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Solid Organ Transplantation in HIV: Multi-Site Study

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SPECIAL NOTE

Note: Organ-Specific and site-specific areas that require modification prior to IRB submission are included in **[bold and bracket]**.

STUDY MANAGEMENT

See section 3 of the Manual of Operations (MOP) for an outline of who to contact for specific questions related to this study, including appropriate contact information.

1 STUDY OBJECTIVES AND HYPOTHESES

1.1 PRIMARY OBJECTIVES AND HYPOTHESES

The primary aim of this study is to evaluate the safety and efficacy of solid organ transplantation in people with HIV disease by conducting a prospective, multi-center cohort study of HIV-positive (+) patients who undergo kidney or liver transplantation. Our long-range goals are: (1) to provide patients and clinicians with information regarding the HIV-specific risks of transplantation, (2) to provide clinicians with information necessary to manage immunosuppressive and antiretroviral (ARV) medications together, and (3) to understand underlying basic science mechanisms that explain patient outcomes so that clinical management may be adjusted to maximize these outcomes. Patients with HIV infection are at significant risk for end-stage organ disease. Prior to the advent of highly active antiretroviral therapy (HAART), such patients were often not considered as transplant candidates based on poor prognosis. However, with the use of HAART, HIV+ patients have experienced significant improvements in morbidity and mortality¹⁻³. Thus, increasing numbers of HIV+ patients with end-stage kidney and liver disease are potential candidates for transplantation.

Data on the safety and efficacy of solid organ transplantation in people with HIV infection are limited and the results are mixed. Prior to the HAART era, some transplant centers reported good outcomes following transplantation in HIV+ patients⁴⁻⁹; however, other reports have been less favorable¹⁰⁻¹³. Short of a randomized, controlled trial, the clinical benefit of solid organ transplantation in people with HIV disease can be best established in a large, prospective study as we propose. In addition, we propose to establish a cohort of HIV+ transplant recipients that will provide an ideal opportunity to investigate key medical management issues and underlying mechanisms of disease progression within the proposed study or with additional funding from stored specimens. There are two sets of laboratory studies included in this proposal. The first set includes those that will be performed in real time or in batches throughout the trial that will provide information critical to the development of clinical practice guidelines. Such studies include the pharmacokinetic interactions between immunosuppressive agents and the hepatically metabolized antiretroviral agents, and the impact of immunosuppression on viral co-pathogen organism load. While not all patients in the cohort will participate in each of these studies, and they are not meant to be used for direct clinical management, the findings will be used to develop principles of patient management that will be applied to the entire cohort. The second group of studies includes those that are not anticipated to directly impact clinical management, but are critical for furthering our understanding of pathogenesis-related issues, and will be performed later with separate funding on stored samples obtained in this protocol. Such studies include the impact of HIV infection on the alloimmune response, and the effect of immunosuppression on T cell phenotypes, HIV-specific immune responses, and the HIV viral reservoir.

We have established a multidisciplinary team of investigators and clinicians from high volume transplant centers in areas of high HIV prevalence who have the most scientific and clinical expertise in the management of transplant recipients and people with HIV infection. Our specific aims are:

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

Hypothesis 1.1: Liver and kidney transplant recipients will have survival rates comparable to other patient groups without HIV infection that are currently considered acceptable transplant candidates.

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

Hypothesis 2.1: HIV+ liver and kidney transplant recipients will have graft survival rates comparable to other patient groups without HIV infection that are currently considered acceptable transplant candidates.

Hypothesis 2.2: HIV+ liver transplant recipients co-infected with hepatitis B or C will have graft survival comparable to other patient groups with the same viral hepatitis infections but without HIV infection that are currently considered acceptable transplant candidates.

Hypothesis 2.3: HIV+ kidney transplant recipients with HIV nephropathy (HIVAN) will have recurrence of HIVAN resulting in impaired renal function and graft survival despite the use of HAART.

1.2 SECONDARY OBJECTIVES AND HYPOTHESES

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

Rationale: Post-transplant immunosuppression may cause declines in CD4+ T-cell counts, and lead to HIV-1 RNA breakthrough on HAART. Alternatively, immunosuppression may result in depletion of HIV-1 reservoirs or reductions in viral rebound. Such acceleration may be mediated through viral and/or host immunologic pathways. This question, as well as the effect of immunosuppression on the HIV viral reservoir, will be explored in future studies using stored samples.

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.

Rationale: The combination of immunosuppression and HIV could alter viral activation and/or host immune control of viruses that are associated with the development of recurrent and clinically significant disease post-transplant.

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

Rationale: HIV+ transplant recipients may have perturbations of the immune system that influence the immune response to solid organ allografts that may have implications for immunosuppression requirements. This question will be explored in the current proposal and in future studies using stored samples.

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

Rationale: Many of the immunosuppressive drugs (including cyclosporine [CsA], tacrolimus and sirolimus), as well as the protease inhibitor (PI) and non-nucleoside reverse transcriptase inhibitor (NNRTI) ARVs, are hepatically metabolized by the p450 enzymatic system. These drugs are expected to interact with one another, with similar interactions within drugs in the same immunosuppression or ARV class, resulting in perturbations in drug levels and requiring modifications in dosing.

2 BACKGROUND AND RATIONALE

SIGNIFICANCE

People with HIV infection are living longer and dying less often from AIDS-related complications, but are experiencing morbidity and mortality secondary to organ failure and are increasingly seeking organ transplantation. Patient and graft survival outcomes and the management of complex medication interactions in the HAART era are unknown. The need for an organized, national effort to address the safety and efficacy of solid organ transplantation in HIV+ patients is increasing as more centers offer transplantation to this population. Such a coordinated effort will provide an opportunity to study long-term clinical outcomes and drug interactions, and to conduct exploratory studies focused on underlying mechanisms of disease progression and graft survival. Reliable data on patient and graft survival will not only guide patient and referring provider decisions to seek transplant, but will influence reimbursement policies as well. Similarly, drug interaction and clinical management experience will provide the basis for the development of clinical practice guidelines for managing HIV+ transplant recipients. Finally, understanding the mechanisms underlying disease progression within the current proposal and through additional studies to be performed on stored specimens will help in the development of specific patient management strategies.

HIV Treatment Advances, Disease Burden and Early Transplant Data: The Need for a Prospective Study

Recent Advances in HIV Therapy and Improvements in Morbidity and Mortality: Clinical trials

have demonstrated virologic, immunologic, and survival benefits associated with the use of PI-containing or NNRTI-containing regimens (HAART)¹⁴⁻³¹. Epidemiologic data show decreased mortality, hospitalization rates, and opportunistic infection incidence associated with HAART^{1, 3, 13, 14, 22, 25, 32-36}. There have been dramatic reductions in new AIDS-related opportunistic infections (OI), most of which are now occurring in people with low CD4+ T cell counts and those who are not receiving medical care³.

Prevalence and Natural History of End-stage Renal Disease and HIV-Associated Nephropathy (HIVAN)

HIV+ patients are at risk for end-stage renal disease (ESRD) due to common and HIV-specific diseases, including HIV-associated nephropathy (HIVAN), immune complex glomerulonephropathy (GN), and hepatitis C-associated cryoglobulinemic GN^{37, 38}.

Prevalence and Natural History of End-stage Liver Disease

HIV+ patients are at risk for hepatitis C (HCV) and B (HBV) infection and the development of end-stage liver disease (ESLD)³⁹⁻⁴¹. The prevalence of HCV among HIV+ patients has been reported as 23 to 33%^{42 40}. The prevalence of chronic HBV infection is approximately 9% in HIV+ patients⁴⁰. ESLD progression is significantly accelerated in co-infected patients⁴³⁻⁵³ and may be complicated by ARV toxicity⁵⁴⁻⁵⁸, immune restoration-induced hepatitis⁵⁸, or the development of lamivudine-resistant HBV^{49, 59, 60}. Deaths due to ESLD are of growing significance among patients with HIV infection^{42, 61-63}.

Safety and Efficacy of Solid Organ Transplantation in HIV+ Recipients

United Network for Organ Sharing (UNOS) policy does not consider HIV infection to be a contraindication for transplantation. Although several initial papers reported poor outcomes following transplantation in HIV+ recipients^{10-12, 64}, there have also been reports where there were no apparent adverse effects of HIV infection on allograft survival^{4, 9}. Preliminary data in the HAART era are promising⁶⁵

Antiviral and/or Immune Modulating Effects of Cyclosporine (CsA) and Mycophenolate Mofetil

Ironically, some immunosuppressive agents have direct antiviral properties or are hypothesized to inhibit HIV replication through immune modulating effects. The use of mycophenolate mofetil (MMF) as a synergistic component of HAART is under evaluation.

HIV Disease Progression and the Role of Immunologic and Virologic Mechanisms.

Effect of Immunosuppression on Opportunistic Infections and Changes in CD4+ T Cell Count and HIV-1 RNA: HIV infection is characterized by the progressive loss of CD4+ T cells and alterations in function. AIDS-defining opportunistic complications develop as a result of impaired cell-mediated immune responses. It is important to determine whether HIV+ transplant recipients are at increased risk of accelerated CD4+ T cell depletion (or increased CD4+ T cell dysfunction), the development of opportunistic complications, or difficulty in controlling HIV replication.

Effect of Immunosuppression on T Cell Phenotypes and HIV-Specific Immune Responses:

The underlying hypothesis of the HIV-specific immunologic studies we propose for future evaluation using stored samples is that immunosuppression will be associated with changes in markers of immune function and activity that are not associated with HIV disease progression. Immunosuppression might inhibit protective immune responses against HIV; conversely, it might reverse the immunopathology associated with HIV disease.

Effect of Immunosuppression on the HIV Viral Reservoir:

In future studies from stored specimens, we plan to evaluate the effect of immunosuppression on the reservoir of HIV-infected cells that persist during HAART. Immunosuppression might decrease cell-associated HIV through either direct inhibition of viral replication, potentiation of HAART effects⁶⁶, or depletion of infected cells. Alternatively, decreased immune control of HIV expressing cells may result in enhanced viral reservoirs.

Viral Co-Pathogen Prevalence and Impact of Immunosuppression on Clinical Manifestations, Organism Load, and Host Immune Responses.

Hepatitis B Infection (HBV): Prevalence, Clinical Manifestations and Viral Drug Resistance:

Liver and kidney transplant recipients co-infected with HIV and HBV may be at increased risk of recurrent or progressive HBV infection post-transplantation due to HIV-associated immune deficiencies that allow escape from antiviral therapies, or due to high rates of lamivudine (3TC)-resistant HBV and ALT, and improved liver function⁶⁷. Adefovir has been shown to be safe and effective in non-transplant patients co-infected with HIV and HBV^{68, 69}. *In vitro* studies suggest tenofovir may be effective against 3TC-resistant HBV infection⁷⁰ and thus may be useful in the management of liver transplant recipients with

HBV infection, particularly in HIV+ patients. There are no data on the effectiveness or safety of these agents in kidney recipients. We will characterize HBV viral mutants and use this information to guide decisions regarding the optimal anti-HBV therapy.

Hepatitis C Infection (HCV): Prevalence, Clinical Manifestations, Organism Load, Viral Evolution, and Host Immune Responses: It is estimated that up to 240,000 people are co-infected with HCV and HIV⁵¹ and HCV disease progresses more rapidly in HIV+ patients^{42, 50, 53, 71-73}. HCV disease progression is also accelerated in liver⁷⁴ and renal⁷⁵ transplant recipients, but patient survival is improved due to the benefit of the allograft. The clinical endpoints of greatest importance include patient and graft survival, disease progression (histologic fibrosis and inflammation scores, occurrence of cirrhosis), and incidence and outcome of HCC. We will monitor the same outcomes in cohorts of HCV positive (non-HIV infected) patients undergoing kidney or liver transplantation. We will require standardized use of HCV therapy post-transplant if there is biopsy-proven evidence of significant disease activity. We will also examine virologic and immunologic outcomes.

Human Herpesviruses: Prevalence, Clinical Manifestations, and Organism Load: Opportunistic infections with herpesviruses (cytomegalovirus [CMV], Epstein-Barr virus [EBV], human herpes virus 6 [HHV-6] and human herpesvirus 8 [HHV-8]) are a significant cause of morbidity and mortality in organ transplant recipients and HIV+ patients due to suppression of host anti-herpesvirus T cell immunity. Although the type of herpesvirus-related diseases will likely be similar in HIV+ transplant recipients on HAART as in HIV-transplant recipients, the disease incidence and severity may be increased. In addition, the viral load associated with the development of disease may be lower as viral replication is controlled by T cell immunity to the herpesviruses. To explore these hypotheses, we propose to perform longitudinal assessments on peripheral blood samples for markers of EBV, CMV, HHV-6, and HHV-8 viral replication, and correlate these with markers of host immune response and clinical disease.

Human Papilloma Virus: Prevalence, Clinical Manifestations and Viral Evolution: Transplant recipients are at increased risk for HPV-associated cancers⁷⁶⁻⁷⁸. Not surprisingly, HIV+ patients also have a high prevalence of anogenital HPV infection⁷⁹⁻⁸¹. Since these two forms of immune suppression may affect the immune system differently, it is important – both clinically and scientifically – to assess the effect of immunosuppression on the course of anal HPV infection and AIN in this population.

Host Immune Responses to Viral Co-Pathogens: Post-transplant immunosuppression may lead to reactivation and increased replication of these viral pathogens. Combined with information on host viral burden and clinical disease, these data will help ultimately in the design of immune-based prophylactic strategies to prevent viral-mediated disease in the transplantation setting.

Impact of HIV Infection on the Alloimmune Response

Perturbations of the immune system associated with HIV infection may influence the immune response to allografts.

Pharmacokinetic Interactions Between Immunosuppressive Agents and Antiretrovirals

Many of the immunosuppressive drugs (CsA, tacrolimus and sirolimus), as well as the PIs and NNRTIs, are hepatically metabolized by the cytochrome P-450 enzymatic system. It is also necessary to consider interactions via P-glycoprotein (P-gp), an ATP-dependent drug efflux pump expressed in high levels on the apical surfaces of many epithelial cells. P-gp expression and function and cytochrome P4503A function can be affected by both sets of drugs. Drugs interactions may result in perturbations in drug levels that require dosing modifications to maintain appropriate drug levels; over- or under- dosing carries the risk of toxicity, transplant rejection or HIV rebound.

3 GENERAL STUDY DESIGN

This is a 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. We anticipate enrolling eligible subjects until we have transplanted up to 150 kidney transplant recipients and 125 liver transplant recipients with two to five years of follow-up. Following transplant and post-operative recovery, this will be an outpatient study **[UCSF ONLY: with the exception of 4 or more possible inpatient 14 to 26 hour GCRC or PCRC visits at Screening, Week 2, Week 12, and Week 26, Week 52, Year 2 or Year 5 depending on which antiretroviral and immunosuppressive agents the patient is on.]**. 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. A detailed schedule of events is listed in section 6.2.

3.1 INTERNET-BASED DATA COLLECTION

Data from this study will be entered into a database through a secured web site, utilizing the same high quality encryption technologies used for commercial financial transactions over the Internet. Only authorized personnel requiring a password will be permitted to enter data. Data will be collected and analyzed in three separate phases: the pre-study screening phase, the pre-transplant phase and the post-transplant phase.

3.2 STUDY ENDPOINTS

3.2.1 Primary Endpoints

The primary endpoints are subject survival and graft survival. Graft survival time will be measured from the time of transplantation to the time of graft failure for those with failure, and will be censored at the last follow-up time for those without failure. Graft failure is defined as the first observation of any of the following events:

KIDNEY: death, retransplantation or initial return to chronic dialysis.

