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# Perceptions of HIV-positive kidney donations to HIV-positive recipients

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BOSTON UNIVERSITY  
SCHOOL OF MEDICINE

Thesis

**PERCEPTIONS OF HIV-POSITIVE KIDNEY DONATIONS TO HIV-POSITIVE  
RECIPIENTS**

by

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B.S., Lehigh University, 2014

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Master of Science

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RECIPIENTS**

**JULIE STOMEL**

**ABSTRACT**

Background

Kidney transplantation is the preferred standard of care for patients who have both end stage renal disease (ESRD) and human immunodeficiency virus (HIV) infection. The first successful kidney transplant was done in 1954 and the first case of HIV/AIDS occurred in 1981. Until recently, HIV-positive patients who required an organ transplant received an HIV-negative organ because it was illegal to use HIV-positive organs in transplants in the United States. The HIV Organ Policy Equity (HOPE) Act was signed in 2013 and legalized the use of HIV-positive donor organs in organ transplants. The first of these transplants was completed in March 2016 with good results.

Literature review

Renal transplants have lower mortality than dialysis. HIV damages the kidney in multiple ways, including HIV associated nephropathy and HIV immune complex kidney disease, putting HIV patients at higher risk of ESRD. Studies from before the utilization of anti-retroviral therapy show that transplantation of HIV infected blood or organs do not cause failure of the transplanted organ. However, in 1997 most surgeons would not transplant kidneys to HIV-infected individuals. Success of antiretroviral therapy has allowed HIV patients to live longer, but patients experience complications including end organ damage. Providing transplants to ESRD patients with HIV infection has been preferred

treatment since 2010. Due to improvements in both HIV and transplant science, transplant specialists today are likely to accept HIV-positive organs to HIV-positive transplant recipients.

#### Proposed project

The proposed study is a survey of United States transplant professionals to determine their perceptions about these transplants. Researchers will collect data in the form of Likert scales as well as open-ended responses. The survey will also collect demographic information about surveyors. Investigators will then analyze the collected data for professional knowledge of the legal change, perceptions of efficacy and safety, and concerns. Researchers will analyze the data both as a whole and divided by demographic subgroups.

#### Conclusions

To date, there has been no study that has assessed at the attitudes of the medical community involved in these transplants. This study is unique in that it attempts to obtain the perceptions and concerns the transplant specialists have about HIV-positive donor organs to HIV-positive transplant recipients.

#### Significance

The data from this study will help to establish what opinions are at this time, to determine if there are any regional discrepancies that may affect patient access to care, and to determine the concerns of transplant specialists at this time.

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## LIST OF ABBREVIATIONS

AASPA	American Association of Surgical Physician Assistants
AIDS	Acquired Immune Deficiency Syndrome
ANOVA	Analysis of Variance
AST	American Society of Transplantation
ASTS	American Society of Transplant Surgeons
AZT	Zidovudine
CCR5	Chemokine coreceptor 5
CDC	Centers for Disease Control and Prevention
CXCR4	Coreceptor X4
ESRD	End stage renal disease
HAART	Highly active antiretroviral therapy
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HIVAN	Human Immunodeficiency Virus Associated Nephropathy
HIVICK	Human Immunodeficiency Virus Immune Complex Kidney Disease
IRD	Infectious risk donor
IS	Immunosuppression
KS	Kaposi's Sarcoma
LDKT	Living donor kidney transplant
NITp	North Italy transplant program
OI	Opportunistic infection

PML ..... Progressive multifocal leukoencephalopathy  
SOT ..... Solid organ transplant  
SRTR ..... Scientific registry of transplant recipients  
US ..... United States

## INTRODUCTION

### Background

Organ transplant is often a treatment option for patients with end stage renal disease (ESRD). Kidney transplantation is the process in which a kidney is surgically removed from either a living person or deceased person. The kidney is implanted into the recipient's abdomen, and if successful, allows the recipient to have a functioning kidney. This saves the patient from renal failure and avoidance of dialysis or reduces time on dialysis. The recipient takes immunosuppressive medications both prior to and after the surgery to prevent loss of the new kidney<sup>38</sup>. According to the 2013 Organ Procurement and Transplantation Network/Scientific Registry of Transplant Recipients (OPTN/SRTR) Annual Data Report, in 2013 there were 16,901 adult kidney transplants completed in the United States and there were 96,607 adults on the transplant list waiting for a kidney as of December 31, 2013<sup>38</sup>.

Kidney transplants become more complicated if the patient who needs the kidney is infected with Human Immunodeficiency Virus (HIV). Standard of care for treatment of HIV infection requires decades long therapy with antiretroviral medications<sup>18</sup>. Patients who take the antiretroviral medications, called highly active antiretroviral therapy (HAART), are typically successful at controlling the HIV infection<sup>2,18</sup>. However, HAART therapy does not rid the patient of the infection and is not a cure<sup>2,18</sup>. Poor kidney function is one of the most common complications of HIV infection in the HAART era, with up to 30% of patients having abnormal renal function<sup>58</sup>. The causes of

kidney disease in HIV patients vary and include non-HIV related causes such as hypertension and diabetes associated nephropathy<sup>24, 32, 58, 65</sup>.

However, HIV infection itself can cause kidney damage. HIV associated nephropathy is a severe form of glomerulonephritis that develops in 5-10% of patients on HAART medications<sup>33</sup>. HIVAN is the third leading cause of ESRD in African American males age 20-64 in the United States<sup>8, 24</sup>. HIVAN can lead to ESRD within 6 months<sup>49</sup>. There is also HIV immune complex kidney disease (HIVICK), which is more common in non-African descendants<sup>23</sup>. Additionally, some HAART medications have nephrotoxic effects that can further cause kidney disease<sup>2,8,9,18,19,24,36,49,54,58,67</sup>. Overall, HIV infection is a leading cause of ESRD requiring the need for renal replacement therapy.

