT/PTT	X		X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X ²	X ²
HIV LABS: (Clinical Lab)																				
CD4+/CD8+ T-cell count			X		X	X	X	X ⁹	X	X	X	X	X	X	X ⁹	X	X	X ⁹	X ¹	X ²
HIV-1 RNA (bDNA)	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X ¹	X ²
RPR/VDRL	X		X												X			X	X ²	X ²
Toxoplasmosis Quantitative	X		X												X			X	X ²	X ²
G6PD	X																			
LDH	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X ¹	X ²
Fasting Lipid Panel	X		X												X			X	X ²	X ²

Years:	0		Year 1															Years 2 and 3	Years 4 and 5	
Weeks:	Scr. 1	Scr. 2 ¹⁰	Day 0 ³	Q day ⁴	1	2	3	4	6	8	10	12	16	20	28	36	44	52	53-156	157-260
HepBSAg ⁶	X		X												X			X	X ²	X ²
HepBSAb ⁶	X		X												X			X	X ²	X ²
HepB core Ab ⁶	X		X												X			X	X ²	X ²
HepB DNA ⁷	X		X												X			X	X ²	X ²
MAC-Blood (CD4 nadir <75)	X		X				X					X			X			X	X ²	X ²
MAC-Sputum (CD4 nadir <75)	X		X				X					X			X			X	X ²	X ²
CSF JC virus ⁵	X		X																	
HCV Labs (Lab TBD)																				
HCV Ab	X		X												X			X	X ²	X ²
HCV RNA (Hep C Patients) ⁸	X		X												X			X	X ²	X ²
HCV Genotype ⁸	X		X																	
HCV Quasispecies ⁸	X		X												X			X	X ¹	X ²
Liver Biopsy (Path) ⁸							X												X ¹	X ²
IMMUNOLOGY-HIV (McCune)																				
Phenotype	X						X								X			X	Yr 2	Yr 5
Cytokine Flow Cytometry	X						X								X			X	Yr 2	Yr 5
Lymphoproliferative Assays	X						X								X			X	Yr 2	Yr 5
Natural Killer Cells	X						X								X			X	Yr 2	Yr 5
Soluble Activation Markers (neopterin, B2microglobulin)	X						X								X			X	Yr 2	Yr 5
CT thymus	X						X											X	Yr 2	
(HIV specific CTLs)	X						X								X			X	Yr 2	Yr 5
IMMUNOLOGY – HIV (Levy)																				
CAF	X						X								X			X	Yr 2	Yr 5
CMV ELISA	X						X								X			X	Yr 2	Yr 5
EBV ELISA	X						X								X			X	Yr 2	Yr 5
HHV6 ELISA	X						X								X			X	Yr 2	Yr 5

Years:	0		Year 1															Years 2 and 3	Years 4 and 5	
Weeks:	Scr. 1	Scr. 2	Day 0 ³	Q day ⁴	1	2	3	4	6	8	10	12	16	20	28	36	44	52	53-156	157-260
IMMUNOLOGY-TRANSPL. (Stock)																				
Chimerism	X							X							X			X	Yr 2	Yr 5
Donor alloreactivity	X							X							X			X	Yr 2	Yr 5
PHARMACOLOGY (Benet UCSF)																				
PI/NNRTI/CSA pK	X		X		X			X							X			X	Yr 2	Yr 5
HHV8 (State DPH)																				
HHV8 Ab	X		X												X			X	X²	X²
HHV8 Viral Load (cell-associated)	X		X												X			X	X²	X²
HHV8 Viral Load (plasma)	X		X												X			X	X²	X²
HHV8 Cellular Immunology	X		X												X			X	X²	X²
HHV8 Saliva	X		X												X			X	X²	X²
ASB – (AIDS Specimen Bank)																				
Plasma			X		X			X		X		X			X			X	X¹	X²
Cells			X		X			X		X		X			X			X	X¹	X²

Bold signifies GCRC in-patient visit, 24 hours

1. X¹ = every 12 weeks
2. X² = every 6months
3. Initial day of hospitalization only
4. Every day of hospitalization
5. MRI will be repeated as needed for evaluation of changes in mental status; CSC JC virus if indicated by clinical and MRI findings
6. Studies repeated only if indicated to diagnose new infection, not in patients with evidence of past infection
7. Study performed only if HepBSAg positive
8. Study performed only if HCV Ab positive
9. CD4/CD8 cell counts will be done in McCune lab with phenotyping
10. Screen 2 lab draws should occur as near as possible to baseline: on same day if possible

Monday August 14

1. Pharmacokinetics (ARVs/immunosuppressants)

9:30-10:00

A. pK evaluations

Pharmacology Studies: Cyclosporine levels will be monitored at each clinical visit and between study visits and indicated by standard clinical practice. Pharmacokinetic monitoring will be conducted in the GCRC or during the post-operative hospitalization pre-transplant, then at Weeks 1 and 4, month 6, Year 1, and Year 2 and Year 5 post-transplant and whenever there is a change in ARVs, a significant change in immunosuppressants, or an episode of organ rejection. For each study, a peripheral blood sample (5 ml) will be collected at the following times relative to immunosuppressant administration: 0, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 9, 12 and 24 hours. Whole blood and/or plasma will be analyzed for immunosuppressant, PI, and NNRTI concentrations using HPLC/MS assays. Urine toxicology screening for illegal and prescription drugs will be performed while patients are in the GCRC to evaluate any interactions with ARV and/or immunosuppressive medications. All of these studies are considered standard of care in this setting as the drug interactions are unknown.

DISCUSSION POINTS

pK Evaluations

- Interest and capability at each site
- Central specimen analysis and interpretation
- Funding

Monday, August 14

2. IRB/Ethical Issues

10:00 – 10:30 AM

IRB and Ethical issues will not be dealt with in detail at this meeting. Though we felt it was important to establish a basic framework of ethical and IRB-related questions and concerns at this time, these are weighty and complex issues which cannot be addressed adequately at this meeting. An exhaustive discussion of IRB/Ethical will take place at a later date.

