Protocol Synopsis

Title	Impact of CCR5 Blockade in HIV+ Kidney Transplant Recipients
Short Title	HIVTR CCR5
Clinical Phase	Phase II
Number of Sites	10
IND Sponsor/Number	NIAID DAIDS
Study Objectives	The primary clinical objectives are to evaluate the: 1. Impact of CCR5 blockade (maraviroc, MVC) on renal function at week 52 post-transplant. 2. Overall safety and tolerability of CCR5 blockade in the HIV+ kidney transplant recipient. The secondary clinical objectives are to evaluate the: 1. Impact of CCR5 blockade (maraviroc, MVC) on inflammation in the graft at week 26 and week 52 post-transplant. 2. Impact of CCR5 blockade on long term kidney function in the HIV positive kidney transplant recipient at months 3, 6, 9 and years 1, 2, 3. 3. Impact of the addition of CCR5 blockade to cART and immunosuppression on HIV persistence following kidney transplantation 4. Impact of CCR5 blockade on the incidence and severity of rejection 5. Incidence of HIV infection/HIV nephropathy (HIVAN) in the kidney allograft 6. Safety profiles with use of CCR5 blockade 7. Pharmacokinetics and impact of CCR5 blockade exposure to CNIs The primary mechanistic objectives are to: 1. Define immunologic parameters associated with rejection in the HIV positive recipient (versus HIV+ non-rejectors) 2. Determine the impact of CCR5 blockade on the immunologic profiles in the HIV positive recipient.
Study Design	Prospective, multi-center, double-blind phase II study
Primary Clinical Endpoints	1. Measured glomerular filtration rate at 52 weeks by iohexol clearance. 2. Graft loss, toxicities ≥ Grade 3 and/or permanent treatment discontinuation within the first 52 weeks post-transplant.
Secondary Clinical Endpoints	1. Inflammation in the graft a. CD45 gene expression (PTPRC) on the FFPE kidney biopsy sample at 26 weeks post-transplant. b. CD45 quantitative IHC on the FFPE sample at 26 weeks post-transplant.

	c. Gene expression profiling using the 11-gene tCRM module on FFPE biopsy shaves at 26 weeks and the 11-gene uCRM module on urine cell pellets at 26 weeks and 52 weeks post-transplant. 2. Measures of Renal Function and Injury (months 3, 6, 9, years 1, 2, 3) a. Proportion of participants with eGFR by CKD-EPI, cystatin C, and CKD-cystatin C, < 60 mL/min/1.73 m^2. b. Proportion of participants with defined CKD stage 4 or 5. c. Mean calculated eGFR by CKD-EPI, cystatin C, and CKD-cystatin C. d. The slope of eGFR by CKD-EPI, cystatin C, and CKD-cystatin C variable models over time based on serum creatinine. 3. HIV persistence a. HIV reactivation (frequency of CD4+ T cells producing HIV multiply spliced RNAs upon TCR stimulation) b. HIV DNA and RNA in peripheral blood CD4+ T cells c. Plasma HIV RNA levels (single copy assay) 4. Histologic and Serologic Evidence of Rejection a. Incidence of clinically suspected and biopsy proven acute rejection within the first 52 weeks and 156 weeks as defined by histologic evidence of rejection and graft dysfunction as identified on central read of biopsy slides. b. The incidence of acute cellular rejection grade equal to or > than IA, by the Banff 2007 criteria, within the study period (3 years) as identified on central read of biopsy slides. c. The severity of first and highest grade of acute cellular rejection within the study period. d. The incidence of antibody mediated rejection. e. The prevalence of de novo anti-donor HLA antibodies at 52 weeks. 5. Analysis of HIV infection in the renal allograft and HIVAN a. Histology/in situ hybridization to assess HIV infection in the renal allograft 6. Safety Profile measures a. Death b. Graft loss c. Incidence of all adverse events (AEs) >/= Grade 3 d. Incidence of serious adverse events (SAEs) >/= Grade 3 e. Incidence of opportunistic infections or neoplasms f. Incidence of non-opportunistic infections requiring hospitalization or systemic therapy 7. Pharmacokinetics a. Calcineurin inhibitor trough levels and AUC for participants on maraviroc versus placebo b. AUC and trough levels of CCR5 blockade (maraviroc)