Chronic dialysis is defined as 30 days or a treatment plan of permanent ongoing dialysis support. If a patient was preemptively transplanted (i.e. not receiving chronic dialysis at the time of transplant), then the graft failure date is defined by the decision to discontinue futile treatment (i.e. date of discontinuation of immunosuppression) if neither retransplantation or return to dialysis occurs.

LIVER: death or retransplantation

3.2.2 Secondary Endpoints

The secondary endpoints include:

Secondary Aim 1: opportunistic complications and changes in CD4+ T cell counts and HIV-1 RNA levels

Secondary Aim 2: viral markers and host-response (CFC and ELISPOT) to viral co-pathogens, including hepatitis B and C, the human herpesviruses (CMV, EBV, HHV-6, HHV-8) and HPV.

Secondary Aim 3: rejection rates and markers of alloresponse

Secondary Aim 4: pharmacokinetic interactions between immunosuppressive agents and the hepatically metabolized antiretroviral agents, by drug class

4 SUBJECT SELECTION AND ENROLLMENT

All individuals with end-stage [**kidney, liver**] disease and HIV infection who meet standard clinical criteria for transplantation and the study inclusion and exclusion criteria are eligible for registration on the study. When an organ becomes available, patient transplant eligibility will be determined based on an eligible CD4+ T-cell count not more than 16 weeks prior to transplant, and the most recent viral load result not more than 16 weeks prior to transplant.

Patients must be ≥ 1 year in age to participate in this study. Standard consent criteria by age will be applied. With respect to inclusion and clinical management guidelines, patients who are Tanner stage ≤ 4 will be considered children; those who are Tanner stage 5 will be considered as adults.

Final decisions with regard to the application of narrower selection criteria with regard to pre-transplant viral load and history of opportunistic complications are the prerogative of the individual sites. However, individual sites may not enroll patients who are outside the bounds of the inclusion criteria.

4.1 INCLUSION CRITERIA

1. Documented HIV infection (by any licensed ELISA and confirmation by Western Blot, positive HIV ab IFA, or documented history of detectable HIV-1 RNA).
2. Age > 1 year old.
3. Opportunistic Complications:

Per site policy, a previous history of the following opportunistic infections or neoplasms may be allowed if subjects have received appropriate acute and maintenance therapy and no evidence of active disease. Medical record documentation should be provided by the primary medical provider whenever possible.

Condition	Comments
Candidiasis of bronchi, trachea. or lungs	--
Candidiasis, esophageal	
Cryptococcosis, extrapulmonary	Requires negative serum CRAG
Cytomegalovirus disease (other than liver, spleen, or nodes)	--
Cytomegalovirus retinitis	no active disease on optho exam. Presence of an intraocular implant does not imply active disease.

Encephalopathy, HIV-related	Diagnosed prior to HAART and resolved on HAART with marked improvement in mental status and increased CD4+ T-cell count and no evidence of progression of CNS disease AND are otherwise considered eligible from a functional standpoint.
Herpes simplex: chronic ulcer(s) (greater than 1 month's duration); or bronchitis, pneumonitis, or esophagitis	--
Histoplasmosis, disseminated or extrapulmonary	Must be on or restart secondary prophylaxis regardless of CD4 count. (Will be modified if the USPHS/IDSA Guidelines change.)
Isosporiasis, chronic intestinal (greater than 1 month's duration)	--
Kaposi's Sarcoma (cutaneous)	If complete remission with immune reconstitution. No active/vascular residual cutaneous lesions on physical exam and negative chest CT scan.
Lymphocytic interstitial pneumonitis	--
Mycobacterium avium complex, disseminated or extrapulmonary	Completed treatment
Mycobacterium tuberculosis, any site (pulmonary or extrapulmonary)	Completed treatment
Mycobacterium kansasii, any site (pulmonary or extrapulmonary)	Completed treatment
Mycobacterium, other species of unidentified species, disseminated or extrapulmonary	Completed treatment
Pneumocystis carinii pneumonia	--
Pneumonia, recurrent	--
Recurrent bacterial infections	--
Salmonella septicemia, recurrent	--
Toxoplasmosis, CNS	Completed therapy AND MRI without active disease

4. Current CD4+ T-cell count:

[KIDNEY]: $\geq 200/\mu\text{L}$ at anytime in the 16 weeks prior to transplant. Note that the CD4+ T-cell count can be lower on one or more occasions within the 16 weeks prior to transplant as long as it was $\geq 200/\mu\text{L}$ at least once in these 16 weeks.

Subjects on interferon therapy who do not meet this criteria must have a CD4 T-cell count $\geq 200/\mu\text{L}$ within 16 weeks of starting interferon therapy.

For children ages 1 – 2, CD4% $\geq 30\%$ at anytime in the 16 weeks prior to transplant. For children 2 - 10 years, CD4% $\geq 20\%$ at anytime in the 16 weeks prior to transplant. Note that the CD4% can be lower than 30/20 on one or more

occasions within the 16 weeks prior to transplant as long as it was above 30/20 at least once in these 16 weeks.

After eligibility is determined, all patients will be asked to have CD4+ T-cell assays performed by a certified lab every 3 months by their primary care provider and faxed to the study site.

[LIVER]: $\geq 100/\mu\text{L}$ at anytime in the 16 weeks prior to transplant ($\geq 200/\mu\text{L}$ at any time in the 16 weeks prior to transplant if there is a history of any of the conditions outlined in the Opportunistic Complications table in section 4.1). Note that the CD4+ T-cell count can be lower on one or more occasions within the 16 weeks prior to transplant as long as it was $\geq 100/200$ at least once in these 16 weeks.

Subjects on interferon therapy who do not meet this criteria must have a CD4 T-cell count $\geq 100/\mu\text{L}$ (or $\geq 200/\mu\text{L}$ if there is a history of any of the conditions outlined in the Opportunistic Complications table in section 4.1) within 16 weeks of starting interferon therapy.

For children ages 1 – 2, CD4% $\geq 30\%$ at any time in the 16 weeks prior to transplant. For children 2 - 10 years, CD4% $\geq 20\%$ at any time in the 16 weeks prior to transplant. Note that the CD4% can be lower than 30/20 on one or more occasions within the 16 weeks prior to transplant as long as it was above 30/20 at least once in these 16 weeks.

After eligibility is determined, all patients will be asked to have CD4+ T-cell assays performed by a certified lab every 3 months by their primary care provider and faxed to the study site.

5. HIV-1 RNA:

[KIDNEY]: Less than 50 copies/ml if the Amplicor Monitor Ultrasensitive PCR assay is used or less than 75 copies/ml if the bDNA Versant version 3.0 assay is used. If other assays are used, the co-principal investigator will review and define the appropriate cut-off. After eligibility is determined, all patients will be asked to have HIV-1 RNA assays performed by a certified lab every 3 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 HIV-1 RNA, not more than 16 weeks prior to transplant.

[LIVER]: If patient is on chronic ARV therapy, less than 50 copies/ml if the Amplicor Monitor Ultrasensitive PCR assay is used or less than 75 copies/ml if the bDNA Versant version 3.0 assay is used. If other assays are used, the co-principal investigator will review and define the appropriate cut-off. After eligibility is determined, all patients will be asked to have HIV-1 RNA assays performed by a certified lab every 3 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 HIV-1 RNA, not more than 16 weeks prior to transplant.

If the study HIV physician feels it is in the best interest of the patient to remain on a partially suppressive chronic ARV regimen until the post-transplant period rather than modifying the ARV regimen prior to transplant to achieve an undetectable viral load,

and the HIV clinician on the team is confident that they can predict HIV suppression post-transplant with a modified ARV regimen, the subject may be included in the study. When possible, it is strongly encouraged to modify the ARV regimen pre-transplant to achieve or work towards an undetectable viral load, if this modified regimen change is tolerated. Patients who are unable to tolerate antiretroviral therapy due to exacerbation of their underlying liver disease, or who have only recently started or reinitiated ARV therapy may have detectable viral load, only if the HIV clinician on the team is confident that they can predict HIV suppression post-transplant.

The assessment of the likelihood of post-transplant HIV suppression is based on a thorough review of the patient's antiretroviral history, HIV-1 RNA levels while on medications, adherence and any available resistance tests. If there is any significant doubt about the ability to suppress viral replication post-transplant, the patient should not be enrolled under this criterion.

6. Meet standard listing criteria for placement on transplant waiting list.
7. Able to provide informed consent. For children under age 7, only the parent provides consent. For children ages 7 - 12, the parental or legally responsible person will be asked to provide informed consent and the minor will be asked to sign an assent. In the case of a minor between ages 13 and 18, the minor and parent(s) will be asked to provide informed consent.

8. Antiretroviral (ARV) Use

[KIDNEY]: On stable ARV regimen for at least 3 months prior to entry (unless changes are made due to toxicity, drug interactions, or convenience) or able to maintain a persistently undetectable HIV-1 RNA level (less than 50 copies/ml if the Amplicor Monitor Ultrasensitive PCR assay is used or less than 75 copies/ml if the bDNA Versant version 3.0 assay is used. If other assays are used, the co-principal investigator will review and define the appropriate cut-off) without the use of antiretroviral agents (no history of a detectable HIV RNA test).

9. Willing to use PCP, herpes virus and fungal prophylaxis as indicated.

10. HCV-HIV Co-Infection, HBV-HIV Co-Infection and HCV-HBV-HIV Co-Infection

[KIDNEY]: If the patient also has HCV infection, must be willing to undergo frequent monitoring, including liver biopsies and treatment of HCV as mandated by the protocol and as recommended by the study clinicians. Pre-transplant evaluation will consist of liver function tests, HCV RNA determination, HCV genotype and liver biopsy. All subjects with a liver biopsy showing a non-cirrhotic liver will be considered for transplant. Pre-transplant therapy with interferon or pegylated interferon will be offered to those with fibrosis on biopsy, and all those with genotype 2 or 3 regardless of the stage of disease, but will not be required for entry into the study. Patients with bleeding disorders will require clotting factor replacement prior to any invasive procedure under the care of a hematologist familiar with bleeding disorders. If the patient is HBV-HCV-HIV co-infected, each viral hepatitis infection in the tri-infected subject will be managed in terms of diagnostic testing and therapy as outlined for the

individual viral hepatitis infections. It is recommended that HBV co-infected kidney recipients have undetectable HBV RNA at the time of transplant.

[LIVER]: If the patient also has HBV or HCV infection, must be willing to undergo frequent monitoring, including liver biopsies and treatment as mandated by the protocol and as recommended by the study clinicians. Patients with bleeding disorders will require clotting factor replacement prior to any invasive procedure under the care of a hematologist familiar with bleeding disorders. Pre-Transplant anti-HCV therapy with interferon or pegylated interferon will be considered in each patient with HCV infection but will not be a requirement for entry into the study. If the patient is HBV-HCV-HIV co-infected, each viral hepatitis infection in the tri-infected subject will be managed in terms of diagnostic testing and therapy as outlined for the individual viral hepatitis infections.

11. For subjects with a history of aspergillus colonization or disease, no current clinical evidence of active disease.
12. The patient must have or be willing to start seeing a primary medical care provider with expertise in HIV management. The primary medical care provider must be willing to submit laboratory studies within 7 days of draw and willing to notify the transplant team/study coordinator prior to any change in medication. Medical record documentation must be provided for all testing and interventions by the primary medical provider.
13. Female subjects of child-bearing potential must have a negative serum beta-HCG pregnancy test within 14 days of screening. All subjects participating in sexual activity that could lead to pregnancy must practice two reliable methods of contraception simultaneously.
14. Not suffering from significant wasting.

4.2 EXCLUSION CRITERIA

1. 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.
2. Opportunistic Complication History: Any history of progressive multifocal leukoencephalopathy (PML), chronic intestinal cryptosporidiosis of > 1 month duration, or primary CNS lymphoma. History of pulmonary coccidiomycosis will be treated per local site policy regarding this infection in HIV negative transplant candidates, generally requiring a 5-year disease-free interval.
3. History of documented multi-drug resistant fungal infection not expected to respond to available oral antifungal agents (*krussii*, *glabrata*, *candida*).
4. History of documented influenza or RSV in the past 30 days.
5. History of any 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 5 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.)
6. Inability or unwillingness to comply with immunosuppression protocol, ARV therapy and/or HCV monitoring and therapy if indicated.
 7. Substance use per local site policy.
 8. Advanced cardiac or pulmonary disease per local site policy.
 9. Documented anatomic abnormalities precluding transplantation.
 10. Pregnancy (pre transplant). Patients who become pregnant post-transplant will continue to be followed in the study and will be managed per local site practice.
 11. Concomitant conditions that, in the judgment of the investigators, would preclude transplantation or immunosuppression.
 12. Use of IL-2 or GM-CSF in the prior six months.
 13. [**KIDNEY**]: HCV - Cirrhosis on liver biopsy in patients with hepatitis C co-infection unless being listed for combined liver and kidney transplant. Exceptions to the requirement for combined kidney-liver transplant will be made when sequential rather than simultaneous transplant is appropriate (eg if the patient is ineligible for liver transplant due to medical contraindications such as severe cardiopulmonary disease or has stable, compensated cirrhosis deemed by the investigator to not necessitate transplant at this time).

4.3 SUBJECT RECRUITMENT

Subjects meeting center-specific criteria for listing and transplantation will be recruited according to local practice. Registration will occur following EMMES training on the Internet Data Entry System (IDES) per their protocol. The primary medical care provider will ascertain continued eligibility by monitoring CD4+ T cell count, HIV RNA viral load and the development of new opportunistic infections or neoplasms.

4.4 STUDY ENROLLMENT PROCEDURES

Prior to implementation of this protocol, sites must have the protocol and consent form approved by their local institutional review board (IRB). Sites must be registered with and approved by EMMES. Site registration must occur before any subjects can be enrolled in this study.

Once a candidate for study entry has been identified, details will be carefully discussed with the subject. The subject (or parent or legal guardian if the subject is younger than 18 years of age or under guardianship) will be asked to read and sign the consent form that was approved by the IRB. Data will be collected in the pre-transplant phase as in the schedule of events (section 6.2)

To enroll into the post-transplant phase of the study, eligibility must be re-assessed when a donor organ is available. If eligibility is maintained at the time of organ availability

(including an eligible CD4+ T-cell at any time in the 16 weeks prior to transplant and the most recent HIV-1 RNA not more than 16 weeks prior to transplant), the subject will be enrolled in the transplant phase of this study. Eligible subjects will be transplanted according to protocol.

The Division of AIDS has concluded that this protocol meets Federal requirements governing prisoner participation in clinical trials (45.CFR 46.306). Local IRBs have the final decision as to whether prisoners may participate in the study.

5 STUDY INTERVENTIONS

5.1 SPECIAL CONSIDERATIONS FOR CHILDREN

All medications will be dose adjusted for pediatric use. Medication doses should be determined based upon standard of care for pediatric dosing.

5.2 IMMUNOSUPPRESSION PROTOCOL

Maintenance immunosuppressive regimen will include a calcineurin inhibitor (cyclosporine or tacrolimus) or sirolimus, mycophenolate mofetil (MMF), and prednisone. Induction with an IL-2 receptor inhibitor (anti-CD25 antibody) or Thymoglobulin may be utilized for kidney transplants, but no induction will be used for liver transplants unless the transplant team feels that it is essential. Immunosuppressant doses will be modified to obtain routine trough levels standard for kidney and liver transplants. Modification of dosages and drugs will be made for toxicity as outlined below. In the case of HIV disease progression, immunosuppressive doses may be reduced to prevent clinical decline. The transplant team/study coordinator must be notified of any change in immunosuppressive dosing because there may be interactions with antiretroviral drug dosing and visa versa.

5.2.1 Calcineurin Inhibitor

Cyclosporine or tacrolimus administration, per local site discretion. See section 9 of the MOP for recommended starting doses based on antiretroviral class use.

