PROTOCOL RTB-008

HOPE in Action Prospective Multicenter, Clinical Trial of HIV+ Deceased Donor Kidney Transplants for HIV+ Recipients

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National Institute of Allergy and Infectious Diseases

SITE INVESTIGATOR SIGNATURE PAGE	
Protocol Number: RTB-008	**Version Number/Date: 6.0/ February 1, 2021**

Protocol Title: *Prospective Multicenter, Clinical Trial of HIV+ Deceased Donor Kidney Transplants for HIV+ Recipients*

IND/IDE Sponsor: The National Institute of Allergy and Infectious Diseases (NIAID)

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I confirm that I have read the above protocol in the latest version. I understand it, and I will work according to the principles of Good Clinical Practice (GCP) as described in the United States Code of Federal Regulations (CFR) – 45 CFR part 46 and 21 CFR parts 50, 56, and 312, 812 and in the International Conference for Harmonisation (ICH) document entitled *Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2)*. Further, I will conduct the study in keeping with local legal and regulatory requirements.

As the site Principal Investigator, I agree to carry out the study by the criteria written in the protocol and understand that no changes can be made to this protocol without the written permission of the IRB and NIAID.

*[*The site Principal Investigator should sign and date at the indicated location below. A written signature/date is acceptable (e.g., scanned and sent via email as a PDF version). An electronic signature is also acceptable (e.g., sent via email as a PDF version).]*

_____

Site Principal Investigator (Print)

_____ _____

Site Principal Investigator (Signature) **Date**

Protocol Synopsis

Title	Prospective Multicenter, Clinical Trial of HIV+ Deceased Donor Kidney Transplants for HIV+ Recipients
Short Title	HOPE in Action Multicenter Kidney Study
Number of Sites	~29 clinical sites
Study Objectives	The primary objective is to determine if an HIV+ kidney donor transplant is safe with regards to major transplant-related and HIV-related complications. The secondary objectives are to compare other clinical outcomes between HIV+ transplant recipients of kidneys from HIV+ and HIV- donors. Exploratory objectives are to explore HIV-superinfection, changes in the HIV latent reservoir, ethical, and patient reported psychosocial outcomes.
Study Design	Prospective multicenter, interventional clinical trial
Accrual Objective	Full Study Arm: 100 HIV+ transplant recipients of kidneys from HIV+ deceased donors (HIV D+/R+) 100 HIV+ transplant recipients of kidneys from HIV- deceased donors (HIV D-/R+) Observational Arm: Up to 200 HIV+ kidney transplant recipients of HIV- deceased donors (HIV D-/R+) in a nested observational cohort
Study Duration	3 years accrual + 1 year minimum (up to 4 years) follow-up post-transplant
Primary Endpoint(s)	The primary endpoint of the study is time to a composite event of all-cause-mortality, graft failure, serious adverse event, HIV breakthrough, HIV virologic failure, or opportunistic infection.
Secondary Endpoint(s)	1. Patient survival 2. Graft survival 3. Serious adverse events 4. Graft rejection: incidence, severity (biopsy month 6, year 1, and for cause) 5. Graft function Glomerular filtration rate (GFR) (months 3, 6, 9, years 1, 2, 3) a. Proportion of participants with eGFR by CKD-EPI < 60 mL/min/1.73 m2 b. Mean calculated eGFR by CKD-EPI c. The slope of eGFR by CKD-EPI, over time based on serum creatinine 6. Analysis of renal diseases including HIV-related renal disease (HIV-AN, HIVICK, HIV-associated FSGS, HIV-associated thrombotic angiopathy) and HIV infection in the renal allograft as identified on central read of biopsy slides a. Protocol biopsy at 6 months and 1 year with histologic findings as identified on central read of biopsy slides b. APOL1 variant testing in donors and recipients 7. HIV disease progression:

	a. HIV plasma RNA at weeks 1, 2, 3, 4, 8, 13, 26, 39, 52, and every 6 months through follow-up b. Absolute CD4 count and %CD4 at weeks 4, 8, 13, 26, 39, 52, and every 6 months through follow-up 8. Development of antiretroviral resistance and X4 tropic virus: resistance testing and viral tropism testing with any episodes of HIV breakthrough 9. Bacterial, fungal, viral and other opportunistic infections: captured during hospitalizations and/or by retrospective medical record view at all scheduled study visits through end of follow-up 10. Incidence of surgical and vascular complications transplant during the first year of follow-up 11. Incidence of other viral-related malignancies (HPV-related tumors, EBV-related tumors, KSHV related tumors, hepatocellular carcinoma associated with HBV and/or HCV) as determined by local pathology 12. Prevalence of donor-specific antibody at one year in central lab 13. Time to composite event of all-cause-mortality, graft failure, renal allograft rejection, HIV breakthrough, virologic failure, or AIDS defining illness (composite event from prior version of the protocol)
Exploratory Endpoints	1. Incidence of systemic HIV-superinfection in blood in recipients 2. Incidence of tissue specific HIV-superinfection measured by HIV in the allograft 3. Changes in HIV latent reservoir populations by viral outgrowth and next-generation sequencing of resting CD4+ T-cells 4. Quality of Life measures and patient reported outcome measures
HIV+ Deceased Donor Criteria	1. Donation after brain death or cardiac death. 2. HIV+ donors have confirmed or suspected HIV infection* (by medical record history and/or a licensed HIV test.) If HIV infection is diagnosed during the donor evaluation process, a second confirmatory test will be required). 3. Donor has no active opportunistic infections, neoplasms, and or severe acute retroviral syndrome; if previous history of an opportunistic infection, donor has received appropriate treatment. 4. Donor may have any HIV-1 RNA viral load provided a safe, tolerable and effective post-transplant antiretroviral regimen to be prescribed for the recipient is anticipated, described and justified. 5. Donors with active hepatitis C virus infection (detectable HCV nucleic acid by licensed assay in a CLIA certified lab) are acceptable based on local site practice.
Recipient Inclusion Criteria	1. Participant meets the standard criteria for kidney transplant at the local center. 2. Participant is able to understand and provide informed consent. 3. Participant meets with an independent advocate per the HOPE Act Safeguards and Research Criteria. 4. Documented HIV infection (by any licensed assay, or documented history of detectable HIV-1 RNA). 5. Participant is ≥ 18 years old.

	6. Opportunistic complications: prior history of certain opportunistic infections is not an exclusion if the participant has received appropriate therapy and has no evidence of active disease. Medical record documentation should be provided whenever possible.* 7. CD4+ T-cell count: ≥ 200/µL 8. HIV-1 RNA is below 50 copies RNA/mL.* Viral blips between 50-400 copies will be allowed as long as there are not consecutive measurements > 200 copies/mL. *Organ recipients who are unable to tolerate ART due to organ failure or recently started ART may be eligible despite a detectable viral load if safe and effective ART to be used by the recipient after transplantation is described. 9. Participant is willing to comply with all medications related to their transplant and HIV management. 10. For participants with a history of aspergillus colonization or disease, no current clinical evidence of active disease. 11. The participant must have or be willing to start seeing a primary medical care provider with expertise in HIV management. 12. Agreement to use contraception (see section 4.3 for further details). 13. Participant is not suffering from significant wasting (e.g. body mass index < 21) thought to be related to HIV disease.
Recipient Exclusion Criteria	1. Participant has a history of progressive multifocal leukoencephalopathy (PML), or primary CNS lymphoma.* 2. Participant is pregnant or breastfeeding. (Note: Participants who become pregnant post-transplant will continue to be followed and will be managed per local site practice. Women that become pregnant should not breastfeed.) 3. 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. *These eligibility criteria align with the eligibility in the H*uman Immunodeficiency Virus (HIV) Organ Policy Equity (HOPE) Act Safeguards and Research Criteria for Transplantation of Organs Infected with HIV.*
Study pausing rule	Study enrollment will be paused for Data Safety and Monitoring Board review if any of the following adverse events occur at an unexpected rate: one-year graft loss, rejection requiring hospitalization, complications of kidney biopsy; HIV breakthrough or persistent HIV virologic failure. The study will be stopped if the Data Safety and Monitoring Board determines that there are unexpected fatal, or life threatening adverse events related to the use of HIV+ donor or study procedures.

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Table of Contents

Glossary of Abbreviations

AIDS	Acquired Immunodeficiency Syndrome
AE	Adverse Event
AR	Acute Rejection
ART	Antiretroviral therapy
ARV	Antiretroviral
CDC	Centers for Disease Control
CFR	Code of Federal Regulations
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration equation
CLIA	Clinical Laboratory Improvement Amendments
CMV	Cytomegalovirus
CNS	Central Nervous System
CRAG	Cryptococcal Antigen
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DAIT	Division of Allergy, Immunology, and Transplantation
DRAI	Donor Risk Assessment Interview
DSA	Donor Specific Antibodies
DSMB	Data Safety Monitoring Board
EBV	Epstein Barr Virus
eGFR	Estimated Glomerular Filtration Rate
ELISA	Enzyme-Linked Immunosorbent Assay
ESKD	End Stage Kidney Disease
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HIV-AN	Human Immunodeficiency Virus Associated Nephropathy
HIV-SI	Human Immunodeficiency Virus Superinfection
HIV D+	Human Immunodeficiency Virus Infected Deceased Donor
HIVICK	Human Immunodeficiency Virus Associated Immune Complex Kidney Disease
HOPE Act	HIV Organ Policy Equity Act

HPV	Human Papilloma Virus
HRSA	Health Resources and Services Administration
ICH	International Conference on Harmonization
IRB	Institutional Review Board
IS	Immunosuppression
IVDU	Intravenous Drug Use
KSHV	Kaposi's Sarcoma Associated Herpesvirus
MOP	Manual of Procedures
NIAID	National Institute of Allergy and Infectious Diseases
NOTA	National Organ Transplantation Act
OCT	Optimal Cutting Temperature
OI	Opportunistic Infection
OPO	Organ Procurement Organization
OPTN	Organ Procurement Transplantation Network
PI	[Site] Principal Investigator
PBMC	Peripheral Blood Mononuclear Cells
PCP	Pneumocystis Pneumonia
PML	Progressive Multifocal Leukoencephalopathy
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Suspected Adverse Reaction
SOP	Standard Operating Procedure
SUSAR	Serious Unexpected Suspected Adverse Reaction
UNOS	United Network of Organ Sharing
USRDS	United States Renal Data System

Study Definitions Page

Acute Cellular Mediated Rejection	Renal: A clinical and histologic event that meets the Banff 2015 criteria for acute cellular rejection [44].
Acute Renal Allograft Rejection	Acute kidney injury defined as a rise in serum creatinine of at least 0.3 mg/dL (26.5 micromol/L) over a 48-hour period and/or ≥1.5 times the baseline value presumed to have occurred in the seven previous days (according to The Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guidelines). PLUS Histologic evidence of rejection on biopsy meeting Banff 2015 criteria and confirmed on central read of biopsy slides.
Antibody Mediated Rejection	A clinical and histologic event that meets the Banff 2015 criteria for antibody mediated rejection.
ARV Drug Resistance	Presence of major drug resistance mutations in reverse transcriptase, protease, and integrase as determined by any licensed assay in a CLIA certified lab.
Banff 2015 Scoring Criteria (Kidney)	**1. Normal biopsy or nonspecific changes** **2. Antibody-mediated changes** (may coincide with categories 3, 4, 5 and 6) **Acute/active ABMR; all three features must be present for diagnosis** Histologic evidence of acute tissue injury, including one or more of the following: • Microvascular inflammation (g>0 in the absence of recurrent or *de novo* glomerulonephritis and/or ptc>0) • Intimal or transmural arteritis (v>0)4 • Acute thrombotic microangiopathy, in the absence of any other cause • Acute tubular injury, in the absence of any other apparent cause Evidence of current/recent antibody interaction with vascular endothelium, including at least one of the following: • Linear C4d staining in peritubular capillaries (C4d2 or C4d3 by IF on frozen sections, or C4d>0 by IHC on paraffin sections) • At least moderate microvascular inflammation ([g + ptc]≥2) • Increased expression of gene transcripts in the biopsy tissue indicative of endothelial injury, if thoroughly validated Serologic evidence of donor-specific antibodies (DSAs) (HLA or other antigens) **Chronic, active ABMR; all three features must be present for diagnosis** Histologic evidence of chronic tissue injury, including one or more of the following: • Transplant glomerulopathy (TG) (cg>0), if no evidence of chronic thrombotic microangiopathy • Severe peritubular capillary basement membrane multilayering (requires EM) • Arterial intimal fibrosis of new onset, excluding other causes

Evidence of current/recent antibody interaction with vascular endothelium, including at least one of the following:

- Linear C4d staining in peritubular capillaries (C4d2 or C4d3 by IF on frozen sections, or C4d>0 by IHC on paraffin sections)
- At least moderate microvascular inflammation ([g + ptc]≥2)
- Increased expression of gene transcripts in the biopsy tissue indicative of endothelial injury, if thoroughly validated

Serologic evidence of DSAs (HLA or other antigens)

C4d staining without evidence of rejection; all three features must be present for diagnosis

- Linear C4d staining in peritubular capillaries (C4d2 or C4d3 by IF on frozen sections, or C4d>0 by IHC on paraffin sections)
- g=0, ptc=0, cg=0 (by light microscopy and by EM if available), v=0; no TMA, no peritubular capillary basement membrane multilayering, no acute tubular injury (in the absence of another apparent cause for this)
- No acute cell-mediated rejection (Banff 97 type 1A or greater) or borderline changes)

3. **Borderline changes**: 'Suspicious' for acute T-cell mediated rejection (may coincide with categories 2 and 5 and 6). This category is used when no intimal arteritis is present, but there are foci of mild tubulitis (t1, t2, or t3) with minor interstitial infiltration (i0 or i1) or interstitial infiltration (i2, i3) with mild (t1) tubulitis.
4. **T-cell mediated rejection** (may coincide with categories 2 and 5 and 6).

   Acute T-cell-mediated rejection (Type/Grade):

   IA Cases with significant interstitial infiltration (>25% of parenchyma affected, i2 or i3) and foci of moderate tubulitis (t2)

   IB Cases with significant interstitial infiltration (>25% of parenchyma affected, i2 or i3) and foci of severe tubulitis (t3)

   IIA Cases with mild-to-moderate intimal arteritis (v1), with or without interstitial inflammation and tubulitis

   IIB Cases with severe intimal arteritis comprising >25% of the luminal area (v2), with or without interstitial inflammation and tubulitis

   III Cases with 'transmural' arteritis and/or arterial fibrinoid change and necrosis of medial smooth muscle cells with accompanying lymphocytic inflammation (v3)

   Chronic active T-cell mediated rejection

   'Chronic allograft arteriopathy' (arterial intimal fibrosis with mononuclear cell infiltration in fibrosis, formation of neo-intima)
5. **Interstitial fibrosis and tubular atrophy**

   Grade I Mild interstitial fibrosis and tubular atrophy (<25% of cortical area)

   Grade II Moderate interstitial fibrosis and tubular atrophy (26-50% of cortical area)

	Grade III Severe interstitial fibrosis and tubular atrophy/loss (>50% of cortical area) **6. Other:** Changes not considered to be due to rejection-acute and/or chronic; may include isolated g, cg, or cv lesions and coincide with categories 2, 3, 4, and 5.
Biopsy Proven Rejection	Histologic evidence of rejection on biopsy meeting Banff 2015 criteria.
Chronic Active Hepatitis B	A history of a positive hepatitis B surface antigen and/or positive hepatitis B DNA PCR test. Participants with a positive surface antibody or positive core antibody only are NOT considered to have active infection.
Chronic dialysis	Need for renal replacement therapy for more than 90 days
Clinically Suspected and Treated Rejection	Clinical suspicion for and treatment for renal allograft rejection for > 2 days, including but not limited to increases in the doses of immunosuppressive medications in the absence of a biopsy if the managing physician feels a biopsy is unsafe.
CMV Disease	**Primary CMV disease** refers to a patient with a positive blood pp65 antigenemia, or positive blood culture, shell vial, or PCR, and who was seronegative for CMV before transplantation. **Secondary or reactivated CMV disease** refers to a patient with a positive blood pp65 antigenemia, or positive blood culture, shell vial, or PCR, and who was seropositive for CMV before transplantation. **Invasive end organ CMV disease:** 1. Signs and symptoms compatible with invasive CMV disease 2. Biopsy of visceral site with site-specific definitions for disease with histopathology consistent with CMV infection. Sites: **CMV gastrointestinal disease**: 1. Macroscopic mucosal lesions on endoscopy 2. Demonstration of CMV infection (by culture, histopathologic testing, immunohistochemical analysis, or in situ hybridization) in a gastrointestinal tract biopsy specimen. **CMV hepatitis (definite):** 1. Abnormal liver function tests (LFTs) (e.g., transaminases at least 2X the upper limit of normal for at least 2 days) 2. Histopathologic evidence of viral hepatitis on liver biopsy specimen 3. CMV identified in liver biopsy by culture, immuno-histochemistry, *in situ* hybridization or PCR. **CMV hepatitis (probable):** 1. Abnormal liver function tests (LFTs), (e.g., transaminases at least 2X the upper limit of normal for at least 2 days 2. Histopathological evidence of viral hepatitis on liver biopsy specimen **CMV neurologic disease:** 1. Signs and/or symptoms of encephalitis transverse myelitis or other diffuse CNS disease