DISCUSSION POINTS:

**Ethical Issues
Cadaveric, Living-Related, High Risk Donors
Stopping Rules**

1. Cadaveric Donors
 - Donor pool

2. Living Related Donors
 - Risk to donor
 - Disclosing HIV status

3. High Risk Donors
 - Additional risk and consent
 - Availability to others

4. Stopping Rules
 - To avoid stopping too early or too late

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

CONSENT TO BE A RESEARCH SUBJECT

Clinical, Immunologic and Pharmacologic Consequences of Solid Organ Transplantation in People with HIV Infection

- Liver Transplant –
- (See Kidney as well)

BACKGROUND/PURPOSE

Dr. Peter Stock and Dr. Nancy Ascher at the Department of Surgery, Dr. Michelle Roland at the Department of Medicine, and Dr. Leslie Floren at the Department of Biopharmaceutical Sciences, University of California, San Francisco are conducting a research study to evaluate the safety and effectiveness of kidney and liver transplants and post-transplant immunosuppression (weakening of the immune system with drugs) in HIV-infected patients. People with HIV infection are at great risk for both kidney and liver disease. Up until now, people with HIV infection have been excluded from this procedure due mainly to concerns that the immunosuppression required for organ transplantation might worsen the patient's HIV infection. However, due to improvements in the treatment of HIV, resulting in improved overall health and long-term survival, HIV-infected patients may now be eligible for a liver or kidney transplant.

A second purpose of this study is to evaluate the action between the immunosuppressive drugs used for the transplant procedure and my antiretroviral drugs.

Up to ten people will be enrolled in this study at UCSF over a two-year period. Total study participation will be five years.

I am being asked to participate in this research study because I am HIV-infected with end-stage liver disease.

PROCEDURES

If I agree to participate and sign this consent form, the following will occur:

Screening: I will have examinations and tests to determine my eligibility to participate. I will have a review of my medical history and any anti-HIV and other medications I am taking, a complete physical examination and a chest x-ray. A urine sample, sputum sample, and 4 tablespoonsful of blood will be collected for lab tests including tests for syphilis, hepatitis B and C, other opportunistic diseases, safety labs, T-cell counts, viral load (HIV RNA; amount of HIV in my blood), and immunology studies (tests to evaluate my immune system).

If I am a woman who can become pregnant, a portion of the blood collected will be tested for pregnancy. If I am pregnant, I will not be allowed to participate in this study. I must not become or plan to become pregnant during the study. I will have a Pap smear

to collect cells from my cervix. For this procedure, I will have a pelvic examination and an instrument called a speculum will be used to examine my cervix. A small plastic brush and a wooden spatula will be used to collect the cells for examination under a microscope. The cells will also be tested for cervical human papilloma virus (HPV) infection. HPV is the cause of genital warts (condyloma acuminata) and is thought to be important in the development of cancer in the anogenital area.

Patients who are immunosuppressed for any reason are thought to be at a higher risk for the development of HPV-associated cancer in the cervix as well as in the anua. The study investigators would like to learn more about anal HPV infection and the course of anal disease over time. Because HPV infection of the anus is common in both men and women, if I am 18 years or older, I will be asked to have an anal examination and a Pap smear of my anus to collect cells to test for anal HPV infection. The purpose of the Pap smear in the cervix and/or the anus is also for early detection of any pre-cancerous changes so treatment can be offered. If a potentially pre-cancerous area is found, the information will be shared with my primary clinician. Arrangements for appropriate followup or treatment will be made.

For the anal Pap smear, I will have a swab inserted into my anal canal to collect cells and to look for HPV. After this, I will have a visual examination of my anal region. An instrument called an anoscope will be inserted into the anal canal. The anoscope allows the nurse practitioner or physician to look at the inside of the anal canal. Three percent acetic acid (diluted vinegar) will be applied to the surface of the anal canal as well as to the inside of the canal. During the anoscopy, if any areas of abnormality are seen, a biopsy (removal of a small piece of anal skin) may be required. To perform this biopsy, the anal skin will be numbed by injecting a numbing medicine (similar to that used by a dentist) with a small needle. After the skin becomes numb, a very small piece of anal skin will be removed. This biopsy skin will be sent to the Department of Pathology for assessment. If the area of abnormality is large enough, a second piece of anal skin may be needed for analysis. These procedures take about 30 minutes and will be done at Mount Zion Medical Center.

I may choose not to participate in the studies of the anal region or I may stop participating in them at any time. My decision will not affect my participation in the rest of the study.

I will have a review of any immunizations and skin test reactions I may have had in the past. I will have a skin test for tuberculosis (PPD) which will be given by injecting a small amount of the skin test fluid just under the skin on my inner arm. I must remain in the clinic for at least 20 minutes after the TB test to check for any reaction. I will be required to return to the clinic 48 hours afterwards to have my response to the skin test measured. If my immunizations are not current or my hepatitis antibody tests are negative, I will receive one injection each of a vaccine for pneumonia, hepatitis A and hepatitis B, which will be given in the muscle of my upper arm.

If the study doctors are concerned about my neurologic examination or mental status, I will have a MRI (Magnetic Resonance Imaging study) of my head to rule out certain infections. For this procedure, I will lie down on a narrow bed which will then be placed in a tunnel that is 6 feet long by 22 inches wide and open at each end. I will lie there quietly for about one hour during which time I will hear a loud noise.

Based on the findings of the MRI, it may be necessary to obtain a sample of my cerebrospinal fluid (the fluid surrounding my brain and spine). For this procedure, I will be asked to curl up on my side on a table with my knees drawn up to my chest and both arms clasped around my knees. A local pain killer will be applied at the site where the fluid is to be withdrawn. A thin needle is inserted between two bones in my lower back. Once the needle is in place, approximately 2 teaspoonsful of fluid are withdrawn. The procedure usually takes about 30 minutes.