5.2.2 Mycophenolate mofetil (Cellcept)

See section 9 of the MOP for standard dosing for both kidney and liver recipients.

5.2.3 Steroids

Steroid induction, taper, and maintenance will be according to local site practice.

5.3 REJECTION TREATMENT PROTOCOL

A biopsy will be performed in all cases of suspected rejection (see section 5.3.1 definition of kidney and liver rejection). Treatment for rejection for > 1 day, including increases in the dose of immunosuppressive medications, cannot be sustained without a biopsy, unless the managing physicians believe biopsy is unsafe. However, therapy may be initiated \leq one day prior to the results of the biopsy if clinically indicated. Treatment of rejection episodes will be according to local site practices and may include sirolimus. OKT3 and polyclonal anti-lymphocyte preparations have resulted in prolonged reduction in CD4+ counts in HIV infected transplant recipients, and their use should be restricted to treatment for severe rejection.

5.3.1 Definition of Rejection

5.3.1.1 Kidney

The definition for kidney rejection is as defined by the NIH supported Cooperative Clinical Trials in Transplantation:

- Type I: mononuclear infiltrate in > or =5% of cortex, a total of at least three tubules with tubulitis in 10 consecutive high-power fields from the most severely affected areas, and at least two of the three following features: edema, activated lymphocytes, or tubular injury.
- Type II: arterial, or arteriolar, endothelialitis with or without the preceding features.
- Type III: arterial fibrinoid necrosis or transmural inflammation with or without thrombosis, parenchymal necrosis, or hemorrhage.

5.3.1.2 Liver

Liver rejection will be defined by the Banff global grading scheme as well as the Banff rejection activity index.

5.4 HCV TREATMENT PROTOCOL [LIVER TRANSPLANT PATIENTS]

HCV treatment should not be initiated preemptively (e.g. in all patients regardless of clinical and histologic status) post-transplant. There are no data currently available to suggest that HCV RNA clearance rates are higher when antiviral therapy is started preemptively post-transplantation versus when recurrent disease is documented. In addition, reserving HCV therapy only for those with documented recurrence may potentially avoid drug interactions and additive toxicity with HAART and immunosuppression, especially in the early post-transplant period.

HCV treatment should be initiated post-transplant when there is liver biopsy documentation of recurrent HCV infection and disease is severe or progressive. Biopsies will be obtained at 6 and 12 months post transplant, and annually thereafter regardless of serum aminotransferase activity, and at any time as clinically indicated at the discretion of the physician responsible for the care of patient. HAI score > 8 and/or fibrosis stage >2 are considered indications for treatment by most transplant physicians but the decision to treat will ultimately be determined by the treating physician. Biopsies will be read by a central pathologist and will be scored using the Ishak version of Knodell (Ishak K et al, J Hepatol 1995; 22:696-9).

5.4.1 Biopsies

Biopsies will be performed under the following circumstances:

1. Routine protocol mandated biopsies will be performed at 6 and 12 months post transplant, and annually thereafter regardless of serum aminotransferase activity. Non-protocol biopsies may be used for protocol purposes as long as the biopsy is within 3 months of the protocol scheduled biopsy date.
2. Clinical indications: any significant increase in serum aminotransferase activity above baseline levels will be considered a possible reason for liver biopsy to determine

etiology (e.g. recurrent HCV, acute rejection, drug toxicity, etc) per investigator discretion. Note that abnormal liver biochemistry indicators are not specifically defined in the liver transplant recipient (as they are in the kidney transplant recipient) due to multiple potential etiologies of abnormal liver enzyme levels post-liver transplant.

5.4.2 Therapeutic Regimen

Peg-INF or standard INF plus ribavirin will be the standard treatments. Therapy should not be altered based upon prior INF experience or genotype.

Doses:

Target dose of Peg-INF a-2b 1.0-1.5 ug/kg weekly or peg-INF a-2a is 135 ug weekly (note: if currently acceptable dosing regimens change, use the currently acceptable dose). Note that it is recommended to start at half dose and increase to full-dose in 2 weeks if blood counts are acceptable. In order to increase tolerability, dose titration should be managed on a case-by-case basis.

Ribavirin 200 mg PO BID to start and increase to 400 mg PO BID after 2 weeks if lower dose tolerated. Increase after 2 weeks to 10-13 mg/kg as divided dose if 800 mg PO QD dose is tolerated. Note that transplant patients have renal clearance issues that make increasing ribavirin doses to high and/or too quickly result in drug-limiting anemia. Thus, ribavirin should be titrated up slowly as tolerated.

Absolute Contraindications to ribavirin use:

1. Dialysis
2. Prior serious adverse reaction to ribavirin
3. Hgb<10 and inability to correct with growth factors

Relative contraindications to ribavirin use:

1. Cr>2.0 mg/dL
2. Hemolytic anemia

Absolute Contraindications to interferon use:

1. Uncontrolled depression or other psychiatric disease
2. Uncontrolled thyroid disease
3. Severe acute rejection in preceding 2 weeks
4. History of significant retinopathy (visual loss)

Relative contraindications to interferon use:

1. Autoimmune disease (e.g. lupus, ulcerative colitis, psoriatic arthritis)
2. Platelet count <40,000

5.4.3 Monitoring on Treatment (in addition to all standard protocol studies)

Laboratory:

- Baseline pre-therapy: CBC, liver panel, TSH, lipid panel, CXR (if none in past 12 mo), renal function, HCV genotype (if none)
- Months 1-2 post-therapy initiation: CBC weekly in addition to usual monthly transplant labs

- Months 3, 6, 9, 12 post-therapy initiation: TSH
- HCV RNA quantitation for all HCV co-infected patients, regardless of therapy at Baseline, Month 3, Month 6, Month 12 and Years 2 and 5. Subjects receiving HCV therapy must have additional HCV RNA at 1, 3, 6 and 12 months post-therapy initiation. Qualitative HCV RNA if quantitative negative. Subjects will also have additional HCV RNA at 6 and 12 months post therapy discontinuation.
- Lactate monitoring for hyperlactataemia is recommended for subjects on HCV therapy, especially those who develop an increase in AST or ALT.

Clinical:

- Vital signs at each clinic visit
- Adverse event inquiry including depression monthly for first 3 months, then every 3 months thereafter

Patient will be provided with 24-hour clinical contact number for adverse effect notification.

5.4.4 Length of Treatment

12 month minimum. At 12 months, response will be determined by measurement of HCV RNA (quantitative and qualitative if negative by quantitative assay), AST/ALT and liver histology.

Types of Response and Actions:

1. HCV RNA negative at 6 and 12 months of treatment: stop treatment and observe for possible relapse.
2. HCV RNA positive but liver histology improved: Discontinue therapy and observe for biochemical and histological change. Consider re-initiation of therapy if disease activity increases.
3. HCV RNA positive but liver histology unchanged or worse: Continue treatment for another 12 months (or consider for experimental therapies).

5.4.5 Additional Supportive Therapy

Erythropoietin should be initiated at any point when the hemoglobin is <10g/dl. Dose of erythropoietin will be 40,000 IU subcutaneously weekly. Dosing should be continued until the end of treatment or until hemoglobin is >12 g/dL (women) >14 g/dL (men). If hemoglobin decreases below 8.0 g/dL, ribavirin will be discontinued until the Hgb >10 g/dL (women) or >12 g/dL (males) and patient has demonstrated response to erythropoietin. If ribavirin is restarted, the dose used is 50% of the dose when ribavirin was discontinued.

G-CSF will be administered to any participant whose absolute neutrophil count is <1,000/mm³. Starting dose is 300 ug twice weekly. If subsequent trough ANC >3000/mm³, reduce dose to 150 ug twice weekly or 300 ug once weekly. Dosing will be continued until the end of treatment.

5.5 HCV TREATMENT PROTOCOL [KIDNEY TRANSPLANT PATIENTS]

If the patient has HCV infection, pre-transplant evaluation will consist of liver enzymes (serum aminotransferase levels, alkaline phosphatase), liver function tests (total bilirubin, albumin, prothrombin time), HCV RNA determination, HCV genotype and liver biopsy. All subjects with a liver biopsy showing a non-cirrhotic liver are considered eligible for kidney transplantation. Subjects with cirrhosis should be considered for joint liver and kidney transplant. Exceptions to the requirement for combined kidney-liver transplant will be made if the patient is ineligible for liver transplant due to medical contraindications or has stable compensated cirrhosis deemed by the investigator to not necessitate transplant at this time. Pre-transplant anti-HCV therapy with interferon or pegylated interferon will be considered in each patient but will not be a requirement for entry into the study. Post-transplant monitoring will include liver biopsies. Advanced or progressive liver disease will be targeted for anti-HCV treatment.

5.5.1 Biopsies

Biopsies will be performed under the following circumstances:

1. Pre-transplantation to assess severity of histological disease and to rule out cirrhosis.
2. Routine protocol biopsies will be performed at Month 6, Year 2.5, and Year 5 post-transplant regardless of serum aminotransferase activity. Non-protocol biopsies may be used for protocol purposes as long as the biopsy is within 3 months of the protocol scheduled biopsy date.
3. Clinical indications as indicated by:
 - a. abnormal liver biochemistry (AST or ALT >2 ULN for at least 3 months)
 - b. significant change in AST, ALT, alkaline phosphatase or total bilirubin from baseline in order to rule out concurrent conditions (e.g. drug toxicity, biliary disease, fibrosing cholestatic hepatitis or other progressive HCV disease).

5.5.2 Indications for initiation of anti-HCV therapy

Pre-transplantation therapy will be strongly recommended due to the risks of post-transplant INF therapy, but not mandated, in the following circumstances:

1. Biopsy shows stage of fibrosis consistent with stage 2 or greater (periportal fibrosis with early septae, bridging fibrosis)
2. All patients with non-1 genotypes, regardless of stage of disease, since the viral clearance rates with INF treatment are >50% for this subgroup.

Post-transplantation therapy will be offered but not required in the following circumstances:

1. Biopsy evidence of progressive disease (increase in fibrosis score)
2. Any biopsy showing stage 3 or 4 disease (bridging fibrosis or cirrhosis)
3. Biopsy and clinical features of fibrosing cholestatic hepatitis

5.5.3 Therapeutic Regimen

Pre-transplant therapy will be pegylated INF or standard INF. Therapy will not be altered based upon prior INF experience. The dose of standard INF will be 3 million units three times weekly; the dose of pegylated INF will be 1.0-1.5 ug/kg (peg-INF alfa-2b) weekly or 135 ug weekly (peg-INF alfa-2a) [note if currently acceptable dosing regimens change, use the currently acceptable dose]. Absolute and relative contraindications as indicated in section 5.4.2 .

Post-transplant therapy will be pegylated INF or standard INF plus ribavirin. Therapy will not be altered based upon prior INF experience. Doses, absolute and relative contraindications are the same as in section 5.4.2.

5.5.4 Monitoring on Treatment (in addition to all standard protocol studies)

Laboratory:

- Baseline pre-therapy: CBC, liver panel, TSH, lipid panel, CXR (if none in past 12 mo), renal function, HCV genotype (if none)
- Months 1-2 post-therapy initiation: CBC weekly in addition to usual monthly transplant labs
- Months 3, 6, 9, 12 post-therapy initiation: TSH
- HCV RNA quantitation for all HCV co-infected patients, regardless of therapy at Baseline, Month 3, Month 6, Month 12 and Years 2 and 5. Subjects receiving HCV therapy must have additional HCV RNA at 1, 3, 6 and 12 months post-therapy initiation. Qualitative HCV RNA if quantitative negative. Subjects will also have additional HCV RNA at 6 and 12 months post therapy discontinuation.
- Lactate monitoring for hyperlactataemia is recommended for subjects on HCV therapy, especially those who develop an increase in AST or ALT.

Clinical:

- Vital signs at each clinic visit
- Adverse event inquiry including depression monthly for first 3 months, then every 3 months thereafter

Patient will be provided with 24-hour clinical contact number for adverse effect notification.

5.5.5 Length of Treatment

5.5.5.1 Pre-transplantation

Duration of therapy is determined by initial virological response and HCV genotype. All patients will receive a minimum of 3 months treatment. At 3 months an assessment of virological response will be made. If the patient has achieved a 2-log reduction in HCV RNA levels or is HCV RNA negative, treatment will be continued for a total of 6 to 12 months (depending upon genotype and stage of fibrosis). If the patient does not achieve at least a 2-log reduction in HCV RNA by month 3 of treatment, the treatment will be discontinued.

Note that liver transplant candidates and combined kidney-liver candidates will not be encouraged to treat HCV pre-transplant (as kidney candidates are) as it is assumed that they have already exhausted all medical therapy options for the treatment of HCV.

5.5.5.2 *Post-transplantation*

Duration of treatment is 12 months. HCV RNA quantitation will be measured at 3 and 12 months post-therapy initiation. If quantitative results are negative at 12 months, HCV RNA (qualitative) will be obtained. Repeat liver biopsy following 12 months of treatment is recommended to assess histological response in virological non-responders.

5.5.6 **Types of Response and Actions**

HCV RNA negative at end of treatment: stop and observe for possible relapse.

HCV RNA positive at end of treatment: stop and observe for histological progression.

Consider re-initiation of therapy if histological activity or fibrosis score increases.

5.5.7 **Additional Supportive Measures**

Same as HCV+ liver patients. See section 5.4.5 for additional supportive measures.

5.6 **HBV TREATMENT PROTOCOL [LIVER TRANSPLANT PATIENTS]**

5.6.1 **Biopsies**

Biopsies will be performed as follows:

1. Abnormal liver enzymes (AST or ALT > 1.5 ULN)
2. Any HBV virological breakthrough
3. Suspicion of drug hepatotoxicity

Annual biopsies are recommended for those at highest risk for progressive disease post-liver transplant:

1. Any patient who fails prophylactic therapy (i.e. becomes HBsAg positive)
2. Patients with HDV co-infection

5.6.2 **Therapeutic Guidelines**

5.6.2.1 *Pre-transplant Therapeutic Options*

If no prior exposure to lamivudine or emtricitabine, treatment options include:

lamivudine 150 mg BID or 300 mg QD as part of HAART
tenofovir 300 mg QD as part of HAART
entecavir 0.5 mg QD (not active against HIV) ¹

¹ Entecavir should not be used unless a full HIV ARV regimen can be used as entecavir has anti-HIV activity and can cause the development of HIV resistance.

adefovir 10 mg QD (not active against HIV)

If prior exposure to lamivudine or emtricitabine (and drug resistance suspected or proven), treatment options include:

adefovir 10 mg QD (with or without continued lamivudine)
entecavir 1.0 mg QD¹
tenofovir 300 mg QD, as part of HAART

5.6.2.2 Peri-transplant and Early Post-Transplant Therapeutic Options

Continue lamivudine, adefovir, entecavir¹ or tenofovir if prescribed pre transplant, and adjust for renal insufficiency. If unable to start HIV antiretroviral therapy post liver transplant, hold HBV antiviral medication until able to start HIV antiretroviral therapy unless the subject had a detectable pre-transplant HBV DNA titer in which case adefovir and/or entecavir 0.5 mg QD (if no prior lamivudine or emtricitabine exposure) or 1.0 mg QD (if prior lamivudine or emtricitabine exposure) may be started without HIV antiretrovirals (the risk of developing HIV resistance associated with adefovir is thought to be low and warranted in this situation with a high likelihood of HBV recurrence in the absence of therapy).

HBIG Dosing Schedule: 10,000 IU during the anhepatic phase and on admission to ICU and 10,000 IU daily for a total of 7 days. Check HBsAg on day 2 and if positive, give 10,000 IU every 12 hours until HBsAg negative.