	2. Evidence of CMV in CSF by PCR, cytospin, or culture **CMV pneumonia:** 1. Symptoms compatible with pneumonia 2. New or changing radiographic evidence of pulmonary infiltrates 3. Bronchoalveolar lavage (BAL) or lung biopsy specimen positive for CMV by culture, histopathologic testing, or immunohistology (e.g., direct fluorescent antibody staining). **CMV retinitis:** 1. Signs and/or symptoms of CMV retinitis 2. CMV retinal lesions visualized by an ophthalmologist. **CMV syndrome:** 1. CMV in blood (culture, antigen or PCR) and at least one of the following: a) Fever (>38C) b) New or increased malaise c) Leucopenia d) ≥5% atypical lymphocytes e) Thrombocytopenia f) Elevation of ALT (2X upper limit of normal)
Donor Risk Assessment Interview	Uniform interview forms used by Organ Procurement Organizations optimized for obtaining medical history, behavioral risk, and travel information for a donor of organs and/or tissues developed by experts representing donation and transplantation organizations and government agencies.
Donor Specific Antibodies	The presence of antibodies against antigens encoded by the HLA (human leukocyte antigen) complex that are expressed on the donor allograft. Techniques to determine presence and HLA specificity of DSAs may include complement dependent cytotoxicity (CDC) or flow cytometric cell based crossmatch tests and Luminex multi-analyte bead immunoassays.
Epstein Barr virus-associated smooth muscle tumors	Low grade smooth muscle neoplasm with minimal atypia and mitotic activity. Characterized mostly by spindle cell morphology but can also display primitive-looking round cell areas and prominent infiltration by T-lymphocytes. Immunohistochemistry shows consistent actin positivity and desmin in only a subset of cases. In situ hybridization for EBV early RNAs is positive in all cases. May occur in soft tissue, GI tract, lung, liver, spleen, adrenal gland and other sites.
Graft Failure (Kidney)	Any of the following events: initiation of post-donation chronic dialysis; re-transplantation; death.
HIV-Associated Renal Diseases	HIV-Associated Nephropathy HIV-Associated Focal Segmental Glomerulosclerosis, non-collapsing type HIV-Associated Immune Complex Kidney disease HIV-Associated Thrombotic Microangiopathy
HIV-Associated Nephropathy	Light microscopy:

	• Glomerular collapse, podocyte hypertrophy and hyperplasia can resemble cellular crescents, protein droplets in podocyte cytoplasm • Glomeruli can have global and/or segmental sclerosis, the latter with relative expansion of the urinary space • Tubular microcystic dilatation, variable degree of tubular atrophy can be present • Interstitial inflammation predominantly lymphocytic, can have lymphoid follicle-like infiltrate • Variable degree of interstitial fibrosis • Variable degree of arterial intimal thickening and arteriolar hyalinosis Immunofluorescence • Typically negative for immune complex type deposits, can have nonspecific glomerular staining for IgM and C3 Electron microscopy • Glomerular capillary loops collapse with wrinkled glomerular basement membrane • Podocyte enlargement, with protein droplet in the cytoplasm, vacuolization, microvillous changes, effacement of the foot processes (usually diffuse but can be variable), focal detachment of the foot processes from the glomerular basement membrane with intervening fluffy electrolucent material • Tubuloreticular inclusions in the cytoplasm of endothelial cells • Typically no electron dense immune type deposits
HIV-Associated Focal Segmental Glomerulosclerosis, non-collapsing type	Light microscopy • Segmental (and global) glomerulosclerosis without glomerular collapsing changes • No/mild and focal tubular microcystic dilatation • Variable interstitial inflammation • Variable degree of interstitial fibrosis and tubular atrophy • Variable degree of arterial intimal thickening and arteriolar hyalinosis Immunofluorescence • Typically negative for immune complex type deposits, can have nonspecific glomerular staining for IgM and C3 Electron microscopy • Podocyte enlargement, with protein droplet in the cytoplasm, vacuolization, microvillous changes, variable effacement of the foot processes • Tubuloreticular inclusions in the cytoplasm of endothelial cells • Typically no electron dense immune type deposits
HIV-Associated Immune Complex Kidney Disease	Light microscopy • Variable patterns and degrees of glomerular changes, including but not limited to glomerular mesangial expansion, endocapillary proliferation, membranous thickening and double contours, cellular and fibrocellular crescents, global and segmental glomerular scarring • Variable interstitial inflammation • Variable degree of interstitial fibrosis and tubular atrophy

	• Variable degree of arterial intimal thickening and arteriolar hyalinosis Immunofluorescence • Positive for immune complex type deposits with various patterns, including "full-house" positivity Electron microscopy • Electron dense deposits with variable patterns • Tubuloreticular inclusions in the cytoplasm of endothelial cells
HIV-Associated Thrombotic Microangiopathy	Light microscopy • Glomerular severe ischemia, congestion, fragmented red blood cells in the glomerular capillaries, fibrin thrombi in the glomerular capillaries, double contours in the capillary walls • Arterial/Arteriolar edema and narrowing/occlusion, fragmented red blood cells in the arterial wall, fibrinoid necrosis of the arterial wall, concentric "onion skin-like" thickening of the arterial wall • Variable interstitial inflammation • Variable degree of interstitial fibrosis and tubular atrophy Immunofluorescence • Can have positive fibrinogen staining of fibrinoid necrosis/fibrin thrombi • Typically negative for immune complex type deposits Electron microscopy • Endothelial cells swelling, widening of subendothelial space, cytoplasmic interposition with double contours, can have fibrin • Tubuloreticular inclusions in the cytoplasm of endothelial cells
HIV+ Donor, Known	Donor with HIV infection based on medical record review or DRAI plus a licensed HIV antibody, antigen or nucleic acid test from a CLIA-approved laboratory.
HIV+ Donor, Discovered	Donor with no known history of HIV based on medical record review or DRAI where HIV status is diagnosed during the donor evaluation process by a licensed HIV antibody, antigen or nucleic acid test and confirmed by a second test.
HIV+ Donor, Discovered Acute Infection	Donor who is HIV Ab (-) NAT (+) in which a quantitative HIV NAT is positive.
HIV+ Donor, Suspected False Positive	Donor with no known history of HIV per the medical record or DRAI who has a discordant HIV antibody (Ab) and HIV qualitative nucleic acid test (NAT) in the donor evaluation process. This includes both HIV Ab (+) NAT (-) or Ab (-) NAT (+) cases.
HIV+ Donor, Confirmed False Positive	A suspected false positive HIV Ab (+) NAT (-) donor in which an HIV Western blot or combination HIV Ag/Ab assay on the donor blood is negative OR a suspected false positive HIV Ab (-) NAT (+) donor in which a quantitative HIV NAT is negative.
HIV Persistent Virologic Failure	HIV viral load > 1000 copies/mL post-transplant for more than 90 days that is not the result of an investigator/physician-approved interruption in antiretroviral treatment. This would include instances in a recipient receives an HIV+ donor with

	a detectable HIV plasma RNA and the recipient has persistent high levels of virus despite ART more than 90 days post-transplant.
HIV Viral Breakthrough	2 consecutive plasma HIV viral load > 200 copies/mL or one HIV viral load > 1000 copies/mL after virologic control post-transplant. *In cases in which an HIV+ donor has detectable HIV plasma RNA, at early post-transplant timepoints the recipient may have transient detectable plasma due to HIV transferred from the donor organ. This would not meet criteria for HIV viral breakthrough. With effective recipient ART this plasma viremia is expected to decay according to standard viral dynamics. If detectable viremia does not decline with recipient ART, the criteria for HIV persistent virologic failure may be met.
HIV Viral Reservoir	Presence of cells in either blood or tissues from recipients that contain integrated HIV provirus, which can be induced to either produce fully infectious virions as determined by a viral outgrowth assay, or generate multiple complete viral transcripts without major deletions or hypermutations.
HIV Superinfection, systemic	Systemic HIV superinfection is defined as the detection of HIV viral sequences that phylogenetically cluster with the donor's viral population at two or more time points in circulating blood cells, plasma, or recipient tissues other than the allograft.
HPV-related anal invasive squamous cell carcinoma	Histologically proven invasive squamous cell carcinoma arising in the anal canal. 80-90% of these stain for p16, which is a surrogate marker for high risk HPV.
Lost to Follow-up	Missing all in-person follow up visits and cannot be reached by telephone or mail after 12 months.
Medical Monitor	The physician who is responsible for the safety aspects of this trial. The medical monitor is responsible for making the final causal relationship assessment of each serious adverse event.
NIAID Project Manager	NIAID assigned project manager who is responsible for all day to day protocol related issues, including version control, consent review, etc.
Opportunistic infections and conditions	Aspergillosis, invasive Bartonella Candidiasis of bronchi, trachea, or lungs Candidiasis of esophagus Cervical cancer, invasive Coccidioidomycosis Cryptococcosis Cryptosporidiosis Cytomegalovirus disease Encephalopathy, HIV related Herpes simplex: chronic ulcers (>1 month's duration) or bronchitis, pneumonitis, or esophagitis HHV-6 disease Histoplasmosis

	Isosporiasis Kaposi sarcoma Lymphoid interstitial pneumonia or pulmonary lymphoid hyperplasia complex Lymphoma Mucormycosis, invasive Mycobacterium avium complex or Mycobacterium kansasii, disseminated or extrapulmonary Mycobacterium tuberculosis of any site Mycobacterium, other species or unidentified species, disseminated or extrapulmonary Nocardia Pneumocystis jirovecii pneumonia, previously known as PCP Progressive multifocal leukoencephalopathy Salmonella septicemia, recurrent Toxoplasmosis of brain Varicella zoster, disseminated disease Wasting syndrome attributed to HIV
Post-transplant lymphoproliferative disorder (PTLD)	Lymphoid or plasmacytic proliferations due to immunosuppression in a transplant recipient. Comprise a spectrum ranging from EBV driven infectious mononucleosis-type polyclonal proliferations to EBV positive or negative proliferations indistinguishable from a subset of B-cell or less often T-cell lymphomas that occur in immunocompetent individuals. May occur in lymph nodes, GI tract, lungs, liver, CNS, and bone marrow.
Premature Termination	Participants who are lost to follow up, withdraw consent, or die during the study. Data and specimens will no longer be expected from participants who are terminated from the study.
Primary Endpoint	Composite endpoint of time to all-cause-mortality, serious adverse event, graft failure, HIV breakthrough, HIV virologic failure or opportunistic infection.
Principal Investigator	Investigator awarded NIH funding for the grant.
Program Officer	NIAID official who oversees the scientific and budgetary aspects of the grant.
Protocol Mandated Procedures	A procedure or intervention that is a study requirement at the specified time point in the protocol.
Recurrent Disease	Biopsy proven disease in the allograft that is the same as what was seen in the organ prior to transplant.
Regulatory Affairs Officer	NIAID assigned officer responsible for regulatory aspects of the study.
Site Principal Investigator	Lead investigator listed on the Investigator of Record Agreement at a particular center who is responsible for the conduct of the study at that center.
Subclinical Renal Allograft Rejection	Histologic evidence of rejection on biopsy meeting Banff 2015 criteria, which is not accompanied by acute kidney injury defined as a rise in serum creatinine of at least 0.3 mg/dL (26.5 micromol/L) over a 48-hour period and/or ≥1.5 times the baseline

	value presumed to have occurred in the seven previous days (according to The Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guidelines).

1 Study Hypotheses/Objectives

1.1 Hypotheses

Use of an HIV+ deceased donor could increase the risk of death, transplant-related or HIV-related complications; alternatively with effective antiretroviral treatment and careful HIV+ donor selection, these risks may be comparable to kidney transplant using an HIV-negative donor.

We hypothesize that receiving a kidney transplant from an HIV+ donor will be ***non-inferior*** to receiving a kidney transplant from an HIV-negative deceased donor.

1.2 Primary Objective(s)

The primary objective is to determine if receiving a kidney transplant from an HIV+ deceased donor is safe with regards to survival and major transplant-related and HIV-related complications compared to receiving a kidney transplant from an HIV-negative donor.

The primary endpoint is time to a composite of all-cause-mortality, graft failure, serious adverse event, HIV breakthrough, HIV virologic failure or opportunistic infection events.

1.3 Secondary Objective(s)

The secondary objectives are to compare other clinical outcomes between HIV+ kidney recipients of HIV+ and HIV- donors, including:

1. Survival
2. Graft survival
3. Serious adverse event
4. Rejection
5. Graft function
6. Incidence of HIV-associated renal diseases
7. HIV disease control (viral load and CD4 cell count)
8. Detection of new antiretroviral drug resistant and X4 tropic HIV
9. Incidence of bacterial, fungal, viral and other opportunistic infections
10. Incidence of surgical and vascular transplant complications
11. Incidence of post-transplant malignancies
12. Formation of *de novo* donor-specific HLA antibodies

Exploratory objectives area to measure:

1. Incidence of systemic HIV-superinfection
2. Incidence of tissue specific HIV-superinfection measured by viral infiltration in allograft
3. Changes in HIV latent reservoir
4. Quality of Life measures and ethical/psychosocial outcomes

2 Background and Rationale

2.1 Background and Scientific Rationale

Increasing Need for Solid Organ Transplantation in HIV-infected (HIV+) Individuals

Effective antiretroviral therapy (ART) has increased the life expectancy in HIV+ individuals [1]. Thus, end stage kidney disease (ESKD) is increasingly prevalent [2]. Up to 30% of HIV+ individuals have renal dysfunction due to HIV, nephrotoxic ART, or comorbidities, e.g. HBV/HCV glomerulonephritis [3]. Although the incidence of HIV-associated nephropathy (HIV-AN) is decreasing, ESKD due to hypertension, diabetes, and cardiovascular disease is on the rise [4]. Medicare claims show the number of prevalent HIV+ ESKD patients has increased >14-fold since 1999 (USRDS).

Success of Transplantation in HIV+ Individuals Using HIV- Donors (HIVD-)

Transplantation in HIV+ recipients using HIV-uninfected (HIV-) donors (HIV D-/R+) has excellent outcomes [5-15]. In the NIH study, 4-year outcomes of kidney transplant (KT) were excellent (88% patient survival) [10, 15] and similar outcomes have been achieved in national cohorts outside of the NIH study [8, 9, 12-14].

Demand for HIV+ organs and the organ shortage

With these excellent outcomes, there has been a 42-fold increase in HIV D-/R+ kidney transplants (2015 versus 2000) and this upward trend is expected to continue (SRTR). A novel source of organs specific to HIV+ individuals is needed. There are currently more than 120,000 individuals awaiting organ transplantation in the US [UNOS data]. However, only about 10,000 donors are available annually, and thousands of organ transplant candidates die while waiting. Waiting times for kidneys in some regions can be > 10 years. As such, for many today, the probability of dying on the waiting list is higher than the probability of receiving even one viable organ offer [16].

HIV+ Individuals Have Higher Waitlist Mortality

HIV+ individuals with ESKD have shorter survival than their HIV- counterparts. Despite advancements afforded by ART, studies demonstrate 5-year survival of 9-35% for HIV+ ESKD patients [17-19]. As such, the need for transplantation described above is even higher for HIV+ patients.

Use of HIV+ Deceased Donors (HIV D+) as a Novel Source of Donors

Organs from HIV D+ represent a unique resource for HIV+ individuals on the waitlist. In addition, every HIV+ recipient that receives an organ from a HIV D+ would allow HIV- individuals to move up on the general waitlist and potentially attenuate the organ shortage for everyone, resulting in a far-reaching public health impact.

South Africa Experience in HIV D+ Kidney Transplantation. Dr. Elmi Muller, a transplant surgeon in South Africa (SA), has reported excellent outcomes in > 30 HIV D+ kidney transplants [20, 21]. This experience has generated tremendous optimism for HIV D+ transplant. However, the SA experience is limited in that it remains small and cannot be generalized to the US due to key differences between the US and SA, such as general population differences in race, comorbidities, underlying causes of end-organ diseases, and access to health care and differences in the HIV epidemic such as overall prevalence, age, gender, HIV subtypes, mean HIV viral load and CD4 count, common opportunistic infections, access to ART, and prevalence of ART drug resistance.

Federal Regulatory Aspects of HIV D+

The use of organs from HIV D+ was forbidden by the National Organ Transplant Act of 1984 until profound advances in the treatment of HIV and excellent outcomes in HIV+ transplant recipients motivated the HIV Organ Policy Equity (HOPE) Act. The HOPE Act was supported by over 50 medical and patient organizations, unanimously passed the Senate and the House of Representatives, and was signed into law by President Obama on November 21, 2013 [22]. Per the HOPE Act,

the Department of Health and Human Services (DHHS) revised the federal ban on HIV+ donors on June 8, 2015 to allow for these transplants to take place under research protocols [23]. Second, the Organ Procurement Transplant Network (OPTN) revised standards of quality for donated HIV+ organs in November 2015 [24]. Finally, DHHS had to create safeguards and research guidelines, which was delegated to the National Institutes of Health (NIH) with input from the Centers for Disease Control and Prevention, the Health Resources and Services Administration, Centers for Medicare & Medicaid Services, the Food and Drug Administration (FDA) and community stakeholders. Accordingly, the Final Human HOPE Act Safeguards and Research Criteria were published on November 25, 2015 [25].