Transplant eligibility monitoring: If these examinations and tests determine that I am eligible to participate and I agree to continue my participation, I will be put on a list and scheduled to receive a liver transplant once a liver becomes available. Waiting for a liver could take from several months to 5 years. Participation in this study does not guarantee that an organ will become available. While I am waiting for an available liver, I will be asked to have T cell counts and viral load measurements performed every two months by my primary care doctor and have the results faxed to research staff. Research staff will provide me with a fax number. My continued eligibility will be determined based on my most recent T-cell count and viral load test results, not more than 10 weeks prior to transplant.

Hospitalization: During hospitalization for the transplant procedure I will be seen daily for a physical examination, collection of blood for safety laboratory tests and immunology studies, review of my medications and any symptoms I may be having. Hospitalization may be for at least one week.

Medication: I will be treated with immunosuppressive drugs consisting of cyclosporine, mycophenolate mofetil (MMF) and prednisone. Antiretroviral therapy will consist of combinations of approved drugs for the treatment of HIV and will be guided by the study doctors in consultation with my primary care provider.

Post-transplant study visits: After hospitalization, I will have 14 clinic visits in the first year. I will be seen every 12 weeks in Years 2 and 3 and every 6 months in Years 4 and 5. At most visits I will have a brief physical examination, a review of my symptoms and medications, a chest x-ray, and collection of blood for safety laboratory tests and immunology studies. I will have a repeat PPD test every 6 months. If I am a woman or if I have had receptive anal intercourse I will have a repeat Pap smear at Week 4 and then every 6 months.

If I test positive for hepatitis C virus, I will have a biopsy of my liver at Month 4, every 12 weeks in Years 2 and 3 and every 6 months in Years 4 and 5. For this procedure, the biopsy site will be cleaned with an antiseptic and the skin and tissues between the skin and the liver will be injected with a local anesthetic. Usually a small incision (less than ¼ inch in size) is made in the skin. A small needle will be inserted a short distance under the skin and a small piece of my liver will be removed. I will be asked to hold my breath and remain completely still during this procedure. I will be asked to sign a separate consent form for this procedure.

For safety reasons, I should keep research staff informed about any medications (over-the-counter or prescription) I am taking or intend to take while enrolled in this study. I will have additional tests and evaluations as clinically necessary to monitor my condition.

Drug level measurements: A portion of the blood collected at each clinic visit will be used to measure the level of drugs in my body. Additionally, multiple blood samples will be collected at various times over a 24-hour period during study participation, as follows: during hospitalization prior to the transplant procedure and whenever HIV medicines are changed, immunosuppressive medicines are significantly changed, and if my body rejects the liver. Multiple blood samples will also be collected during an overnight stay in the UCSF General Clinical Research Center (GCRC) at Weeks 1 and 4, 6 months, and Years 1, 2 and 5 after the transplant procedure. A small plastic tube will be inserted in a vein in order to avoid multiple needlesticks for the collection of these blood samples. Approximately 1 teaspoonful of blood will be collected at each of 13 time points over 24 hours (a total of approximately ¼ cupful of blood). At each GCRC stay I will also provide a sample of my urine which will be tested for illegal drugs and prescription drugs to evaluate any interactions with my anti-HIV and/or immunosuppressive medications. This test is called a urine toxicology screen.

My stay in the GCRC may take up to 26 hours.

Storage of blood: A portion of the blood drawn at each study visit, except during hospitalization, will be frozen and stored for future clinical tests and research studies. Samples will be stored with a coded number at the AIDS Specimen Bank at UCSF. Only the researchers will have access to them. I will be provided with any information from the future tests that may be important to my clinical care. These tests may not be done for several months, and it is possible these studies may never be performed. Storage of blood is optional. I may agree or refuse to have blood samples stored by checking a box at the end of this consent form.

Birth control: I must practice an effective method of birth control while participating in this study. A barrier protection such as a latex condom with spermicidal foam or diaphragm with spermicidal cream or jelly must be used. Because of the possible interaction between the protease inhibitors and birth control pills, birth control pills alone should not be used as an effective means of birth control during my participation in this study.

Total blood: Approximately 2½ pintful of blood will be collected in Year 1; a little more than 1 cupful will be collected in Years 2 and 5; less than 1 cupful will be collected in Years 3 and 4.

Early study discontinuation: I may be removed from the study without my consent for the following reasons:

- I am a woman who becomes pregnant or who is breast-feeding a young child;
- I no longer meet eligibility criteria;
- The investigator(s) decides that continuing in the study would be harmful to me;
- I am unable to keep appointments or follow study instructions;
- I experience serious side effect(s) to the study medications;
- The study is cancelled;
- Other administrative reasons.

RISKS/DISCOMFORTS

Transplant procedure: Liver transplantation in an HIV-infected individual is investigational. There may be risks that are currently unknown.

Waiting period: Because I may have a long wait for a compatible liver, I may no longer meet the eligibility requirements for a transplant within this study.

Transplant immunosuppression therapies including cyclosporine, MMF and steroids required for transplant may worsen my HIV infection, which could result in a more rapid progression to AIDS, increased opportunistic infections, and death. These drugs may also result in a more rapid progression of viruses which effect the liver, including hepatitis B and hepatitis C.

Cyclosporines weaken the immune system, causing an increased susceptibility to infection. In a study of patients with advanced HIV disease (AIDS) this resulted in an increased risk of AIDS-related infections. Common side effects seen in patients taking cyclosporines include headache, diarrhea, nausea, vomiting, shaking and numbness. Kidney toxicity and elevated blood sugar are possible but would be uncommon after a single dose. Chronic treatment with cyclosporine includes kidney toxicity, elevated blood sugar, high blood pressure and an increased risk of infection and cancer through immune suppression.

Cyclosporines are known to cause side effects in the unborn child and should not be taken by pregnant or breast-feeding women.

Cyclosporines in combination with antiretrovirals: It is unknown how immunosuppressants will interact with antiretroviral medications. Combination treatment may cause increased side effects. There is also the possibility that the combination of these drugs may increase or decrease the levels of the antiretroviral medications, which may cause incomplete suppression of the HIV virus resulting in a worsening of my HIV disease and causing my antiretroviral medications to become ineffective. Incorrect levels of medication could make my HIV disease worsen and make me more likely to develop an opportunistic infection(s).