If patient is HBV DNA detectable (10^3 copies/mL) pre liver transplant, closer monitoring of HBIG dosing is advised, especially if HBV antivirals are on hold. If HBV antivirals are on hold, check HBsAg daily and use HBIG 5000 IU Q6 hours until HBsAg is negative, then use 10,000 IU daily for a total of 7 days of treatment.

5.6.2.3 Post-transplant (after first week) Therapeutic Guidelines

Continue HBV and HIV antivirals post liver transplant indefinitely. Monitor HBsAg and anti-HB titers prior to each HBIG infusion. Monitor HBV DNA levels as clinically indicated (AST or ALT > 1.5 ULN) and every 3 months.

HBIG Dosing Schedule Post-Transplant:

Step 1	10,000 IU monthly for 3 months, If anti-HB titers > 100 IU/L, proceed to Step 2.
Step 2	5,000 IU monthly for 3 months. If anti-HB titers > 100 IU/L, proceed to Step 3.
Step 3	2,500 IU (IM or IV) monthly for 6 months. If anti-HB titers > 100 IU/L, proceed to Step 4.

¹ Entecavir should not be used unless a full HIV ARV regimen can be used as entecavir has anti-HIV activity and can cause the development of HIV resistance.

Step 4	2,500 IU (IM or IV) every two months for 12 months as long as anti-HB titers remain > 100 IU/L, then proceed to Step 5. If anti-HB titers become < 100 IU/L, revert to step 3.
Step 5	2,500 IU (IM or IV) every three months for 12 months as long as anti-HB titers remain > 100 IU/L. If anti-HB titers become < 100 IU/L, revert to Step 4.

5.6.3 Monitoring Guidelines

Pre-transplant Monitoring Guidelines: HBV DNA every 3 months pre-transplant.

Peri-Transplant Monitoring Guidelines: Check HBV DNA immediately pre-transplant to detect virological breakthrough.

Post-Transplant Monitoring Guidelines: In addition to the protocol-mandated lab evaluations listed in the schedule of events, it is recommended for clinical management that HBV DNA be followed every three months and as clinically indicated by abnormal liver enzymes (AST or ALT > 1.5 ULN) and that HBSAg and HBSAb be followed monthly.

5.7 HBV TREATMENT PROTOCOL [KIDNEY TRANSPLANT PATIENTS]

5.7.1 Biopsies

Biopsies will be performed as follows:

1. Persistently abnormal liver enzymes (AST or ALT > 1.5 ULN) for 3 months
2. Any HBV virological breakthrough
3. Suspicion of drug hepatotoxicity or other clinical indications per investigator

5.7.2 Therapeutic Guidelines

5.7.2.1 Pre-transplant Therapeutic Options

If no prior exposure to lamivudine or emtricitabine, treatment options include (all drugs must be adjusted for renal function):

lamivudine 150 mg BID or 300 mg QD as part of HAART
tenofovir 300 mg QD as part of HAART
entecavir 0.5 mg QD (not active against HIV)¹

If prior exposure to lamivudine or emtricitabine (and drug resistance suspected or proven), treatment options include (all drugs must be adjusted for renal function):

entecavir 1.0 mg QD¹
tenofovir 300 mg QD, as part of HAART

¹ Entecavir should not be used unless a full HIV ARV regimen can be used as entecavir has anti-HIV activity and can cause the development of HIV resistance.

adefovir 10 mg QD (with or without continued lamivudine).

Adefovir is the least favored option due to potential renal toxicity issues associated with continued use post-transplantation. It is not active against HIV.

5.7.2.2 *Peri-transplant and Early Post-Transplant Therapeutic Options*

Continue lamivudine, adefovir, entecavir¹ or tenofovir if prescribed pre transplant, and adjust for renal insufficiency. If unable to start HIV antiretroviral therapy post kidney transplant, hold HBV antiviral medication until able to start HIV antiretroviral therapy.

5.7.2.3 *Post-transplant (after first week) Therapeutic Options*

Continue HBV antivirals post kidney transplant for a minimum of 12 months. Monitor HBV DNA levels as clinically indicated and every 3 months. If patient has stage 3 or 4 fibrosis, antiviral therapy should be continued indefinitely as risk of progressive disease is significant. For patients with \leq stage 2 fibrosis, antiviral therapy can be stopped after 12 months if the following criteria are met:

1. Normal liver enzymes
2. Minimal (5 mg QD or QOD) or no prednisone
3. No recent change in immunosuppression (stable for preceding 3 months)
4. Normal AST and ALT

HBV Antiviral therapy will be restarted and continued indefinitely if AST or ALT increase to > 1.5 ULN *and* HBV DNA > 105 copies/mL after treatment is stopped.

Additionally, HBV antiviral therapy will be given whenever a patient receives treatment for rejection, and should be continued for a period of at least 4 months and then stopped after 4 months when:

1. Normal liver enzymes
2. Minimal (5 mg QD or QOD) or no prednisone
3. No recent change in IMS (stable for preceding 3 months)

5.7.3 **Monitoring Guidelines**

Pre-transplant Monitoring Guidelines: HBV DNA every 3 months pre-transplant

Peri-Transplant Monitoring Guidelines: Check HBV DNA immediately pre-transplant.

Post-Transplant Monitoring Guidelines: In addition to the protocol-mandated lab evaluations listed in the schedule of events, it is recommended for clinical management that HBV DNA be followed every three months and as clinically indicated by abnormal liver enzymes (AST or ALT > 1.5 ULN)] and that HBSAg and HBSAb be monitored annually.

¹ Entecavir should not be used unless a full HIV ARV regimen can be used as entecavir has anti-HIV activity and can cause the development of HIV resistance.

5.8 HBV-HCV-HIV CO-INFECTION

Each viral hepatitis infection in the tri-infected subject will be managed in terms of diagnostic testing and therapy as outlined for the individual viral hepatitis infections as it pertains to the specific organ.

5.9 OPPORTUNISTIC INFECTION PROPHYLAXIS

5.9.1 Pneumocystis Carinii Pneumonia (PCP)

5.9.1.1 Primary Prophylaxis (Patients with No Prior History of PCP)

Indications:

Primary prophylaxis is indicated in all patients for life and should start immediately post-transplant.

Regimen:

See section 9 of the MOP for recommended regimen.

5.9.1.2 Secondary Prophylaxis (Patients with a Prior History of PCP)

Indications:

Secondary PCP prophylaxis is indicated in all patients for life and should start immediately post-transplant.

Regimen:

See section 9 of the MOP for recommended regimen.

5.9.2 Toxoplasmosis

5.9.2.1 Primary Prophylaxis (Patients with No Prior History of Toxoplasmosis)

Indications:

Primary prophylaxis is indicated for Toxo IgG-positive subjects with CD4+ T-cell count \leq 200.

Regimen:

See section 9 of the MOP for recommended regimen.

5.9.2.2 Secondary Prophylaxis (Patients with a Prior History of Toxoplasmosis)

Indications:

Secondary prophylaxis must be reinstated immediately post-transplant for one month (unless the CD4 count is below 200 cells/ μ L – see below).

Secondary prophylaxis must be reinstated during the treatment of acute rejection for one month following completion of acute rejection therapy (unless the CD4 count is below 200 cells/ μ L – see below).

Secondary prophylaxis must be reinstated whenever the CD4 cell count drops below 200 cells/ μ L. Secondary prophylaxis will be discontinued when CD4+ T-cell count is above 200 cells/ μ L for six months (unless the patient is within one month of completion of therapy for a rejection episode).

Regimen:

See section 9 of the MOP for recommended regimen.

5.9.3 Mycobacterium Avium Complex (MAC)

5.9.3.1 Primary Prophylaxis (Patients with No Prior History of MAC)

Indications:

Indicated when CD4+ T-cell count \leq 75. Discontinue when the CD4 count is above 100 cells/ μ L for six months

Regimen:

See section 9 of the MOP for recommended regimen.

5.9.3.2 Secondary Prophylaxis (Patients with a Prior History of MAC)

Indications:

Secondary prophylaxis must be reinstated immediately post- transplant for one month (unless the CD4 count is below 75 cells/ μ L – see below).

Secondary prophylaxis must be reinstated during the treatment of acute rejection for one month following completion of acute rejection therapy (unless the CD4 count is below 75 cells/ μ L – see below).

Secondary prophylaxis must be reinstated whenever the CD4 cell count drops below 75 cells/ μ L, and will be discontinued when the CD4 count is above 100 cells/ μ L for six months (unless the patient is within one month of completion of therapy for a rejection episode).

Regimen:

See section 9 of the MOP for recommended regimen.

5.9.4 Cytomegalovirus (CMV)

5.9.4.1 Primary Prophylaxis (Patients with No Prior History of CMV)

Per site practice as long as this is within the generally accepted standard of care.

5.9.4.2 Secondary Prophylaxis (Patients with a Prior History of CMV)

Indications:

Secondary prophylaxis must be reinstated immediately post- transplant for one month (unless the CD4 count is below 100 cells/ μ L – see below).

Secondary prophylaxis must be reinstated during the treatment of acute rejection for one month following completion of acute rejection therapy (unless the CD4 count is below 100 cells/ μ L – see below).

Secondary prophylaxis must be reinstated whenever the CD4 cell count drops below 100 cells/ μ L and will be discontinued when CD4 count is above 200 cells/ μ L for six months (unless the patient is within one month of completion of therapy for a rejection episode).

Regimen:

See section 9 of the MOP for recommended regimen.

5.9.5 Epstein Barr Virus (EBV)

5.9.5.1 Primary Prophylaxis for EBV

Indications:

Indicated for EBV negative recipient/positive donor.

Regimen:

See section 9 of the MOP for recommended regimen.

5.9.6 Candidiasis

5.9.6.1 Prophylaxis for Candidiasis

Per site practice, but fluconazole 100mg once per week for 3 months, supplemented with Mycelex troches is highly recommended.

Severe toxicity from calcineurin inhibitors may result if daily fluconazole or another azole antifungal agent is combined with calcineurin inhibitors or protease inhibitors and levels must be monitored closely. At a minimum, the dose of calcineurin inhibitors should be reduced by 50%, but the amount is variable and sometimes more significant dose reduction is required. Daily calcineurin inhibitor trough levels should be monitored during the first week of therapy, or longer if necessary. Similar adjustments are required in the dosing of sirolimus and tacrolimus.

5.9.7 Cryptococcosis, extrapulmonary

5.9.7.1 Primary Prophylaxis (Patients with No Prior History of Cryptococcosis)

None recommended.

5.9.7.2 Secondary Prophylaxis (Patients with a Prior History of Cryptococcosis)

Indications:

Secondary prophylaxis must be reinstated immediately post- transplant for one month (unless the CD4 count is below 200 cells/ μ L – see below).

Secondary prophylaxis must be reinstated during the treatment of acute rejection for one month following completion of acute rejection therapy (unless the CD4 count is below 200 cells/ μ L – see below).

Secondary prophylaxis must be reinstated whenever the CD4 cell count drops below 200 cells/ μ L and will be discontinued when CD4 count is above 200 cells/ μ L for six months (unless the patient is within one month of completion of therapy for a rejection episode).

Regimen:

See section 9 of the MOP for recommended regimen.

5.9.8 Histoplasmosis

5.9.8.1 Primary Prophylaxis (Patients with No Prior History of Histoplasmosis)

None recommended.

5.9.8.2 Secondary Prophylaxis (Patients with a Prior History of Histoplasmosis)

Indications:

Secondary prophylaxis must be continued regardless of CD4+ T-cell count. (This criterion will be modified if/when the DHHS guidelines are modified).

Regimen:

See section 9 of the MOP for recommended regimen.

5.10 VACCINATIONS

5.10.1 Vaccinations Prior To Transplant

Pneumovax, Hepatitis A & B (if not immune), Influenza.

Adult patients should NOT be vaccinated against varicella, however patients exposed who are IgG(-) should receive varicella-zoster immune globulin (VZIG) 5 vials (1.25 mL each) IM administered # 96 hours after exposure, ideally within 48 hours.

5.10.2 Vaccinations Post Transplant

Patients should receive annual influenza vaccination.

Household contacts should not receive oral polio vaccine, and in most cases, should not receive smallpox inoculation

5.10.3 Special Considerations for Children

Children should be vaccinated with all vaccines, except some live vaccines, as early in life as possible following the routine schedule. Vaccines that can be used include DTaP, HiB, HepB, IPV, Prevnar, Pneumovax, HepA, and Influenza.

Live vaccines (MMR, Varicella) should only be administered pre-transplant and should not be administered 6 weeks or less before transplant.

HIV infected children who are eligible for this study can be immunized with MMR.

Live Varicella vaccine (varivax) can be used as long as patients are eligible for this study.

Varicella post-exposure prophylaxis: For patients with significant exposure and no prior history of Varicella (regardless of titer, or immunization status), per American Academy of Pediatrics Guidelines.

VZIG

1. <10kg 1 vial
2. 10.1-20kg 2 vials
3. 20.1-30kg 3 vials
4. 30.1-40kg 4 vials
5. >40kg 5 vials

Acyclovir (if more than 96h post exposure)

1500 mg/m²/day IV divided Q8 or 1500-3000 mg/m²/day PO in 4-5 doses

5.11 PPD TESTING AND TB PROPHYLAXIS

PPD testing (or chest x-ray if history of positive PPD) will be performed by the primary medical care provider at screening and every 12 months. For subjects who have a PPD that cannot be interpreted (eg they have anergy testing and are anergic, or have a history of BCG vaccination and a positive PPD), a chest x-ray should be performed. If PPD positivity noted prior to transplant, prophylaxis should be instituted pre-transplant. The course does not need to be completed pre-transplant and can be continued in the post-transplant period.

Prophylaxis is indicated for TST reaction \geq 5 mm or previous positive TST reaction without treatment or contact with a person with active tuberculosis.

Regimen:

See section 9 of the MOP for recommended regimen.

5.12 SPECIAL CONSIDERATIONS WITH ANTIRETROVIRALS

For patients who enter the study at any phase on maraviroc, or start maraviroc during the study at any phase, the site should request documentation from primary provider of tropism assay pre-maraviroc initiation and any subsequent tropism assays. For post-transplant subjects taking maraviroc with HIV RNA > 1,000 copies on 2 successive measurements, request repeat tropism assay results from primary provider.

See section 9 of the MOP for other special considerations with antiretrovirals, including interactions between MMF and nucleoside analogues, calcineurin inhibitors and protease inhibitors, and specific antiretroviral toxicities and interactions requiring special monitoring and/or dose adjustments.

5.13 ANTIRETROVIRAL DOSE ADJUSTMENTS FOR HEPATIC AND RENAL INSUFFICIENCY

ARV therapy choices will be guided by study physicians with expertise in HIV management in consultation with the primary medical care provider. ARV therapy will be initiated post-transplantation when the patient is able to take oral agents and renal function is stable, at the discretion of the study team. In those subjects for whom Mycophenolate mofetil is likely to be used for immunosuppression, attempts will be made to minimize the use of zidovudine and stavudine, due to *in vitro* antagonism seen with these agents. Because of the potential for acute hepatic necrosis with Viramune (nevirapine), attempts will be made to minimize the use of this drug when reasonable alternatives are available. Attempts will also be made to choose those antiretrovirals with the least likelihood for significant drug interactions with the immunosuppressants through the P450 metabolism pathways. Antiretrovirals will be dose adjusted for renal and hepatic function.

See section 9 of the MOP for recommended dosing adjustments for hepatic and renal insufficiencies

6 STUDY PROCEDURES

6.1 TIMING OF EVALUATIONS

6.1.1 Screening and Pre-Screening Data Collection

A Screening section of the EMMES IDES will capture information regarding initial and ongoing transplant and study eligibility and subject outcome (i.e. transplanted on study, transplanted off study, elected no transplant, or died) on those subjects who have not yet made it to the Pre-Transplant (Segment A) phase of the EMMES Internet Data Entry System (IDES). A separate Pre-Screening informed consent, or signature on the main study consent, will be required to collect this information. This portion of the EMMES IDES will function as the screening log for this study.