Current State Regulations Regarding HIV-to-HIV Transplantation

While many states have restrictions related to HIV organ donation and transplant, all 50 states allow HIV-to-HIV transplants as described in this protocol.

Biologic Risks specific to HIV-to-HIV Transplantation

Although transplantation in HIV+ individuals using HIVD- has been highly successful, the practice of HIV-to-HIV transplantation could be more complex because of the following theoretical risks/challenges associated with an HIV D+.

Acute Rejection (AR)

HIV+ recipients have been shown to have 2-4 fold higher rates of AR, in both the NIH HIV Transplant Recipient Multisite Study in which the one year rejection rate was 31% [10] and in the national experience in which the one year rejection rate was 15% [12]. There are multiple potential mechanisms for this increased rejection rate. First, it could be due to drug interactions between immunosuppression and ART. Problematic interactions can be avoided by using ART regimens that do not that contains potent cytochrome P450 inhibitors (ritonavir or cobicistat) [26] and this is now part of recommended clinical care for HIV+ recipients [27].

Elevated rejection rate may also be due to biologic factors specific to the viral infection and resulting immune dysregulation. Host HLA antibodies are packaged with the HIV virion which could lead to an increased risk of antibody mediated rejection [28, 29]. Some studies have shown higher frequencies of alloantibodies in HIV+ individuals [30, 31]. In addition, HIV+ individuals often have an immune responses with a larger repertoire of memory T cell responses due to chronic infection which can enhance alloreactivity and this could be further perturbed by homeostatic proliferation of T cells after lymphocyte depleting immunosuppression strategies [32-35].

Recurrent HIV-Associated Nephropathy

There has been concern about HIV-AN after kidney transplant; this occurred in 38% of HIV+ recipients using HIVD- in a French cohort [36], but was not observed in the NIH Multisite study [10,15]. In South Africa, histologic changes consistent with HIV-AN without graft dysfunction were observed in 3 of 27 patients [21]. In individuals of African descent, HIV-AN may be related to genetic factors such as polymorphisms in the apolipoprotein 1 (APOL1) [34], but whether this contributes to post-transplant HIV-AN is not clear. This risk needs to be better understood.

Opportunistic Infections and Hospitalizations

In the NIH Multisite study kidney cohort there were 13 occurrences of serious opportunistic infections reported (Kaposi's sarcoma, candidiasis, *Pneumocystis jirovecci* pneumonia, cryptosporidiosis) [15]. In a larger national analysis including over 300 HIV+ kidney transplant recipients with HIV-negative donors, 12% of individual had an AIDS defining illness (Kaposi's sarcoma, candidiasis, *Pneumocystis jirovecci* pneumonia, CMV, coccidiodiomycosis, tuberculosis) [38]. Whether the use of HIV D+ in the US will be associated with an increased risk of opportunistic infections requires further investigation.

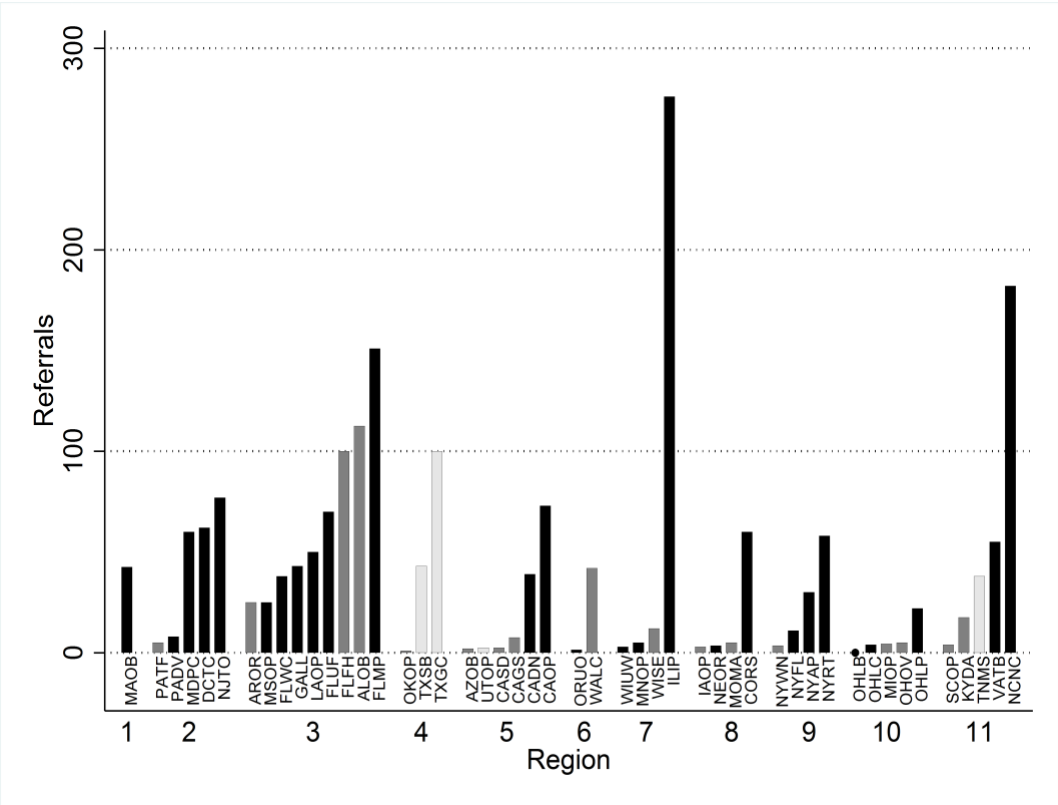
HIV Superinfection (HIV-SI)

HIV+ recipients of HIV D+ may become systemically superinfected, i.e. acquire a second, new HIV strain from the donor [39]. Superinfection occurs at varying rates in populations with differing modes of transmission, including intravenous drug use (IVDU) and sexual transmission [40-42]. Although HIV+ transplant candidates are on ART [43], which should protect against HIV-SI, there is concern of increased risk of HIV-SI with an HIV D+ because, (i) the viral inoculum that occurs with transplant is likely higher than with IVDU or sexual transmission, (ii) if an HIV D+ is infected with an ART resistant or X4 tropic virus, this might not be suppressed by the HIV+ recipient's ART regimen [43-44], and (iii) stably integrated HIV-infected resting CD4+ T-cells may be transplanted. Additionally, ART regimens in HIV+ recipients ideally will avoid ritonavir or cobicistat-boosting regimens [27]. However, boosted protease inhibitor (PI) regimens in particular are potent and in some cases may be required to treat drug resistant virus. It will be important to study whether HIV-SI leads to clinical consequences such as HIV breakthrough or disease progression.

Size of the HIV D+ Pool in the US

The size of the potential HIV D+ pool in the US is unknown. Organ procurement organizations (OPOs) are mandated to receive calls from hospitals regarding all deaths or imminent deaths regardless of HIV status. We obtained annual referral data from 55/58 OPOs. Many OPOs track exact numbers of annual HIV+ referrals (black bars) while others provided accurate estimates (dark gray bars) or estimates they considered inaccurate (light gray bars).

Figure 1. Estimated Annual HIV+ Referrals by OPO.



Feasibility of HIV+ Donor Accrual Targets

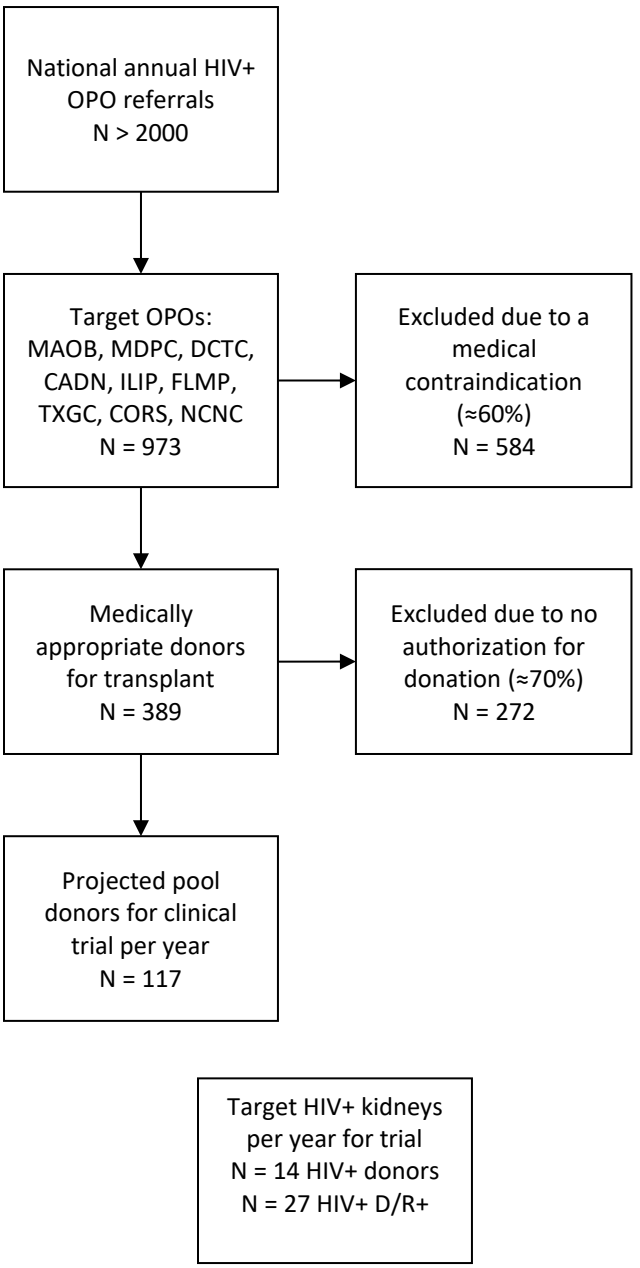
The accrual target in this trial is 80 HIV D+/R+ transplants over 3 years, i.e. 27 HIV D+/R+ recipients per year. If 2 kidneys were recovered from each HIV+ donor, about 14-15 HIV+ donors per year is needed for our accrual goals.

In this trial, any OPO who meets the Federal Criteria may identify an HIV D+. Evaluating HIV+ donors requires staff time, effort, education and training. To facilitate identification of HIV D+ for this study, we have targeted 9 OPOs with high annual HIV+ referrals numbers (MAOB, MDPC, DCTC, CADN, ILIP, FLMP, TXGC, CORS, NCNC). These OPOs are active partners in our NIH-funded HIV+ Donor study (1R01AI120938-01A1). Collectively, these 9 OPOs reported 973 HIV+ referrals per year. A subset of these referrals will have medical contraindications to kidney donation. In two prior retrospective studies examining the potential HIV+ donor pool in the US 40-60% of HIV+ individuals who died in the hospital had a medical contraindication to donation. In addition, average donation authorization rates are about 50%. Applying an estimated medical exclusion rate of 60% and a declined authorization rate of 70%, we project these 9 OPOs will identify 117 medically-appropriate authorized HIV+ donors per year, which is above our target.

Successful Proof of Concept HIV D+/R+ Transplants

As of October 2017, there have been 32 transplants which have occurred under the HOPE in Action pilot protocols (NCT02602262) at 6 US transplants centers. These transplants were the result of 14 HOPE donors; 8 HIV+ donors as well as 6 donors with false positive HIV+ screening tests. As of October 2017, 20 US transplant centers have approved HOPE in Action pilot protocols and > 250 HIV+ candidates on the UNOS waitlist are consented to accept kidneys from HIV+ donors.

Figure 2. Anticipated HIV+ Donor Accrual.



3 Study Design

3.1 Description of Study Design

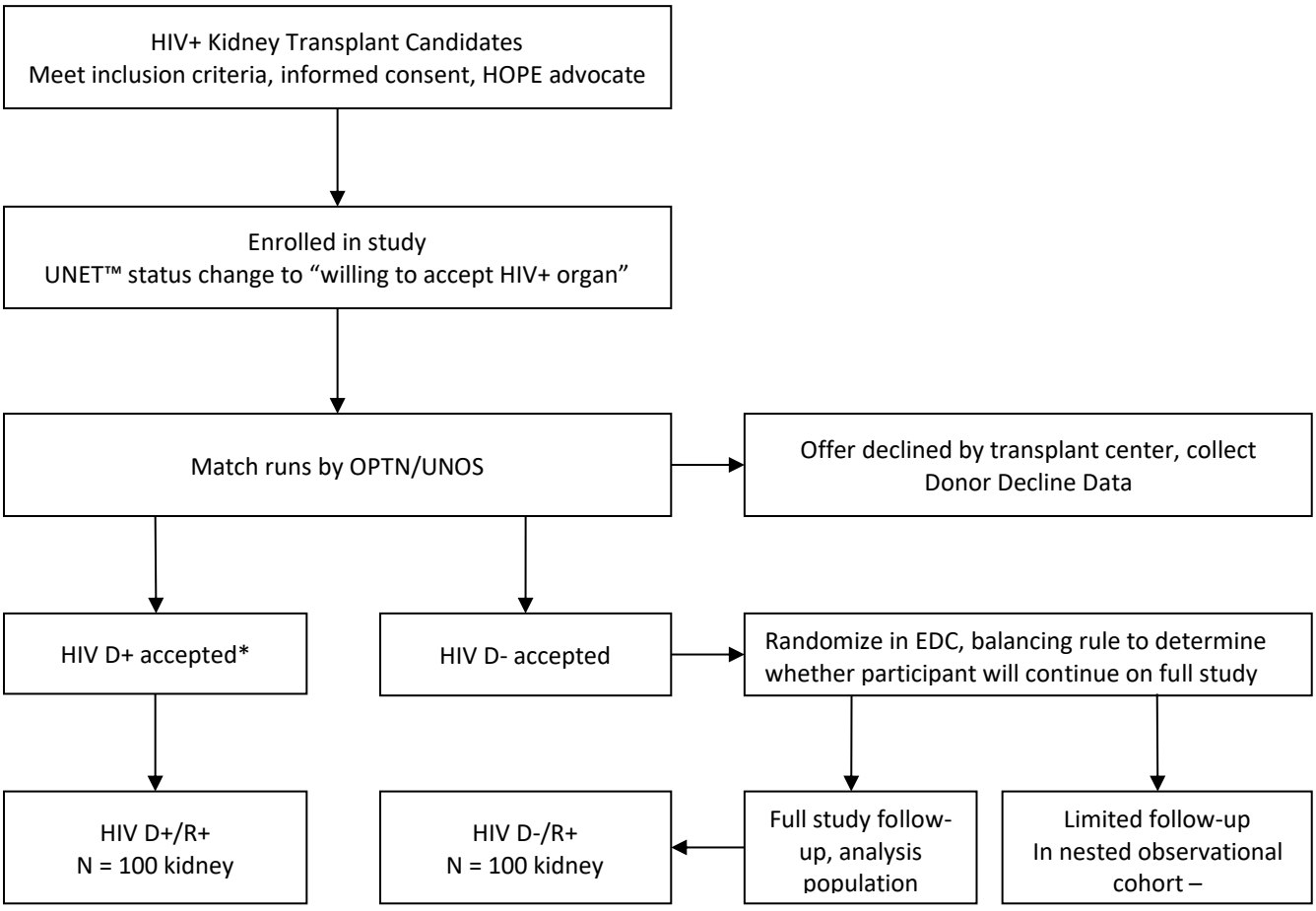
Participants

HIV-infected adults in need of a kidney transplant, who meet standard transplant clinical criteria and HIV/HOPE criteria are eligible. Patients who provide informed consent and meet with a HOPE recipient advocate will be enrolled. Pre-transplant, HIV-specific eligibility will be confirmed every 16 weeks.

Donor/group assignment

HIV-positive or HIV-negative donor offers will be made by OPTN which serves as a process of "natural randomization." We will collect basic information on donor primary offer declines for study participants. As the evaluation of HIV+ donors is a novel practice, we anticipate that there may be more HIV- donors than HIV+ donors. In order to maintain equal numbers in D- and D+ groups, a balancing rule has been designed. If a study participant is allocated an HIV+ donor, the participant will be assigned to the HIV D+/R+ group. If a study participant is allocated an HIV D- , the site will use the EDC, which will apply a balancing rule to randomize the participant (see section 3.5 Randomization) in order to determine if the participant continues on study for full follow-up or whether the participant will remain in a nested observational HIV D-/R+ cohort with limited annual follow up to collect major outcomes.

Figure 3. Study Design.

