

Protocol Synopsis – HIV-TR

Solid Organ Transplantation in HIV: Multi-Site Study Version 7.0, July 2009

Principal Investigators: Peter Stock, MD (University of California, San Francisco)
Michelle Roland, MD (University of California, San Francisco)

Participating Sites:

University of California, SF (K,L)* (Peds K,L)*	Mount Sinai School of Medicine (K,L) (Peds K)
Cedars-Sinai, LA (L)	Columbia University (L) (Peds L)
University of Maryland (K)	Georgetown Medical Center (K,L)
Tulane University (K,L) (Peds K,L)	(Peds K, L)
Drexel (K, L)	Beth Israel/Harvard (K, L)
University of Virginia (K,L)	University of Chicago (K,L) (Peds K)
University of Pennsylvania (K,L)	University of Cincinnati (K,L)
University of Pittsburgh (K,L)	University of Miami (K, L) (Peds K)
Washington Hospital Center (K)	Cleveland Clinic Foundation (K,L)
Rush University (K,L)	Emory University (K)
Northwestern (K, L)	Johns Hopkins (K,L) (Peds K)

*K=kidney, L=liver, Peds=Pediatric Centers

Activation Date: October 2003

Accrual Objective: 150 kidney transplants and 125 liver transplants

Accrual Period: Open enrollment until accrual objective is reached.

Study Design: Prospective, open-label, non-randomized clinical trial evaluating the safety and efficacy of [kidney, liver] transplants performed in HIV positive patients over the age of 1 year. All patients who are being considered for transplant will be registered when eligibility is confirmed and after informed consent is obtained. Following transplant, patients are seen daily during the initial hospitalization, then weekly (x2), every other week (x5), monthly (x2), every 8 weeks (x4), every 12 weeks (beginning of Year 2 to the end of Year 3), then every 6 months for the final 2 years of follow-up.

Primary Study Objectives: Primary Aim 1: Evaluate the impact of immunosuppression (IS) in HIV+ liver and kidney transplant recipients on patient survival.

Primary Aim 2: Evaluate the impact of HIV infection and HAART on graft survival.

Secondary Study Objectives: Secondary Aim 1: Explore the impact of post-transplant immunosuppression on changes in CD4+ T cell counts and HIV-1 RNA levels.

Secondary Aim 2: Explore the impact of post-transplant immunosuppression on the host-response to viral co-pathogens, including hepatitis B and C, the human herpesviruses (CMV, EBV, HHV-6, HHV-8) and HPV.

Secondary Aim 3: Explore the impact of HIV infection on the alloimmune response and rejection rates.

Secondary Aim 4: Explore the pharmacokinetic interactions between immunosuppressive agents and the hepatically metabolized antiretroviral agents.

Eligibility Criteria: Inclusion Criteria:

- Documented HIV infection.
- Age > 1 year old.
- Opportunistic Complications - multiple prior conditions permitted, provided there is no active disease.
- CD4+ T-cell count within 16 weeks of transplant for subjects >10 years old:
For kidney patients: $\geq 200/\mu\text{L}$
For liver patients: $\geq 100/\mu\text{L}$ (≥ 200 if history of opportunistic complications).
- Current HIV-1 RNA assay - non-detectable except for liver candidates with controllable viral loads.
- Meet standard listing criteria for placement on transplant waiting list.
- Able to provide informed consent.
- Kidney candidates must be on stable antiretroviral (ARV) for three months.
- Willing to use PCP, herpes virus and fungal prophylaxis as indicated.
- If HBV or HCV positive, must undergo frequent monitoring, including biopsies. HCV+ kidney candidates must have non-cirrhotic liver
- For subjects with a history of aspergillus colonization or disease, no current clinical evidence of active disease.
- The patient must have or be willing to start seeing a primary medical care provider with expertise in HIV management.
- Female subjects of child-bearing potential must have a negative serum beta-HCG pregnancy test within 14 days of screening. All subjects must practice barrier contraception.
- Not suffering from significant wasting.

Eligibility Criteria: Exclusion Criteria

- Patients who have received a prior transplant will be excluded only if they have received immunosuppressant medication in the 6 months prior to re-transplantation in the current study. Low dose maintenance steroids (≤ 10 mg per day of prednisone, or equivalent strength steroid) will not be considered immunosuppression.
- Opportunistic Complication History: Any history of progressive multifocal leukoencephalopathy (PML), chronic intestinal cryptosporidiosis of >1 month duration, or primary CNS lymphoma. History of pulmonary coccidioidomycosis will be treated per local site policy regarding this infection in HIV negative transplant candidates, generally requiring a five-year disease-free interval.
- History of documented resistant fungal infection not expected to respond to available oral antifungal agents (*krussii*, *glabrata*, *candida*).
- History of documented influenza or RSV in the past 30 days.
- History of other neoplasm is an exclusion except for the following: cutaneous kaposi's sarcoma, in situ anogenital carcinoma, adequately treated basal or squamous cell carcinoma of the skin, solid tumors (except primary CNS lymphoma) treated with curative therapy and disease free for more than five years. History of renal cell carcinoma requires disease free state for 2 years. History of leukemia and disease-free duration will be per site policy. (Liver: hepatocellular carcinoma is not an exclusion.)

- Inability or unwillingness to comply with immunosuppression protocol, ARV therapy and/or HCV monitoring and therapy if indicated.
- Substance use per local site policy.
- Advanced cardiac or pulmonary disease per local site policy.
- Documented anatomic abnormalities precluding transplantation.
- Pregnancy (pre transplant).
- Concomitant conditions that, in the judgment of the investigators, would preclude transplantation or immunosuppression.
- Use of IL-2 or GM-CSF in the prior six months.
- For kidney patients, HCV - Cirrhosis on liver biopsy in patients with hepatitis C co-infection unless being listed for combined liver and kidney transplant. Exceptions may be made per protocol specifications.

Treatment:

Patients will be monitored with considerations detailed in the protocol for:

- Immunosuppression Strategy
- Rejection Treatment
- HCV Therapy
- HBV Therapy
- Opportunistic Infection Prophylaxis
- Vaccinations
- PPD Testing and TB Prophylaxis
- Special Considerations for Antiretrovirals
- Antiretroviral Dose Adjustments for Hepatic and Renal Insufficiency
- Pediatric Issues

Primary Endpoints:

Participant survival and graft survival

Study Duration:

5 years