Once transplant eligibility is determined, subjects will begin screening evaluation to determine study eligibility. Screening tests indicated on the schedule of events (footnote 3) in section 6.2 must be completed no more than 12 months prior to transplantation. All others only need to be completed once, regardless of timing of screening, unless otherwise indicated in the schedule of events. Once a subject has met all study inclusion and exclusion criteria and all screening labs that affect eligibility have been obtained, the subject should be enrolled into the Pre-Transplant (Segment A) phase of the EMMES IDES while waiting for organ availability.

6.1.2 Pre-Transplant On-Going Eligibility Monitoring

Once subjects have been enrolled into Pre-Transplant (Segment A) phase of the EMMES IDES, both kidney and liver transplant candidates will have CD4+ T-cell count and HIV RNA testing every 3 months (may be provided by primary medical care provider), and no more than 16 weeks prior to organ availability.

For liver transplant candidates only: total bilirubin, INR and creatinine will also be recorded every 3 months (may be provided by primary medical care provider).

All interval opportunistic complications will be recorded. If the subject is no longer eligible for transplant, or for the study, or wishes to withdraw from the study, the reasons(s) will be recorded on the appropriate case report form. Subjects in the Pre-Transplant phase may fluctuate between eligibility and ineligibility, but must meet study eligibility at the time of organ availability.

6.1.3 On-Study Evaluations

Once the patient has been transplanted, study related visits will occur at Day 0, Weeks 1, 2, 4, 6, 8, 10, 12, 16, 20, 26, 36, 44, and 52, every 3 months in Years 2 and 3, and every 6 months in Years 4 and 5.

Although it is preferred that all study visits occur at the transplant center, only the weeks 12, 26, 52, and year 2 study visits must occur at the transplant center. If the patient is unable to return to the transplant center for any other post-transplant study visits, a complete medical review should be conducted by telephone. In addition, all necessary lab work as outlined in the schedule of events should be performed locally at a CLIA-

certified laboratory and the results faxed to the transplant center for data entry along with the associated normal laboratory reference ranges.

Attempts should be made to complete study visits as close as possible to the defined study visit date. Study visits may occur within 2 weeks prior to the defined visit time point. Study visits may occur after the defined study visit time point up to the mid-way point between the target date of the study visit and the subsequent study visit. For example, Week 26 visit may occur up to Week 31 [eg $26 + (36 - 26)/2 = 31$].

6.1.4 Study Discontinuation Evaluation

Patients who register for this study and withdraw their consent prior to transplant will be terminated from this study with no additional follow-up necessary.

Subjects terminating from this study after transplantation for reasons other than reaching a study endpoint (death, loss of graft function) will continue to be followed every 6 months until they are 5 years post-transplant, if they are willing. These assessments will include questions about patient and graft survival, rejection and HIV status (opportunistic complications, CD4 cell count and HIV RNA).

6.2 SCHEDULE OF EVENTS

6.2.1 Pre-Transplant On-Going Eligibility Monitoring

KIDNEY PATIENTS	
Ongoing Eligibility Monitoring	Every three months
CD4+T-cell count	X*
HIV-1 RNA (bDNA or PCR)	X*

LIVER PATIENTS	
Ongoing Eligibility Monitoring	Every three months
CD4+T-cell count	X*
HIV-1 RNA (bDNA or PCR)	X*
Total bilirubin	X
Creatinine	X
INR	X

* Must be within 16 weeks of transplant

6.2.2 Schedule of Events

Years:	Year 0	Year 1														Years 2 & 3 every 3 m ¹ every 6 m ²	Years 4 & 5 every 6 m			
		Weeks:	Screen	Day 0	Week 1	2	4	6	8	10	12	16	20	26	36			44	52	53-156
CLINICAL																				
	X																			
	X																			
	X ³																	X	Y2	Y5
	X ³	X								X			X					X	Y2	Y5
	X ³																	X	Y2, Y3	Y4, Y5
	X																			
	X ³																	X	X ²	X
	X ³	X																		
RADIOLOGY																				
	X																			

Years:	Year 0	Year 1															Years 2 & 3 every 3 m ¹ every 6 m ²	Years 4 & 5 every 6 m
Weeks:	Screen	Day 0	Week 1	2	4	6	8	10	12	16	20	26	36	44	52	53-156	157-260	
Biopsies																		
HCV+ Liver Subjects ⁷												X			X	Y2, Y3	Y4, Y5	
HCV+ Kidney Subjects ⁷	X ¹⁰											X				Y2.5	Y5	
HBV+ Kidney and Liver Subjects ⁸																		
Biopsy for all suspected rejection episodes																		
Pharmacokinetics (UCSF ONLY)																		
PI/NNRTI/CSA pK	X			X					X			X			X	Y2	Y5	
Urine toxicology	X								X			X			X	Y2	Y5	
pGP Phenotype												X						
CLUSTER 1: SeraCare Specimen Collection – Specimens collected and shipped to SeraCare																		
Recipient Blood	X								X			X			X	Y2		
Recipient Saliva	X								X			X			X	Y2		
Donor Blood and/or Spleen		X																
Biopsy Slides (kidney and liver bx post-tx)																		
Anal Pap (UCSF, U MD, Cedars-Sinai only)	X ¹¹											X			X	X ²	X	
Biopsy Tissue – All kidney rejection episodes (UCSF only)																		
CLUSTER 2: SeraCare Specimen Collection – Specimens collected and shipped to SeraCare																		
Recipient Blood	X								X			X			X	Y2		
Recipient Saliva	X								X			X			X	Y2		
Donor Blood		X																
Biopsy Slides (kidney and liver bx post-tx)																		
CLUSTER 3: SeraCare Specimen Collection – Specimens collected and shipped to Seracare																		
Recipient Blood	X								X			X			X	Y2		
Donor Blood and/or Spleen		X																
Biopsy Slides (all kidney and liver bx post-tx)																		
Anal Pap (Mt. Sinai liver subjects, Columbia, and Beth Israel Deaconess only)	X ¹¹											X			X	X ²	X	
Biopsy Tissue – All kidney rejection episodes (Mt. Sinai only)																		

1. every 3 months
2. every 6 months
3. Must be completed no more than 12 months prior to transplantation.

4. MRI will be performed as needed for evaluation of abnormal neurologic examination or changes in mental status; CSC JC virus if indicated by clinical and MRI findings. Factor replacement will be required for individuals with bleeding disorders.
5. Expected every 12 weeks. Must be completed no more than 16 weeks prior to transplantation.
6. Repeat only if indicated based on prior results. See section 9.2 of the MOP for guidelines.
7. The use of non-protocol biopsies for protocol purposes is allowed as long as the biopsy is within 3 months of the protocol scheduled biopsy date.
8. As clinically indicated.
9. Every 3 or 6 months per protocol.
10. HCV+ kidney patients will have a liver biopsy pre-transplant if none performed already.
11. At the time of organ availability, obtain peri-transplant anal pap if it has been > 6 months since last anal pap.
12. Not required if subject is anuric.
13. Must be completed no more than 30 days prior to day 0.
14. If not done pre-transplant, get at one point post transplant.

6.2.3 Schedule of Events (Additional monitoring for subjects on HCV Therapy)

Patients starting HCV Therapy are required to have the following additional monitoring performed:

	Pre-Therapy Initiation	Post Therapy Initiation												Month 6 Post Therapy Discontinuation	Month 12 Post Therapy Discontinuation
		Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Month 3	Month 6	Month 9	Month 12		
General															
CBC-diff	X	X	X	X	X	X	X	X	X						
LFTs (ALT, AST, T Bili, ALP, PT/INR)	X														
TSH	X									X	X	X	X		
Fasting Lipid Panel	X														
CXR (if none in past 12 months)	X														
Renal/Electrolytes (Na, K, Cl, HCO ₃ , Ca, P)	X														
HCV Genotype	x														
HCV RNA VL	x				X					X	X		X	X	X

6.3 DEFINITIONS FOR SCHEDULE OF EVENTS

6.3.1 Definitions for Schedule of Events

6.3.1.1 *Documentation of HIV Infection*

HIV documentation will be required at screening using any licensed ELISA and confirmation by Western Blot or any HIV RNA-based viral load test.

6.3.1.2 *Informed Consent*

A signed and dated, IRB approved consent form is required prior to participation in this study. Surrogate consent can be used for liver transplant candidates with hepatic encephalopathy who have not been previously screened for the study, thus have not previously signed a consent form. Once the patient is able to consent in the post-transplant phase, the consent process will need to be completed with the patient in order to continue in the study.

Living donors must sign an informed consent document prior to any invasive procedures that indicates that their donation is intended for use in a patient with HIV infection and that the outcome of transplantation in people with HIV infection has not been defined and is under investigation.

6.3.1.3 *SF-36 Quality of Life Questionnaire*

The SF-36 is a measure of quality of life and disease impact on physical, psychological, and social functioning. The SF-36 is a short form measure of generic health status and is designed for self-administration.

6.3.1.4 *Symptom & Medical Review plus Physical Exam*

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 will focus on signs and symptoms suggestive of HIV disease progression, impaired allograft function, and rejection. Clinical evaluation will concentrate on symptoms and examination findings of the oropharynx, respiratory, cardiac, gastrointestinal, skin, lymphatic and nervous system. CD4+ T-cell numbers and percents, and quantitative HIV-1 RNA by Ultrasensitive bDNA or PCR assays, will be monitored at outpatient and GCRC/PCRC* clinical visits as outlined in the schedule of events.

A medical history must be present in source documents. The medical history should include any previous HIV-related diagnosis and non-HIV related diagnosis of major organ systems.

A complete current medication history (prescription, non-prescription and alternative therapies) must be present in source documents, with estimated start dates. All medications will be recorded on the case report forms (CRFs).

* If no GCRC/PCRC is available, these studies can be done in a clinic setting per local site discretion.

All concomitant medications taken since the last report will be recorded in the source documentation and recorded on the case report forms (CRFs).

6.3.1.5 PPD

PPD testing (or chest x-ray if the patient has a history of positive PPD) is to be performed by the primary medical care provider every 12 months.

6.3.1.6 Vaccination Review

Patient records should be reviewed for history of vaccinations for pneumovax, hepatitis A and B and, for children, childhood vaccinations. See section 5.10 for complete details on vaccinations.

6.3.1.7 Cervical PAP and Pregnancy Test

A cervical PAP smear will be performed in women with a cervix and sexually active adolescents at least every 6 months. This can be done by the primary medical care provider or the study team. Female subjects of child-bearing potential must have a negative serum beta-HCG pregnancy test within 14 days of screening and pre-transplant. All subjects must practice barrier contraception and express intent not to become pregnant while participating in this study. Documentation that counseling was provided regarding the importance of contraception during participation in the study should be recorded in the participant's medical chart. Any pregnancy (and outcome) that occurs during participation in this study will be reported to EMMES on a case report form .

6.3.1.8 Radiology

A chest x-ray (CXR) will be obtained at baseline and as clinically indicated. An MRI of the head will be performed as needed for evaluation of abnormal neurologic examinations or changes in mental status. If the MRI is suspicious for progressive multifocal leukoencephalopathy (PML), cerebrospinal fluid (CSF) will be tested for JC virus. Abdominal imaging should be performed at screening for all HCV+ subjects. **[UCSF only: A whole body DEXA (Dual Energy X-Ray Absorptiometry) may be performed for body composition and bone mineral density evaluation at each GCRC visit.]**

6.3.1.9 Safety Labs

Standard baseline and follow-up laboratory tests will be performed at each outpatient and GCRC/PCRC visit per Schedule of Events (Section 6.2):

- complete blood count with platelets and differential (CBC-diff)
- blood urea nitrogen (BUN)
- creatinine (Cr)
- electrolytes (sodium, potassium, chloride, bicarbonate, calcium, and phosphorous)
- glucose

- albumin
- liver function tests (bilirubin, SGOT/AST, SGPT/ALT, alkaline phosphatase) for all patients, plus PT/INR for liver recipients
- Fasting lipid panel (Chol, LDL, HDL, TGL)
- urinalysis (kidney subjects only)
- Immunosuppressant levels

6.3.1.10 CD4+ T-Cell Count and HIV RNA Changes

Monitored as outlined in Schedule of Events (Section 6.2).

6.3.1.11 RPR/VDRL, Toxoplasmosis, G6PD

Monitored as outlined in Schedule of Events (Section 6.2). Monitor only if indicated based on results of prior testing.

6.3.1.12 Histoplasmosis

If patient has a history of histoplasmosis, urine histoplasmosis antigen every 3 months while CD4+ <200 cells/ μ L.

6.3.1.13 CMV

CMV antibody testing will be done at screening, day 0, then every 6 months if indicated based on prior results

6.3.1.14 HBV Monitoring

HepBSAg, HepBSAb, and HepB Core Ab testing done at Screening, day 0, then every 6 months in Years two one through five if indicated based on prior results. Patients with hepatitis B infection (HbsAg+) will have hepatitis B DNA and anti-HB titers at Screen, day 0, and every 6 months post transplant. HbsAg+ subjects will also have anti HDV, HbeAg and anti-Hbe at screening. If HbeAb and Anti-Hbe are not collected pre-transplant, obtain at one point post transplant.

6.3.1.15 HCV Monitoring

HCV antibody testing done at screening, day 0, then every 6 months in Years one through five if indicated based on prior results. Patients with hepatitis C co-infection will have hepatitis C RNA at Screen, day of transplant, and annually post transplant.

6.3.1.16 EBV Monitoring

Patients will be EBV tested at screening, day 0, then every 6 months only if indicated based on prior results.

6.3.1.17 Biopsies

For HCV+ kidney patients, biopsies will be performed at pre-transplant if none performed already, 6 months, 2.5 years and 5 years post transplant. HCV+ liver patients will have biopsies at month 6 and Month 12, then annually post-transplant. HBV+ kidney and liver patients will have biopsies as clinically indicated. A biopsy will also be performed in all cases of suspected rejection.

6.3.2 Definitions for Schedule of Events: Site Specific Sub-Studies

6.3.2.1 Pharmacokinetics (UCSF Only)

Pharmacokinetic monitoring will be conducted in the GCRC³ or PCRC pre-transplant if patient is taking a PI or NNRTI⁴, then at Weeks 2, 12, 26, 52, Year 2 and Year 5 post-transplant. Once target accrual has been reached for the pharmacokinetics substudy, only subjects on one of the new antiretroviral agents for HIV currently available in expanded access will have pharmacokinetic monitoring at screening, weeks 2, 12, and 26. If additional funds are obtained, Year 3 and 4 studies will be added. Additional studies will be performed when there is a change in PI or NNRTI type or dose, a change in immunosuppressant type (CSA, Tacrolimus, or Sirolimus), a rejection episode requiring a change in immunosuppressant type, or following the development of an opportunistic infection. The appropriate time frame after an opportunistic infection is defined as when the acute illness is resolved and the patient is clinically stable on stable chronic therapy or is off anti-infective therapy, in either case within 6 weeks of the diagnosis. When any of these events occur, the timing of the pK analysis will restart (new baseline, Week 2, etc.), necessitating more visits for these analyses. For each study, a peripheral blood sample (5 mL for adults and 2mL for pediatrics) will be collected at the following times relative to their immunosuppressant administration: 0, 0.25, 0.5, 2, 2.5, 3, 4, 6, 9, and 12 hours. In some cases (e.g., subjects on efavirenz, a once daily drug), a 24-hour analysis would be preferred. Study coordinators should contact Lynda Frassetto and Michelle Roland prior to scheduling to determine optimum timing of pK studies based on specific antiretrovirals (frassetto@gcrc.ucsf.edu and mroland@php.ucsf.edu). An optional Week 12 pK analysis may be added for sites with funding and capacity.