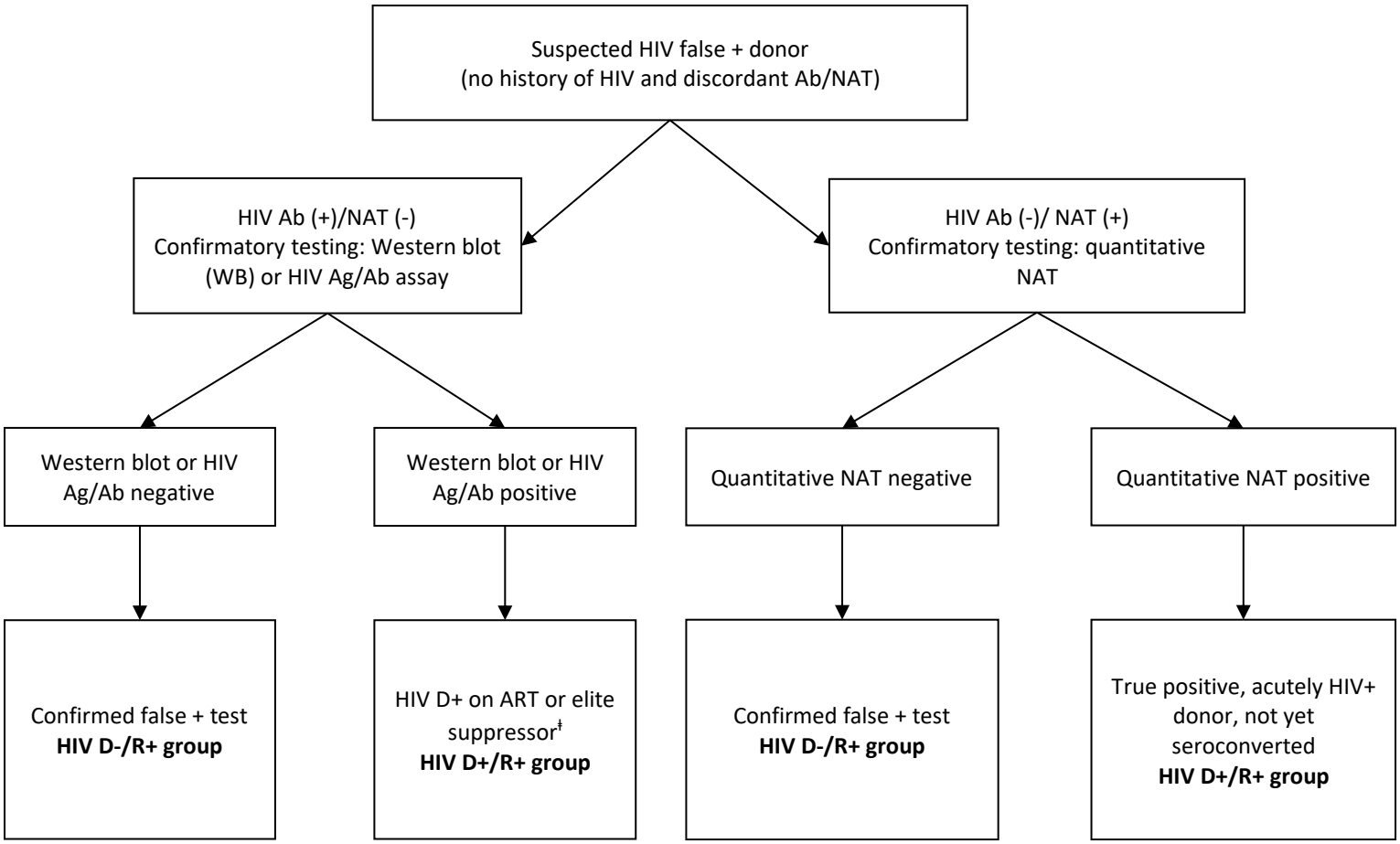


*For suspected false positive HIV donors, see Figure 4.

Suspected false positive donors

Deceased donors are screened for HIV infection using anti-HIV antibody (Ab) and nucleic acid testing (NAT). These assays have false positive rates of 0.1-0.5%; therefore, when screening > 30,000 potential deceased donors annually, a significant number of false positive results will occur. Historically, in cases of a suspected false positive HIV screen, organs from the donor were not considered. Under HIV Organ Policy Equity (HOPE) Act research protocols, organs from donors with suspected false positive HIV tests can now be used for transplants in HIV+ study participants who have consented to receive HIV+ organs. We define suspected false positive donors as individuals with 1) no history of HIV infection in the medical record or UNOS Donor Risk Assessment Interview and 2) discordant HIV Ab and NAT. In these cases, the transplant center will request that a confirmatory test be performed by the OPO/UNOS. If the OPO cannot perform the indicated test, the donor blood will be tested in the central study lab (Figure 5). The recipient will be initially assigned to the HIV D+/R+ group. Confirmatory results will be available within 7 days of transplant, accounting for the turnaround time of the assay (Western blot or quantitative PCR) and the different facilities that may perform testing (OPO facility versus central core lab). Participants will be reassigned to the HIV D-/R+ group if the confirmatory test is negative. Both the physician and transplant recipient will know the final HIV status of the donor as per OPTN policy.

Figure 4. False Positive HIV Donor Algorithm.



3.2 Primary Endpoint(s)

The primary endpoint of the study is time to a composite event of all-cause-mortality, graft failure, serious adverse event, HIV breakthrough, HIV virologic failure, or opportunistic infection.

3.3 Secondary Endpoint(s)

1. Patient survival
2. Graft survival
3. Serious adverse event: time to first serious adverse event
4. Allograft rejection defined as biopsy proven rejection or clinically suspected and treated rejection.
5. Graft function defined as glomerular filtration rate (GFR) (months 3, 6, 9, years 1, 2, 3)
    a. Proportion of participants with eGFR by CKD-EPI < 60 mL/min/1.73 m2.
    b. Mean calculated eGFR by CKD-EPI.
    c. The slope of eGFR by CKD-EPI, over time based on serum creatinine.
6. Analysis of renal diseases including HIV-related renal disease (HIV-AN, HIVICK, HIV-associated FSGS, HIV-associated thrombotic angiopathy) and HIV infection in the renal allograft as identified on central read of biopsy slides
    a. Protocol biopsy at 6 months and 1 year with histologic findings as identified on central read of biopsy slides
    b. APOL1 variant testing in donors and recipient
7. HIV disease progression
    a. Weekly HIV RNA viral load by any licensed assay in a CLIA approved laboratory at weeks 1, 2, 3, 4, 8, 13, 26, 39, 52, and at least every 6 months through the remainder of follow-up
    b. Absolute CD4 count and %CD4 by any licensed assay in a CLIA approved laboratory at weeks 4, 8, 13, 26, 39, 52, and at least every 6 months through the remainder of follow-up
8. Development of antiretroviral resistance mutations and/or X4 tropic virus
    a. If a participant has an HIV breakthrough, defined as 2 consecutive HIV viral loads >200 copies/mL or one HIV viral load >1000 copies/mL, then HIV resistance testing will be performed by a CLIA certified laboratory, including resistance in the integrase gene and viral tropism.
9. Incidence of bacterial, fungal, viral and other opportunistic infections
    a. Using standardized definitions, data will be collected on infectious complications at scheduled study visits and by review of patient medical records every 3 months during year 1 and every 6 months thereafter to identify and record infectious complications, treatments administered, and outcomes. During these intervals, participants will be contacted by phone to review the same outcomes.
10. Incidence of other transplant complications (surgical and vascular)
    a. Surgical complication including re-exploration, anastomotic leak, post-operative hematoma, delayed closure, wound dehiscence. See appendix for standard definitions.
11. Incidence of other viral-related malignancies (HPV-related tumors, EBV-related tumors, KSHV related tumors, hepatocellular carcinoma associated with HBV and/or HCV) as determined by local pathology
12. The prevalence of de novo anti-donor HLA antibodies at one year (central lab).
13. Time to composite event of all-cause-mortality, graft failure, renal allograft rejection, HIV breakthrough, virologic failure, or AIDS Defining Illness (composite event from prior version of the protocol)

3.4 Exploratory Endpoint(s)

The following research studies will be conducted as a part of the study:

1. Incidence of systemic HIV-superinfection in blood in HIV D+/R+ participants utilizing next-generation sequencing
2. Incidence of tissue specific HIV-superinfection measured by viral infiltration in the allograft
3. Changes in HIV latent reservoir by viral outgrowth and next-generation sequencing of resting CD4+ T-cells
4. Quality of Life measures and ethical/psychosocial

3.5 Stratification, Randomization, and Blinding/Masking

Group assignment/donor allocation will occur per standard OPTN allocation policy, which acts as a process of "natural randomization." We anticipate that the number of HIV D- may exceed the number of HIV D+ so we have designed a balancing rule. When an HIV D- organ is allocated to a transplant candidate, the transplant center will use the EDC to randomize the participant to continue on full study or to continue in a nested cohort with limited observational follow up. The data center will implement a balancing rule: a computer will draw a random number from a uniform distribution on the interval (0,1). The recipient will be selected for participation in the full study if the random number falls below a certain value, *v*. V will be chosen as follows: if the number of participants so far who have received an HIV D+ organ, n_{pos}, exceeds the number of participants who have received an HIV- organ, n_{neg}, select v=1. Otherwise, select v=max(1-(n_{neg}-n_{pos})/10, 0.1). Examples of this rule are:

$n_{neg}<=n_{pos}$	Always enroll
$n_{neg}-1=n_{pos}$	Enroll with probability 0.9
$n_{neg}-2=n_{pos}$	Enroll with probability 0.8
$n_{neg}-5=n_{pos}$	Enroll with probability 0.5
$n_{neg}-9>=n_{pos}$	Enroll with probability 0.1

V will be recalculated after every transplant; as such, the ratio of on-study HIV D+/R+ recipients to HIV D-/R+ recipients will stay close to 1. Thus, all recipient of organs from HIV+ donors, and a random subset of those from HIVD-, will be followed on full study. This is to ensure time of transplant will not confound the association between donor HIV status and patient outcomes, and balance will be consistently maintained between the two groups. As per standard OPTN allocation policy, both physician and transplant recipient will know the HIV status of the donor prior to transplantation.

False positive HIV+ donors

In the event that there is a suspected false positive HIV+ donor, the recipient will initially be assigned to the HIV D+/R+ group and the balancing rule described above will not be applied. If confirmatory testing reveals the donor is HIV-negative and the screen was a false positive, the recipient will be reassigned to the HIV D-/R+ group and this will be the designation for purposes of outcome analysis.

$n_{neg}<=n_{pos}$	Always enroll
$n_{neg}-1=n_{pos}$	Enroll with probability 0.9
$n_{neg}-2=n_{pos}$	Enroll with probability 0.8
$n_{neg}-5=n_{pos}$	Enroll with probability 0.5
$n_{neg}-9>=n_{pos}$	Enroll with probability 0.1

4 Selection of Participants and Clinical Sites

4.1 Rationale for Study Population

This study will evaluate the use of HIV D+ in HIV+ kidney transplant candidates who are willing to accept an HIV+ organ. Potential donors will meet specific criteria based on the HOPE Act Research Criteria published in November 2015. Further HIV D+ criteria are outlined below. Transplant recipients included in this study will have controlled HIV disease and be on a stable ART regimen. Participants who receive kidneys from HIV D- will be included in the study as part of the control population.

4.2 HIV+ Deceased Donor Criteria

All deceased donors will meet the following criteria in order for the organ to be accepted for transplant under this protocol.

1. Donation after brain death or cardiac death.
2. HIV+ donors have confirmed or suspected HIV infection* (by medical record history plus a licensed HIV antibody, antigen or nucleic acid test from a CLIA-approved laboratory.) If there is no record of known HIV history, and HIV status is diagnosed during the donor evaluation process by a licensed HIV antibody, antigen or nucleic acid test, HIV status will need to be confirmed by a second test). Organs from donors with suspected false positive HIV screening tests can be used under this protocol as per section 3.5.
3. Donor has no active opportunistic infections or neoplasms and no active signs or symptoms of severe acute retroviral syndrome including meningoencephalitis, fevers, or disseminated rash; if previous history, donor has received appropriate treatment.*
4. Donor may have any HIV-1 RNA viral load provided a safe, tolerable and effective post-transplant antiretroviral regimen to be prescribed for the recipient is anticipated and justified.*
5. Organs from donors with active hepatitis C virus co-infection (detectable HCV nucleic acid using any licensed assay in a CLIA certified lab) are acceptable based on local site practice..

4.3 Inclusion Criteria

All individuals with end-stage kidney disease and HIV infection who meet the study inclusion and exclusion criteria will be eligible for participation in the study.

1. Participant meets the standard criteria for kidney transplant at the local center.
2. Participant is able to understand and provide informed consent.
3. Participant meets with an independent advocate per the HOPE Act Safeguards and Research Criteria.
4. Documented HIV infection (by any licensed assay, or documented history of detectable HIV-1 RNA).*
5. Participant is ≥ 18 years old.
6. Opportunistic complications: if prior history of an opportunistic infection, the participant has received appropriate therapy and has no evidence of active disease. Medical record documentation should be provided whenever possible.*

Condition	Comments
Candidiasis of bronchi, esophagus, trachea, or lungs	--
Cryptococcosis	Requires negative serum CRAG
Cryptosporidiosis (>1 month duration)	--
Cytomegalovirus disease	--
Encephalopathy, HIV-related	Diagnosed prior to ART and resolved on ART with marked improvement in mental status 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	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	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	Completed treatment
Pneumonia, recurrent	--
Recurrent bacterial infections	--
Salmonella septicemia, recurrent	--
Toxoplasmosis, CNS	Completed therapy AND MRI without active disease

7. CD4+ T-cell count: ≥ 200/µL within 16 weeks of transplant.*
8. HIV-1 RNA is below 50 copies RNA/mL.*/** Viral blips between 50-400 copies will be allowed as long as there are not consecutive measurements > 200 copies/mL. **Organ recipients who are unable to tolerate ART due to organ failure or recently started ART may have detectable viral load and still be eligible if a safe and effective antiretroviral regimen to be used by the recipient after transplantation is described.
9. Participant is willing to comply with all medications related to their transplant and HIV management.
10. For participants with a history of aspergillus colonization or disease, no evidence of active disease.

11. The participant must have or be willing to start seeing a primary medical care provider with expertise in HIV management.
12. Agreement to use contraception; according to the FDA Office of Women's Health (http://www.fda.gov/birthcontrol), there are a number of birth control methods that are more than 80% effective. Female participants of child-bearing potential must consult with their physician and determine the most suitable method(s) from this list to be used from the time that study treatment begins until after study completion.
13. Participant is not suffering from significant wasting (e.g. body mass index < 21) thought to be related to HIV disease.

4.4 Exclusion Criteria

Individuals who meet any of these criteria are not eligible for enrollment as study participants:

1. Participant has a history of progressive multifocal leukoencephalopathy (PML or primary CNS lymphoma).*
2. 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.)
3. 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.

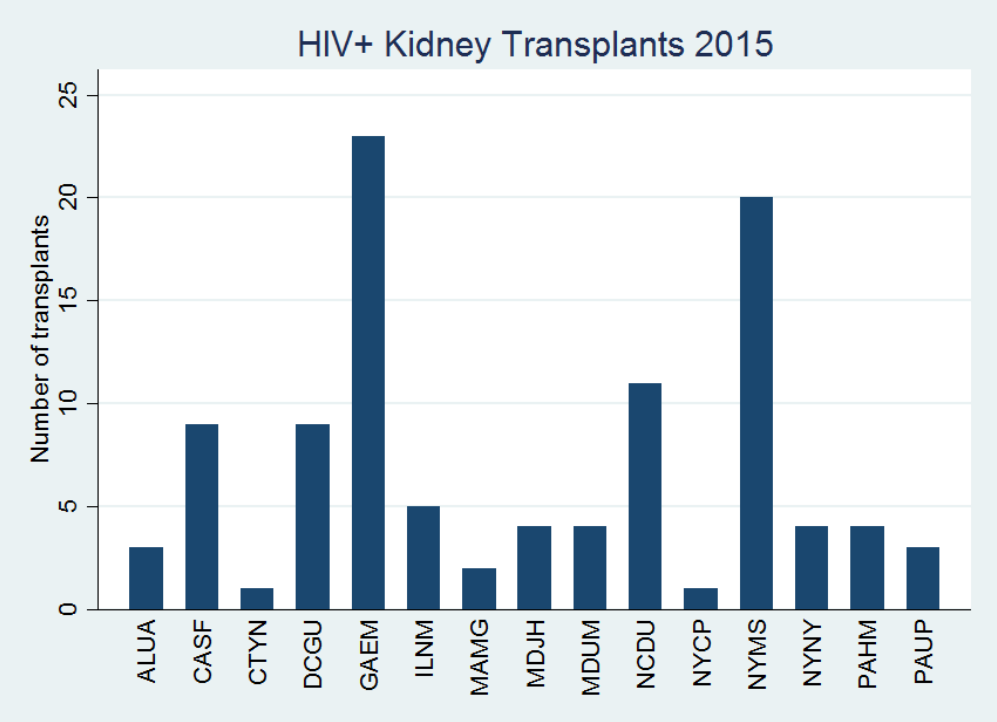
*These eligibility criteria align with the eligibility in the H*uman Immunodeficiency Virus (HIV) Organ Policy Equity (HOPE) Act Safeguards and Research Criteria for Transplantation of Organs Infected with HIV.*

4.5 Selection of Clinical Sites

All participating clinical sites will require an open variance from the United Network of Organ Sharing and ensure that their local Organ Procurement Organizations are aware that they are participating in this research and can therefore, accept HIV+ organs. Approximately 29 clinical sites will participate in this study, however, sites may be added and/or replaced if enrollment becomes an issue.