Mycophenolate mofetil is a potent immunosuppressive drug that has been very effective in preventing rejection of the kidney. The most common adverse effects of MMF are diarrhea, nausea, vomiting, abdominal pain, constipation, loss of appetite, and indigestion. Decreases in red blood cells (anemia), platelets (blood cells involved in clotting), and white blood cells (blood cells involved in fighting infection) may also be observed.

Prednisone is a potent immunosuppressive drug that is used to help maintain the function of the transplanted organ as well as an acute treatment in the event of organ rejection. The immunosuppressive effects of the drug may make me more susceptible to infection.

Common side effects seen in patients taking prednisone chronically are behavioral changes, increased appetite, ulcers, changes in fat and muscle pattern, thinning of the skin, increased blood sugar as well as an increased risk of adrenal suppression and increased susceptibility to viral, bacterial and fungal infections.

Pneumococcal Vaccination (Pneumovax® 23): Soreness, warmth, redness, and swelling at the site of injection, usually lasting less than 48 hours, are common. The development of hardness of the skin at the site of injection is less common. Low grade fever occurs occasionally and is usually limited to the 24-hour period following

vaccination. Although rare, fever over 102 degrees has been reported. A vague feeling of being unwell, muscle aches, headache, nausea, vomiting and weakness have been reported. There have been rare reports of severe allergic reactions, rash, hives, arthritis, joint pain, and lymph gland swelling. Patients with a certain type of disease affecting the number of platelets (a type of blood cell important for clotting of the blood) in their blood have, on rare occasions, developed a temporary decrease in the number of platelets in their blood after vaccination. In addition, there have been rare reports of a type of anemia occurring in patients who have had other blood diseases.

In a recent study, reactions at the site of injection of pneumococcal vaccine were more common among those subjects who had been revaccinated, compared with those receiving the vaccine for the first time. In addition, a greater percentage of patients (11%) who received a second vaccine shot developed large amounts of redness and swelling at the injection site compared with those who received the vaccine for the first time (3%).

Hepatitis A Vaccination (HAVRIX®): Most of the side effects caused by this vaccine are mild and do not last for more than 24 hours. The most frequent side effect is soreness at the site of injection (up to 56%). Headache was reported by 14% of adults. Side effects occurring in association with 1 to 10% of injections include hardness, redness, or swelling at the injection site, tiredness, fever, a vague sense of feeling unwell, loss of appetite or nausea. Fewer than 1% of injections are associated with bruising at the injection site, itching, rash, hives, sore throat, pain in the stomach, diarrhea, a change in taste, vomiting, joint pain, muscle pain, lymph gland swelling, or neurologic (nerve) problems. Hepatitis A vaccination is recommended for people at increased risk for hepatitis A infection, such as men who have sex with men and people who inject unprescribed drugs. Up to 50% of men who have sex with men already have antibodies (protection against hepatitis A). Vaccination of a person who is already immune to hepatitis A does not increase the risk of side effects.

Liver biopsy: Needle liver biopsy may result in significant bleeding into the abdominal cavity in approximately 1 case in 1000. If severe bleeding occurs, this may require surgery. The risk of death from a liver biopsy is approximately 1 in 10,000 liver biopsies. In rare cases, biopsy may result in trauma to other abdominal or intra-thoracic tissue. About 1 subject in 50 will have temporary significant pain after the biopsy procedure.

TB skin testing (PPD): Reactions at the site of injection may include tenderness, itching, and blister formation. Repeat testing in persons who have had positive PPD skin tests sometimes leads to large, painful skin reactions, which may blister.

MRI: Because the MRI machine acts like a large magnet, it could move iron-containing objects in the MRI room during my examination, which could in the process harm me. Precautions have been taken to prevent such an event; loose metal objects, like pocket knives or key chains, are not allowed in the MRI room. If I have a piece of metal in my body, such as a fragment in my eye, aneurysm clips, ear implants, spinal nerve stimulators, or a pacemaker, I will not be allowed into the MRI room and cannot have an MRI. I may be bothered by feelings of claustrophobia and by the loud banging noise during the procedure. Temporary hearing loss has been reported from this loud noise, which why I will wear earplugs. At times during the test, I may be asked not to swallow for a while, which can be uncomfortable. I may feel warm during this procedure.

Additionally, I may experience a reaction to the dye used for this procedure, which could cause difficulty breathing, swelling, hives, itching, and sudden death.

The risks to a fetus from MRI are unknown.

Lumbar puncture may cause local discomfort, pain, decreased blood pressure and rarely, infection at the site of injection. The most common complication is headache caused by leaking of cerebral spinal fluid after the procedure. In some cases the headache may be severe and may last several days to a week. Very rarely will the headache last for several weeks. If headache occurs I will be offered pain medication.

Radiation: As a result of participating in this study, I will receive a significant amount of radiation. The amount is similar to that received in many standard x-ray procedures, but is far more than I would receive from natural daily exposure or in my normal course of treatment and carries at least a theoretical risk. If I am especially concerned with radiation exposure, I might wish to discuss this with the investigators.

Reporting of sexually transmittable diseases: Positive test results for syphilis, Hepatitis B and C, will be reported to the San Francisco Department of Health, as required by law.

Collection of blood may cause slight discomfort, pain, bleeding or bruising at the injection site and rarely, infection may occur.

Pap smear: This procedure may be slightly uncomfortable from the position and the speculum. Slight bleeding may occur.

Anal procedures: Insertion of an anal swab, an anoscope and application of acetic acid may cause some discomfort. Anal biopsy may be associated with discomfort from the needle stick for anesthesia, bleeding, temporary discomfort after the anesthetic wears off and rarely, infection. Time will be required to travel to and from the clinic at Mount Zion Medical Center where the procedures are performed.

Catheter placement may cause slight discomfort, bleeding or bruising at the site of placement and rarely, infection may occur.