There are two main options for renal replacement therapy: dialysis and organ transplant. Until 2005, transplantation was often not an option for HIV-positive patients in the United States for fear that the necessary immunosuppression required for transplantation would cause increased morbidity and mortality<sup>33</sup>. However, studies published in 2005 show that HIV-positive kidney recipients can achieve survival rates similar to HIV-negative patients<sup>33, 49</sup>.

Although HIV-positive patients are able to accept organs, HIV-positive patients were not able to donate organs until 2013 when the HOPE Act was approved. Therefore, prior to the HOPE act HIV-positive organs could not be used in organ transplants. The new law allows HIV-positive donor to HIV-positive recipient organ transplants in the United States. The first of these transplants was done in March 2016.

## **Statement of the Problem**

The HOPE Act was first approved in November 2013 and updated in November 2015.

The first HIV-positive to HIV-positive organ transplants in the United States were completed in the spring of 2016. There has been no analysis into what transplant surgeons, transplant nephrologists, and transplant PAs' perceptions are about HIV-positive donor organs to HIV-positive organ transplant recipients in the United States.

It is important to know the transplant specialists' perspective of HIV-positive donor to HIV-positive recipient transplants at this point of time for multiple reasons. First, it is important to establish a baseline for future researchers to understand the attitudes and perspectives of these specialists at the beginning of the HOPE era. Be it a failure or a success, future scholars will want to know what the community is thinking at this moment. Additionally, the perceptions of specialists can help point us in a direction to spend funding.

The study proposed will yield a way to determine the perceptions of transplant surgeons, transplant nephrologists, and transplant surgical physician assistants on the topic of HIV-positive to HIV-positive organ donations.

## **Hypothesis**

Transplant surgeons, transplant nephrologists, and transplant physician assistants will be aware of the legality of HIV-positive donor organ to HIV-positive recipient transplants, and perceive HIV-positive donor organ to HIV-positive organ recipient transplants as

effective and an ethical treatment option for their patients on a qualitative survey of perceptions.

### **Objectives and specific aims**

HIV-positive donor organ donation to HIV-positive recipient in the United States is a new endeavor, with the first surgery occurring in March 2016. There is no data about the beliefs of the teams completing these transplants. The overall goal in conducting this research is to understand the perspective of transplant specialists involved in HIV-positive to HIV-positive organ transplants.

Specific aims of this study are to:

1. Establish if transplant specialists are aware of the legislative change that makes HIV-positive donor organs to HIV-positive organ transplant recipients legal in the United States
2. Determine if transplant specialists believe HIV-positive to HIV-positive transplants will be safe and effective treatment options for their patients
3. Understand the concerns that transplant specialists have about HIV-positive to HIV-positive transplants

## REVIEW OF THE LITERATURE

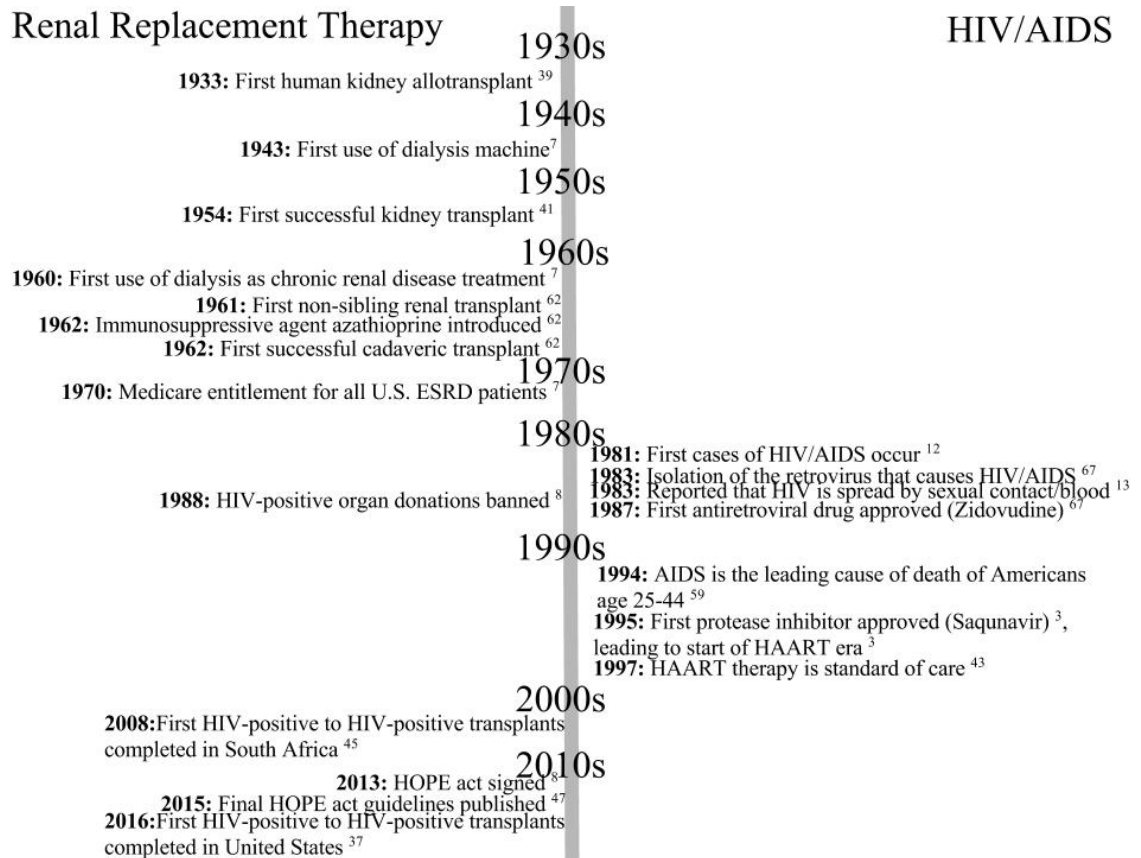
### Overview

#### Renal transplants

To fully understand transplantation of HIV-positive kidneys into HIV-positive recipients, it is important to first appreciate treatment of end stage renal disease via renal transplants and HIV infection individually (See figure 1, page 6 for timeline). On April 3, 1933 Yurii Voronoy in Ukraine completed the first human kidney allotransplant<sup>39</sup>. He took a six-hour anoxic cadaver kidney and transplanted it into the thigh of the recipient<sup>39</sup>. Although the patient died after 2 days secondary to ABO incompatibility, Voronoy is credited by future transplant surgeons as having completed the first human allotransplant<sup>39</sup>.

