

**Prospective Observational Study of Heart and Lung Transplantation from Deceased Donors with HIV to Transplant Recipients with HIV**

**VERSION 0.9.2 / May 27, 2025**

**Protocol Committee**

Vagish Hemmige, MD (Montefiore Einstein)

Maryjane Farr, MD, MSc (University of Texas Southwestern)

Saima Aslam, MD, MS (University of California San Diego)

Sarath Raju, MD MPH (Johns Hopkins University)

Emily Blumberg, MD (University of Pennsylvania)

Christine Durand, MD (Johns Hopkins University)

Allan Massie, PhD (New York University)

Moreno Rodrigues, PhD (Johns Hopkins University)

***PROTOCOL***

*Prospective Observational Study of Heart and Lung Transplantation from Deceased Donors with HIV to Transplant Recipients with HIV: HOPE in Action Thoracic Pilot*

*Version 0.9.2 / May 27, 2025*

# Protocol Synopsis

|  |  |
| --- | --- |
| **Title** | Prospective Observational Study of Heart and Lung Transplantation from Deceased Donors with HIV to Transplant Recipients with HIV |
| **Short Title**  | HOPE Thoracic Pilot Study |
| **Number of Sites**  | Approximately 25 clinical sites |
| **Study Objectives** | Primary Objective: The primary objective is to determine whether receiving a heart and/or lung from a donor with (D+) vs without HIV (D-) is safe in regard to major transplant-related and HIV-related complications.Secondary Objectives: The secondary objective is to measure post-transplant outcomes of D+ and D- heart (HT) and/or lung transplant (LT) in HIV+ recipients (R+). |
| **Study Outcomes** | Primary Outcome: Patient survival at one yearSecondary Outcomes: 1. Patient survival over time
2. Incidence of graft failure (relisting/retransplantation) over time
3. Incidence, type (cellular or antibody mediated), and severity (grade) of rejection, biopsy proven or hemodynamic compromise rejection in absence of a biopsy or histological rejection, by local site
4. Proportion with primary graft dysfunction
5. Development of cardiac allograft vasculopathy (HT only) over time
6. Development of chronic lung allograft dysfunction (CLAD) (LT only) in lung transplant over time
7. HIV disease control (viral load and CD4 cell count) over time
8. Incidence of bacterial, fungal, viral and other opportunistic infections
9. Incidence of post-transplant malignancies
10. Estimated glomerular filtration rate over time
 |
| **Study Design** | Prospective observational study  |
| **Accrual Objective** | Prospective transplants: * Approximately 20 HIV+ recipients of a heart and/or lung from HIV+ deceased donors (HIV D+/R+)
* Approximately 20 HIV- recipients of a heart and/or lung from HIV- deceased donors (HIV D-/R+)

  |
| **Study Duration** | 1-year minimum (up to 10 years) follow-up post-transplant |
| **Recipient Inclusion Criteria** | 1. Participant meets local criteria for thoracic transplant. Participants listed for simultaneous heart/lung, heart/kidney or lung/kidney are eligible if they meet the standard criteria for both organs at the local center.
2. Participant is able to understand and provide informed consent.
3. Participant has documented HIV infection by any licensed assay or documented history of detectable HIV-1 RNA.
4. Participant is ≥ 18 years old.
5. HIV-1 RNA < 50 copies/mL.\* Viral blips between 50-400 copies will be allowed as long as there are not consecutive measurements >200 copies/mL.
6. Participant is not suffering from significant wasting thought to be related to HIV disease.\*
 |
| **Recipient Exclusion Criteria** | 1. Participant has prior progressive multifocal leukoencephalopathy, cryptosporidiosis of > 1 month, or primary CNS lymphoma.\*
2. Participant is pregnant or breastfeeding. *Note: Participants who become pregnant post-transplant will be followed on study and managed per site practice.*
3. Medical problems which, in the opinion of the investigator, may pose additional risks.
 |
| **Deceased Donor Criteria** | 1. Donation after brain death or circulatory death.
2. HIV+ donors have confirmed HIV infection\* (by medical record history and 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.
 |

\*These eligibility criteria align with the *Final Revised Human Immunodeficiency Virus (HIV) Organ Policy Equity (HOPE) Act Safeguards and Research Criteria for Transplantation of Organs From Donors with HIV*.