Whole blood and/or plasma will be analyzed for immunosuppressant (mycophenolate at time 0 only), 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/PCRC to evaluate any interactions with ARV and/or prescription medications.

A plasma sample for baseline P450 genotyping will be stored. Additional genetic testing may be warranted in the future and samples will be stored for this possibility with subject consent.

³ If no GCRC is available, these studies can be done in a clinic setting per local site discretion.

⁴ If pre-transplant pharmacokinetics are unable to be completed, baseline studies should be done as early as possible in the post-transplant hospitalization if the subject is taking a PI and/or NNRTI.

6.3.2.2 *SeraCare Specimen Collection*

Specimens are collected and shipped to SeraCare for sub-study analysis.

Sites participating in each sub-study have been organized into “Sub-Study Clusters.” See section 4 of the MOP for composition of each Sub-Study Cluster and participation of each site in each sub-study. See section 2 of the Laboratory Manual for an exact summary of which specimens will need to be collected and shipped by each center, appropriate time points, and shipping instructions. For a complete list of testing that will be performed on research specimens, see Appendix B: Sub-Study Testing Performed on Specimens Sent to SeraCare.

6.4 BLOOD VOLUME CONSIDERATIONS FOR CHILDREN

Blood volumes for children will be based on weight. No more than 10% of the blood volume may be withdrawn in any 6 week period and no more than 5% may be withdrawn over a 4 week period. No more than 5 mL/kg can be withdrawn at any single draw.

Laboratory studies will be sent based on the following priorities (and at investigator’s discretion based on patient care needs)

1. Safety Labs in the following order of priority: LFT, renal/electrolytes, CBC-diff, Immunosuppressant level, PT/PTT, CMV ab
2. HIV labs in the following order of priority: CD4/CD8, HIV RNA, Lipids, Hep B studies, Toxo, G6PD, EBV, MAC
3. HCV labs
4. PK samples
5. Storage
6. Virology and immunology sub-studies

6.5 REQUIREMENTS FOR CONFIRMATION OF OPPORTUNISTIC INFECTIONS AND NEOPLASMS

All occurrences of suspected opportunistic infections or neoplasms will be confirmed microbiologically and/or pathologically when possible.

See Appendix A: Confirmation of Opportunistic Infections and Neoplasms for guidelines.

6.6 REQUIREMENTS FOR CONFIRMATION OF REJECTION

All presumptive episodes of rejection will be confirmed with biopsy within 1 day of initiation of presumptive therapy (including increases in immunosuppression doses). Etiology of organ dysfunction or failure will be determined by the local study team. See section 5.3.1 for definition of rejection. All study-mandated kidney and liver biopsies will be sent to the core pathology laboratory for central pathology review.

7 SPECIMENS

All specimens from this study will be shipped fresh to SeraCare for processing. They will be batch shipped from SeraCare for testing at specified laboratories, or will be stored for future testing. No identifying information will be used to mark specimens; the study ID will be used. Specimens not used after 5 years from the date of collection will be destroyed unless consent is obtained for further storage. Any specimens remaining at SeraCare at the end of this 5-year grant will be destroyed, or stored at SeraCare or other repository if funding is available.

See the Laboratory Manual for specific specimen collection, shipping, and tracking information.

8 ADVERSE EVENT MANAGEMENT AND REPORTING

8.1 ADVERSE EVENTS

8.1.1 Adverse Event Definition

An adverse event is any occurrence or worsening of an undesirable or unintended sign, symptom (including an abnormal laboratory finding), or disease temporally associated with the use of a medicinal product/procedure, whether or not considered related to the medicinal product/procedure.

Adverse events include, but are not limited to:

- Worsening (change in nature, severity, or frequency) of conditions present at the onset of the study
- Intercurrent illnesses
- Drug reactions or interactions of antiretroviral agents, immunosuppressant agents, or other concomitant medications used on study
- Infections
- Events related or possibly related to concomitant medications
- Abnormal laboratory values (significant shifts from baseline within the range of normal that the investigator considers to be clinically important)
- Clinically significant abnormalities in physical examination, vital signs, weight, and/or tests and procedures.
- Surgical complications of kidney or liver transplantation

The investigator should treat participants with adverse events appropriately and observe them at suitable intervals until the events resolve or stabilize. Adverse events may be discovered through observation of the participant, questioning of the participant, complaint by the participant, or by abnormal clinical laboratory values or other studies.

8.1.2 Adverse Event Reporting Procedures

Throughout this study, the investigator must record all grade 3 or higher events (based on the Division of AIDS Table for Grading The Severity of Adult and Pediatric Adverse Experiences Version 1.0, publish date December 2004), not present at baseline, on the appropriate Adverse Event Form within 5 business days of identification of the event. Adverse events must be reported from the time of transplant through study completion unless a participant is prematurely terminated from the trial. Adverse Events will not be captured during the pre-transplant phase of the trial. Baseline condition is determined during the screening visit. If an event is present at baseline, is clearly documented, and does not change in severity throughout the study, it does not need to be captured on an Adverse Event Form. However, if the event resolves, or begins to resolve, and then worsens again to a grade 3 or higher, it must be captured on an Adverse Event Form.

Within 5 business days of recognition of an adverse event, the Study Coordinator will:

- Complete an Adverse Event Form in the EMMES Internet Data Entry System (IDES) found at www.emmes.com.
- Record information on the adverse event in the participant's medical chart.
- Enter follow-up information into the EMMES IDES when it becomes available.

8.2 SERIOUS ADVERSE EVENTS

8.2.1 Serious Adverse Event Definition

A serious adverse event (SAE) or reaction is defined as any adverse event that suggests a significant contraindication to ongoing therapy. This includes, but may not be limited to any of the following events:

- Death: A death occurring during the study or after a participant prematurely withdraws from the study (for as long as they are willing to be contacted by study staff), whether or not considered treatment-related, must be reported;
- Life-threatening: Any adverse experience that places the patient or participant, in the view of the investigator, at immediate risk of death from the reaction as it occurred;
- Inpatient hospitalization or prolongation of existing hospitalization;
- Persistent or significant disability/incapacity;
- Congenital anomaly/birth defect;
- An event that requires intervention to prevent permanent impairment or damage.

An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

8.2.2 Serious Adverse Event Reporting Procedures

Serious Adverse Events must be reported from the time of transplant through study completion unless a participant is prematurely terminated from the trial. Serious Adverse Events are not reported during the pre-transplant phase of the trial. When an investigator identifies an SAE, as defined above, EMMES must be notified within 72 hours of the discovery of the event. If there is any doubt whether the information constitutes an SAE, the information should be treated as an SAE for the purposes of this protocol.

Within 72 hours of recognition of a serious adverse event, the Investigator or Study Coordinator will:

- Complete a Serious Adverse Event Form in the EMMES IDES. An email will be automatically generated real-time to notify the appropriate study staff.

- Fax supporting documentation to the EMMES Data Manager (see section 3 of the MOP for fax number) attn: HIV-Transplant Data Manager. This includes a narrative summary of the event, discharge summary, laboratory test(s), consultation and biopsy summary reports, and any other pertinent reports. The site investigator should determine if the SAE is related to the intervention, or not, and should include the rationale for this determination in the report. This report can be completed by the study nurse, but must be reviewed and signed by the site principal investigator. All available supporting documentation should be submitted to EMMES within 5 days of the onset of the SAE. Additional information will be included in the follow-up report.
- In the event of death, complete a Death Form in the EMMES IDES, sending supporting information (death certificate, medical notes, etc.) when available.
- Record information on the serious adverse event in the participant's medical chart.
- Enter follow-up information in the EMMES IDES, in addition to faxing follow-up source documents to EMMES, when it becomes available. Follow-up information will be provided to EMMES until the event has subsided or, in case of permanent impairment, until the condition(s) stabilizes.

8.3 REPORTING GUIDELINES

The following adverse events and serious adverse events do not need to be reported for this study. However, remember to report all serious adverse events to your IRB as per your institutional guidelines.

8.3.1 Adverse Events Exempt from Reporting

- Elevated liver enzymes in liver recipients or creatinine elevation in kidney recipients in the first week post-transplant if they are within expected ranges
- Decline in CD4+ T-cell counts during the first year following thymoglobulin treatment for rejection

8.3.2 Serious Adverse Events Exempt from Reporting

- Hospitalizations for uncomplicated protocol-mandated biopsies or study PK GCRC visits

8.4 GRADING ADVERSE EVENTS

Use the Division of AIDS Table for Grading The Severity of Adult and Pediatric Adverse Experiences Version 1.0, publish date December 2004.

8.4.1 Serious Adverse Event Review

The Protocol chairpersons (Drs. Stock/Roland) will have day-to-day supervisory responsibility for reviewing outcomes and responding to urgent serious safety

issues that arise during the study. EMMES will notify the protocol co-chairs and NIAID co-medical monitors within 72 hours of any unexpected SAE. Expected events will be reviewed on a monthly basis. The protocol co-chairs and NIAID co-medical monitors will review the reports and determine if any modifications in procedures should be implemented, if other site PIs should be notified and/or whether procedural changes in the protocol are required. Investigators should follow institutional requirements when reporting AEs and SAEs to their respective Institutional Review Boards. EMMES will assist in site notification, and, when necessary, will draft a letter to be submitted to site IRBs. EMMES will also notify the DSMB of all SAEs and will provide monthly summary reports of all adverse events to NIAID and the protocol co-chairs.

8.5 COMMITTEE REPORTING

The following table summarizes strategies to monitor accumulating information about transplant efficacy and safety. In particular, formal statistical continuing/stopping boundaries for monitoring patient and graft survival during the first post transplant year will be reported monthly to the operations committee. Reporting frequency for the DSMB may be at shorter intervals and will include immediate notification if patient or graft survival continuation boundaries are crossed.

Reports	Operations		Steering	Endpoint	DSMB
	Daily	Monthly	Quarterly	Quarterly	At least Annually
Accrual	X	X	X		X
Patient Survival		X	X	X	X
Graft Survival		X	X	X	X
Adverse Experiences					
Serious	X	X	X	X	X
Other		X	X	X	X
Laboratory Abnormalities		X	X	X	X
PK Dosing Analyses		X	X		X
Other secondary Endpoints			X	X	X
Data Quality	X	X	X		X

8.6 DATA SAFETY AND MONITORING

This study will be monitored by the NIAID Therapeutic Data Safety Monitoring Board (TDSMB). An initial design review of the protocol will be scheduled to precede the start of subject enrollment and interim administrative and safety reviews will be performed at least annually. Additional interim evaluation of accrual, safety, and/or endpoint data will be scheduled as necessary.

To monitor recruitment, retention, and overall data quality, as well as to review serious adverse events, the study investigators and statistician will provide to the Board periodic reports on expected versus observed accrual, expected versus losses to follow-up as well as anticipated versus observed adverse events. The Board will review such reports to evaluate safety data and to assure that original

design assumptions and power considerations remain valid as the study progresses. The Board will make recommendations to NIAID and/or provide general guidance to the study investigators on alternate strategies if design assumptions fall short of original expectations.

The DSMB defines its responsibilities which may include, but are not limited to, any or all of the following: to monitor trial progress in recruitment and retention; to monitor factors such as protocol adherence and data quality that affect the integrity of the study; to consider factors external to the study that may impact participant safety or trial conduct; to review serious adverse events and determine if it is safe to continue the study; and to report and advise NIAID on trial-related matters.

8.7 EXTERNAL MONITORING

Site monitors under contract to the National Institute of Allergy and Infectious Diseases (NIAID) will visit participating clinical research sites to review the individual subject records, including consent forms, CRFs, supporting data, laboratory specimen records, and medical records (physicians' progress notes, nurses' notes, individuals' hospital charts), to ensure protection of study subjects, compliance with the protocol, and accuracy and completeness of records. The monitors also will inspect sites' regulatory files to ensure that regulatory requirements are being followed. The investigator will make study documents (e.g., consent forms, drug distribution forms, CRFs) and pertinent hospital or clinic records readily available for inspection.

9 DATA ANALYSIS

9.1 SAMPLE SIZE

As the study is a single arm evaluation of transplantation in stable HIV infected patients, the analysis will be descriptive and include statements of observed results and their associated precision. The targeted sample size of 150 kidney transplant patients and 125 liver transplants was obtained as follows. A sequential probability ratio test was constructed for the survival endpoints and both error rates were set to .05. The boundaries were modified to be closed at the maximum sample size. Uniform accrual over three years was assumed as was exponential survival over a truncated 1-year follow-up period. The size requirements were evaluated by simulation with monthly inspection of results. The continuation boundary was calculated using type I and type II error rates of 0.075 and 0.05 so as to give the truncated SPRT error rates matching those planned. For each organ the upper parameter value was selected to be the one year result from the UNOS 2000 report for patients >65 years of age. We enter the study anticipating, as with older subjects, that transplantation of HIV+ patients is an acceptable but high-risk procedure. We expect survival may be less than that of age matched controls (where the national age matched average 1 year survival for kidneys transplants is 97%) but that results should be similar to those seen in other poor prognosis groups (e.g. diabetics, hospitalized patients, etc). The >65 year old normative group was selected because it is relatively common (9% of deceased kidneys, 7% of livers) and represents patients with additional co-morbidities. The null and alternatives used in the test construction were .88 vs .76 for kidney patient survival at 1 year, and .82 vs .67 for liver patient survival at 1 year. Note that we have selected a less stringent equivalence criterion for the liver transplants since the event rate is higher and because liver failure patients not receiving transplants have higher mortality risks.

9.2 DATA ANALYSIS PLAN FOR PRIMARY AIM 1

9.2.1 Data Analysis Plan for Primary Aim 1, Hypothesis 1.1

HIV+ liver and kidney transplant recipients will have survival rates comparable to other patient groups without HIV infection that are currently considered acceptable transplant candidates. Survival distributions will be estimated by the product-limit method and variability at 1 year and subsequent time points will be estimated with Greenwood's formula. For the purpose of providing monitoring guidelines for DSMB review, the upper confidence limit for the 1-year survival estimate will be calculated using a one-sided .0001 significance level. The confidence limit will be calculated every six months and examined to determine those that fail to include the targeted national survival rate. Operating characteristics for the probability of failing the monitoring guidelines prior to completing accrual, under the assumed study structure, are provided in the table below. When sufficient follow-up events are available at 3 and 5 years, we will compare results against 2 control groups from the national registry. One will comprise randomly selected age-race-donor source-year-of-transplant matched controls. The second will be constructed from similarly matched patients, but the patient at the 90th risk percentile will be selected. Finally, the effect of transplantation on mortality will be examined by

comparing the mortality rate of registered study subjects awaiting transplant to those receiving an allograft. This will be formally tested using a proportional hazards model with a time-varying indicator of transplant status. This approach is not primary since it can be affected by listing decisions made by the participating sites.

9.3 DATA ANALYSIS PLAN FOR PRIMARY AIM 2

9.3.1 Primary Aim 2, Hypothesis 2.1

HIV+ liver and kidney transplant recipients will have graft survival rates comparable to other patient groups without HIV infection that are currently considered acceptable transplant candidates. Patient survival may not be negatively affected by transplantation but graft failure may still be excessive. Therefore, we will monitor one year graft failure as described for the survival endpoint. For each organ, the targeted parameter value was selected to be the reported one year result from the UNOS 2000 report for patients >65 years of age (ie .83 for kidney, .78 for liver). Inclusion of the target in the confidence interval will be taken as evidence of similarity of graft survival to that for current acceptable organ transplant candidates, and cause for continued sampling. Operating characteristics are detailed in the table below. As additional analyses, we will compare results to comparable national data in the 3rd and 5th project years with consideration of appropriate covariates, including age, race, and donor source. These comparisons will also examine the graft rejection experience that is available in the national registry at selected time points, including 1, 6, and 12 months post-transplant. Differences from national registry rejection rates exceeding .1 are detectable with adequate power for both organ groups.