Further research in renal transplantation occurred in both humans and animals. The next significant event was the first successful renal transplantation in 1954<sup>41</sup>. A 24-year-old male named Richard Herrick was transferred to Peter Bent Brigham Hospital with chronic glomerulonephritis after unsuccessful treatment with conservative therapy<sup>41</sup>. Herrick had an identical monozygotic brother, and after testing for 21 identical antigens for blood subgroups and successful skin grafting between the twins to confirm monozygoticity, the surgeons decided that they were good candidates for renal transplantation<sup>41</sup>. On December 23<sup>rd</sup>, 1954, the transplant was completed with survival of both brothers and the transplanted kidney<sup>41</sup>. This transplant proved that

## Timeline of select important events in the history of renal replacement therapy and HIV/AIDS



**Figure 1- Timeline of select important events in the history of renal replacement therapy and HIV/AIDS. See text for full details and additional events.**

“homotransplantation of the kidney in man is at least a technically feasible procedure” and provided proof of concept of homotransplantation<sup>41</sup>. Richard Herrick did not take any immunosuppressive medications<sup>62</sup> and lived for 8 years after his surgery before death from myocardial infarction unrelated to the surgery<sup>46</sup>. This operation is considered the first successful kidney transplant<sup>41</sup>.

In 1961, the first successful living donor kidney transplant between non-siblings occurred, setting the way for future transplants between people who are not related<sup>62</sup>. In 1962, the immunosuppressive drug azathioprine was introduced, decreasing the acute graft rejection rate<sup>62</sup>. Also in 1962, cadaveric donor transplants occurred successfully for the first time (using azathioprine and actinomycin for immunosuppression), opening up new sources of organs for patients<sup>62</sup>. Renal transplants were on the path to being the gold standard treatment for end stage renal disease.

Dialysis is the alternative treatment for end stage renal disease. Dialysis machines were first constructed in 1943, and were initially used for acute renal failure<sup>7</sup>. Patients were first treated for chronic renal failure via intermittent hemodialysis in 1960 at the University of Washington<sup>7</sup>. Three of the first four patients survived the first year on intermittent hemodialysis (and would live for more than 10 years), making it a success<sup>7</sup>. However, funding was a problem and initially severely limited the number of patients that could have dialysis treatments<sup>7</sup>. In 1970, a report with 170 patients studied showed 90% survival at 1 year and 61% survival at 5 years<sup>7</sup>. On October 30, 1972 President Nixon signed a bill that established Medicare entitlement for patients needing dialysis or transplantation, making renal replacement treatment available and affordable to all renal failure patients<sup>7</sup>.

As surgeons gained experience in transplanting kidneys, many studies came out comparing dialysis and transplantation. A systematic review published in 2011 that analyzed 110 studies and 1,961,904 patients with renal failure revealed renal transplants are associated with significantly lower mortality and significantly increased quality of life

compared to chronic dialysis<sup>69</sup>. From the first successful transplant in 1954 to the systematic review published in 2011, transplantation science has become the gold standard in treating end stage renal disease for those fortunate enough to receive a transplant.

### Human Immunodeficiency Virus / Acquired Immune Deficiency Syndrome

HIV/AIDS was a public health emergency in the United States and other developed nations from its discovery until the success of antiretroviral medications, and is still an emergency in developing regions<sup>21</sup>. Retrospectively, the first cases of what is now known as the AIDS epidemic was published on June 5, 1981 in a US Center for Disease Control and Prevention (CDC) Morbidity and Mortality Weekly Report that highlighted five previously healthy young homosexual men who were diagnosed with *Pneumocystis carinii* pneumonia, indicating severe immunodeficiency<sup>12</sup>. By the end of 1981, there were 270 reported cases of severe immune deficiency among homosexual men, with 121 deaths<sup>29</sup>. On September 24, 1982, the CDC used the term Acquired Immune Deficiency Syndrome (AIDS) for the first time, and defined AIDS as “a disease at least moderately predictive of a defect in cell-mediated immunity, occurring in a person with no known case for diminished resistance to that disease”<sup>14</sup>. In March 1983, the CDC released a report that suggested AIDS may be caused by an infectious agent that is transmitted via sexual contact and blood products<sup>13</sup>. Because of the nature of its transmission, the CDC was able to give recommendations to prevent the spread of HIV for the first time. On

May 20<sup>th</sup>, 1983, Dr. Françoise Barre-Sinoussi and her team isolated the retrovirus that they proposed and was later proven to cause AIDS<sup>5</sup>. The first antiretroviral drug zidovudine (AZT) was approved in 1987<sup>67</sup>. In 1988, HIV-positive organ donations were banned which made HIV infection the only exclusion criteria written into the transplant legislation<sup>8</sup>.

In 1992, AIDS was the number one cause of death for US men ages 25-44<sup>14</sup> and in 1994 AIDS became the leading cause of death of all Americans ages 25-44<sup>59</sup>. In June 1995 the first protease inhibitor, Saquinavir, was approved by the FDA and is now considered the start of the HAART era<sup>3</sup>. In 1997, HAART therapy was the standard of care for HIV patients<sup>43</sup>, and the first substantial decline in AIDS-related deaths was reported in British Columbia, Canada<sup>30</sup>.