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# Glossary of Abbreviations

|  |  |
| --- | --- |
| AIDS  | Acquired Immunodeficiency Syndrome  |
| AE  | Adverse Event  |
| AR  | Acute Rejection  |
| ART  | Antiretroviral therapy  |
| BALF | Bronchoalveolar Lavage Fluid |
| CAV | Cardiac Allograft Vasculopathy |
| 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  |
| GCP  | Good Clinical Practice  |
| HBV  | Hepatitis B Virus  |
| HCV  | Hepatitis C Virus  |
| HDC | Hemodynamic Compromise |
| 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  |
| 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  |
| 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  |

# Study Definitions Page

|  |  |
| --- | --- |
| Acute Cellular Rejection (Heart)1  | According to ISHLT definitions |
| Antibody Mediated Rejection (Heart)1  | According to ISHLT definitions |
| Acute Cellular Rejection (Lung)2  | According to ISHLT definitions |
| Antibody Mediated Rejection (Lung)2  | According to ISHLT definitions |
| Cardiac Allograft Dysfunction | Ejection fraction of <40% |
| Cardiac Allograft Vasculopathy3 | According to ISHLT definitions |
| Chronic Lung Allograft Dysfunction (CLAD)4 | According to ISHLT definitions |
| Chronic dialysis  | Need for renal replacement therapy for more than 90 days  |
| Clinically Suspected and Treated Rejection  | Clinical suspicion for and treatment for 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. |
| Cardiomyopathy (native heart) | Ischemic:Myocardial dysfunction primarily due to native atherosclerotic coronary artery disease (CAD).Non‐ischemic:Myocardial dysfunction NOT primarily due to native atherosclerotic coronary artery disease. CAD may be present but disproportionate to the degree of myocardial dysfunction.Dilated cardiomyopathy:Left ventricular end diastolic volume indexed to BSA (indexed LV EDV) > 75 mL/m2 (males) or > 61 mL/m2 (females). |
| 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. |
| Graft Failure (Heart) | Any of the following events: death; re-listing or re‐transplantation;  |
| Graft Failure (Kidney)  | Any of the following events: initiation of post-donation chronic dialysis; re-transplantation; death. |
| Graft Failure (Lung) | Any of the following events: death, relisting or retransplantation |
| Hemodynamic Compromise (HDC) | The following criteria are required for hemodynamic compromise rejection whether or not a biopsy is performed and whether or not there is histological rejection: * Need for inotropic agents due to either a Cardiac Index (CI) <2.0 L/min/m2 or clinical evidence of acute decompensated heart failure and,
* Ejection fraction of <40%
 |
| HIV-Associated Renal Diseases  | HIV-Associated NephropathyHIV-Associated Focal Segmental Glomerulosclerosis, non-collapsing typeHIV-Associated Immune Complex Kidney diseaseHIV-Associated Thrombotic Microangiopathy |
| 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 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. |
| KSHV | Kaposi Sarcoma Associated Herpes Virus |
| Lost to Follow-up  | Missing all in-person follow up visits and cannot be reached by telephone or mail after 12 months. |
| Opportunistic infections and conditions  | Aspergillosis, invasive Bartonella Candidiasis of bronchi, trachea, or lungs Candidiasis of esophagus Cervical cancer, invasive Coccidioidomycosis Cryptococcosis Cryptosporidiosis Cytomegalovirus end-organ disease Encephalopathy, HIV related Herpes simplex: chronic ulcers (>1 month's duration) or bronchitis, pneumonitis, or esophagitis HHV-6 disease Histoplasmosis Isosporiasis Kaposi sarcoma (KS) KSHV associated disease lymphoproliferative such as Castleman’sKSHV associated inflammatory cytokine syndrome (KICS)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. |
| Primary graft dysfunction (heart)5 | Left ventricular, right ventricular, or biventricular dysfunction that occurs within 24 hours after surgery and is not associated with an identifiable cause such as hyperacute rejection, pulmonary hypertension, massive blood product transfusion, or prolonged graft ischemic time. |
| Primary graft dysfunction (lung)6 | Presence of diffuse pulmonary opacities on thoracic imaging and hypoxemia without other identifiable cause, developing in the first 72 hours after lung allograft implantation. |
| 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. |

# Study Objectives

## Objectives

### 1.1.1 Primary Objective

The primary objective is to determine whether receiving a heart and/or lung from a donor with (D+) vs without HIV (D-) is safe in regard to major transplant-related and HIV-related complications.