New findings: There may be risks that are currently unknown. I will be informed of any new findings during the study that may affect my decision to continue participating.

CONFIDENTIALITY: PARTICIPATION IN RESEARCH WILL INVOLVE A LOSS OF PRIVACY. IN THIS STUDY, I WILL BE TESTED FOR ILLEGAL DRUGS. THE RESEARCHERS WILL KEEP INFORMATION ABOUT ME AS CONFIDENTIAL AS POSSIBLE, BUT COMPLETE CONFIDENTIALITY CANNOT BE GUARANTEED. ON RARE OCCASIONS, RESEARCH RECORDS HAVE BEEN SUPOENAED BY A COURT. ALL RECORDS WILL BE IDENTIFIED BY A CODE, THAT IS, NO NAMES WILL BE USED. IN ORDER TO VERIFY THE STUDY DATA, REPRESENTATIVES FROM THE FOOD AND DRUG ADMINISTRATION (FDA) MAY NEED TO REVIEW MY RECORDS. BY SIGNING THIS CONSENT FORM, I CONSENT TO INSPECTION OF MY MEDICAL RECORDS. NO INDIVIDUAL IDENTITIES WILL BE USED IN ANY REPORTS OR PUBLICATIONS RESULTING FROM THIS STUDY. IF I AGREE TO PARTICIPATE, A MEDICAL RECORD WILL BE CREATED FOR ME AT UCSF.

Treatment and Compensation for Injury

If I am injured as a result of being in this study, treatment will be available. The costs of such treatment may be covered by the University of California, depending on a number of factors. The University does not normally provide any other form of compensation for injury. For further information, I may call the office of the Committee on Human Research at 415/476-1814, or write: Committee on Human Research, Box 0962, University of California, San Francisco, CA 94143.

Benefits

I may receive no benefit from participating in this study. However, I will be contributing to the understanding of liver transplantation in HIV-infected individuals.

ALTERNATIVES

I may choose not to participate. If I choose not to participate in this study, a similar protocol will be available for transplantation. In addition, I may choose at any time after transplantation to discontinue my participation in the study.

COSTS

If I have insurance, all clinic visits, inpatient hospitalization, routine laboratory monitoring, procedures and x-rays will be billed to my insurance. If I have no insurance or my insurance does not pay for one or more of these charges, the study will pay. My insurance will not be billed for any research-related tests including immunology studies performed in the laboratories of Dr. McCune, Levy, Baxter and Stock, pharmacokinetic studies, special studies on liver or kidney tissue, GCRC visits, or HPV testing.

REIMBURSEMENT

I will not be reimbursed for my participation in this study.

QUESTIONS

This study has been explained to me by Dr. Peter Stock or Dr. Nancy Ascher and my questions have been answered. If I have any other questions about the study or if I experience a study-related injury, I can call Dr. Stock or Dr. Ascher at 415/353-1117. If I have any questions about my rights as a subject participating in a research study, I may contact the office of the Committee on Human Research at 415/476-1814.

CONSENT

I have been given copies of the signed and dated consent form and the Experimental Subject's Bill of Rights to keep.

PARTICIPATION IN RESEARCH IS VOLUNTARY. I have the right to decline to participate or to withdraw at any point in the study without jeopardy to my medical care. If I wish to participate, I should sign below.

Patient's Printed Name

Signature of Patient

Date

The person being considered for this study is unable to consent for himself/herself because he/she is a minor. I have been asked to give my permission to include my child in this study.

Signature of Parent or Legally Authorized Representative

Date

Signature of Person Obtaining Consent

Date

Signature of Translator

Date

I agree to have blood stored for future tests or research studies.

Yes No

Subject's initials

I agree to have procedures for the detection of HPV (Pap smear, anoscopy and if necessary, anal biopsy).

Yes No

Subject's initials

Pending IRB Approval

Additional information and signature line for high-risk donor interest. Draft language

H. High risk organ donation

I have been offered the possibility of kidney/liver donation from a donor who is considered to be at “high risk” of having one of the following infections that is in the early stages and can not yet be detected with the tests that are used to screen the donors of organs: HIV, hepatitis B, hepatitis C or other infections that are spread through sexual activity or drug use but have not yet been identified. People are considered to be at high risk if they are known to have recently used injection drugs, be men who have sex with men, be commercial sex workers, or have been recently incarcerated. I will not be offered an organ from a donor who is known or found to have any of these infections during the screening process after the donor has died. If the transplant surgeons feel the donor is otherwise healthy, and all their tests are negative for known infections, they will offer me the organ if I indicate below that I wish to be offered such an organ. Even though the tests are negative, the donor could be in the “window period” – the period shortly after they are infected with the HIV or hepatitis viruses - when it is too early for the body to make enough antibody to be seen on the diagnostic tests that are used to screen the donor.

The additional risks of accepting a transplant from such an organ donor include being exposed to another HIV or hepatitis infection in addition to those I already have. It is not known if people who already have HIV infection can get infected again with another strain of HIV, although a case has been described that suggests that this can happen. It is not known if a person were to become infected in such a way, if their HIV infection would progress more rapidly, be more severe, or be more difficult to treat. It is possible that a strain of HIV that is resistant to my antiviral medications could be passed on to me in this way and make my HIV treatment much more difficult. If this did happen, it is possible that I could become ill with HIV-related diseases and die more quickly.

Accepting the possibility of being offered a kidney/liver from a high risk donor does not guarantee that I will be offered such an organ. However, it is likely that I will be offered a high risk organ before a non-high risk organ becomes available to me since waiting lists for these organs are so long.

I do not need to accept any organ that is offered to me at any time, whether from a high risk donor or any donor. I can ask questions about the risk factor(s) the donor has. I can change my mind at any time. By signing below, I indicate that should such an organ become available, I would like it to be offered to me.

Monday August 14

3. Next Steps

10:30 - Noon

A. Common Protocols to IRBs

- Discuss anticipated delays
- Discuss unresolved issues

B. Central vs. site labs/storage

- Finalize agreements
- Other options to be explored

C. National DSMB

- UARP to take the lead?