## Kidney Disease and HIV

Renal disease is one of the most common complications of HIV infection, with abnormal kidney function in up to 30% of HIV patients<sup>58</sup>. HIV affects the kidney in multiple ways. Both diabetes and hypertension are more common in HIV patients than the general population, and both can lead to chronic kidney disease<sup>24, 32, 58, 65</sup>. Acute renal failure is also more common in HIV patients than in the general population, with underlying CKD, HIV infection, and HCV infection as risk factors<sup>58</sup>. Additionally, some antiretroviral agents are nephrotoxic<sup>2,8,9,18,19,24,36,49,54,58,67</sup>. For example, tenofovir is a first-line HAART agent that has a small nephrotoxic effect that can overtime cause clinically significant

kidney damage<sup>18</sup>. Therefore, HIV patients are at higher risk for renal disease than the general population<sup>18</sup>.

There are two common types of chronic kidney disease found in HIV patients that are not found in non-HIV patients, called HIV-associated nephropathy (HIVAN) and HIV immune complex kidney disease (HIVICK). HIVAN is caused by “direct viral infection of kidney cells (particularly the visceral epithelial cells of the glomerulus and the tubular epithelial cells) and it is more common in patients with high plasma HIV-RNA viral load”<sup>15</sup>. Expression of the HIV transgene induces dedifferentiation as well as proliferation of glomerular epithelial cells while also impairing cytokinesis in tubular epithelial cells<sup>4</sup>. This causes a collapsing form of focal sclerosing glomerulosclerosis that also has interstitial inflammation and microcystic tubular dilation<sup>34</sup>. HIVAN affects mainly patients of sub-Saharan African descent<sup>24</sup> and is the 3<sup>rd</sup> most common etiology of renal disease in African Americans aged 20-64 after diabetes and hypertension<sup>24</sup>. Overall, HIVAN occurs in approximately 10% of all patients with HIV<sup>24</sup> and is considered the most aggressive HIV-related renal disease<sup>24</sup> because it can progress to ESRD within weeks to months<sup>24</sup>, making it the most common cause of renal failure in HIV-1-seronegative patients<sup>4</sup>.

HIVICK occurs when HIV infection causes deregulation of the immune system and causes “increasing gamma globulin contributing to immune complex formation”<sup>23</sup>. HIVICK patients have lupus-like lesions on renal histology without other evidence of lupus<sup>23</sup>. Patients present with various renal disease manifestations depending on where the lesions are, but proteinuria and hematuria are common findings<sup>23</sup>. HIVICK appears

to be more common in patients with non-African descent, and prognosis is better than for HIVAN<sup>23</sup>.

Despite high prevalence of renal failure amongst HIV patients, a survey conducted in the Spring of 1997 and subsequently published in the journal *Transplantation*, concluded that the “majority (88%) of US transplant centers will not transplant kidneys to HIV-infected patients with end-stage renal disease, even if their infection is asymptomatic”<sup>61</sup>. The timing of this survey is significant because in 1997, HAART therapy became standard of care for treating HIV-infected patients<sup>43</sup> and is when for the first time prognosis started to improve<sup>30,35</sup>. However, “transplantation was thought to be contraindicated [by surgeons] because of the poor prognosis militated against using scarce organs for HIV-infected people, and it was feared that allogenic stimulation and immunosuppressive drugs (used to prevent rejection) might accelerate the patient’s demise”<sup>61</sup>. As opposed to the surgeons, the authors of the study suggest that HIV-infection is “not a valid reason for automatically excluding” from transplantation<sup>61</sup>. Thus, from the beginning of the HAART era, HIV-positive transplantation had both opponents and proponents.

Between 1998 and 2003, the overall perception of HIV in developed countries changed from “a terminal to chronic illness [and] accordingly, transplantation in HIV-infected patients [had] been initiated at a handful of centers”<sup>28</sup>. A study published in *American Journal of Transplantation* in 2005 regarding the perceptions of surgeons of transplantation in HIV, Hepatitis B (HBV), and Hepatitis C (HCV) infected patients showed that surgeons had greater fear of becoming infected with HIV than with HBV or

HCV, and that most surgeons still considered HIV infection to be a contraindication to transplantation<sup>28</sup>. However, surgeons surveyed in this study believed that HIV-positive patients would receive benefit receiving a transplant<sup>28</sup> versus the 1998 study when surgeons were fearful the transplant would hasten the patient demise<sup>61</sup>. It is important to note that despite the surgeons' fear, there were HIV-positive transplants being done in 2003<sup>28</sup>.

Much progress has been made in prevention and treatment of HIV since the 1980s. HIV infection incidence has been decreasing, down from 3.3 million in 2002 to 2.3 million in 2012<sup>36</sup>. However the prevalence of HIV infection is increasing worldwide because patients are living longer with the infection<sup>36</sup>. Globally, AIDS-related deaths peaked in 2005 at 2.3 million and had decreased to 1.6 million by 2012<sup>36</sup>. Much of this decrease is due to decreased heterosexual transmission<sup>36</sup>. In 2012, an estimated 35.3 million people were living with HIV<sup>36</sup>. Advances in both treatment and prevention have even lead some to envision a future where "HIV infections and deaths from AIDS are rare"<sup>21</sup>.

In the past 22 years, since AIDS was noted to be the leading cause of death among Americans ages 25-44, HIV infection has gone from a "modern day plague"<sup>21</sup> to a chronic disease. This success is due to highly active antiretroviral therapy (HAART)<sup>8</sup> which is the practice of using multiple drugs that target the virus at different enzymes required for its replication<sup>2,43</sup>. Patients who have access to and who take their prescribed HAART regimen for decades can expect improved health and prolonged life compared to those who do not take HAART medications<sup>18</sup>. Patients who start taking HAART in their

20s can live into their 70s<sup>57</sup>. However, new complications have come forth, underscoring the disease portion of the phrase ‘chronic disease’<sup>18</sup>. Several inflammation-associated and immunodeficiency complications arise in HAART treated HIV patients, such as cardiovascular disease<sup>25</sup>, kidney disease, liver disease, and cancer<sup>18</sup>. For example, HIV infected adults had a 50% increased risk of having a myocardial infarction as a non-infected adult when traditional risk factors were controlled for<sup>18,25</sup>. Additionally, the antiretroviral agents have toxic side effects that build up after decades of use that can cause clinically important end organ damage<sup>18</sup>. Together, all these complications of having chronic HIV infection are termed non-AIDS morbidity. Therefore, while people are living longer with HIV on HAART, the antiretroviral medications are not a cure for HIV infection and complications do arise.