The sites that are currently participating performed over 100 HIV D-/R+ transplants in 2015, which represented a significant increase from the prior year. For this protocol, we expect approximately 53 transplants per year to meet the accrual target of 160 transplants over three years.

Figure 5. Number of HIV+ Kidney Transplants Performed at Each Site in 2015.



5 Known and Potential Risks and Benefits to Participants

5.1 Risks associated with solid organ transplant from HIV+ Deceased Donors

Although transplantation in HIV+ individuals using HIVD- is highly successful, the practice of HIV-to-HIV transplantation is potentially more complex because of the following theoretical additional risks/challenges associated with an HIV D+.

5.1.1 Acute Rejection (AR)

HIV+ recipients have 2-4 fold higher rates of AR, in both the NIH HIV Multisite Study [10] and in the national experience [12]. This may be due to drug-drug interactions between immunosuppression and antiretroviral therapy or due to a dysregulated immune system from HIV infection. Proposed interventions to address this include avoiding ritonavir-containing ART and induction immunosuppression. It is unknown whether AR rates will be increased in HIV-to-HIV transplantation.

5.1.2 HIV-Associated Renal Disease

There is concern that HIV D+ may carry a higher risk of HIV-related kidney disease after transplant. In a French cohort of HIV D-/R+, 5 of 19 participants had evidence of HIV infection of the allograft with graft dysfunction [36], but this was not observed in the NIH Multisite study of HIVD-/R+ [10]. In South African experience of HIV D+/R+, histologic changes consistent with HIVAN without graft dysfunction were observed in 3 /27 patients [21]. This risk needs to be better understood.

5.1.3 Infections

In the NIH Multisite study kidney cohort there were 13 occurrences of serious opportunistic infections reported (Kaposi's sarcoma, candidiasis, *Pneumocystis jirovecci* pneumonia, cryptosporidiosis) [15]. In a larger national analysis including over 300 HIV D-/R+, 12% of individual had a serious opportunistic infection (Kaposi's sarcoma, candidiasis, *Pneumocystis jirovecci* pneumonia, CMV, coccidiodiomycosis, tuberculosis) [38]. Whether the use of HIV D+ in the US will be associated with an increased risk of serious opportunistic infection requires further investigation.

5.1.4 HIV superinfection (HIV-SI)

HIV+ recipients of HIV D+ may become systemically superinfected, i.e. acquire a second, new HIV strain from the donor that is found at multiple time points post-transplantation outside of the allograft. It will be important to study whether HIV-SI leads to clinical consequences such as HIV breakthrough or disease progression. HIV-SI although very rare in individuals who are on effective antiretroviral therapy, it is possible that it could occur in the HIV D-/R+ group if participants are exposed to a multidrug resistant virus or if ART is interrupted. Therefore, in cases of HIV breakthrough and/or virologic failure in both groups, we will perform viral sequencing to allow for phylogenetic analysis to determine the source of the viremia (donor, recipient, outside/unlinked source).

5.2 Risks of Other Protocol Specified Medications

There are no specified protocol medications.

5.3 Risks of Study Procedures

5.3.1 Collection of Blood

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

5.3.2 Kidney Biopsy

In this study, protocol mandated biopsies will be performed at month 6 and year 1 post-transplant. In addition, an additional research core will be collected during each biopsy, including "for cause" biopsies. The most frequent complications of a kidney biopsy include pain and hematuria (blood in the urine). In rare cases, bleeding from the biopsy may cause a drop in blood pressure or cause anemia. This may require the administration of intravenous fluids or blood. Blood transfusions are required in about 1-5% of cases. Surgery to repair a tear or to stop persistent or massive bleeding is required in less than 1 per 500 biopsies and in less than 1 per 2000 cases is it necessary to remove the kidney. Other uncommon complications include puncture of other organs (liver, spleen, bowel) or the creation of a fistula (a connection between an artery and vein).

5.3.3 Lymph Node Collection

One large or 2-3 smaller whole lymph nodes will be excised at the time of transplant. These nodes will be taken while in surgery for the transplant. There is a slight risk of bleeding, fluid collection and discomfort where the nodes are removed.

5.3.4 Anal PAP Smear

The anal PAP smear is considered standard of care at many of the participating sites. This procedure may be slightly uncomfortable from the position and the cotton-tipped swab. Slight bleeding may occur.

5.3.5 Internet-Based Data Collection

Data from this study will be entered into a computerized database through a secured web site. All information will be saved and transmitted in a coded form. Only authorized personnel requiring a password will be permitted to enter data. There is risk, although minimal, of unauthorized persons obtaining confidential information.

5.4 Potential Benefits

Currently there is a national organ shortage crisis, with more than 120,000 individuals awaiting organ transplantation [UNOS data]. Less than 10,000 deceased donors are available per year, and thousands of candidates die while waiting. Waiting times for kidneys in some regions can be > 10 years. As such, for many today, the probability of dying on the waiting list is higher than the probability of receiving even one viable organ offer.

For participants in this study, the use of HIV D+, could increase access to kidney transplantation which has a known survival benefit, could decrease wait time on the list, and thereby decrease the risk of waitlist mortality [51]. From a public health perspective, the use of HIV D+ could lead to the largest expansion of the donor pool in the last decade.

6 Investigational Agent/Device/Intervention

6.1 Investigational Agents/Devices/Interventions

There is no investigational agent for this study nor is there a prescribed standard of care regimen for each participant.

6.2 Drug Accountability

This section is not applicable.

6.3 Assessment of Participant Compliance with Investigational Agent

This section is not applicable.

6.4 Toxicity Prevention and Management

This section is not applicable.

6.5 Premature Discontinuation of Investigational Agent

This section is not applicable.

7 Other Medications

7.1 Concomitant Medications

7.1.1 Protocol-mandated Medications

There are no protocol-mandated concomitant medications. Each participant will be prescribed an appropriate immunosuppressive regimen post-transplant according to the judgment of the site transplant team.

7.1.2 Antiretroviral Guidelines

There is no protocol-mandated antiretroviral regimen. The site HIV/Transplant Infectious Diseases study team must describe the anticipated post-transplant antiretroviral regimen to be prescribed for the recipient and justify that the regimen will be safe, tolerable, and effective. This regimen will be determined on a case-by-case basis, taking into account the participant's clinical history of prior antiretroviral treatment, tolerance, known or suspected antiretroviral resistance-associated mutations, and preferences. In participants who receive an HIV+ donor, the specifics of the HIV+ donor's history of prior antiretroviral treatment, documented or suspected antiretroviral resistance-associated mutations will also be considered. As per current clinical guidelines [27], to avoid drug interactions, ritonavir or cobicistat-containing antiretroviral regimens should be avoided, unless in the opinion of the HIV/Transplant Infectious Disease team there is no alternative regimen expected to control HIV replication. To assist with this decision-making process, refer to the Manual of Operations guidance on "Determining a post-transplant regimen for HIV+ recipients."

7.1.3 Hepatitis C Antiviral Treatment Guidelines

For participants with chronic hepatitis C virus (HCV+) co-infection (detectable HCV nucleic acid using any licensed assay in a CLIA certified lab) or recipients of organs from donors with hepatitis C infection, we recommend that the recipient is treated for hepatitis C infection as soon as possible and within 90 days post-transplant according to the best judgment of the site clinical specialist in hepatitis C and/or Transplant Infectious Diseases. For recipients who receive an HCV+ donor (with a positive HCV nucleic acid test), a post-transplant HCV genotype test should be performed. The specific direct acting antiviral regimen can be selected according to hcvguidelines.org, HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C, published jointly by the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America. If both the recipient and donor are hepatitis C infected, the possibility of dual infection with different HCV genotypes should be considered.

7.2 Prophylactic Medications

Participants will receive prophylactic medications based on the current standard of care at their institution.

7.3 Prohibited Medications

There are no prohibited medications for this study.

7.4 Rescue Medications

This section is not applicable.

8 Study Procedures

8.1 Informed Consent

The research study will be explained in lay terms to each potential research participant, and the potential participant will sign an informed consent form before undergoing any study procedures and then be assigned a unique participant number. Centers will identify potential study participants who are HIV+ organ transplant candidates listed for transplant.

During the screening period for study eligibility, the study personnel will review the participant's medical record for previous and current medical history, perform a physical examination, and record the participant's demographic information.

8.2 Screening/Baseline Visit

The following procedures, assessments, and laboratory measures will be collected for the screening/baseline visit. Many of these laboratory assessments may have been collected as a part of standard of care and can be used for this study if they fall within the specified visit window. The screening/baseline research specimens are solely for the purpose of this study and will be collected prior to the administration of immunosuppressive therapy at the time transplant. See Appendix 1 for a detailed schedule of assessments.

- Symptom & medical review plus physical exam
- Cervical PAP for women
- Anal PAP for men who have sex with men or women who have receptive anal sex (if this is considered standard of care)
- Pregnancy test (serum or urine) on all female participants of child-bearing potential
- Safety labs (see schedule of events)
- CD4+ T-cell count
- HIV-1 RNA
- Serologies (CMV Ab, EBV Ab, hepatitis B and C)
- Review of PPD history and/or FDA approved assay for detection of latent tuberculosis infection
- Screening/baseline research specimens: the collection of all baseline/screening samples are not necessarily drawn at initial screening for the study when all other screening laboratory measures and procedures are performed. All baseline/screening research specimens (blood and urine) should be collected on the day of transplant (day 0) if they were not previously collected prior to transplant. If the baseline research samples were not collected prior to day of transplant, they should be collected on the day of transplant, prior to transplant and administration of immunosuppression.

8.3 Enrollment

Once a participant has met all study inclusion and exclusion criteria, the participant will be enrolled into the Pre-Transplant phase of the study. During this phase, CD4+ T-cell count and HIV RNA testing results will be reviewed and

recorded per the Schedule of Events in Appendix 1. CD4+ T-cell count must be ≥ 200/µL within 16 weeks prior to transplant. This testing may be ordered by the participant's local PCP and performed at a local CLIA certified lab, but results should be sent to the transplant center for review and entry into the clinical database. Entry into the Post-Transplant phase of the study will occur on the day of transplant.

After consent and eligibility is confirmed, study participants will have a status change to "willing to accept an HIV+ organ" as per HRSA and OPTN policy 15.6 in UNET™, the secure database used by both transplant hospitals and OPOs to coordinate organ recovery and waitlist candidate matching. As per standard OPTN allocation policy, when an HIV D+ is identified, a national "match run" is performed by UNOS.

For any given study participant, if an HIV+ offer becomes available first and is accepted by a candidate, he/she will be assigned to the HIV D+/R+ group; alternatively, if an HIV- offer becomes available first and is accepted by a candidate, the transplant center should use the EDC to randomize the participant prior to transplant. The EDC will determine if the participant will continue on the full study according to a randomization rule designed to minimize bias (see section 3.5). If the balancing rule indicates that the individual should not continue on in the full study, the participant will continue in the nested observational cohort and be followed annually for the remainder of the funding period in order to collect major clinical outcomes (see section 13.4.1 and Appendix 2).

8.4 Post-Transplant Study Visits

Study visits for both groups will occur at day 0, weeks 1, 2, 3, 4, 8, 13 (month 3), 26 (month 6), 39 (month 9), 52 (year 1), 78 (year 1.5), 104 (year 2), 130 (year 2.5), 156 (year 3), 182 (year 3.5) and 208 (year 4). At each study visit, a clinical evaluation and physical examination will focus on signs and symptoms suggestive of HIV disease progression, impaired allograft function, rejection, and opportunistic infection. 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 percent, and quantitative HIV-1 RNA by PCR assays will be determined. All necessary lab work outlined in the Schedule of Events should be performed at the study visits outlined below. At each study visit, the study coordinator will collect and enter data into the web based data system, including medications, adverse events (AEs)/serious adverse events (SAEs), hospitalizations, infections, and standard of care labs.

If the participant is unable to return to the transplant center for any post-transplant study visit, a medical review should be conducted by telephone by a study team nurse or physician. 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 sent to the transplant center for data entry along with the associated normal laboratory reference ranges.

- **Biopsy**: A kidney biopsy will be performed at month six and year one post-transplant unless the clinical team does not feel this is safe for the participant. If a biopsy is performed for a standard clinical indication at any other time an additional tissue core for research will be collected if the clinical team feels this is safe.
- **Recipient lymph node tissue**: At the time of transplant, then one large or 2-3 smaller lymph nodes will be collected if the surgeon determines it is safe. These are lymph nodes that would generally be excised and discarded during the transplant procedure and no additional risk is anticipated beyond the standard clinical risk of kidney transplant.
- **Collection of research blood (~100 mL):** Whole blood specimens will be obtained pre-transplant, baseline on the day of transplant, and at weeks 13 (month 3), 26 (month 6), 52 (year 1), 104 (year 2), 156 (year 3), 208 (year 4).
- **Collection of research urine (~100 mL) (optional for sites):** Urine specimens will be obtained from kidney transplant recipients pre-transplant if possible, baseline on the day of transplant, and at weeks 26 (month 6), and 52 (year 1).

- **Collection of research blood (~30 mL):** Whole blood specimens will be obtained at time of "for cause" biopsy is performed or HIV viral breakthrough as defined by the protocol.

8.5 Unscheduled Visits

If disease activity increases or other concerns arise between regularly scheduled visits, participants should be instructed to contact study personnel and may be asked to return to the study site for an "unscheduled" visit. When participants return for unscheduled visits, additional data will be collected related to suspected rejection episodes, "for cause" biopsies, suspected and/or confirmed infections, and HIV breakthrough events.

8.6 Visit Windows

Study visit numbers 1 through 4 may occur within +/- 3 days of the target window date. The window for visit 4 will close on the median date between the visit 4 target window date and the visit 5 target window date.

Study visits 5 through 14 may occur within 2 weeks prior to the target window date and up to the median date between the target window date and subsequent study visit target window date.

8.7 Follow-up for Participants with Graft Failure

Participants who experience graft failure will remain on study and continue to follow their original schedule for key assessments such as patient survival, HIV monitoring (CD4 count, viral load measurements, and mechanistic studies) and infections. If the participant is re-transplanted on study, a final disposition form will be completed for the initial transplant and the participant will re-enroll and begin the Schedule of Events from the time of their re-transplant.

9 Mechanistic Assays

All recipient and donor samples will be banked at the Johns Hopkins Sample Repository and analyzed in batches.

9.1 Recipient Samples

Peripheral blood mononuclear cells (PBMC) and plasma will be processed from peripheral blood collected in 12 8.5 mL ACD tubes at pre-transplant, day of transplant, and months 3, 6, 12, 24, and 36 after transplant. Peripheral blood mononuclear cells (PBMC) and plasma will be processed from peripheral blood collected in 3 8.5 mL ACD tubes at any time of rejection or HIV viral breakthrough. The samples will be stored in aliquots as live cells in cryopreservation medium in the vapor phase of liquid nitrogen.

9.1.1 Donor Specific Antibody

Detection and characterization of HLA-specific IgG antibodies will be performed using multi-analyte bead assays performed on the Luminex™ platform. Luminex™ based assays include the Luminex™ screen (LMX), Luminex specificity by phenotypes panels and Luminex™ specificity by single antigen panels (Lifecodes class I and II ID panels, Immucor Gen-Probe, San Diego, CA and Single Antigen Beads, One Lambda, Canoga Park, CA). The core lab will test all samples at one year.

9.1.2 APOL1 Testing

HIV infection is associated with a spectrum of kidney diseases. In particular, HIV-associated nephropathy (HIV-AN) is a rapidly progressive form of focal segmental glomerulosclerosis, which is the leading cause of kidney disease in African American individuals and is of particular concern. HIV-AN is associated with specific genetic variants of apolipoprotein type 1 (APOL1). Therefore, APOL1 polymorphisms will be examined and included in the subsequent analysis as a possible risk factor.

9.1.3 HIV Latent Reservoirs and HIV Superinfection

There is concern that the kidney may represent an additional viral reservoir for HIV. This could have clinical implications increasing the risk of superinfection, viral rebound and may increase the risk of HIV-associated renal diseases [20]. Therefore, we will quantify and characterize donor HIV (from blood, PBMCs, and lymph nodes at donor recovery described in donor sample section) and HIV in the recipient from lymph nodes at transplant, and from plasma, PBMCs, and kidney allograft biopsies post-transplant. Tissue samples will be used to assess HIV source location by laser capture microdissection and gene expression analysis, and these will be compared to viral sequences derived from the quantitative viral induction assay of circulating CD4+ cells pre- and post-transplant.