D. Emmes to get all sites on the web

- What is needed?

E. Funding for Site Coordinators/Data Managers

- All information requested to Steve Rose

F. On-going conference calls and meetings

- Central administrative structure and funding at UCSF

G. Mechanisms for referrals between sites

-

H. RO1 preparation

Transplantation in HIV+ Patients Workshop – August 12-14, 2000
Contact List

Cleveland Clinic

Leonard Calabrese, M.D.
HIV Specialist
Ph : (216) 444-5258
Email: Calabri@ccf.org

Cornell

David Serur, M.D.
Nephrologist
New York Hospital, Cornell Medical
Center
505 East 70th Street
New York, NY 10021
Ph : (212) 746-1583

Emmes Corp.

Donald Stablein, Ph.D.
Statistician
President, The Emmes Corporation
11325 Seven Locks Road, Suite 214
Potomac, MD 20854
Tel: (301) 299-8655
Fax: (301) 299-3991
Email: dstablein@emmes.com

Matthew McIntosh, Ph.D.
Statistician
The EMMES Corporation
11325 Seven Locks Road, Suite 214
Potomac, MD 20854
Ph: (301) 299-8655 x 137
Fx: (301) 299-3991
Email: mmcintosh@emmes.com

Georgetown

Paul C. Kuo, M.D.
Surgeon: Kidney
4 PHC, 3800 Reservoir Rd NW
Georgetown University Medical Center
Washington, DC 20007
Ph: (202) 784-3700
Fx: 202-687-2969
e-mail: KUOP@gunet.georgetown.edu

Amy Lu, M.D.
Surgeon: Liver
Ph: (202) 784-6395
Email: Adl7@gunet.georgetown.edu

Bill Sachau
Study/Site Coordinator
Ph: 202-784-3700
Email: Sachauw@gunet.georgetown.edu

Joseph Timpone, M.D.
HIV Physician

Mary Young
HIV Physician
Ph: (202) 687-6845
Email:
Youngm2@gunet.georgetown.edu

Harvard

Sandy Feng, M.D.
Sfeng@PARTNERS.ORG

Jay Alan Fishman, M.D.
American Society of Transplantation
Infectious Disease Division
Massachusetts General Hospital
Room 5238, 149- 13th Street
Charlestown, MA 02129
Ph: 617-726-5772
Fx: 617-726-5411
Jfishman@partners.org

--or--

Associate Professor of Medicine,
Harvard Medical School
Clinical Director, Transplant Infectious
Disease Program
Physician, Infectious Disease, Mass
General Hospital
32 Fruit Street
Boston, MA 02114

Loyola of Chicago

Paul O'Keefe
HIV Specialist
Head, HIV/AIDS Program
Division of Infectious Diseases
Loyola University Medical Center
Building 54, Room 101
2160 S First Avenue
Maywood, IL 60153
Ph: (708) 216-3232
Fx: (708) 216-8198
Email: pokeefe@luc.edu

Sherry Hannon
Asst to Dr. O'Keefe
sshanno@luc.edu

Lode J. Swinnen, M.D.
HIV Specialist
Associate Professor of Medicine
Loyola University Chicago
Division Hematology/Oncology
Ph: 708-327-3142
Fx: 708-327-3219
Lswinne@luc.edu

David Vanthiel, M.D.
Hepatologist
2160 So. First Avenue
Building 114, Room 48
Maywood, IL 60153
(708) 216-0364

Katina Shehie
Asst to Dr. Vanthiel
kshehie@lumc.edu

Mayo Clinic, Jacksonville

Christopher Hughes
Surgery
Hughes.christopher@mayo.edu

Mt. Sinai

Jon Bromberg, M.D.
Surgeon: Kidney
Jon.bromberg@mountsinai.org
Ph: (212) 241-8684

Rosemarie Gagliardi
Study/Site Coordinator
Rosemarie.gagliardi@mountsinai.org
Ph: (212) 241-3665

Jeffrey Jacobson, M.D.
HIV/ID Specialist, liver transplant patients
Director, HIV/AIDS Center
Mt. Sinai Medical Center
1 Gustave Levi Place, Box 1009
New York, NY 10029
Ph : (212) 241-0700
Fx : (212) 876-7613
Email : jeffrey.jacobson@mssm.edu

Marla Keller, M.D.
HIV Specialist
AIDS Center, Infectious Disease
Mount Sinai Medical Center
1 Gustave L. Levy Place, Box 1090
New York, NY 10029-6574
Ph: (212) 241-5890
Fx: (212) 534-3240
e-mail: marla.keller@mssm.edu

Leona Kim, M.D.
Hepatologist
Leona.kim@mountsinai.org
Ph: (212) 241-2892

Charles Miller, M.D.
Surgeon: Liver
Charles.miller@mountsinai.org
Ph: (212) 241-0106

Barbara Murphy, M.D.
Nephrologist
Assistant Professor, Renal Division
Mount Sinai School of Medicine
1 Gustave L. Levy Place, Box 1243
New York, NY 10029
Ph: 212-241-5850
Email: barbara.murphy@mssm.edu

National Institutes of Health

Sandra Bridges, Ph.D.
Deputy Chief, Targeted Interventions
Branch
NIH/NIAID/Division of AIDS
6700B Rockledge MSC 7626
Room 4128
Bethesda, MD 20892-7626
(For Federal Express, use 20817-7626)
Ph: (301) 496-8198
Fx: (301) 402-3211
Email: sb33j@nih.gov

Doug Brust, M.D.
Clinical Associate
Laboratory of Immunoregulation
National Institute of Allergy and
Infectious Diseases
National Institutes of Health
Building 10, Room 6A11
10 Center Drive, MSC 1576
Bethesda, Maryland 20892-1576
Ph: 301-402-2617
FAX: 301-402-4122
Page: 301-496-1211
E-mail: dbrust@niaid.nih.gov