Because patients are living longer with HIV infection, organ failure is a problem. Organ transplant is a solution, but was only determined definitively to be so for HIV patients in the US in 2010<sup>64</sup>. The first US study published was in 2006 and followed 38 donor kidney pairs that were transplanted into one HIV-positive patient and one HIV-negative patient. In this study there was a non-statistically significant higher patient and graft survival in HIV-positive patients at 5 years<sup>49</sup>. Adjusted analysis showed HIV was not associated with graft loss<sup>65</sup>. A more conclusive study was the NIH-sponsored US HIV-TR trial published in 2010. This study looked at 150 HIV-positive patients who had kidney transplants between 2003 and 2009. In this study, “both patient- and graft-survival rates were high at 1 and 3 years, with no increase in complications associated with HIV infection”<sup>64</sup>. However, a “higher than expected rejection rate was observed”

which is “of serious concern and indicate[s] the need for better immunotherapy”<sup>64</sup>. The study concluded that, “the major issues encountered in HIV-TR were achieving therapeutic, but nontoxic drug levels, a high rejection rate, and future management of HCV coinfection. HIV remained well controlled, and renal transplantation was shown to be a viable option and feasible in selected patients”<sup>65</sup>. A follow up study published in 2015 confirmed these results and concluded that “kidney transplantation should be standard of care for well managed HIV-positive patients”<sup>54</sup>. Overall, HIV infection is no longer a contraindication to kidney transplant, and good patient outcomes have been described in numerous studies.

The question becomes which HIV infected patients are eligible for renal transplant. The Guidelines for Kidney Transplant in Patients with HIV disease written on behalf of the British HIV Association and reviewed and endorsed by the British Transplantation Society Standards Committee is a set of recommendations used by transplant centers, including Boston Medical Center<sup>6</sup>. These guidelines suggest that “any patient with end stage renal disease is eligible for transplantation if medically fit. Life expectancy of at least five years is considered appropriate before embarking on transplantation”<sup>6</sup>. The Guidelines also lay out HIV specific inclusion criteria, including CD4>200 cells/microliter for at least six months, undetectable HIV viremia (< 50 copies/ml) for at least 6 months, demonstrable and a stable HAART regimen for > 6 months, absence of AIDS defining illness following successful immune reconstitution after HAART, and available anti-retroviral treatment options in the future<sup>6</sup>. HIV-disease specific exclusion criteria include documented history of progressive multifocal

leukoencephalopathy (PML), extracutaneous Kaposi's Sarcoma (KS), EBV and HHV8-related lymphoproliferative disorders, CD4 count < 200 cells/microliter, persistent HIV viremia despite HAART, continuing non-compliance with anti-retroviral therapy, and more than three-class HIV resistance and lack of future HIV treatment options<sup>6</sup>. The guidelines also contain inclusion and exclusion criteria that are not specific to HIV infection, include criteria for pre-transplant assessment and vaccinations, and immunosuppressant protocols<sup>6</sup>.

#### HIV-positive organs for HIV-positive transplant recipients

The first HIV-positive organs intentionally transplanted into HIV-positive patients were in South Africa. In South Africa, like most places in the world, the HIV infection was considered an absolute contraindication for organ transplant. However, unlike other places in the world, dialysis in South Africa is only used as a bridge to transplantation due to lack of public resources<sup>17</sup>. Therefore, HIV-positive renal failure patients in South Africa were ineligible for dialysis<sup>17</sup> unless they had private insurance, which very few South Africans have<sup>50</sup>. Because HIVAN is the number one cause of ESRD in South Africa, this allocation of resources caused many patients to be "sent home to die"<sup>45</sup>. In fall 2008, Dr. Elmi Muller "undertook four renal transplantations involving HIV-positive recipients and HIV-positive donors" at Groote Schuur Hospital in Cape Town, South Africa<sup>45</sup>. The transplants involved "two deceased donors who had not received any antiretroviral therapy, did not have a history of serious opportunistic infection or cancer,

and had normal renal biopsies without evidence of proteinuria<sup>45</sup>. The four initial transplants were deemed a success<sup>51</sup>. Muller's initial triumph changed South African policy and stopped "the exclusion of HIV-infection persons from the general renal-transplantation program" in 2009<sup>44</sup>, which allowed "HIV-infected patients to receive kidneys from HIV-negative donors or from HIV-positive deceased donors" at Groote Schuur Hospital<sup>44</sup>. Muller and her team proved that HIV-positive to HIV-positive kidney transplants were safe and effective in carefully selected patients<sup>44</sup>.

Colleagues in the United States, where transplants using HIV-positive organs were still illegal, were watching Muller's success. Advocates who wanted to make HIV-positive transplants legal in the United States knew that knowing an estimated number of lives saved per year would be essential when talking to members of congress<sup>9</sup>. Because UNOS does not track HIV-positive donors, researchers had to look elsewhere for this data. One study estimates that in the United States there would be 500-600 HIV-positive donors per year who would be eligible transplant candidates<sup>9</sup>. This study utilized the Nationwide Inpatient Sample and the HIV Research Network to generate its data<sup>9</sup>. A second study that looked at a single center and then extrapolated data estimated approximately 356 HIV-positive deceased donors each year<sup>52</sup>. By utilizing these donors, it could help with the current organ shortage and waitlist mortality<sup>9, 52</sup>. If a HIV-positive patient is willing to accept a HIV-positive organ in the United States, wait time "would likely be less than 1 year"<sup>63</sup> compared to the excess of 7 years many patients currently wait for a deceased donor kidney<sup>63</sup>. Furthermore, if all 356-600 HIV-positive organs are

used by HIV-positive patients each year, there are more organs available for non-HIV patients with ESRD which shortens the overall wait time and decreases overall morbidity.