Operating Characteristics for Stopping Guidelines Using Semi-Annual Confidence Limits with .0001 1- Sided Significance Level.

% of Trials Recommended for Stopping Prior to Completing 3 Year Accrual Period, 2000 replicates per cell

	Kidney Survival	Kidney Graft Survival	Liver Survival	Liver Graft Survival
Targeted 1-Year Rate	.88	.83	.82	.78
True 1-Year Rate				
.85	0.1	0	0	0
.80	1.4	0	0	0
.75	16.1	1.6	0.5	0
.70	56.8	16.4	6.2	1.1
.65	89.5	51.4	29.5	8.7
.60	98.5	84.7	63.7	32.9
.55	99.9	97.6	89.4	66.7
Mean 1-Year Estimate For Terminated Studies	0.596	0.561	0.535	0.504

9.3.2 Primary Aim 2, Hypothesis 2.2

HIV+ liver transplant recipients co-infected with hepatitis B or C will have graft survival comparable to other patient groups with the same viral hepatitis infections but without HIV infection that are currently considered acceptable transplant candidates. These analyses will be performed as special studies to be initiated 3 years after the start of recruitment since it requires acquiring additional comparison data. A request will be made to the scientific registry of the OPTN for extraction of a contemporaneous control cohort of liver transplant patients with hepatitis B and HCV. Minimally, demographics, infectious disease serology, diagnosis, and graft status will be obtained. We have previous experience and established working relationships with national registry staff, and mechanisms to execute this approach are in place. Powerful contrasts of covariate-controlled graft survival will be possible because of the large national registry cohort.

9.3.3 Primary Aim 2, Hypothesis 2.3

This study will estimate the proportionate importance of HIVAN as a cause of renal transplant candidacy in HIV+ patients. The study will also have the unique opportunity to contrast, via the logrank test, graft survival results from patients with the HIVAN diagnosis versus all other ESRD causes. The study size provides an estimated 70% power to detect a difference in graft survival curves of .2 at 5 years with power exceeding 80% after 2 additional follow-up years. We will estimate the proportion (and confidence interval) of patients who have graft failure attributed to HIVAN in patients with and without pre-transplant HIVAN.

9.4 DATA ANALYSIS PLAN FOR SECONDARY AIM 1

HIV-1 RNA and CD4+ Tcell counts will be characterized through time with a focus on initial peri-transplant response and subsequent repeated measures analysis with generalized estimating equations. Sentinel infections, CD4+ T cell counts and HIV-1 RNA will be examined as a predictor of graft loss. This will be associated with examination of cause specific graft loss to determine frequency of loss associated with withdrawal of immunosuppression attributed to lack of viral control.

9.5 DATA ANALYSIS PLAN FOR SECONDARY AIM 2

A series of parallel studies of 7 viral co-pathogens will be executed. For each, the incidence and prevalence of viral infections and accompanying 95% confidence interval will be estimated. Each will consider organ-specific post-transplant response and pathogen co-infection as a risk factor for both organ rejection and HIV disease progression in this group receiving chronic immunosuppression. Survival analytic methods including time-varying covariates will be used for the graft survival endpoint. Pathogen burden (in plasma, PBMC and saliva, as appropriate) will be modeled with repeated measures techniques to evaluate the independent roles of transplant-related immunosuppressive agents, HIV plasma viral load, and CD4+ lymphocyte count as predictors. While these approaches are common across pathogens, there are special features for the various viruses, including: (1) HBV: comparison of liver disease progression among all subjects with and without 3TC resistance; a single arm study of HBIG/3TC prophylaxis in liver recipients and; correlation of emergence of viral mutations with clinical

outcomes; (2) a retrospective comparison to HIV- liver transplant recipients with HCV of pathologic progression of liver disease; (3) quantitative DNA and RNA assessment of herpesvirus, peak viral load and time to disease progression, and drug-resistant CMV emergence in clusters 1 and 2 (n=132); and (4) evaluation of HPV disease progression (AIN and anogenital carcinoma) in a cohort of 100+ transplanted individuals with comparison to multiple HIV positive and negative control cohorts. Given the projected sample sizes, there is sufficient statistical power to determine disease and viral load correlations. For example, we estimate a CMV disease rate of at least 10%, resulting in 13 cases out of 132 patients. Using a test of two proportions, the difference between the percentage of patients above and below the disease cutoff can be as low as 35%, and still achieve 80% power with a type I [alpha] error = 0.05 and one sided test of hypothesis. Functional cellular responses will be measured in parallel by CFC (~20 antigens) and ELISPOT (peptide pools from 4 co-pathogens and HIV). The critical comparison will be the change in these responses from pre transplant to week 12. Because of the multiplicity of endpoints, type I error control will be maintained with Bonferoni adjustment although power varies with disease prevalence and cohort size. These disease-specific change scores will be used in discriminant analyses to determine if those who develop subsequent infection can be predicted from the early cellular responses. Finally, CFC and ELISPOT measures relating to the co-pathogens and the functional HIV assays will be correlated with incidence and time to OI with the covariates of organ type and immunosuppression type.

9.6 DATA ANALYSIS PLAN FOR SECONDARY AIM 3

Acute rejection rates in study subjects will be compared to rejection rates for HIV-transplant recipient controls selected from participating centers, and matched for age, race, disease, immunosuppressive regimen, and center. Assuming that the rate of acute rejection is 20% in HIV- recipients, the sample of 275 HIV+ transplant recipients and 275 matched HIV- controls will provide 80% power to detect an increase in rejection rates among HIV+ patients of only 10 percentage points, to 30%. This is a smaller rejection rate than the 38% observed in the preliminary data for 13 HIV+ patients at UCSF. Response to allostimulation (third party positive controls) and donor-specific responses will be assessed using MLC assays for cluster 1 subjects (n = 62) and an equal number controls from UCSF, matched on race, age, and disease selection criteria. These data will be compared with relevant parameters (e.g., rejection, graft survival), HIVAN, and host response to viral pathogens.

9.7 DATA ANALYSIS PLAN FOR SECONDARY AIM 4

The pharmacokinetic parameters C_{max} , C_{min} , t_{max} , AUC_{0-12} , CL/F, and $t_{1/2}$ will be determined. The values for C_{max} and the time to reach C_{max} (t_{max}) will be obtained directly from the concentration-time profile of the data. AUC_{0-12} , CL/F, and $t_{1/2}$ will be based on non-compartmental methods using WinNonlin Professional software (version 2.1, Pharsight Inc., Mountain View, CA). Individual concentration-time profiles will be plotted, and the elimination rate constant determined by the logarithmic regression of the time points in the terminal elimination phase. Exposure, defined as AUC/dose, will be calculated to determine if there is a change in the dose concentration relationship, as would be expected if two drugs significantly interact with each other. Assessments of interactions will use the

calculated pharmacokinetic parameter endpoints and compare them within patients at times of drug changes and between subjects at fixed time points to evaluate drug (or drug class) interactions. Repeated measurement techniques using generalized estimating equation methods will be used to examine the pharmacokinetic endpoints as functions of immunosuppressive and antiviral therapy programs.

10 STUDYING LIVER TRANSPLANT RESULTS OF HCV-INFECTED, HIV NEGATIVE RECIPIENTS

10.1 PURPOSE AND RATIONALE SPECIFIC TO SUBJECTS

The Solid Organ Transplantation in HIV study (HIVTR study) is seeking institution-specific matched controls who are HCV-infected and HIV negative in order to compare HCV disease progression outcomes between the 2 groups. Approximately 60% of the liver recipients in the Solid Organ Transplantation in HIV study are HCV-infected, and outcomes are predicted to be poorer in this cohort compared to HIV-infected liver transplant recipients who do not have HCV and compared to HCV mono-infected liver transplant recipients. However, the specific factors associated with poor outcome in co-infected patients are not understood. Therefore, it is important to establish a control cohort to evaluate HCV recurrence, severity, treatment, treatment success, graft failure and graft rejection.

10.2 ENROLLMENT INFORMATION

Each participating center will identify three controls for each HCV-infected, HIV positive liver transplant recipient enrolled in the HIVTR study. Control subjects should be HCV-infected, HIV negative liver transplant recipients transplanted during the course of the HIVTR study, be greater than 12 years of age, and be chosen consecutively based on the HIVTR transplant recipient's date of transplant and should be matched first on single/dual organ transplant, and second on HCC status (if single organ transplant).

10.3 DATA COLLECTION

Each center will apply for waiver of consent approval from their institutional review board and will be required to have IRB approval before collecting control group data. The HIVTR study team at the site will be responsible for reviewing the medical charts and collecting specific data points. This information will be de-identified, and then submitted to the study investigators for review and statistical analysis. Data will be collected through a 5 year follow-up period.

10.4 SAMPLE SIZE

The expected number of HCV positive, HCV RNA positive liver transplant recipients in the HIVTR study by the end of year 2008 is 64 by assuming a continued average accrual rate of 1.2/month. We plan to enroll three controls from the same center for each case. This will yield a total sample size of 256 subjects. From the UNOS database, the 1-year graft survival rate for liver recipients with detectable HCV RNA at baseline is about 0.83. By assuming a lost-to-follow-up rate of 0.02 and proportional hazard rates, a one-sided log rank test achieves at least 80% power at a 0.05 significance level to detect a reduction of 0.15 or more in the survival rate for HIV positive HCV-infected subjects. Assuming an HCV recurrence rate of 0.5 for the control group, a two-sided Fisher's exact test achieves at least 80% power at a 0.05 significance level to detect a difference of 0.21 or more between the rates of HCV recurrence in the two patient groups.

10.5 DATA COLLECTION FOR HCV CONTROL GROUP

BASELINE (PRE-TRANSPLANT- at or closest to the date of liver transplant)

- Age, race, gender, BMI, dual organ transplant, HCC status, HBsAg, anti-HBc, anti-HBs
- HCV viral count - quantitative (in IU/ml), genotype
- most recent serum creatinine, total bilirubin, and INR pre-transplant (or MELD score if not available)

OTHER

- Transplant date, graft status, graft failure date and cause (if applicable), survival status, death date and cause (if applicable), last follow-up date
- Treated rejection dates (treated = steroids, lymphocyte-depleting agent)
- HCV RNA levels annually post-tx (if available)

IF TREATED FOR HCV

- Date of HCV therapy initiation
- Medications used [ribavirin, interferon alpha, peg-alpha, alfacon]
- Date of HCV therapy discontinuation
- HCV RNA level at therapy initiation
- HCV RNA level as close to 6 months post therapy discontinuation as is available (at least 3 months post therapy discontinuation)

HCV HISTOLOGY

- Liver biopsy reports pre-transplant: a copy of at least one pre/peri-transplant biopsy report (including grade and presence of steatosis) with diagnosis of HCV should be de-identified and faxed to EMMES.
- Liver biopsy reports post transplant: copies of all liver biopsy reports (including fibrosis score and scoring method used) post-transplant should be de-identified and faxed to EMMES.

DONOR

Source, age, race, gender, HCV status, HBsAg, anti-HBc, anti-HBs status, split/partial graft

11 HUMAN SUBJECTS

11.1 INSTITUTIONAL REVIEW BOARD (IRB) REVIEW AND INFORMED CONSENT

This protocol and the informed consent document and any subsequent modifications will be reviewed and approved by the IRB or ethics committee responsible for oversight of the study. A signed consent form will be obtained from the subject (or parent, legal guardian, or person with power of attorney for subjects who cannot consent for themselves, such as those below the legal age). The subject's assent must also be obtained if he or she is able to understand the nature, significance, and risks associated with the study. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the subject, parent, or legal guardian, and this fact will be documented in the subject's record.

12 BIOHAZARD CONTAINMENT

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the Centers for Disease Control and Prevention and the NIH.

All infectious specimens will be transported using packaging mandated in the Federal Code of Regulations, CDC 42 CFR Part 72. Please see section the Laboratory Manual for the guidelines and specific instructions.

13 APPENDICES

APPENDIX A: CONFIRMATION OF OPPORTUNISTIC INFECTIONS AND NEOPLASMS

	CONFIRMED	PROBABLE
CONSTITUTIONAL DISEASE		
HIV wasting syndrome	None	A plus B plus C: (A) unexplained, involuntary weight loss >10% from baseline, (B) persistent diarrhea with >2 liquid stools/d for >1 month or weakness for >1 month or fever for >1 month, (C) tests for alternate causes of weight loss, such as cancer, TB, MAC, cryptosporidiosis or other specific causes of weight loss, if obtained, should be negative
INFECTIONS		
Aspergillosis, invasive pulmonary	A plus B plus C: (A) CXR abnormality compatible with aspergillosis, (B) invasive mycelia consistent with Aspergillus on lung biopsy, (C) positive culture from lung biopsy or sputum collected by any method	A plus B: (A) CXR abnormality compatible with aspergillosis, (B) invasive mycelia consistent with Aspergillus on lung biopsy or positive culture of lung tissue or positive culture of sputum collected by any method
Aspergillosis, other invasive	A plus B plus C: (A) compatible clinical course, (B) invasive mycelia consistent with Aspergillus on tissue biopsy or clinical evidence of infection, (C) positive culture from the affected tissue	A plus B: (A) clinical evidence of invasive infection, (B) invasive mycelia consistent with Aspergillus on tissue biopsy or positive culture at a normally sterile site (e.g., blood) apart from the involved tissue
Bartonellosis	A plus B: (A) Clinical or histologic evidence of bacillary angiomatosis or bacillary peliosis, (B) a positive culture or PCR for <i>B. quintana</i> or <i>B. henselae</i>	A plus B: (A) Clinical evidence of bacillary angiomatosis or bacillary peliosis, (B) positive silver stain for bacilli from a skin lesion or an affected organ
Candidiasis of bronchi, trachea or lungs	Macroscopic appearance at bronchoscopy or autopsy plus microscopic evidence of yeasts or	None

	pseudo hyphae	
Candidiasis, esophageal	A plus B: (A) Macroscopic appearance at esophagoscopy or autopsy, (B) microscopic evidence of yeasts or pseudo hyphae	A plus B plus C: (A) Recent onset of retrosternal pain or difficulty on swallowing, (B) a clinical diagnosis of oral candidiasis plus microscopic evidence of yeasts or pseudo hyphae from oropharyngeal mucosa, (C) clinical response to treatment
Chagas disease (American trypanosomiasis) of the CNS	Histologic evidence obtained by brain tissue biopsy or autopsy	A plus B plus C plus D: (A) Focal, typically hemispherical neurological dysfunction with onset over several days or weeks; (B) enhancing focal lesion(s) with mass effect, and surrounding edema and contrast enhancement, typically located in grey matter; (C) serum antibodies to <i>T. cruzi</i> , (D) response to standard therapy with documented clinical or radiographic improvement (if radiography was done, it must be improved), or peripheral blood smear or CSF smear positive for <i>T. cruzi</i>
Coccidioidomycosis, disseminated or extrapulmonary	From tissue other than lung or hilum, A or B or C: (A) Microscopic demonstration of spherules, (B) positive culture, (C) antigen detection -	None
Cryptococcosis, meningitis or extrapulmonary	From tissue other than lung or hilum, A or B or C or D: (A) microscopic demonstration of narrow based budding yeast, (B) for meningitis, if done, a positive CSF India ink test, (C) positive culture, (D) antigen detection	None
Cryptosporidiosis	Diarrhea for >1 month and positive microscopy	None
CMV retinitis	Autopsy demonstration	Typical appearance on funduscopy of discrete patches of retinal whitening, spreading along blood vessels, associated with vasculitis, hemorrhage and necrosis, confirmed by ophthalmologist
CMV radiculomyelitis	Autopsy demonstration	A plus B plus C plus D plus E plus