Recipient kidney allograft biopsy samples will be collected at month 6, year 1 post-transplant and any time a “for cause” biopsy is performed. For these post-transplant recipient biopsies, three cores of at least 2 cm should be obtained. Two cores should be sent to pathology at the local site for standard clinical review, and one core should be immediately flash frozen in OCT medium, remain at -80^{0}C or less, and sent to the HOPE Core Lab to assess HIV by laser capture microdissection and gene expression analysis. After completion of standard clinical histology review, all slides will be sent to HOPE Core lab. The stained slides will be scanned, and returned to the local site. The unstained slides will remain with the HOPE Core lab. See Laboratory Manual for details.

Recipient lymph nodes: at the time of transplant 1 large or 2-3 smaller whole lymph nodes should be excised, placed in OCT media, flash frozen, remain at -80^{0}C or less, and sent to the HOPE Core lab.

Urine will be collected in kidney transplant recipients at day of transplant, month 6 and year 1.

9.2 Donor Samples

Donor blood (200 ml) will be collected prior to implantation by the Organ Procurement Organization and shipped directly to the HOPE in Action Core Laboratory as part of a separate protocol, *Unlocking the Potential of HIV-Infected Deceased Donors for Organ Transplantation (1R01AI120938-01A1).*

Graft biopsy samples will be collected prior to implantation with two possible methods: 1) one wedge can be done with ~2/3 of the tissue going to pathology at the local site for standard clinical review, and ~1/3 should be immediately flash frozen in OCT medium, remain at -80^{0}C or less, and sent to the HOPE Core Lab to assess HIV by laser capture microdissection and gene expression analysis; or 2) three cores of at least 2 cm can be done with two cores sent to pathology at the local site for standard clinical review, and one core should be immediately flash frozen in OCT medium, remain at -80^{0}C or less, and sent to the HOPE Core Lab to assess HIV by laser capture microdissection and gene expression analysis. The additional research sample (1/3 wedge or 3rd core) is only collected when the donor is HIV+ (or false positive).

10 Biospecimen Storage

Biological specimens obtained under this protocol may be used in future assays to reevaluate biological responses as additional research tests are developed over time. These may include, but are not limited to, tests examining aspects of host immunology, virology, cell biology, or human genetics as it relates to any of these aspects. Appropriate informed consent will be obtained for both the collection and storing of samples. The specimens from these evaluations will be labeled with a coded ID and may be stored beyond the funding period.

11 Criteria for Participant and Study Completion and Premature Study Termination

11.1 Participant Completion

Participants will have completed the study at the week 208 (year 4) study visit, or once the study has been closed. All participants will be followed for at least 52 weeks (1 year) post-transplant.

11.2 Participant Withdrawal Criteria

Participants may be prematurely terminated from the study for the following reasons:

1. The participant elects to withdraw consent from all future study activities, including follow-up.
2. The participant is pre-transplant and no longer qualifies for the study (e.g. delisted).
3. 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).
4. The participant dies.

11.3 Participant Replacement

Participants who withdraw or are withdrawn will not be replaced.

11.4 Follow-up after Early Study Withdrawal

If participants are prematurely terminated from the study, no further follow-up will take place.

11.5 Study Pausing Rules

DSMB review of all adverse events related to study procedures will occur at regular intervals, with a minimum of an annual review. In addition, the NIAID Medical Monitor may request an enrollment pause/DSMB review if there is concern at any time based on ongoing reporting of SAEs. In this section, we have outlined thresholds for investigator pausing rules for serious rejection requiring hospitalization or treatment with intravenous steroids, one-year graft loss, complications of kidney biopsy, HIV breakthrough, or persistent HIV virologic failure.

In cases in which there are unexpected rates of biopsy complications triggering an ad hoc DSMB review, all protocol-mandated biopsies will be stopped until after DSMB review and determination; enrollment and transplantation may still occur until the ad hoc DSMB review. For all other pausing rules, enrollment and transplantation can continue until after ad hoc DSMB review, unless the medical monitor and/or PI determine enrollment and/or transplant should stop.

Renal allograft rejection: The pausing rule is based on serious rejection requiring hospitalization or treatment with intravenous steroids. Stock et al reported a 1-year rejection rate of 30% among HIV+ kidney transplant recipients of kidneys with HIV-negative donors [13]. We assume not all of these rejection episodes resulted in hospitalization and as such, our pausing rules for rejection requiring hospitalization or treatment with intravenous agents will be based on a prior distribution of beta (1, 4) for each subgroup of kidney recipients (corresponding to anticipated rejection rate of 25%). Following each episode of serious rejection requiring hospitalization or treatment with intravenous agents, the data center will review the number of serious rejection events to date and determine if any pause in study enrollment and DSMB review is needed according to the methods described in 13.4.5

The table here provides examples of thresholds for pausing.

With this many enrollees in each arm	If there are this many rejections in D- group	Pause if ≥ this many rejections in D+ group	If there are this many rejections in D- group	Pause if ≥ this many rejections in D+ group
10	2	6	5	9
20	4	9	10	15
30	6	12	15	22
40	8	16	20	28
50	10	19	25	34
60	12	22	30	41
70	14	26	35	47

Kidney biopsy complications: Complications of kidney biopsy include need for blood transfusion, need for angiographic intervention or need for surgical intervention due to persistent bleeding, perforation of other organs, or the creation of a fistula.

Need for transfusion after kidney biopsy: Prior studies of kidney biopsy report need for transfusion in up to 8% [45-47], including a recent report at our center in HIV+ individuals which reported a transfusion rate of 3.3% and elevated risk in those who have HCV co-infection [48]. As such, we will apply an expected need for transfusion rate of 7.5% % using a prior beta distribution of (3,37). After any reported transfusion required due to bleeding after biopsy, the data center will review the number of transfusion episodes to date and determine if any pause in protocol biopsies and DSMB review is required according to the methods described in 13.4.5. The table here provides examples of thresholds for pausing based on transfusions and protocol biopsies.

If there are this many total protocol biopsies performed	It will take this many transfusion events to trigger a pause
20	6
40	8
60	10
80	12
100	14
120	16
140	19
160	21

Need for angiographic intervention after kidney biopsy: Prior studies report angiographic interventional radiology (IR) procedure rates between 0.4-1.5% [45-48]. As such we will apply an expected rate of 1% using a prior beta distribution of (0.1, 9.9). After any reported angiographic intervention after kidney biopsy, the data center will review the number of events to date and determine whether a pause in study biopsies and DSMB review are required according to the methods described in 13.4.5. The table here provides examples of thresholds for pausing:

If there are this many total protocol biopsies performed	It will take this many angiographic intervention events to trigger a pause
20	3
40	4
60	5
80	7

100	8
120	9
140	10
160	11

Need for surgical intervention after kidney biopsy: Prior studies report that he need for surgical procedures due to hemorrhage or injury after kidney biopsy is extremely low between 0-.01% [45-48]. As such we will apply an expected rate of 0.01% using a prior beta distribution of (0.01, 99.99). After any reported surgical intervention after kidney biopsy, the data center will review the number of events and determine whether a pause in study biopsies and DSMB review are required according to the methods described in 13.4.5. The table here provides examples of thresholds for pausing:

If there are this many total protocol biopsies performed	It will take this many surgical intervention events to trigger a pause
94 or fewer	2
95-248	3
249-400	4

Graft loss: A prior study reported a 1-year graft loss rate of 10% in 510 HIV+ kidney transplant recipients [13]. As such, after any reported graft loss in the first 12 months, the data center will review the number of complications to date and determine if any pause in study enrollment and DSMB review is required according to the methods described in 13.4.5. The table below provides examples of thresholds for pausing based on 1-year graft loss rates and enrollment.

If there are this many participants in each kidney treatment group	And there are this many graft loss events in the HIV- recipient group	It will take this many events in the HIV D+KT group to trigger a pause
10	0	6
20	1	8
30	1	8
40	2	10
50	2	10
60	3	12
70	3	13
80	4	14

NOTE: Despite the thresholds outlined in the charts below, the NIAID Medical Monitor may request an enrollment pause/DSMB review if there is concern regarding the number of graft losses at any time.

HIV Breakthrough: Based on outcomes from the NIH Multisite Study of HIV+ transplant recipients of HIVD-, we expect detectable HIV viremia to occur in about 8-12% of kidney transplant recipient [15]. As such, after any reported HIV breakthrough, the data center will review the number of breakthrough episodes to date and determine if any pause in study enrollment and DSMB review is required according to the methods described in 13.4.5. The table below provides examples of thresholds for pausing based on breakthrough event rates and enrollment.

If there are this many participants in each treatment group	And there are this many HIV breakthrough events in the HIV- recipient group	It will take this many events in the HIV D+KT group to trigger a pause
10	1	7
20	3	10
30	4	12

40	6	15
50	7	16
60	9	19
70	10	21
80	12	23

Persistent HIV virologic failure is distinct from HIV breakthrough, defined as HIV viral load > 1000 copies/mL for more than 90 days that is not the result of an investigator/physician approved interruption in antiretroviral treatment. We have added an absolute threshold of persistent virologic failure that would lead to study pause and DSMB review, irrespective of comparisons between groups. After every event of persistent HIV virologic failure post-transplant, the data center will review the number of virologic failures and determine if any pause in study enrollment and DSMB review is required according to the methods described in 13.4.5. The table below provides examples of thresholds for pausing based on virologic failure event rates and enrollment

If there are this many total participants	It will take this many episodes of persistent HIV virologic failure to trigger a pause
5	4
10	6
15	8
20	9
30	13
40	16
50	19
60	22
80	29
100	35
120	41
140	47
160	54

In addition, when there are few participants enrolled (< 10), if at any time more than 50% experience persistent virologic failure, the operations committee will act as internal safety committee and will review the data to determine if study pause and DSMB review is required. Study enrollment will be stopped if the Data Safety and Monitoring board determines that there are unexpected fatal or life threatening adverse events related to the use of HIV D+/R+ or study procedures.

12 Safety Monitoring and Reporting

12.1 Overview

This section defines the types of safety data that will be collected under this protocol and outlines the procedures for appropriately collecting, grading, recording, and reporting those data. Adverse events that are classified as serious according to the definition of health authorities must be reported promptly (per Section 12.5, *Reporting of Serious Adverse Events and Adverse Events*) to the NIAID. Appropriate notifications will also be made to site principal investigators, Institutional Review Boards (IRBs), and health authorities, if applicable.

Information in this section complies with *ICH Guideline E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, ICH Guideline E-6: Guideline for Good Clinical Practice*, 21CFR Parts 312 and 320, and applies the standards set forth in the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0: http://rsc.tech-res.com/safetyandpharmacovigilance/gradingtables.aspx.

Participants undergoing solid organ transplantation will have frequent adverse events (AEs) related to the organ transplant surgery and immunosuppressive medications, which are not the subject of this protocol. This protocol focuses on the use of HIV+ deceased donors. Therefore, a number of adverse events outlined below in section 12.4.3 will not be collected in this study unless meeting specified criteria. AEs relevant to the use of HIV D+ include donor-transmitted AIDS related infections and HIV breakthrough related to systemic HIV-superinfection. Collection of these HIV-related infections are described in Section 12.4.4. AEs associated with study mandated blood draws and kidney biopsy at month 6 and year one post-transplant will also be captured. Further detail regarding what events will be captured are summarized below.

12.2 Definitions

12.2.1 Adverse Event (AE)

Any untoward or unfavorable medical occurrence associated with the participant's participation in the research, whether or not considered related to the participant's participation in the research (modified from the definition of adverse events in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice) (from OHRP "Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events (1/15/07)" http://www.hhs.gov/ohrp/policy/advevntguid.html#Q2)

12.2.2 Serious Adverse Event (SAE)

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or Sponsor [DAIT/NIAID], it results in any of the following outcomes (21 CFR 312.32(a)):

1. Death.
2. A life-threatening event: An AE or SAE is considered "life-threatening" if, in the view of either the investigator or Sponsor (DAIT/NIAID), its occurrence places the subject at immediate risk of death. It does not include an AE or SAE that, had it occurred in a more severe form, might have caused death.
3. Inpatient hospitalization or prolongation of existing hospitalization.
4. Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5. Congenital anomaly or birth defect.

6. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

Any instance of COVID-19, regardless of grade, will be reported as a Serious Adverse Event.

12.3 Grading and Attribution of Adverse Events

12.3.1 Grading Criteria

The study site will grade the severity of adverse events experienced by the study participants according to the criteria set forth in the NIAID/Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0. This document (referred to herein as the DAIDS Grading Table) provides a common language to describe levels of severity, to analyze and interpret data, and to articulate the clinical significance of all adverse events. The DAIDS Grading Table has been reviewed by the Protocol Chair and NIAID Medical Monitor and has been deemed appropriate for the participant population to be studied in this protocol.

For additional information and a printable version of the DAIDS Grading Table, consult the DAIDS web site: http://rsc.tech-res.com/safetyandpharmacovigilance/gradingtables.aspx.

Adverse events will be graded on a scale from 1 to 5 according to the following standards in the DAIDS Grading Table:

Grade 1 = mild adverse event

Grade 2 = moderate adverse event

Grade 3 = severe and undesirable adverse event

Grade 4 = potentially life-threatening

Grade 5 = death

Adverse events Grade 3 or higher according to the DAIDS Grading Table will be collected regardless of relationship to study procedures or interventions.

In addition to the DAIDS Grading Table, the following table will be used to grade infections for the purpose of adverse event reporting. All infections, regardless of grade or severity, will be reported on a separate case report form.

Infection Grading Scale

Grade 1 = none

Grade 2 = Oral intervention indicated (e.g. antibiotic, antifungal or antiviral)

Grade 3 = IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated

Grade 4 = life-threatening consequences; urgent intervention indicated

Grade 5 = death

12.3.2 Attribution Definitions

The relationship, or attribution, of an adverse event to the study intervention/procedure will initially be determined by the site investigator and recorded on the appropriate AE case report form. Final determination of attribution for safety reporting will be determined by DAIT/NIAID. The relationship of an adverse event to the study procedure or intervention will be determined using the descriptors and definitions provided in Table 12.3.2.

Table 12.3.2 Attribution of Adverse Events

Code	Descriptor	Relationship (to primary intervention and/or other concurrent mandated study therapy or study procedure)
UNRELATED CATEGORY		
1	Unrelated	The adverse event is clearly not related: there is insufficient evidence to suggest a causal relationship.
RELATED CATEGORIES		
2	Possible	The adverse event has a reasonable possibility to be related; there is evidence to suggest a causal relationship.
3	Definite	The adverse event is clearly related.

For this study, an adverse event will include any untoward or unfavorable medical occurrence associated with, but not limited to:

- **HIV D+ (kidney)**
- **Study mandated procedures**:
  - Protocol kidney biopsy
  - Lymph node collection
  - Research blood draws

12.4 Collection and Recording of Adverse Events

12.4.1 Collection Period

Adverse events will be collected from the time of transplant until a participant completes study participation or until 30 days after he/she prematurely withdraws (without withdrawing consent) or is withdrawn from the study.

12.4.2 Collecting Adverse Events

Adverse events (including SAEs) may be discovered through any of these methods:

- Observing the participant.
- Interviewing the participant [e.g., using a checklist, structured questioning, diary, etc.].
- Receiving an unsolicited complaint from the participant.
- In addition, an abnormal value or result from a clinical or laboratory evaluation can also indicate an adverse event, as defined in Section 12.3, *Grading and Attribution of Adverse Events.*

12.4.3 Exemptions to collection

Certain adverse events commonly occur in this study population and are not relevant to the conduct of this study. Conditions listed below will not be reported as an adverse event unless the event is Grade 3 or higher according to the DAIDS Grading Table AND meets the definition of a serious adverse event.

- Occurrence of upper respiratory infection, nasopharyngitis, bronchitis, diarrhea, constipation, nausea, vomiting, abdominal pain, post-op pain, hypocalcaemia, hypercalcemia, hypercholesterolemia, hypomagnesaemia, hyperglycemia, hyperuricemia, edema, pyrexia, hematuria, proteinuria, dysuria, cough, dyspnea, arthralgia, back pain, hip pain, fracture, headache, dizziness, tremor, acne, insomnia, anxiety, depression, stomatitis/aphthous ulcers, wound complications, AVF thrombosis, neutropenia, anemia, thrombocytopenia, renal impairment, renal artery stenosis, incontinence, hydronephrosis, hematoma, lymphocele, musculoskeletal pain, alopecia, hyperhidrosis, atrial fibrillation.

Elective hospitalizations or hospital admissions for the purpose of conduct of protocol mandated procedures are not to be reported as an SAE unless hospitalization is prolonged due to complications.

There is a nested observational cohort that may have research blood collected at screening/baseline prior to the determination that they will be included in this group. Only adverse events related to the research blood draw will be collected. Following transplant, all follow-up is observational and there will be no adverse event reporting.

12.4.4 HIV Breakthrough and Opportunistic Infections

HIV breakthrough defined as 2 consecutive plasma HIV viral load > 200 copies/mL or one HIV viral load > 1000 copies/mL after a period of virologic control post-transplant.

HIV persistent virologic failure defined as a HIV viral load > 1000 copies/mL for more than 90 days that is not the result of an investigator/physician approved interruption in antiretroviral treatment will be recorded as adverse events, regardless of grade or attribution.

Below is a list of what will be defined as opportunistic infections and conditions for the composite primary endpoint. The events below will be recorded as adverse events, regardless of grade or attribution.