In November 2013, the HOPE Act was signed into law in the United States. It mandated that the Secretary of Health and Human Services develop “criteria for the conduct of clinical research involving [HIV-positive deceased donor] organs” by November 2015<sup>8</sup>. The final guidelines were published on November 25, 2015. These guidelines state that “the goal of this research is to increase the knowledge about the safety, efficacy, and effectiveness of solid organ transplantation (SOT) utilizing HIV-positive donors in HIV-positive recipients”<sup>47</sup>. These final guidelines also updated the HOPE Act so to allow living donations, which were previously not addressed<sup>47</sup>.

The current version of the HOPE Act includes eligibility criteria for donors, recipients, and transplant hospitals<sup>47, 56</sup>. Donors may be either deceased or living<sup>47</sup>. If deceased, the transplant team must propose a safe antiretroviral regimen for the recipient after taking the donor’s drug regimen history<sup>47, 56</sup>. If a safe combination is not available, the transplant may not continue<sup>47, 56</sup>. If the donor is living, that donor must be assessed for future risk of kidney disease<sup>47</sup>. The living donor must also go through a consent process that documents their understanding of “(1) the possibility that the loss of organ function resulting from donation could preclude the use of certain antiretroviral drugs in the future; (2) the risk of kidney or liver failure in the future; (3) the possibility of transmission of occult opportunistic infections to the recipient; and (4) the absence of U.S. experience in HIV-positive to HIV-positive organ transplantation, and thus the unpredictable nature of donor and recipient outcomes”<sup>42, 47</sup>.

As previously discussed, there is recipient eligibility criteria, however the criteria written into law is less extensive than what hospitals often use and what was previously discussed. The HOPE Act specifically requires HIV-positive recipients to have CD4+ T cell counts >200/uL within 16 weeks prior to transplant, HIV RNA less than 50 copies/mL and on a stable antiretroviral regimen, no evidence of opportunistic infection, and no history of primary central nervous system lymphoma or progressive multifocal leukoencephalopathy<sup>47, 56</sup>. The transplant team must also be confident that they will be able to control the patient's HIV infection after transplant.

The criteria for the hospitals performing the transplants are set to ensure patient safety<sup>47, 56</sup>. The hospital must be “an established program for the care of individuals infected with HIV”<sup>56</sup>. There must also be a study team that has at least a transplant surgeon, a transplant physician, and an HIV physician<sup>47, 56</sup>. In the past 5 years, the transplant physician and HIV physician collectively must have completed 5 transplants of HIV-negative organs into HIV-positive patients in the past 4 years<sup>47, 56</sup>. The hospital must provide an individual advocate to the recipient and to the living donor in the case of living donor transplants<sup>47, 56</sup>.

Currently, all HIV-positive to HIV-positive solid organ transplants “occur under IRB-approved protocols” and must follow the many regulations set forth by the National Institutes of Health<sup>47, 56</sup>. However, in a limited form, the HOPE Act allows HIV-positive to HIV-positive organ transplants to occur in the United States for the first time.

Much progress has been made in organ transplantation since Yurii Voronoy completed the first human kidney allotransplant in 1933<sup>39</sup>. The next horizon in transplantation is the use of HIV-positive organs for HIV-positive patients.

### **Existing research**

By weaving together pieces of existing research that relate to individual aspects of HIV-positive to HIV-positive transplants and opinions of transplant specialists about related topics, as well as views of patients, the perceptions of transplant specialists concerning HIV-positive to HIV-positive organ transplants may begin to become more clear.

Organs or blood product infected with HIV have been transplanted previously, albeit accidentally<sup>19, 70</sup>. As previously discussed, the first organ transplant was completed in 1954 and the HIV virus discovered in 1983, so the transmission of HIV via organ transplant was a concern upon the discovery of the virus<sup>70</sup>. A study by Dummer et al examined pre- and post-transplant sera from 1043 patients who had organ transplants at the University of Pittsburg between 1981 and 1986<sup>19</sup>, before any retroviral drugs were in use<sup>67</sup>. They found that 25 patients (1.7%) were either HIV-positive at the time of the transplant or seroconverted soon afterwards<sup>19</sup>. These patients were then followed and their clinical course and survival monitored<sup>19, 70</sup>. Eleven of the 25 patients were HIV-positive prior to the transplant<sup>19, 70</sup>. Fourteen of the 25 patients seroconverted to HIV-positive status after the transplant, indicating that either the organ that was transplanted or blood products infused during their hospitalization contained the HIV virus<sup>19, 70</sup>. Seven of these 14 patients were still alive at follow-up of 4.8 +/-1.8 (SD) years (range 2.1-6.6)<sup>19</sup>,

<sup>70</sup>. The authors of this study suggest that HIV-positive patients should not be automatically excluded from receiving organ transplants<sup>19, 70</sup>.

A similar study was completed in the North Italy Transplant Program (NITp) when it started screening for anti-HIV antibodies on September 1, 1985<sup>48</sup>. Data was collected on patients with renal transplants between January 1, 1978 and August 31, 1985<sup>48</sup>. When data was published in 1988, there were eight confirmed cases of post-transplantation seroconversion<sup>48</sup>. At time of publication, three of the eight patients had died<sup>48</sup>. Of these eight, one died of overt AIDS, one of Kaposi sarcoma, and one of cerebral hemorrhage without any sign of HIV-related disease<sup>48</sup>. The other five were still alive at time of publication<sup>48</sup>. Two were on dialysis with HIV related illnesses, indicating graft failure<sup>48</sup>. The other three had functioning allografts with no signs of HIV infection<sup>48</sup>.

These two early studies show that even without HAART therapy, which was not being used at the time of the studies<sup>67</sup>, transplantation of HIV infected blood or organs do not cause failure of the transplanted organ<sup>19, 48, 70</sup>. With the addition of HAART therapy, one would expect the results of transplanting HIV-positive organs to be even more successful.