Mechanistic Endpoints	1) Define immunologic parameters associated with rejection in the HIV+ participants by comparing the following parameters in those who experience acute rejection in the first 6 months and those who do not have acute rejections (samples collected prior to and at the time of rejection will be analyzed and compared): a. Circulating leukocyte subsets and their activation phenotypes b. Anti-donor alloimmune responses measured by frequency of total donor-reactive T cells and donor-reactive effector T cells c. Frequencies of T cells with cross-reactivity between donor alloantigens and HIV, CMV, and EBV antigens d. DSA in serum e. Gene expression in for-cause biopsies by RNASeq analysis f. Histological analysis for evidence of cellular and antibody mediated rejection mechanisms. 2) Determine the impact of CCR5 blockade on the immunologic profiles in the HIV + recipients by comparing results from MVC-treated and those receiving standard of care (SOC). Change of the various parameters after initiation of MVC or SOC will be monitored and these changes will be compared between the two groups (Samples collected pre transplant and at various time points post-transplant will be analyzed): a) Change in circulating leukocyte subsets and their activation phenotypes from pre-transplant baseline b) Change in CCR5 and other chemokine receptor expression on subsets of various circulating leukocytes from pre-transplant baseline c) Change on anti-donor alloimmune responses measured by frequency of total donor-reactive T cells and donor-reactive effector T cells d) Change in frequencies of T cells with cross-reactivity between donor alloantigens and HIV, CMV, and EBV antigens after transplant. e) DSA in serum f) Histological analysis of for-cause biopsies for mechanisms of rejection
Accrual Objective	130 randomized (65 maraviroc and 65 placebo)
Study Duration	5 years (all participants followed for 1 – 3 years depending on enrollment date)

Treatment Description	Prior to transplantation, participants should be on a stable non-protease inhibitor-based regimen. At the time of transplantation, eligible participants will be randomized 1:1 to add maraviroc or placebo. Initiation of study drug will occur during the admission for transplantation, prior to transplant. Arm 1: Maraviroc Arm 2: Placebo Dose: Initial dose of 300 mg twice daily (150mg twice daily if co-prescribed with a potent CYP3A inhibitor or 600mg twice daily if co-prescribed with a potent CYP3A inducer). Will be modified if GFR < 30, if co-prescribed with a potent CYP3A inhibitor or inducer, or if the calcineurin inhibitor used for maintenance immunosuppression is changed to cyclosporine (which is only allowed for tacrolimus toxicity). Once GFR >= 30, the dose should be returned to the non-renal dosage. If GFR is consistently fluctuating (especially immediately post-transplant), the site investigator may choose when to resume normal dosing of study products based on clinical assessment of stability.
Inclusion Criteria	1) Participant is able to understand and provide informed consent 2) Documented HIV infection (by any licensed ELISA and confirmation by Western Blot, positive HIV ab IFA, or documented history of detectable HIV-1 RNA). 3) Participant is ≥ 18 years old. 4) CD4+ T-cell count >/= 200/µL at any time in the 26 weeks prior to enrollment. 5) Most recent HIV-1 RNA < 50 copies RNA/mL. Eligibility at the time of enrollment will be determined based on the most recent HIV-1 RNA, not more than 26 weeks prior to enrollment. Subjects who require a switch in cART regimen to become study eligible must also have an eligible HIV-1 RNA result post change in cART. 6) Participant meets standard listing criteria for placement on transplant waiting list. 7) For participants with an HIV+ deceased donor: a) No active opportunistic infections. b) Concurrence by the study team that based on medical history and ART, viral suppression can be achieved in the recipient post-transplant. c) Must be enrolled in an IRB approved research protocol that fulfills the requirements of the DHHA Hope Act Policy (see section 9.1.2).