		F: (A) Loss of sensation, leg weakness, or decreased reflexes, (B) presentation over 3 days to 3 weeks, (C) CT, MRI or myelogram must be done and all imaging studies must not show a mass lesion, (D) CSF shows >10 WBC with >50% polymorphs, (E) CSF shows no other pathogen, (F) persistence of symptoms in the absence of CMV treatment, or elevated quantitative CMV in the CSF by PCR
CMV meningoencephalitis	Autopsy or brain biopsy demonstration	A plus B: (A) Rapid <4 weeks syndrome with progressive delirium, cognitive impairment and fever, (B) CT/MRI demonstration of periventricular abnormalities or elevated quantitative CMV DNA in the CSF by PCR
CMV, other disease	A plus B plus C plus D: (A) compatible illness, (B) histologic demonstration of inclusion bodies from affected tissue, (C) if done, detectible CMV antibodies, (D) if done, detectible CMV DNA or CMV antigen in blood	A plus B plus C plus D: (A) Compatible illness, (B) moderate to markedly high CMV antigen or CMV DNA in blood, (C) response to therapy, (D) if done, detectible CMV antibodies
HSV mucocutaneous ulceration	A plus B: (A) Ulceration for >1 month, (B) histology or culture or detection of antigen from affected tissue	A plus B: (A) Typical HSV ulceration for >1 month, (B) response to an antiviral active against HZV unless resistance is demonstrated
HSV, bronchitis, pneumonitis, esophagitis or other visceral disease	A plus B: (A) Compatible symptoms, (B) histology or culture or detection of antigen from affected tissue	None
HZV, multidermatomal	A plus B: (A) ≥10 ulcerated lesions affecting at least 2 non-contiguous dermatomes, (B) culture or detection of antigen from affected tissue	A plus B: (A) ≥10 typical ulcerated lesions affecting at least 2 non-contiguous dermatomes, (B) response to an antiviral active against HZV unless resistance is demonstrated
Histoplasmosis, disseminated or extrapulmonary	A plus B: (A) Compatible symptoms, (B) histology or culture or elevated blood or urine antigen levels	None
Isosporiasis	Diarrhea for >1 month,	None

	plus microscopic identification of <i>Isospora belli</i>	
Leishmaniasis, visceral	Compatible symptoms, plus microscopic identification of Leishmania	None
Microsporidiosis	Diarrhea for >1 month plus Microscopic identification of Microsporidia	None
MAC and other mycobacterial disseminated disease	A plus B: (A) Fever, fatigue, anemia or diarrhea, (B) positive culture from blood, body fluids or tissue other than pulmonary, hilar or stool	A plus B plus C: (A) Fever, fatigue, anemia or diarrhea, (B) AFB or positive direct MAC PCR in blood, body fluids or tissue other than pulmonary, hilar or stool (C) no concurrent non-pulmonary TB
<i>M. tuberculosis</i> disease, pulmonary	A plus B: (A) Compatible symptoms of fever, dyspnea, cough, weight loss or fatigue, (B) culture or PCR from sputum or bronchial lavage or lung tissue	A plus B plus C plus D: (A) Symptoms of fever, dyspnea, cough, weight loss or fatigue, (B) abnormal chest X-ray, (C) AFBs seen in sputum or lavage or lung tissue but not grown in culture, (D) responds to treatment
<i>M. tuberculosis</i> disease, extrapulmonary	A plus B: (A) Compatible symptoms, (B) culture or PCR from blood or affected tissue	A plus B plus C: (A) Compatible symptoms, (B) AFBs seen from affected tissue or blood (C) concurrent diagnosis of pulmonary TB or responds to treatment
Nocardiosis	Clinical evidence of invasive infection plus a positive culture from the affected tissue or blood	Clinical evidence of invasive infection plus microscopic evidence of bronchial weakly acid fast organisms from the affected tissue
<i>Penicillium marneffe</i> , disseminated	Culture from a non-pulmonary site	Known presence in a <i>P. marneffe</i> endemic area plus characteristic skin lesions plus response to antifungal therapy for penicillosis
PCP	A plus B: (A) compatible clinical syndrome, (B) microscopic or histological demonstration of <i>P. carinii</i> cysts in a pulmonary specimen	A plus B plus C plus D plus E: (A) dyspnea or cough, or fever progressive over >1 week, (B) diffuse chest x-ray abnormality or, if on inhalational pentamidine, diffuse upper lung field abnormality, (C) evidence of hypoxia, (D) not suggestive of bacterial pneumonia (i.e., not purulent sputum or hemoptysis, no bacterial pathogen identified in blood or bronchial wash), (E)

		response to PCP treatment
<i>Pneumocystis carinii</i> , extrapulmonary	Compatible symptoms, plus microscopy	None
Pneumonia, recurrent bacterial	Both pneumonia episodes must occur after enrollment and satisfy criteria (A) plus (B) plus (C). The recurrent pneumonia must also satisfy criteria (D) plus (E): (A) Signs and symptoms suggestive of bacterial pneumonia, (B) focal CXR abnormality compatible with bacterial pneumonia, (C) identification of a bacterial pathogen by positive blood culture, positive bronchoscopic sputum culture, detection of Legionella or pneumococcal antigen in urine or blood or diagnostic serologic findings, (D) the second pneumonia had onset of symptoms <365 days after the first episode, (E) there is strong evidence that the first episode was cured such as an intervening clear CXR or absence of symptoms after >1 month off antibacterials effective against pathogens commonly producing pneumonia	Both pneumonia episodes must occur after enrollment and satisfy criteria (A) plus (B) plus (C). The recurrent pneumonia must also satisfy criteria (D) plus (E): (A) Signs and symptoms suggestive of bacterial pneumonia, (B) focal CXR abnormality compatible with bacterial pneumonia, (C) diagnosed by a doctor, physicians' assistant or nurse practitioner, (D) the second pneumonia had onset of symptoms <365 days after the first episode, (E) there is strong evidence that the first episode was cured such as an intervening clear CXR or absence of symptoms after >1 month off antibacterials effective against pathogens commonly producing pneumonia
PML (progressive multifocal leukoencephalopathy)	A or B: (A) positive histology, (B) compatible clinical and radiologic course and positive CSF PCR for JK virus	A plus B plus C: (A) Consistent symptoms, (B) brain image consistent with PML, (C) no response to toxo treatment or toxoplasma seronegative
<i>Rhodococcus equi</i> disease	Clinical evidence of invasive infection plus microbiologic identification of the organism in the affected tissue or blood	None
Salmonella septicemia, recurrent	Both episodes must occur after enrollment and met	None

	<p>criterion (A). The second episode must meet criteria (B) and C: (A) Positive blood or tissue culture, (B) the second septicemia had onset of symptoms <365 days after the first episode, (C) the second septicemia must be due to a different Salmonella serotype or there must be strong evidence that the first episode was cured such as a negative blood culture off effective antibacterials for >1 week or absence of symptoms off antibacterials for >1 month</p>	
Toxoplasmosis of brain	Microscopy	A plus B plus C: (A) Symptoms of focal intracranial abnormality or decreased consciousness, (B) brain image consistent with lesion(s) enhanced by contrast, (C) positive toxoplasma serology or responds to treatment clinically or by scan
NEOPLASMS		
Cervical carcinoma, invasive	Histology (NOT carcinoma-in-situ)	None
Kaposi sarcoma, (mucocutaneous or visceral)	Histology	Highly typical appearance and persistence for >1 month
Lymphoma, primary, of brain	Histology	Symptoms consistent with lymphoma plus at least one CNS lesion with mass effect plus lack of clinical and radiographic response to at least 2 weeks of treatment for toxoplasmosis
Lymphoma, Hodgkin's	Histology	None
Lymphoma, non-Hodgkin's, all cell types	Histology	None
NEUROLOGICAL		
HIV encephalopathy (including AIDS Dementia Complex)	None	Cognitive or motor dysfunction interfering with usual activity, progressive over weeks or months plus no other condition to explain the findings plus brain image

		obtained and suggests no other causes plus grade 2 or worse impairment in at least 2 domains by NARS (see below) excluding abnormal domains at trial entry. (For persons with abnormal domains at entry worsening by at least two grades meets criteria.)
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Abbreviated NARS (Neuropsychiatric AIDS Rating Scale) Grading for HIV Encephalopathy
Adapted from: Price RW, Brew BJ. The AIDS dementia complex. J Infect Dis 1988; 158 (5): 1079-83, and Hughes CP, Berg L, Danziger WL. A new clinical scale for the staging of dementia. Brit J Psych 1982; 140: 566-92.

Cognitive-Behavioral Domains						
NARS stage	Orientation	Memory	Motor	Behavior	Problem solving	Activities of daily living
0.5	fully oriented	complains of memory problems	fully ambulatory slightly slowed movements	normal	has slight mental slowing	slight impairment in business dealings
1	fully oriented, may have brief periods of "spaciness"	mild memory problems	balance, coordination and handwriting difficulties	more irritable, labile or apathetic, withdrawn	difficulty planning and completing work	can do simple daily tasks, may need prompting
2	some disorientation	memory moderately impaired, new learning impaired	ambulatory but may require walking aid	some impulsivity or agitated behavior	severe impairment, poor social judgement, gets lost easily	needs assistance with ADLs
3	frequent disorientation	severe memory loss, only fragments of memory remain	ambulatory with assistance	may have organic psychosis	judgement very poor	cannot live independently
4	confused and disoriented	virtually no memory	bedridden	mute and unresponsive	no problem solving ability	nearly vegetative

APPENDIX B: SUB-STUDY TESTING PERFORMED ON SPECIMENS SENT TO SERACARE

As noted in the Schedule of Events in section 6.2.2, specimens are collected and shipped to the central repository, SeraCare, for sub-study testing. These tables do not reflect additional events to be performed at the site. The results of these sub-study tests are not used for patient management and are not sent back to the sites. These tests are for research purposes. The following tables provide a breakdown of the testing that will be performed on the specimens that are collected and shipped to SeraCare as shown in the Schedule of Events in section 6.2.2.

HCV Co-infected (All HCV+ Patients in All Clusters)

Years:	Year 0	Year 1														Years 2 & 3	Years 4 & 5
Weeks:	Pre-Tx	Day 0	Week 1	2	4	6	8	10	12	16	20	26	36	44	52	53-156	157-260
HCV (Oldach)																	
HCV RNA ²	X								X			X			X	Y2	
HCV Genotype	X																
HCV Quasispecies	X								X			X			X	Y2	
HCV Ab-RIBA	X																
CTL (Brander)																	
HCV Elispot	X								X			X			X	Y2	

HBV Co-infected (All HBV+ Patients in All Clusters)

Years:	Year 0	Year 1														Years 2 & 3	Years 4 & 5
Weeks:	Pre-Tx	Day 0	Week 1	2	4	6	8	10	12	16	20	26	36	44	52	53-156	157-260
HBV (Terrault)																	
HepBSAb	X								X			X			X	Y2	
HepBSAg	X								X			X			X	Y2	
HepB DNA	X								X			X			X	Y2	
Anti HDV	X								X			X			X	Y2	

Sub-Study Cluster # 1 (UCSF, Cedar’s Sinai, Umd, Tulane, Cleveland Clinic, Johns Hopkins)

Years:	Year 0	Year 1														Years 2 & 3	Years 4 & 5
Weeks:	Pre-Tx	Day 0	Week 1	2	4	6	8	10	12	16	20	26	36	44	52	53-156	157-260
Co-Pathogen CTL (Brander)																	
Co-Pathogen ELISPOT	X								X			X			X	Y2	
HHV8 (Martin)																	
HHV8 Ab	X								X			X			X	Y2	
HHV8 Viral Load (plasma)	X								X			X			X	Y2	
HHV8 PBMC Associated Viral Load	X								X			X			X	Y2	
HHV8 Saliva Viral Load	X								X			X			X	Y2	
Herpes Viruses (Rinaldo)																	
TaqMan Viral Load (CMV, HHV6, EBV)	X								X			X			X	Y2	
NASBA (CMV pp67) assay	X								X			X			X	Y2	
RT-PCR (5 EBV RNAs) assay	X								X			X			X	Y2	
Transplant Immunology (Stock)																	
MLC (UCSF only real time; others stored)	X								X			X			X	Y2	
Donor tissue or blood	X																
Specimen Storage																	
Fresh blood shipped to SeraCare ¹	X								X			X			X	Y2	
HIVAN (Klotman) – UCSF Only																	
Biopsy Tissue – All kidney rejection episodes																	
HPV (Palefsky) - UCSF, UMD, Cedars-Sinai only																	
Anal PAP	X ²											X			X	X ³	X ³
Central pathology read for all kidney and liver biopsies post-transplant																	
Biopsy Slides																	

Sub-Study Cluster # 2 (Pitt, Washington, Drexel, Penn, U Va, Rush)

Years:	Year 0	Year 1														Years 2 & 3	Years 4 & 5
Weeks:	Pre-Tx	Day 0	Week 1	2	4	6	8	10	12	16	20	26	36	44	52	53-156	157-260
Co-Pathogen CTL (Brander)																	
Co-Pathogen ELISPOT	X								X			X			X	Y2	
HHV8 (Martin)																	
HHV8 Ab	X								X			X			X	Y2	
HHV8 Viral Load (plasma)	X								X			X			X	Y2	
HHV8 PBMC Associated Viral Load	X								X			X			X	Y2	
HHV8 Saliva Viral Load	X								X			X			X	Y2	
Herpes Viruses (Rinaldo)																	
TaqMan Viral Load (CMV, HHV6, EBV)	X								X			X			X	Y2	
NASBA (CMV pp67) assay	X								X			X			X	Y2	
RT-PCR (5 EBV RNAs) assay	X								X			X			X	Y2	
Specimen Storage																	
Fresh blood shipped to SeraCare ¹	X								X			X			X	Y2	
Central pathology read for all kidney and liver biopsies post-transplant																	
Biopsy Slides																	

Sub-Study Cluster # 3 (Mt. Sinai, Georgetown, Emory, Chicago, Cincinnati, Columbia, U Miami, Beth Israel)

Years:	Year 0	Year 1														Years 2 & 3	Years 4 & 5
Weeks:	Pre-Tx	Day 0	Week 1	2	4	6	8	10	12	16	20	26	36	44	52	53-156	157-260
Co-Pathogen CTL (Brander)																	
Co-Pathogen ELISPOT	X								X			X			X	Y2	
HHV8 (Martin)																	
HHV8 Ab	X								X			X			X	Y2	
HHV8 Viral Load (plasma)	X								X			X			X	Y2	
HHV8 PBMC Associated Viral Load	X								X			X			X	Y2	
Herpes Viruses (Rinaldo)																	
TaqMan Viral Load (CMV, HHV6, EBV)	X								X			X			X	Y2	
NASBA (CMV pp67) assay	X								X			X			X	Y2	
RT-PCR (5 EBV RNAs) assay	X								X			X			X	Y2	
Specimen Storage																	
Fresh blood shipped to SeraCare ¹	X								X			X			X	Y2	
Central pathology read for all kidney and liver biopsies post-transplant																	
Biopsy Slides																	
HIVAN (Klotman) – Mt. Sinai Only																	
Biopsy Tissue – All kidney rejection episodes																	
HPV (Palefsky) – Mt. Sinai liver, Columbia, and Beth Israel Deaconess Only																	
Anal PAP	X ²															X ³	X ³

1. Stored blood includes specimen for future HIV Phenotyping, Cytokine Flow Cytometry, ELISPOT, and latent reservoir assays with additional funding.
2. At the time of organ availability, obtain peri-transplant anal pap if it has been > 6 months since last anal pap.
3. Every 6 months

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