Scott Cairns, Ph.D.
Targeted Interventions Branch
Division of AIDS, NIAID
Room 4130
6700-B Rockledge Drive MSC 7628
Bethesda, MD 20892-7626
[Courier delivery: 20817-7626]
Ph: (301) 402-4239
Fx: (301) 402-3211
Email: scairns@niaid.nih.gov

Carole Cole
Assistant to Dr. William Duncan
Office of the Associate Director
Treatment Research Program
Division of AIDS, NIAID, NIH
6700B Rockledge Dr. Rm 5100
Bethesda, MD 20892
Phone : 301-402-5127
Fax : 301-480-4582
Ccole@niaid.nih.gov
Cc40u@nih.gov

William Duncan, Ph.D.
HIV
Associate Director, Therapeutics
Research Program
Division of AIDS
National Institute of Allergy and
Infectious Diseases
National Institutes of Health
6700B Rockledge, Rm 5101 MSC 7624
Bethesda, MD 20892-7624
Ph: 301-496-8210
Fx: 301-480-4582
e-mail: wd6u@nih.gov

Lawrence Fox, M.D., Ph.D.
HIV
HIV Research Branch
Therapeutics Research Program
Division of AIDS
National Institute of Allergy and
Infectious Diseases
National Institutes of Health
6700B Rockledge, Rm 5104 MSC 7624
Bethesda, MD 20892-7624
Ph: 301-402-0139
Fx: 301-435-9282
e-mail: lf6h@nih.gov

Lawrence D. Kerr, Ph.D.
Surgery
Chief, Transplantation Section
Genetics and Transplantation Branch
Division of Allergy, Immunology and
Transplantation (DAIT)
National Institute of Allergy and
Infectious Diseases (NIAID)
6700-B Rockledge Drive, Rm. 5129
Bethesda, MD 20892
Ph : (301) 496-5598
Fx : (301) 402-2571
Email : Lkerr@niaid.nih.gov

Allan D. Kirk, M.D.
Surgery
Section Chief, Transplant and
Autoimmunity Branch
NIDDK, NIH
Building 10, Rm. 115219
Bethesda, MD 20892
Email : AllanK@intra.niddk.nih.gov

Jeffrey Kopp, MD
Kidney Disease Section
Bdg 10, Rm 3N116
NIDDK, NIH
Bethesda, MD 20892-1268
Ph: (301) 594-3403
Fx: (301) 402-0014
Email: jbkopp@nih.gov

Joseph Kovacs, M.D.
HIV
Head, AIDS Section
NIAID, NIH
Building 10, Rm. 4D04
Bethesda, MD 20892
Ph : (301) 496-9907
Email : jkovacs@niaid.nih.gov
Email2 : jk27y@nih.gov

Alice K. Pau, Pharm.D.
**Clinical Pharmacy Specialist for
NIAID**
NIH Clinical Center Pharmacy Dept
Bldg 10 Rm 1N257
10 Center Drive
Bethesda, MD 20892
Ph: 301-402-7077
Fx: 301-496-0210
e-mail: ap124z@nih.gov

Stephen Piscitelli, Pharm.D.
Pharmacologist
Clinical Center Pharmacy Department
Bldg 10, 1N257
National Institutes of Health
Bethesda, MD 20892
Ph: 301-496-2997
Fx: 301-496-0210
e-mail: spisc@nih.gov

Diane Lepley, RN, MPH
Study Coordinator
Transplant Coordinator NIDDK
Email: DianeL@intra.niddk.nih.gov

Stephen Rose, Ph.D.
Surgery: Kidney
Chief, Genetics and Transplantation
Branch
Division of Allergy, Immunology and
Transplantation
National Institute of Allergy and
Infectious Diseases
National Institutes of Health
6700B Rockledge Drive, Rm 5130
Bethesda, MD 20892-7640
Ph: 301-496-5598
Fx: 301-402-2571
e-mail: Steve_Rose@nih.gov

Mary Smolskis, RN, MA
Nurse Consultant
NIAID
Division of Allergy, Immunology and
Transplantation
Ph : (301) 496-2827
Email : msmolskis@niaid.nih.gov

Michael Sneller, M.D.
Chief, Immunologic Diseases Section
Laboratory of Immunoregulation,
NIAID
National Institutes of Health
Building: 10 Room: 11B-13
Bethesda, MD 20892-1876
Phone: (301) 496-0491
FAX: (301) 402-8477
Email: MSNELLER@niaid.nih.gov

**University of California, San
Francisco**

Lee Ann Baxter-Lowe, Ph.D.
Surgery: Immunology
UCSF Immunogenetics and
Transplantation Laboratory
Box 0508
San Francisco, CA 94143-0508
Ph: 415-476-0658
Fx: 415-476-0379
e-mail: BaxterLoweL@surgery.ucsf.edu

Laurie Carlson, R.N.
UCSF Study Coordinator
Ph: (415) 715-2385
Ph2: (415) 476-3304
Email: CarlsonL@surgery.ucsf.edu

Tom Coates, Ph.D.
**Director, UCSF AIDS Research
Institute**
University of California, San Francisco
74 New Montgomery #600
San Francisco, CA 94105
Ph: 415-597-9157
Fx: 415-597-9213
e-mail: tcoates@psg.ucsf.edu

Charles Everett
Administrative Assistant
AIDS Research Institute, UCSF
74 New Montgomery St., Ste. 600
San Francisco, CA 94117
Ph: (415) 597-9266
Fx: (415) 597-9213
Ceverett@psg.ucsf.edu

Lisa Johnson
Administrative Assistant
AIDS Research Institute, UCSF
74 New Montgomery St., Suite 600
San Francisco, CA 94105
Ph: (415) 597-4668
Fx: (415) 597-9213
Email: ljohnson@psg.ucsf.edu

Jay Levy, M.D.
HIV Specialist – Immunology
University of California, San Francisco
513 Parnassus Avenue
San Francisco, CA 94143-1270
Ph: 415-476-4071
Fx: 415-476-8365
e-mail: jalevy@itsa.ucsf.edu