### 1.1.2 Secondary Objective

The secondary objective is to measure post-transplant outcomes of D+ and D- heart (HT) and/or lung transplant (LT) in HIV+ recipients (R+).

## Outcomes

### 1.2.1 Primary Outcome

The primary outcome is patient survival at one year.

### Secondary and Exploratory Outcomes

 The secondary outcomes include:

1. Patient survival over time
2. Incidence of graft failure (relisting/retransplantation) over time
3. Incidence, type (cellular or antibody mediated), and severity (grade) of rejection, biopsy proven or hemodynamic compromise rejection in the absence of a biopsy or histological rejection, by local site
4. Proportion with primary graft dysfunction
5. Development of cardiac allograft vasculopathy (HT only) over time
6. Development of chronic lung allograft dysfunction (CLAD) (LT only) in lung transplant
7. HIV disease control (viral load and CD4 cell count) over time
8. Incidence of bacterial, fungal, viral and other opportunistic infections
9. Incidence of post-transplant malignancies
10. Estimated glomerular filtration rate over time

# Background and Scientific Rationale

People with HIV are at risk for end stage cardiovascular and lung disease7. Observational data demonstrates good outcomes of heart and lung transplant using organs from donors without HIV for recipients with HIV (HIV D-/R+), comparable to outcomes in transplant recipients without HIV (R-)8.9.

Moreover, with passage of the HIV Organ Policy Equity (HOPE) Act, transplantation from donors with HIV to recipients with HIV (HIV D+/R+) is now feasible with good outcomes in HIV D+/R+ kidney and liver transplantation10,11. Under the HOPE Act, there has also been a successful HIV D+/R+ heart transplant12. Building on these experiences, the objective of our study is to share data on the first HIV D+/R+ thoracic transplants under the HOPE Act in the United States.

# Study Design

## Description of Study Design

This is a prospective observational study to evaluate the safety and clinical outcomes in thoracic transplant recipients with HIV (R+) who receive hearts and/or lungs from donors with (D+) vs without HIV (D-). Adults with HIV in need of a heart or lung transplant who meet study-specified criteria for will be offered enrollment in the study.

## Enrollment of Pre-Transplant Participants

All participants who meet eligibility criteria and who provide informed consent will be enrolled into the pre-transplant phase of the study. In the pre-transplant phase of the study, standard waitlist and study-specific eligibility will be confirmed. As per Organ Procurement and Transplantation Network (OPTN) Policy 15.6, at the time of transplant listing, “willing to accept an organ from donor with HIV” status will be indicated in UNet™, the secure database used by transplant hospitals and organ procurement organizations (OPOs) to coordinate organ recovery and waitlist candidate matching.

If an organ from a donor with or without HIV becomes available for a participant, the transplant center and participant will have an opportunity to accept or decline the organ offer.

Participants who receive a heart or lung from a donor with HIV (D+) will be in the HIV D+/R+ arm and participants who receive a heart or lung from a donor without HIV (D-) will be in the D-/R+ arm. Participants who accept a HIV suspected false positive (FP) organ (details below) will be part of the D-/R+ arm once confirmatory testing confirms negative HIV status of the donor. Participants will be followed for a minimum of 1 year and up to 10 years post-transplant.

## Clarification for the Use of Organs from HIV Suspected False Positive (FP) Donors

Deceased donors are generally screened for HIV with 2 assays, an antibody (Ab), an Ab/antigen (Ag) combination assay and/or a nucleic acid test (NAT). Deceased donors with no history of HIV will occasionally test positive on only one HIV assay, indicating that it might be a false positive (FP) result. In this scenario, either Organ Procurement Organizations (OPOs) or the Johns Hopkins University (JHU) HOPE in Action laboratory will perform confirmatory testing. Once confirmatory testing is complete, the recipient will be assigned to the D+ or D- group as appropriate.