Muller's team in South Africa was the first to intentionally transplant organs infected with HIV<sup>44</sup>. Through February 2014, Muller's team completed a total of 27 HIV-positive kidney transplants<sup>44</sup>. Data published in 2015 showed "the rate of survival among the patients was 84% at 1 year, 84% at 3 years, and 75% at 5 years. The corresponding rates of graft survival were 93%, 84%, and 84%"<sup>44</sup>. Furthermore,

“rejection rates were 8% at 1 year and 22% at 3 years. The HIV infection remained well controlled, with undetectable virus in [sic] blood after the transplantation”<sup>44</sup>. These results “compare favorably with reported outcomes in HIV-positive patients who received kidneys from HIV-negative donors”<sup>44</sup>. However, “rejection rates among HIV-positive recipients have been reported to be approximately 3 times as high as those among HIV-negative recipients. The reason for this is still unknown”<sup>44</sup>.

After the signing of the HOPE Act in November 2015, the first intentional HIV-positive to HIV-positive transplants were done in the United States in March 2016 by Dr. Dory Segev. In an interview published in the Journal of the American Medical Association, Dr. Segev stated the operations “went beautifully. The issues were nothing different from what [they] would normally deal with [when] HIV-positive patients receive HIV-negative organs”<sup>37</sup>.

Recent studies in other countries have been conducted to see if HIV-positive patients would consider donating their organs after their death. A study in Taiwan published in 2016 found that 71.9% of surveyed HIV-positive patients would be willing to donate their organs if it were legal to do so in Taiwan<sup>35</sup>. A recent United Kingdom study of HIV-positive patients found that 62% would donate their organs<sup>66</sup>. While there is no published US study of HIV-positive patient perspectives, a 2014 study that surveyed all volunteering individuals leaving Chicago Department of Motor Vehicle buildings found that 90% of participants would likely donate an organ to a needy family member or friend and 17% would donate to a stranger<sup>27</sup>.

The aforementioned study conducted in the United Kingdom surveyed HIV-positive patients who were attending HIV outpatient clinic for routine follow up<sup>66</sup>. These patients were also asked about their perceptions of HIV-positive to HIV-positive organ donation<sup>66</sup>. When asked if they would accept an HIV-positive organ, 55% stated they would<sup>66</sup>. Of those who would not accept an organ, their main concerns were confidentiality, infection, and quality of organ<sup>66</sup>. Patients who were infected with HIV for longer were less likely to be willing to receive an HIV-positive organ compared to those more recently infected<sup>66</sup>. This data can be compared to a 2015 study of African American hemodialysis patients in Philadelphia that did not look at HIV status and concluded 72.3% would accept a living donor kidney transplant (LDKT), and unwillingness to accept an organ was associated with patients who experience increased recovery time after dialysis, concerns about the donor, and concerns about themselves<sup>26</sup>.

When HIV-positive patients in the UK study “were asked whether they would accept an organ to stay alive and/or improve quality of life” 66% responded that they would<sup>66</sup>. This statistic is most applicable to the patients who would receive HIV-positive kidney transplants in the United States, because they would otherwise be reliant on dialysis and are concurrently dying of end stage renal disease.

Although HIV-positive organs were not intentionally transplanted in the United States until 2016, organs from high infectious risk patients have been transplanted. These organs test negative for disease, but the donor has behavioral risk factors that increase the chance that they recently contracted an infection and it is too soon to show up on the screening tests<sup>55</sup>. These risk factors include, but are not limit to, IV drug use, men who

have sex with men, non-sterile tattooing in the past 12 months, or a prison stay for more than 72 hours in the last 12 months<sup>16</sup>. Infectious risk donors (IRDs) comprise about 9% of the deceased donor pool and have a very low incidence of actual infection<sup>55</sup>.

Recipients of increased risk donor organs should have post-transplant testing for HIV, HBC, and HCV<sup>16</sup>. “[S]ignificant variation exists in provider willingness to utilize IRD kidneys”<sup>55</sup> and patient “attitudes toward transplantation with IRD kidneys were negative overall” but “patients reported increased willingness to consider IRD kidney transplantation after receiving education” about IRDs<sup>55</sup>. Of note, the potential recipients questioned in this study did not already have any infectious disease<sup>55</sup>.

Perhaps most akin to HIV-positive to HIV-positive transplants are Hepatitis C (HCV) positive donors to HCV-positive recipients. Kidneys from donors with known HCV infection have been transplanted into patients who also have HCV<sup>71</sup>. Because legislation specifically banned organs infected with HIV<sup>20</sup>, HCV positive status is not and was never a contraindication to organ donation<sup>10</sup>. Although there are risks involved, patients with HCV (but not HIV) who receive a HCV-positive kidney transplant have better survival rate than remaining on dialysis<sup>31</sup>.

The 2015 update to the HOPE Act also permits clinical trials to be done utilizing living donors, which was not initially included in the 2013 version of the act<sup>47, 56</sup>.

Previous research into HIV-positive patient perceptions of receiving an organ from a HIV-negative living donor has been completed<sup>53</sup>. This research shows that “HIV-infected patients have less knowledge about Living Donor Kidney Transplants (LDKT), and there are were more concerns about LDKT, and are less willing to pursue LDKT than

those without HIV<sup>53</sup>. Moreover, most perceive their HIV status to be a barrier to LDKT<sup>53</sup>. Most patients in the study did not want to disclose their HIV status to a potential living donor, and felt that this was a barrier<sup>53</sup>. Guidelines are inconclusive if disclosing HIV status to a potential donor is necessary<sup>53</sup>.

A study was done to see what transplant surgeons and transplant nephrologists thought about disclosing recipient information to potential living donors<sup>40</sup>. The goal of the survey study was to determine attitudes about disclosing information to the living donor about potential recipient health, health-associated behaviors, and lifestyle choices<sup>40</sup>. Even though recipient health and behavior does not affect the donor, it may influence the donor's decision making process<sup>40</sup>. Overall, both transplant surgeons and nephrologists believed one should disclose information about the donor's health that would affect the graft survival and the patient survival, but not information about the patient's lifestyle choices<sup>40</sup>.