- Aspergillosis, invasive
- Bartonella
- Candidiasis of bronchi, trachea, lungs
- Candidiasis of esophagus
- Cervical Cancer, invasive
- Coccidioidomycosis
- Cryptococcosis
- Cryptosporidiosis
- Cytomegalovirus disease
- Encephalopathy, HIV related
- Herpes simplex: chronic ulcers (>1 month's duration) or bronchitis, pneumonitis, or esophagitis
- HHV-6 disease

- Histoplasmosis
- Isosporiasis
- Kaposi sarcoma
- Lymphoid interstitial pneumonia or pulmonary lymphoid hyperplasia complex
- Lymphoma
- Mucormycosis, invasive
- Mycobacterium avium complex or Mycobacterium kansasii, disseminated or extrapulmonary
- Mycobacterium tuberculosis of any site
- Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
- Nocardia
- Pneumocystis jirovecii pneumonia
- Progressive multifocal leukoencephalopathy
- Salmonella septicemia, recurrent
- Toxoplasmosis of brain
- VZV disseminated disease
- Wasting syndrome attributed to HIV

12.4.5 Recording Adverse Events

Throughout the study, the investigator will record adverse events and serious adverse events as described previously (Section 12.2, *Definitions)* on the appropriate case report form.

The investigator must record pertinent information including, but not limited to, dates that each adverse event occurred, what treatment was prescribed, the outcomes, any follow up information and the investigator's opinion of the attribution of the event. All reports should include:

- Protocol number
- Participant ID
- Site PI
- Date of the event
- Last study intervention
- Description of the event-including intervention(s)
- Outcome-state if resolved or not; with or without residual sequela; if not completely resolved, a follow-up report will be submitted to the coordinating center
- Grade of each toxicity
- Attribution for each toxicity and for each agent

Note: Unavailable details of the event will not delay submission of the known information. As additional details become available, the AE/SAE will be updated and submitted.

A designated monitor from the Coordinating Center will be responsible for reviewing medical records at site visits in order to ensure that these guidelines are maintained.

Once recorded, an AE/SAE will be followed until it resolves with or without sequelae, or until the end of study participation, or until 30 days after the participant prematurely withdraws (without withdrawing consent) or is withdrawn from the study, whichever occurs first.

12.5 Reporting of Serious Adverse Events and Adverse Events

12.5.1 Reporting of Serious Adverse Events to Sponsor

This section describes the responsibilities of the site investigator to report serious adverse events to the sponsor. Timely reporting of adverse events is required by 21 CFR and ICH E6 guidelines.

SAE Reporting Guidelines:

1) All SAEs will be reported to the Data Coordinating Center within 24 hours of awareness to the clinical study data management system. Notification of these events will be made to the Coordinating Center Principal Investigator and NIAID Medical Monitor by email via the data management system.
2) Any unanticipated study problem that does not fit the definition of an adverse event, but which may, in the opinion of the affiliate site Principal Investigator, involve risk to the participant, affect others in the research study, or significantly impact the integrity of research data will also be reported to the Coordinating Center within 24 hours of awareness to the clinical study data management system. These events will also be reported separately to the Coordinating Center by email and are relayed simultaneously to the NIAID Medical Monitor via the data management system.
3) The DCC will submit the SAE report to NIAID via the CRIS system within 72 hours of the event being reported by the site to the DCC.
4) Reporting to local affiliate site IRBs will follow local regulations and guidelines, but these reports and responses must be forwarded to the Coordinating Center as they occur.

Site personnel:

Affiliate site personnel must monitor the medical records of all study participants with a frequency that affords adherence to the guidelines above. Site personnel must notify the site PI and/or designee of any suspected serious adverse events. The PI and/or designee will gather appropriate information and determine if the event meets the criteria above. Upon determination that one or more events have occurred at his/her site, the PI and/or designee will follow the applicable reporting guidelines above. Note that a single event may represent more than one class of event. Site personnel and the awardee institutions will follow the strictest requirement for reporting these events, including U.S. Federal, State, country, local laws and regulations, and institutional policies.

12.5.2 Reporting of Adverse Events to IRBs

All investigators shall report adverse events in a timely fashion to their respective IRBs in accordance with applicable regulations and guidelines. If a centralized IRB is implemented during the study, reporting will follow the regulations of the central IRB.

12.6 Pregnancy Reporting

The investigator shall be informed immediately of any pregnancy in a study participant or a partner of a study participant. A pregnant participant shall be instructed on their medication regimen. The investigator shall counsel the participant and discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the pregnant participant shall continue until the conclusion of the pregnancy.

The investigator shall report to DAIT/NIAID all pregnancies within 3 business days of becoming aware of the event using the Pregnancy CRF. All pregnancies identified during the study shall be followed to conclusion and the outcome of each must be reported. The Pregnancy CRF shall be updated and submitted to the DAIT/NIAID when details about the outcome are available. When possible, similar information shall be obtained for a pregnancy occurring in a partner of a study participant.

Information requested about the delivery shall include:

- Gestational age at delivery
- Birth weight, length, and head circumference
- Gender
- Appearance, pulse, grimace, activity, and respiration (APGAR) score at 1 minute, 5 minutes, and 24 hours after birth, if available
- Any abnormalities

All pregnancy complications that result in a congenital abnormality, birth defect, miscarriage, and medically indicated abortion will be considered an SAE. Such pregnancy events shall be submitted to the DAIT/NIAID using the SAE reporting procedures described above.

12.7 Reporting of Other Safety Information

An investigator shall promptly notify the site IRB as well as the Coordinating Center when an "unanticipated problem involving risks to participants or others" is identified, which is not otherwise reportable as an adverse event. The Coordinating Center will immediately inform NIAID of these reports.

12.8 Review of Safety Information

12.8.1 Medical Monitor Review

The Medical Monitor shall receive real-time reports from the Coordinating Center Data Management System regarding Serious Adverse Events and monthly reports compiling new and accumulating information on grade 3 AEs, SAEs, and pregnancies recorded by the study site(s) on appropriate CRFs.

In addition, the Medical Monitor shall review and make decisions on the disposition of the SAE and pregnancy reports received by the Coordinating Center (See Sections 12.5.1, *Reporting of Serious Adverse Events to Sponsor*, and 12.6, *Pregnancy Reporting*).

12.8.2 DSMB Review

12.8.2.1 Planned DSMB Reviews

The Data and Safety Monitoring Board (DSMB) shall review safety data at least yearly during planned DSMB Data Review Meetings. Data for the planned safety reviews will include, at a minimum, a listing of all reported AEs and SAEs.

The DSMB will be informed of an Expedited Safety Report in a timely manner.

12.8.2.2 Ad hoc DSMB Reviews

In addition to the pre-scheduled data reviews and planned safety monitoring, the DSMB may be called upon for *ad hoc* reviews. The DSMB will review any event that potentially impacts safety at the request of the protocol chair or DAIT/NIAID. In addition, the following events will trigger an *ad hoc* comprehensive DSMB Safety Review:

- Any death in the study which is considered possibly or definitely related to a study procedure or use of HIV+ deceased donor.
- If any of the following adverse events occur at a significant higher rate than expected in the HIV+ deceased donor group: one-year graft loss, serious complications of kidney biopsy, or HIV breakthrough as defined in Section 13.4.5

After review of the data, the DSMB will make recommendations regarding study conduct and/or continuation.

12.8.2.3 Temporary Suspension of enrollment for ad hoc DSMB Safety Review

A temporary halt in enrollment/transplant at all participating centers will be implemented if an *ad hoc* DSMB safety review is required.

13 Statistical Considerations and Analytical Plan

13.1 Overview

This study is a prospective clinical trial of deceased donor kidney transplants in HIV+ recipients using HIV+ and HIV- donors. The primary objective is to assess the safety and efficacy of the practice of using HIV+ kidney donors.

13.2 Endpoints

The primary endpoint is time to a composite of all-cause-mortality, graft failure, serious adverse event, HIV breakthrough, HIV virologic failure, or opportunistic infection at any point after transplant, as ascertained by participating centers per study protocol or through normal clinical post-transplant follow-up. We will compare time to event in HIV D+/R+ vs HIV D-/R+ participants using Cox regression.

13.3 Measures to Minimize Bias

Group assignment/ donor organ HIV status is determined by so-called "natural randomization" as described in Section 3.5. We anticipate that this will be independent of recipient risk, with the possible exceptions of hepatitis C infection (since patients with hepatitis C have higher rates of organ transplantation due to availability of the HCV+ donor pool) and receipt of lymphocyte-depleting agents (since physicians may selectively utilize these agents for patients receiving D+ kidneys). As such, our Cox regression will adjust for these two characteristics (each specified as a binary covariate). In addition, we will adjust for patient participation in the Impact of CCR5 Blockade in HIV+ Kidney Transplant Recipients Trial. CCR5 participation might be associated with transplant rate and therefore, potentially, HIV D- vs D+ exposure and also with the outcome since the trial intervention (maraviroc) might reduce rejection, and because participation and CCR5 might lead to added surveillance or a Hawthorne effect. We considered adjusting for treatment in CCR5 but timely access to treatment assignment may not be possible.

We will also collect information on organ offers that are declined by transplant teams and/or study participants. We will evaluate reasons for organ decline and declined donor covariates.

In this study, neither transplant recipients nor treating physicians will be blinded to the HIV status of the donor as per OPTN policy.

In addition, a centralized laboratory will be used for pathologic, virologic, and immunologic secondary endpoints.

13.4 Analysis Plan

13.4.1 Analysis Populations

In this clinical trial, we will compare HIV+ recipients of HIV D+ and HIV D- kidneys. As the use of organs from HIV D+ is novel, we anticipate that there could be over-enrollment in the HIV D-/R+ group. All HIV D+/R+ transplants will be included in the final analysis population. Alternatively, if a study participant is allocated an HIV D- kidney, the site will contact the Data Center to apply a balancing rule in order to determine if the participant continues in study with full follow-up or in a nested observational cohort with limited follow up for major outcomes.

13.4.2 Analysis of Primary Endpoint(s)

Time to a composite event of all-cause-mortality, graft failure, serious adverse event HIV breakthrough, HIV virologic failure or opportunistic infection will be assessed using Cox regression.

As a sensitivity analysis, the primary analysis will be run again, with the current covariates, but also including the additional covariates: age, gender, race, CD4 count at transplant, years of renal replacement at transplant, and induction type.

13.4.3 Analyses of Secondary and Other Endpoint(s)

Graft function (eGFR) will be analyzed using multilevel mixed-effects linear regression. We will analyze the following time-to-event outcomes using Cox regression: first serious adverse event, incidence of bacterial, fungal, viral infections (time to first infection); incidence of surgical and vascular complications (time to first complication); incidence of HIV-associated renal disease; incidence of malignancies. Additionally, we will analyze each component of the composite primary endpoint using Cox regression. We will analyze the following binary outcomes using logistic regression: KSHV serology, APOL1 variant types. For these secondary analyses we will use a frequentist rather than a Bayesian approach, reporting point estimates and 95% confidence intervals of hazard ratios as per standard methods. Additionally, we will compare incidence of opportunistic infections over time using Poisson regression.

13.4.4 Analyses of Secondary Immunologic and Virologic Endpoints

HIV superinfection

We will explore for the incidence of systemic HIV-superinfection in plasma and PBMCs isolated from blood in HIV D+/R+ participants at all times post-transplant and in all participants who experience HIV breakthrough or HIV persistent virologic failure. We will also examine for the presence of tissue specific HIV-superinfection in HIV D+/R+ participants by laser capture microdissection, and sequencing of proviral DNA to determine whether there is viral infiltration from the host into the new organ.

The sequences from these assays will be compared to the sequences from donors collected as part of a separate protocol, in which we examine the prevalence of archived antiretroviral-associated drug resistance mutations and X4 tropic virus using commercially available assays. This sequence data will be available for phylogenetic analysis in conjunction with recipient virus sequences collected prior to transplant.

Analysis of HIV reservoir size

PCR measurements of HIV DNA are not limited as they measure non-replication competent defective proviruses that may not be clinically relevant. Therefore, we plan to measure the HIV latent reservoir using a novel intact provirus detection. We will also bank specimens for other assays, including viral outgrowth assays or the best assay available at the time.

13.4.5 Pausing Rules for Safety

Biopsy complications

Complications of biopsy include need for blood transfusion, persistent bleeding or injury requiring angiographic intervention, surgery, perforation of other organs, or the creation of a fistula.

Need for transfusion after kidney biopsy: Prior reports on kidney biopsy report need for transfusion in up to 8%, including a recent report at our center in HIV+ individuals which reported a transfusion rate of 3.3% and elevated risk in those who have HCV co-infection [45-48]. As such, we will apply an expected complication rate including need for transfusion of 7.5%, using a prior distribution of beta (3, 37) which has an expected value of 0.075. At any point during the study, if there have been n biopsies and x serious complications, the posterior distribution of the complication rate will be beta (3+x, 37+n-x). If the 25th percentile of this distribution exceeds

0.1 (indicating a 75% probability that the biopsy complication rate in our study exceeds 10%) we will pause the study enrollment pending DSMB recommendation.

Need for angiographic intervention after kidney biopsy: Prior studies report angiographic interventional radiology procedure rates between 0.4-1.5% [45-48]. As such we will apply an expected rate of 1% using a prior beta distribution of (0.1, 9.9). After any reported angiographic intervention after kidney biopsy, the data center will review the events. If there have been n biopsies and x serious complications, the posterior distribution of the complication rate will be beta (0.1+x, 9.9+n-x). If the 25th percentile of this distribution exceeds 0.05 (indicating a 75% probability that the angiographic intervention rate in our study exceeds 5%) we will pause the protocol biopsies pending DSMB recommendation.

Need for surgical intervention after kidney biopsy**:** Prior studies report that the need for surgical procedures due to hemorrhage or injury after kidney biopsy is extremely low between 0-.01% [45-48]. As such we will apply an expected rate of 0.01% using a prior beta distribution of (0.01, 99.99). After any reported surgical intervention after kidney biopsy, the data center will review the events. If there have been n biopsies and x serious complications, the posterior distribution of the complication rate will be beta (0.01+x, 99.99+n-x). If the 25th percentile of this distribution exceeds .005 (indicating a 75% probability that the surgical intervention rate in our study exceeds 0.5%) we will pause the protocol biopsies pending DSMB recommendation.

These Bayesian analyses are for safety monitoring purposes only, during the course of the study; final analyses will be a traditional frequentist framework and will not use priors.

Graft loss

After every kidney graft loss occurring within 12 months post-transplant, we will perform a Bayesian analysis of the difference in graft loss rates between HIV D+ recipients versus HIV+ recipients of HIV- donor kidneys. A prior study reported a 1-year graft loss rate of 10% in 510 HIV+ kidney transplant recipients [13]. As such, our pausing rules for 1-year graft loss will be based on a prior distribution of beta (5, 45) for each subgroup of kidney recipients (corresponding to anticipated 1-year graft loss rate of 10%). Following each graft loss within the first-year post-transplant, we will analyze the difference of the posterior distributions using a Monte Carlo simulation. If there is a 75% chance that [12-month graft loss in HIV D+ recipients] minus [12-month graft loss in HIV+ recipients of HIV- donor organs] exceeds 5%, we will pause the study pending DSMB recommendation.

HIV breakthrough

After every event of HIV breakthrough post-transplant, we will perform a Bayesian analysis of the difference in breakthrough rates between HIV D+ recipients versus HIV+ recipients of HIV- donor kidneys. Based on outcomes from the NIH Multisite Study of HIV+ transplant recipients of HIVD-, we expect detectable HIV viremia to occur in about 8-12% of individuals [15]. Based on this expectation, we will use a prior distribution of beta (8.5, 41.5) for each subgroup. We will then analyze the difference of the distributions using a Monte Carlo simulation. If there is a 75% chance that [cumulative incidence of breakthrough in HIV D+ recipients] minus [cumulative incidence of breakthrough in HIV+ recipients of HIV- donor kidneys] exceeds 5%, we will pause the study pending DSMB recommendation.

Persistent HIV virologic failure

Persistent virologic failure is distinct from HIV breakthrough, defined as HIV viral load > 1000 copies/mL for more than 90 days that is not the result of an investigator/physician approved interruption in antiretroviral treatment. We have added an absolute threshold of persistent virologic failure in the study population that would lead to

study pause and DSMB review, irrespective of comparisons between groups. After every event of persistent HIV virologic failure post-transplant, we will perform a Bayesian analysis of the overall HIV virologic failure rate. We expect persistent virologic failure to occur in no more than 15% of individuals [15]. Based on this expectation, we will use a prior distribution of beta (1, 7) which corresponds to 12.5% of individuals. At any point during the study, if there have been n participants and x episodes of persistent HIV virologic failure, the posterior distribution of the complication rate will be beta (1+x, 7+n-x). If the 25th percentile of this distribution exceeds 0.3 (indicating a 75% probability that the HIV persistent virologic failure rate in our study exceeds 30%) we will pause the study enrollment pending DSMB recommendation.