# Selection of Participants

**Figure 1**

Thoracic Transplant Candidates with HIV

Meet inclusion criteria, informed consent

HIV D+/R+

Enrolled in pre-transplant phase of study

UNetTM status “willing to accept organ from donor with HIV (HIV D+)”

Match runs by OPTN/UNOS

HIV D-/R+

HIV D+ accepted

HIV D-/FP accepted

## 4.1 Inclusion/Exclusion Criteria

### 4.1.1 Recipient Inclusion Criteria

1. Participant meets local criteria for thoracic transplant. Participants listed for simultaneous heart/lung, heart/kidney or lung/kidney are eligible for the study if they meet the standard criteria for both organs at the local center.
2. Participant is able to understand and provide informed consent.
3. Participant has documented HIV infection by any licensed assay or documented history of detectable HIV-1 RNA.
4. Participant is ≥ 18 years old.
5. HIV-1 RNA < 50 copies/mL. Viral blips between 50-400 copies will be allowed as long as there are not consecutive measurements >200 copies/mL. *(Transplant candidates 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).*
6. Participant is not suffering from significant wasting thought to be related to HIV disease.\*

### 4.1.2 Recipient Exclusion Criteria

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

1. Participant has prior progressive multifocal leukoencephalopathy, cryptosporidiosis of > 1 month, 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.
3. Medical problems, which, in the opinion of the investigator, may pose additional risks.

\* These eligibility criteria align with *the Final Revised Human Immunodeficiency Virus (HIV) Organ Policy Equity (HOPE) Act Safeguards and Research Criteria for Transplantation of Organs From Donors with HIV.11*

## 4.2 Donor Criteria

### 4.2.1 HIV+ Deceased Donor

HIV+ Deceased donors must meet all criteria as per the HOPE Safeguards and Research Criteria.4

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. Organs from donors with suspected false positive HIV screening tests can be used under this protocol as per section 3.2.
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.

\* These eligibility criteria align with *the Final Revised Human Immunodeficiency Virus (HIV) Organ Policy Equity (HOPE) Act Safeguards and Research Criteria for Transplantation of Organs From Donors with HIV.11*

# 5 Study Procedures

## 5.1 Screening/Baseline Visit

Centers will identify potential study participants among people with HIV who are being evaluated for or are waitlisted to receive a heart and/or lung transplant. Although the focus of this study is thoracic organ transplant, simultaneous heart/kidney or lung/kidney will be included. The heart and/or lung transplant will be performed according to the HOPE Act Safeguards and Research Criteria outlined under this protocol. 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.

During the screening period for study eligibility, the study personnel will review the participant’s medical records for medical history and record the participant’s demographic information.

The following procedures, assessments, and laboratory measures will be reviewed via the medical record for the baseline screening visit (after consent has been obtained):

1. Symptom & medical review plus physical exam
2. Vaccination review
3. Safety labs (see schedule of events)
4. CD4+ T-cell count
5. HIV-1 RNA
6. Serologies (CMV Ab, EBV Ab, hepatitis B and C)
7. Review of PPD history and/or latent tuberculosis infection screening

## Enrollment

### 5.2.1 Pre-Transplant Participants

Once a participant has consented, they will be assigned a unique participant number and enrolled into the pre-transplant phase of the study. During this phase, CD4+ T-cell count and HIV RNA viral load testing will be reviewed as available (both may be collected from clinical care labs if done by the medical team) prior to organ availability. Enrollment into the post-transplant phase of the study will occur on the day of transplant.