	d) HIV+ deceased donor must have no evidence of invasive opportunistic complications of HIV infection, and must have a pre-implant biopsy. 8) Antiretroviral (ARV) Use: Participant is on a stable cART regimen for at least 3 months prior to enrollment (unless changes are made due to toxicity, drug interactions, convenience or to an eligible non-protease inhibitor-based regimen). Switch should not be due to virologic failure. A regimen consisting of 2 NTRTIs and an integrase inhibitor is preferred due to minimal drug interaction but any non-protease inhibitor regimen may be used. • If on a protease inhibitor based regimen, participant must be switched to a non-protease inhibitor-based regimen based on lack of any prior drug resistance or antiretroviral-treatment failure, and be willing to remain on indefinitely unless a change is medically necessary. Participants who need to be switched must have been on a stable cART regimen for at least 3 months prior, and must have an eligible HIV-1 RNA result post change in cART. • If already on a stable non-protease inhibitor-based regimen, participant is willing to remain on this regimen indefinitely unless a change in regimen is medically indicated. • If untreated, must initiate and be willing to remain on indefinitely a non-protease inhibitor-based antiretroviral regimen unless a change is medically necessary. 9) No known allergy or intolerance to components of MVC or its formulation. 10) No known contraindication to MVC. 11) Female participants of child-bearing potential must have a negative serum beta-HCG pregnancy test within 30 days of randomization.
Exclusion Criteria	1. Participant is currently on maraviroc. 2. Participant needs multi-organ transplant. 3. Participant has a live donor who is HIV+. 4. Participant is unable to switch to a non-protease inhibitor-based cART regimen. 5. Participant has received immunosuppressant medication in the 6 months prior to enrollment. Note: Low dose maintenance steroids (</= 10 mg per day of prednisone, or equivalent strength steroid) will not be considered immunosuppression. 6. Opportunistic Complication History: Any history of progressive multifocal leukoencephalopathy (PML), chronic intestinal cryptosporidiosis of > 1 month duration, or primary CNS lymphoma. Note: History of pulmonary

	coccidiodomycosis will be treated per local site policy regarding this infection in HIV negative transplant candidates, generally requiring a 5-year disease-free interval. 7. Participant has a history of any neoplasm except for the following: resolved 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. 8. Substance use that in the opinion of the investigator would interfere with compliance with the study requirements. 9. Participant is pregnant or breastfeeding. Note: Participants who become pregnant post-transplant will continue to be followed in the study and will be managed per local site practice. Women that become pregnant should not breastfeed. 10. Participant has used IL-2 or GM-CSF in the prior six months. 11. Participant has received interferon-alpha therapy in the prior 12 weeks. 12. Use of investigational drugs within 4 weeks of enrollment. 13. Past or current medical problems or findings from medical history, physical examination or laboratory testing that are not listed above, which, in the opinion of the investigator, may pose additional risks from participation in the study, may interfere with the participant's ability to comply with study requirements or that may impact the quality or interpretation of the data obtained from the study.
Participant Stopping Rules	**Treatment discontinuation** 1. Participant meets criteria to discontinue study treatment (MVC or placebo) 2. The investigator no longer believes continuing study treatment is in the best interest of the participant. 3. Participant refuses to continue study treatment. 4. Treatment is held or discontinued for clinical reasons for greater than 60 days. **Study discontinuation** 1. The participant elects to withdraw consent from all future study activities, including follow-up. 2. The participant is "lost to follow-up" (i.e., no further follow-up is possible because attempts to reestablish contact with the participant have failed). 3. For those on the waiting list, confirmed or predicted failure to receive transplant by the end of year 4.

	4. Study closed by sponsor or FDA. 5. Despite being randomized and receiving study treatment, participant did not receive a transplant as expected.
Study Stopping Rules	The study may be discontinued at any time by the EC/IRB, NIAID, the pharmaceutical supporter(s) or designee, the FDA, or other government entities as part of their duties to ensure that research participants are protected. In addition, the incidence of specific safety-related events of particular concern will be continuously monitored throughout the study to determine if any of their observed subject-based incidence rates exceed a threshold incidence rate of concern pre-specified for each particular event. These events and their corresponding thresholds of concern are: 1. During year 1 of follow-up, death due to any reason except accidental death above 10%. 2. During year 1 of follow-up, graft loss due to any reason except accidental death above 16%. 3. During year 1 of follow-up, site-reported treated acute rejection above 35%