Michael McCune, M.D.
HIV Specialist – Immunology
Gladstone Institute of Virology and
Immunology
P.O. box 419100
San Francisco, CA 94141-9100
Ph : (415) 695-3828
Fx : (415) 826-1514
e-mail: mmccune@gladstone.ucsf.edu

Michelle Roland, M.D.
HIV Specialist
Ward 84, San Francisco General
Hospital
995 Potrero Avenue
San Francisco, CA 94110
Ph: 415-476-4082, ext. 432
e-mail: mroland@sfaids.ucsf.edu

Peter Stock, M.D.
Surgery: Kidney and Liver
Associate Professor, Division of
Transplant Surgery
University of California, Moffitt
Hospital, Rm M-884
505 Parnassus Ave
San Francisco, CA 94143
Ph: 415-353-1117
Fx: 415-476-6682
e-mail: pgs007@itsa.ucsf.edu

Susie Kliks, Ph.D.
Universitywide AIDS Research Program
300 Lakeside Drive, 12th Floor
Oakland, CA 94612-3550
Ph: 510-987-9855
Fx: 510-835-4220
e-mail: susie.kliks@ucop.edu

University of Maryland

David Oldach, M.D.
HIV – Virology
Institute of Human Virology
Room 556, U of MD Medical
Biotechnology Center
725 W. Lombard St.
Baltimore, MD 21201
Ph: (410) 706-4609
Fx: (410) 706-1992
e-mail: oldach@umbi.umd.edu

University of Miami

Schiff, M.D.
Hepatologist
University of Miami

Tzakis, M.D.
Surgery
University of Miami
Email : Atzakis@miami.edu

University of Minnesota

Abhi Humar, M.D.
Surgery : Liver
Surgery Dept., University of Minnesota
11-100 PWB
516 Delaware St. SE
Minneapolis, MN 55455
Ph: (612) 625-6460
Email: humar001@umn.edu

Melissa Kamps, PharmD.
Pharmacologist
Pharmacy Administration
Box 611 Mayo
420 Delaware St., SE
Minneapolis, MN 55455
Email: kamps001@umn.edu

John R. Lake, M.D.
Surgery : Liver
Medicine – GI, University of Minnesota
A-543 Mayo
420 Delaware St., SE
Minneapolis, MN 55455
Ph 1: (612) 625-0684
Ph 2: (612) 625-2636
Email: lakex009@umn.edu

Arthur Matas, M.D.
Surgery : Kidney
Surgery Dept., University of Minnesota
11-136 Moos T
515 Delaware St., SE
Minneapolis, MN 55455
Ph: (612) 625-6460
Email: matas001@umn.edu

Tim Schachter
HIV Specialist
University of Minnesota

University of Pennsylvania

Kim. Olthoff, M.D.
Surgery : Liver
Liver Transplant Program
University of Pennsylvania and
The Children's Hospital of Philadelphia
Ph : (215) 662-6136
Fx : (215) 662-7476
Email : kim.olthoff@uphs.upenn.edu

Cay Read, RN
Study Coordinator
Ph : (215)662-4716

University of Pittsburgh

C. Andrew Bonham, M.D.
Surgeon: Liver
3601 5th Avenue
4 Falk Medical Building
University of Pittsburgh
Pittsburgh, PA 15213
Ph: (412) 648-3200
Fx: (412) 647-5480
Email: bonhamca@msx.upmc.edu

John Fung, M.D.
Surgery: Liver
Division of Transplant surgery
3601 5th Avenue
4 Falk Medical Building
University of Pittsburgh
Pittsburgh, PA 15213
Ph: 412-648-3200
Fx: 412-647-5480
e-mail: fung@med.pitt.edu

Susan Hunt, M.D.
HIV
200 Lathrop Street, Suite 9West
Pittsburg, PA 15213
Ph : 412-692-4816
Email : huntsc@msx.upmc.edu

Margaret Ragni, M.D.
HIV
Hemophilia Center of Western
Pennsylvania
3636 Boulevard of the Allies
Pittsburgh, PA 15213-4306
Ph: 412-209-7288
Fx : 412-209-7281
Email: ragni@msx.dept-med.pitt.edu

Ronald Shapiro, M.D.
Surgery: Kidney
3601 5th Avenue
4th Floor Falk Clinic
Pittsburgh, PA 15213
Ph: 412-648-3200
Fx: 412-648-3085
Email: shapiror@msx.upmc.edu

Amanda Gregan
Asst to Dr. Shapiro
Ph: (412) 648-3921
Email: greganal@msx.upmc.edu

University of Virginia

Carl Berg, M.D.
Hepatologist
Ph : (804) 924-2626
Email : clb7d@virginia.edu

Peter Lobo, M.D.
Nephrologist
Ph : (804) 924-2187
Email : pil@virginia.edu

Gabriella
Asst to Dr. Lobo
gf2n@virginia.edu

Robb McGory, PharmD
Pharmacologist
Ph: (804) 243-6156
Email: rwm7u@virginia.edu

Timothy Pruett, M.D.
Surgeon : Liver and Kidney
Chief of Transplantation
U. of Virginia, Dept. of Surgery
P.O. Box 800709
Charlottesville, VA 22908
Ph: (804) 924-9462
Email: tp2w@virginia.edu

Terry Ryan, RN
Study Coordinator
Email :TER5G@hscmail.mcc.virginia.edu

Brian Wispelway, M.D.
HIV Specialist
Ph : (804) 982-4470
Email : Bw9g@virginia.edu

SF Community

Jeff Getty
Community Member
3016 Filbert Street, #3
Oakland, CA 94608
Ph: (510) 653-6278
Fx: (510) 653-6099
Email : jeffgetty@aol.com

Brenda Lein
Community Representative
Project Inform
205 13th Street, #2001
San Francisco, CA 94103
Ph: (415) 558-8669
Fx: (415) 558-0684
Blein@projinf.org

Billy Pick, MPH
Assistant Research Chief
SF Department of Public Health
AIDS Office
25 Van Ness Avenue, 5th Floor
San Francisco, CA 94103
Ph: (415) 554-9000 (general #)
Fx: (415) 621-0641