### 5.2.2. Post-Transplant Phase Data Collection

Data collection for all participants will occur at day 0, weeks 1, 2, 4, 8, 13 (month 3), 26 (month 6), 39 (month 9), 52 (year 1), and every 6 months up to 10 years post-transplant. At each study time point, data will be reviewed from the participant’s clinical evaluations and physical examinations, focusing on signs and symptoms suggestive of HIV disease progression, impaired allograft function, rejection, and opportunistic infections. CD4+ T-cell numbers and percent, and quantitative HIV-1 RNA by PCR assays will be reviewed and data entered as per the Schedule of Events (Appendix 1). At each study time point, the study coordinator will collect and enter data into the web-based data system, including medications of interest, labs, and events of interest, such as deaths, infections, and graft loss.

### 5.2.3. Visit Windows

For visits during weeks 1 and 2, data collection should occur within +/- 3 days of the target visit date. For visits after week 2, data collection should occur between 2 weeks prior to the target visit date, up to the mid-way point between the target date and the subsequent study visit. For example, the week 26 visit may occur up to week 33 [(26 + 39)/2 = 32.5, rounds to 33].

# Known and Potential Risks and Benefits to Participants

## Risks Associated with Transplantation using organs from donors with HIV

### 6.1.1 Acute Rejection (AR)

Some studies have shown there is an increased risk of allograft rejection in transplant recipients with HIV compared to transplant recipients without HIV. The reasons for this are not completely understood but it may be due to drug-drug interactions between immunosuppression and antiretroviral therapy or due to a dysregulated immune system secondary to HIV infection13. It is unknown whether this risk will be higher with the use or organs from HIV D+.

### 6.1.4 HIV superinfection

Breakthrough HIV viremia due to a second strain of HIV from the donor (HIV-superinfection) has not been reported in early experiences of HIV D+/R+ transplantation but remains a theoretical risk that needs to be better understood over the long term.

### 6.1.5 HIV-Associated Thoracic Organ Dysfunction

There is a theoretical concern that HIV D+ may have a higher risk of HIV-related thoracic disease which could impact post-transplant graft function, but the specific risk is unknown. How these conditions may affect long-term graft function in the setting of D+/R+ thoracic transplantation remains to be determined.

## Risks of Study Procedures

### 6.2.1 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.

## 6.3 Potential Benefits

For participants in this study, the use of HIV D+, could increase access to transplantation which has a known survival benefit, could decrease wait time on the list, and thereby decrease the risk of waitlist mortality. From a public health perspective, the use of HIV D+ could lead to a significant expansion of the donor pool which will mitigate wait times generally.

# Criteria for Participant and Study Completion and Premature Study Termination

## 7.1 Participant Completion

Participants will have completed the study at the year 10 data collection time point, or once the study has been closed. All participants will be followed for at least 52 weeks (1 year) post-transplant.

## 7.2 Participant Withdrawal Criteria

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

1. The participant elects to withdraw consent from future study activities, including follow-up.
2. The participant is “lost to follow-up” (i.e., no further follow-up is possible because attempts to reestablish contact with the participant have failed).
3. The participant dies.
4. The investigator no longer believes participation is in the best interest of the participant.

# Safety Monitoring and Reporting

## 8.1 Overview (Special Events Reporting)

This section defines the types of safety data that will be collected under this protocol.

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 organs from donors with HIV. Special events related to the use of organs from donors with HIV including graft failure, death, hospitalization, any infection that requires hospitalization, opportunistic infections, and HIV breakthrough will be collected.

## 8.2 Review of Safety Information

The Principal Investigator will conduct interim administrative, statistical, and safety reviews at least annually and more frequently if warranted. The following Special Events will be reported to the Principal Investigator upon being aware of the event: graft failure, death, hospitalizations, any infection that requires hospitalization, opportunistic infections, and HIV breakthrough. The Principal Investigator will also be responsible for providing reports and/or data per the with Final Revised HOPE Act Safeguards and Research Criteria for Transplantation of Organs From Donors with HIV.

# Statistical Considerations and Analytical Plan

## Overview

This study is a prospective study of solid organ transplantation in individuals with HIV assessing whether receiving a heart and/or lung from donor with (D+) vs without (D-) HIV is safe in regard to major transplant-related and HIV-related complications. Analysis of the primary endpoint will be based on outcomes measured at 52 weeks after transplantation, while analyses of most secondary outcomes will be done on measurements taken at months 3, 6, 9. The primary clinical objective is to evaluate patient survival following transplantation in recipients with HIV receiving thoracic transplants from donors with HIV. Furthermore, there are secondary outcomes related to clinical, immunological and virologic aspects.