Renal allograft rejection

We anticipate a 1-year rejection requiring hospitalization rate of 25% among HIV+ kidney transplant recipients. As such, our pausing rules for 1-year rejection will be based on a prior distribution of beta (1, 4) for each subgroup of kidney recipients (corresponding to anticipated rejection rate of 25%). Following each episode of rejection, we will analyze the difference of the posterior distributions using a Monte Carlo simulation. If there is a 75% chance that [rejection in HIV D+ recipients] minus [rejection in HIV+ recipients of HIV- donor organs] exceeds 10%, we will pause study enrollment pending DSMB recommendation.

13.5 Interim Analyses

No interim efficacy analyses are planned. On an annual basis or more frequently as needed, the data center will report a summary of safety events to the DSMB. This will include an open session with the following safety events summarized: number of serious rejection events requiring hospitalization or treatment with intravenous steroids, number of graft losses, number of complications of allograft biopsy, number of HIV breakthrough events and number of persistent HIV virologic failure events. A summary of these events across study participants will be presented in an open session. In a separate closed session, the DSMB will review safety event counts stratified by study arm, as well as details of previously run Bayesian-framework statistical tests as described in Section 13.4.5.

13.6 Statistical Hypotheses

Primary outcome: We will compare cumulative incidence of the composite event among HIV D+/R+ participants to HIV D-/R+ participants in a non-inferiority framework, with a δ of 3.0, where δ represents the non-inferiority margin. The null hypothesis will be that the adjusted hazard ratio for HIV D+ KT exceeds 3.0 (inferiority). The alternative hypothesis will be that the adjusted hazard ratio for HIV D+ KT is less than or equal to 3 (non-inferiority). We will reject the null hypothesis if the upper bound of the two-sided confidence interval of the hazard ratio for HIV D+ KT, obtained via Cox regression is less than 3.0. Since KT in HIV+ recipients is estimated to have a five-fold reduction in mortality risk, a δ of 3.0 is within the likely survival benefit from HIV+ KT compared to remaining on dialysis [50].

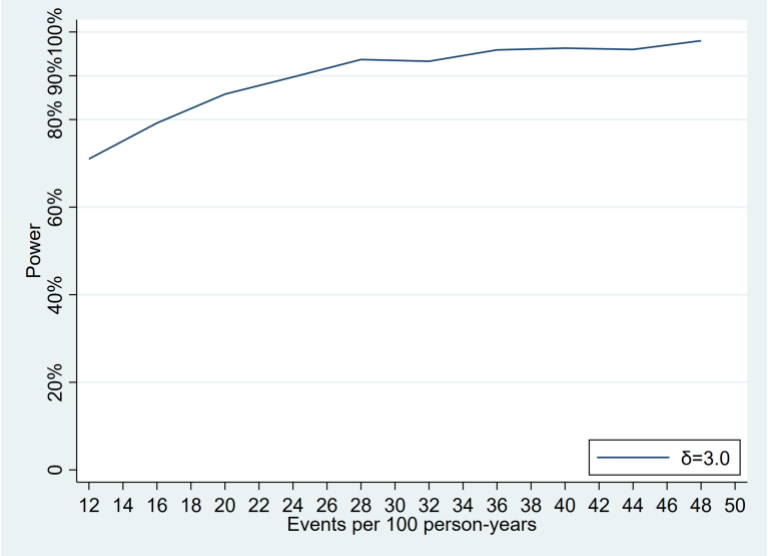
The delta is based on a study of HIV+ kidney transplantation in which the point estimate of the mortality hazard ratio following transplant was 0.23 indicating a > 4-fold survival benefit. The confidence interval for the survival benefit in this study was wide given a small sample size however studies of kidney transplantation in the HIV-uninfected population also support the specified delta. Wolfe and colleagues reported the estimated mortality hazard ratio following transplant was 0.32 (0.30-0.35), corresponding to a survival benefit of 3.12 (95% confidence interval 2.86-3.33) [51].

Secondary outcome, opportunistic infections: We will compare cumulative incidence of opportunistic infections among HIV D+/R+ participants to HIV Ds/R+ participants in a non-inferiority framework, with a non-inferiority margin of 3.0. The null hypothesis will be that the adjusted incidence rate ratio for HIV D+ KT exceeds 3.0 (inferiority). The alternative hypothesis will be that the adjusted incidence rate ratio for HIV D+ KT is less than or equal to 3.0 (non-inferiority). We will reject the null hypothesis if the upper bound of the two-sided confidence interval of the incidence rate ratio for HIV D+ KT, obtained via Poisson regression, is less than 3.0.

13.7 Sample Size Considerations

We will enroll 100 HIV+ KT recipients in each group. Based on data from our pilot study, we assume cumulative incidence of [time to first SAE] at 4 years of approximately 70%, which corresponds to 0.3 events per person-year. Additionally, from prior studies, we assume a rate of 0.1 composite opportunistic infections/breakthrough events per person-year and 0.067 composite graft loss and mortality events per person-year. Time to first SAE may be correlated with other outcomes. Conservatively, we can expect 0.4 total composite outcomes per person-year. If we assume that HIV D+ KT confers 50% increased risk (underlying true HR = 1.5), then with 100 KT recipients in each group followed for 1-4 years post-transplant and α of 0.05 and modeling graft loss as a Poisson process, we calculate via simulation that we will have 96% power if the event rate is 0.4 events per person-year.

Figure 6. Power Curve.



13.8 Sensitivity analyses

Although the primary outcome of the study is a composite outcome, it is possible that there could be a statistically significant difference between groups in mortality or another major outcome, but for the primary analysis to nevertheless demonstrate noninferiority with regards to the composite outcome. As such, we will perform a sensitivity analysis with the outcome of mortality only, comparing D+ recipients vs D- recipients using Cox regression, following all patients until mortality, loss to follow-up, or administrative censorship at end-of-study. For this sensitivity analysis, the null hypothesis will be no association between donor HIV status and mortality; we will test this null hypothesis using a two-sided test with an α of 0.05, and report point estimates and 95% confidence intervals of hazard ratios as per standard Cox regression models. We will then conduct similar sensitivity analyses using other outcomes as follows:

[death or persistent HIV virologic failure]; [death, persistent HIV virologic failure, or graft loss (retransplant)]; [death, persistent HIV virologic failure, graft loss, or SAE]; and [death, persistent HIV virologic failure, graft loss, SAE, or opportunistic infection]. In each case we will report point estimates and 95% confidence intervals for D+ vs D- recipients.

14 Identification and Access to Source Data

14.1 Source Data

Source documents and source data are considered to be the original documentation where participant information, visit consultations, examinations and other information are recorded. Documentation of source data is necessary for the reconstruction, evaluation and validation of clinical findings, observations and other activities during a clinical trial.

14.2 Access to Source Data

The site investigators and site staff will make all source data available to DAIT/NIAID as well as to relevant health authorities. Authorized representatives as noted above are bound to maintain the strict confidentiality of medical and research information that may be linked to identified individuals.

15 Protocol Deviations

15.1 Protocol Deviation Definitions

Protocol Deviation – The investigators and site staff will conduct the study in accordance to the protocol; no deviations from the protocol are permitted. Any change, divergence, or departure from the study design or procedures constitutes a protocol deviation. As a result of any deviation, corrective actions will be developed by the site and implemented promptly.

Major Protocol Deviation (Protocol Violation) - A Protocol Violation is a deviation from the IRB approved protocol that may affect the participant's rights, safety, or well-being and/or the completeness, accuracy and reliability of the study data. In addition, protocol violations include willful or knowing breaches of human subject protection regulations, or policies, any action that is inconsistent with the NIH Human Research Protection Program's research, medical, and ethical principles, and a serious or continuing noncompliance with federal, state, local or institutional human subject protection regulations, policies, or procedures.

Non-Major Protocol Deviation - A non-major protocol deviation is any change, divergence, or departure from the study design or procedures of a research protocol that does not have a major impact on the participant's rights, safety or well-being, or the completeness, accuracy and reliability of the study data.

15.2 Reporting and Managing Protocol Deviations

The study site principal investigator has the responsibility to identify, document and report protocol deviations as directed by the study Sponsor. However, protocol deviations may also be identified during site monitoring visits or during other forms of study conduct review.

16 Ethical Considerations and Compliance with Good Clinical Practice

16.1 Statement of Compliance

This clinical study will be conducted using good clinical practice (GCP), as delineated in *Guidance for Industry: E6 Good Clinical Practice Consolidated Guidance*, and according to the criteria specified in this study protocol. Before study initiation, the protocol and the informed consent documents will be reviewed and approved by the IRB. Any amendments to the protocol or to the consent materials will also be approved by the IRB before they are implemented.

16.2 Informed Consent Process

The consent process will provide information about the study to a prospective participant and will allow adequate time for review and discussion prior to his/her decision. The principal investigator or designee listed on the Investigator of Record Form will review the consent and answer questions. The prospective participant will be told that being in the trial is voluntary and that he or she may withdraw from the study at any time, for any reason. All participants (or their legally acceptable representative) will read, sign, and date a consent form before undergoing any study procedures. Consent materials will be presented in participants' primary language. A copy of the signed consent form will be given to the participant.

The consent process will be ongoing. The consent form will be revised when important new safety information is available, the protocol is amended, and/or new information becomes available that may affect participation in the study. Study participants will be re-consented if new information affecting participant safety is made available.

16.3 Privacy and Confidentiality

A participant's privacy and confidentiality will be respected throughout the study. Each participant will be assigned a unique identification number and these numbers rather than names will be used to collect, store, and report participant information. Site personnel will not transmit documents containing personal health identifiers (PHI) to the study sponsor or their representatives.

17 Publication Policy

The publication guidelines and policies stipulated in the grant will apply to this protocol.

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Appendix 1. Schedule of Events (HIV Positive Transplant Recipient, Groups 1 and 2)

Pre-Transplant On-Going Eligibility Monitoring

HIV+ KIDNEY PATIENTS	
Ongoing Eligibility Monitoring	
CD4+T-cell count every 16 weeks	**X**
HIV-1 RNA (bDNA or PCR)[a]	**X**

[a]Reviewed and recorded every 26 weeks if available. The most recent HIV VL should be < 50 copies, but this result can be documented outside the 26-week window according to the judgment of the local clinical team and site investigator. Candidates who are unable to tolerate ART due to organ failure or who have recently started ART may have detectable viral load and still be eligible if the study team justifies ART regimen post-transplant.

Years:	Year **0**	Year **1**									Years **2** - **4** every 6 m	For Cause Visit
Weeks:	**Screen/ Pre-txp**	Day 0	Week 1	2	3	4	8	**13**	**26**	**39**	**52**	53-208	**FC**
Visit Numbers:	**-1**	0	1	2	3	4	5	**6**	**7**	**8**	**9**	10-15	
STANDARD OF CARE ASSESSMENTS													
CLINICAL													
Medical History	**X**												
Transplant Data (including PRA, antibody testing)		**X**											
Documentation of HIV infection	**X**												
Informed Consent	**X**												
Symptom & Medical Review plus Physical Exam	**X[2]**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Quantiferon or PPD or other latent TB licensed assay		**X[2]**											
Cervical and/or anal PAP (per SOC)		**X**											
Pregnancy Test (serum or urine)		**X[5]**											
Quality of Life Assessment	**X[6]**								**X**		**X**	**Y2, Y3, Y4**	
Patient Reported Outcomes									**X**		**X**	**Y2, Y3, Y4**	
Concomitant Medications		**X**	→	→	→	→	→	→	→	→	→	→	**X**
Adverse/Serious Adverse Event Assessment		**X**	→	→	→	→	→	→	→	→	→	→	**X**
SAFETY LABS													
CBC, Renal/Electrolytes/glucose/albumin LFTs		**X[2]**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Fasting Lipid Panel (Chol, LDL, HDL, TGL)		**X[2]**									**X**	**Y2**	
DSA									**X[3]**	**X[3]**	**X**	**X[3]**	**X[3]**
Immunosuppressant levels			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	

Years:	Year **0**	Year **1**										Years **2** - **4** every 6 m	For Cause Visit
Weeks:	**Screen/ Pre-txp**	Day 0	Week 1	2	3	4	8	**13**	**26**	**39**	**52**	53-208	**FC**
Visit Numbers:	**-1**	0	1	2	3	4	5	**6**	**7**	**8**	**9**	10-15	
HIV LABS													
CD4+ T-cell count	**X[1]**	**X[1]**				**X**	**X**	**X**	**X**	**X**	**X**	**X**	
HIV-1 RNA (PCR)	**X[1]**	**X[1]**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Serology													
CMV Ab, EBV Ab, Toxoplasmosis Ab, Syphilis Ab, RPR		**X[2]**											
HepBSAg, HepBSAb, HepB core Ab, HepB DNA (only if HbsAg+)		**X[2]**											
HCV Ab, HCV RNA (only if HCV Ab+)		**X[2]**											
RESEARCH													
Specimen (Study Participants)													
Recipient Blood collected for research (~100mL) [7]	**X[4]**	**X[4]**						**X**	**X**		**X**	**Y2, Y3, Y4**	
Recipient Lymph node (1 large or 2-3 small nodes)		**X**											
Urine for kidney recipients (~100mL, unless anuric)	**X[4]**	**X[4]**							**X**		**X**		**X**
Recipient Blood Collection for research (~30mL)													**X**
Biopsy													
Recipient biopsy									**X**		**X**		**X**

1. See frequency of pre-transplant monitoring in table above. A repeat Day 0 draw is not necessary if not clinically indicated and there is an available result that meets eligibility criteria.
2. Completed within 12 months prior to transplantation. Do not need to repeat unless clinically indicated (e.g. do not repeat positive Ab). Documentation of prior results with medical record review is allowed.
3. A sample should also be sent to the local HLA lab for testing if a biopsy is performed for suspected rejection.
4. Single baseline blood sample is required, collected during the screening period (within 26 weeks of transplant) or on the day of transplant before administration of immunosuppression. If a subject is randomized to the nested observational cohort, the baseline research blood sample is not required. If the blood is collected prior to randomization, the baseline samples will be stored but no further research blood will be collected.
5. Within 30 days prior to transplant.
6. Completed within 12 months of transplant.
7. For participants co-enrolled in the *Impact of CCR5 Blockade in HIV+ Kidney Transplant Recipients Trial*, sample collection for HOPE is required at baseline (approximately 55 mLs), and at time of HIV viral breakthrough (30 mLs). If the site is unable to obtain a research blood sample for HOPE at weeks 13, 26, 52 and annually it will not be considered a protocol deviation.

Appendix 2. HIV- to HIV+ Nested Observational Cohort

Years:	Year **1**			Years **2** - **4**
Weeks:	Day 0	**26**	**52**	53-208
Visit Numbers:	0	**1**	**2**	3-5
STANDARD OF CARE ASSESSMENTS				
CLINICAL				
Transplant Data (including PRA, antibody testing)	**X**			
Symptom & Medical Review plus Physical Exam	**X**	**X**	**X**	**X**
Quantiferon or PPD or other latent TB licensed assay	**X**[1]			
Cervical and/or anal PAP (per SOC)	**X**			
Pregnancy Test (serum or urine)	**X**[2]			
Post-Transplant Events (Death, rejection, graft failure, AIDS, HIV breakthrough)	**X**	→	→	→
Concomitant Medications	**X**	→	→	→
Adverse/Serious Adverse Event Assessment (only related to research blood draw)	**X**			
SAFETY LABS				
CBC, Renal/Electrolytes/glucose/albumin, LFTs	**X**	**X**	**X**	**X**
DSA		**X**	**X**	**X**
Immunosuppressant levels		**X**	**X**	**X**
HIV LABS				
CD4+ T-cell count	**X**[3]	**X**	**X**	**X**
HIV-1 RNA (PCR)	**X**[3]	**X**	**X**	**X**
Serology				
CMV Ab, EBV Ab, Toxoplasmosis Ab, Syphilis Ab/RPR	**X**[1]			
HepBsAg, HepBsAb, HepB core Ab, HepB DNA (only if HbsAg+)	**X**[1]			
HCV Ab, HCV RNA (only if HCV Ab+)	**X**[1]			

1. Completed within 12 months prior to transplantation. Do not need to repeat unless clinically indicated (e.g. do not repeat positive Ab). Documentation of prior results with medical record review is allowed.
2. Within 30 days prior to transplant.
3. A repeat Day 0 draw is not necessary if not clinically indicated and there is an available result that meets eligibility criteria.

Appendix 3. Schedule of Events (Donor)

		Visit 1
GENERAL ASSESSMENTS		
Donor Information	UNOS ID, Match ID	X
	Donor Risk Assessment Interview (DRAI)	X
	Donor Summary Chart from Donor Net	X
	HIV Specific Data Collection form	X
CORE LABORATORY		
Donor blood (200 mL)[1]	Banked blood specimen, sent by OPO	X
Donor allograft tissue	Biopsy done by Transplant Center ("back table biopsy")	X[2]

[1]HIV+ or suspected false positive donors only; for HIV- donors, a smaller sample for APOL1 testing will be obtained.

[2]Two core samples will be collected for a "standard of care" biopsy. For all HIV+ (or false positive) organs, a third research core sample will be collected and flash frozen.

Appendix 4. HOPE Act Safeguards and Research Criteria