## Primary Analysis of Primary Endpoint

The primary endpoint is patient survival at 1-year post-transplant. Patient survival in each arm (i.e. D+/R+ and D-/R+) will be assessed using the Kaplan-Meier (KM) methods. The 95% confidence intervals will be estimated using the delta method proposed by Greenwood’s to add a standard error on KM estimator. Furthermore, a log-rank test will be used to assess for a difference in survival time between D+/R+ and D-/R+.

## Analysis of Secondary Clinical Endpoints

Patient survival will be assessed using the Kaplan-Meier methods. The 95% CI will be estimated using the Greenwood’s formula. The following incidences: (i) graft failure, (ii) rejection, (iii) bacterial, fungal, virus or other opportunistic pathogen and, (iv) post-transplant malignancies; and the development of cardiac allograft vasculopathy and chronic lung allograft dysfunction will be assessed using Cox regression. HIV disease control (viral load and CD4) and the estimated glomerular filtration over time will be assessed using generalized estimating equations (GEE) with an unstructured covariance matrix.

# 10. Ethical Considerations and Compliance with Good Clinical Practice.

## 10.1 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.

## 10.2 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 (or FDA 1572 if applicable) will review the consent and answer questions. The prospective participant will be told that being in the study 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.

## 10.3 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).

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# Appendix 1. Schedule of Events

### Study Visits

| **Years:** | **Year 0** | **Year 1** | **Years 1.5 - 4q6 months** | **For Cause** |
| --- | --- | --- | --- | --- |
| **Weeks:** | **Screen** | **Day 0** | **Week 1** | **2** | **4** | **8** | **13** | **26** | **39** | **52** | **53-208** | **FC** |
| **STANDARD OF CARE ASSESSMENTS** |  |  |  |  |  |  |  |  |  |  |  |  |
| **CLINICAL** |  |  |  |  |  |  |  |  |  |  |  |  |
| Eligibility Review1 | **X** | **X** |  |  |  |  |  |  |  |  |  |  |
| Transplant Data (e.g. PRA, antibody testing) | **X** |  |  |  |  |  |  |  |  |  |  |  |
| Medical Review of symptoms and physical exam | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** |
| Pregnancy Test | **X2** | **X2** |  |  |  |  |  |  |  |  |  |  |
| Concomitant Medications | **X** | **→** | **→** | **→** | **→** | **→** | **→** | **→** | **→** | **→** | **→** | **X** |
| Adverse Event Assessment |  | **→** | **→** | **→** | **→** | **→** | **→** | **→** | **→** | **→** | **→** | **X** |
| **LABS**  |  |  |  |  |  |  |  |  |  |  |  |  |
| CBC | **X2** | **X2** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** |  |
| CMP | **X2** | **X2** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** |  |
| General Serology Labs3 | **X2** |  |  |  |  |  |  |  |  |  |  |  |
| Pulmonary or Cardiac Function Tests | **X2** | **X2** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **Y2** |  |
| CD4+ T-cell Count | **X4** | **X4** |  |  | **X** | **X** | **X** | **X** | **X** | **X** | **X** |  |
| HIV-1 RNA (PCR) | **X5** | **X5** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** |  |

* 1. As detailed in Section 5.1.
	2. Collect prior to transplant as standard of care and repeat according to site-specific clinical practice.
	3. General serology labs including CMV IgG, HBsAg, HBsAb, HBcAb, HBV DNA (if HBsAg+), HCV Ab, HCV RNA, EBV Ab, T. pallidum/RPR, and Toxoplasmosis IgG.
	4. Reviewed every 26 weeks pre-transplant, if available. A repeat Day 0 draw is not necessary if not clinically indicated and there is an available result that within the prior 26 weeks.
	5. Frequency per clinical team. Recipients unable to tolerate ART recent start may have detectable viral load if the study team is confident there will be effective ART post-transplant. A repeat Day 0 draw is not necessary if not clinically indicated and there is an available result that meets eligibility criteria.