There are certain differences between HIV-disease differences between South Africa and the United States that may cause US transplant specialists to be wary of HIV-positive to HIV-positive transplants. The predominant HIV Subtype in South Africa is HIV-1, Group M, Subtype C, which uses chemokine coreceptor R5 (CCR5) throughout infection<sup>68</sup>. The predominant HIV subtype in the United States it is HIV-1, Group M, Subtype B which uses CCR5 coreceptor early in infection and uses coreceptor X4 (CXCR4) in late infection<sup>8,68</sup>. CCR5 and CXCR4 are coreceptors on CD4 cells for HIV entry into the cell<sup>8</sup>. Additionally, the transmitted drug resistance in newly infected individuals in South Africa is less than 5% while in the United States it is 10-18%<sup>8</sup>.

However, it is still very rare in the United States for a strain that is resistant to all HAART classes to be passed<sup>8</sup>. These statistics suggest it is less risky to transplant HIV-positive organs in South Africa than in the United States, which may affect transplant professionals' opinions.

Other differences between South Africa and the United States that may affect transplant specialists' beliefs include the transplant waiting list, which is less than 5000 in South Africa, but over 100,000 in the United States<sup>8</sup>. The number of kidney transplants performed in 2013 was 229 in South Africa and 16, 896 in the United States<sup>8</sup>. The data may suggest that there is both greater number of potential transplants for HIV-positive kidney transplants and total renal transplant experience in the United States.

Transplant specialists may also be wary of theoretical HIV superinfection if the recipient receives an organ with a different strain of HIV than they already have<sup>8, 15, 20, 51</sup>. HIV superinfection has previously transmitted via IV drug use and sexual contact<sup>8</sup>. By putting an entire organ into the body, a larger viral inoculum of the second HIV strain is introduced and it is unknown if HAART therapy will be able to fight off the new HIV strain to stop the superinfection<sup>8, 20</sup>. It is difficult to assess the strain of HIV during the organ procurement process and HIV strain of the donor may not be previously known<sup>15</sup>. One proposed method to decrease risk of superinfection is to only use donors with undetectable viral loads<sup>51</sup>.

Other concerns may include the quality of the kidneys in HIV-positive donors. Will a kidney with HIV-positive status lead to reduction of the allograft survival? Many HIV-positive patients have early kidney abnormalities, as seen by the “high prevalence of

early renal dysfunction e.g. proteinuria, among the HIV-positive population even among individuals with normal serum creatinine”<sup>8</sup>. Therefore, the transplanted kidney may already show early stages of damage<sup>8</sup>.

Transplant specialists may also fear the risks of the immunosuppression (IS) necessary for kidney transplant. The incidence of opportunistic infection (OI) after kidney transplant in HIV-positive recipients using HIV-negative donors has been 8.6%, which is low<sup>8</sup>. However, there is increased risk with using HIV-positive organs that must be closely monitored<sup>20</sup>. Additionally, there has been 2-4x increased incidence of immunologic rejection of all donations in HIV-positive recipients for unclear reasons<sup>20</sup>. Potential mechanisms to the rejection include specific HAART drug reactions with IS or the underlying immunocompromised state caused by HIV infection<sup>20</sup>.

The guidelines and protocols set forth by the HOPE act criteria were created in a way to minimize all of these risks. At first, all HIV-positive to HIV-positive transplants must be done in a clinical research setting<sup>20, 22</sup>. This setting ensures many safety and protective components for patients<sup>20</sup>. Additionally, the National Institute of Health guidelines require minimum outcome data, specific inclusion criteria, and minimum prior experience for the transplant center<sup>20</sup>. Moreover, patients will undergo a formal consent process<sup>20</sup> acknowledging that they understand the process is unproven in the United States, ensuring that the patient is well informed.

There is also the risk that HIV-positive organs will inadvertently be transplanted into an HIV-negative patient<sup>20</sup>. However, this has not happened in analogous settings, such as HCV organs being accidentally transplanted into HCV-negative patients<sup>20</sup>.

Hospitals also have experience with taking precautions and enforcing proper protocols with ABO compatibility<sup>56</sup>. Additionally, there are protocols written into the HOPE act to ensure this will not take place<sup>47, 56</sup>. The law requires that “each transplant hospital shall have an institutional biohazard plan for handling of HIV-positive organs... that is designed to prevent and/or manage inadvertent transmission of or exposure to HIV”<sup>56</sup>. Therefore, the transplantation of HIV positive organs should not put others at risk of HIV transmission.

With all the risks that are inherent with HIV-positive donors to HIV-positive recipients, one may ask ‘why venture there in the first place?’ The problem includes the mismatch between supply and demand for organs, and the waste of HIV-positive organs that occurs if these organs could be used successfully for transplantation but are not<sup>9</sup>. The ability to choose between receiving an HIV-positive organ when one is offered and waiting potentially years to receive a HIV-negative organ would likely alter one’s life expectancy. As previously discussed, waitlist mortality is increased for HIV-positive patients compared to HIV-negative patients<sup>8, 9, 20</sup>. Trials have been successful elsewhere in the world, thus it is time for these transplants to help patients in the United States. The controlled clinical trial environment in which the first HIV-positive to HIV-positive transplants will be done to allow for precise scientific monitoring that will benefit both the patients in the trial and future patients.

Since April 3, 1933, when Yurii Voronoy completed the first human kidney allotransplant<sup>39</sup>, transplantation has been a science that pushed the boundaries of medicine<sup>22</sup>. Transplant specialists inherently want to continue to push that boundary, and

are likely to accept HIV-positive donor organs to HIV-positive transplant recipients as the next frontier in transplant science.

## **METHODS**

### **Study design**

This study will be an electronic mail survey sent to transplant surgeons, transplant nephrologists, and transplant physician assistants and seek to obtain their opinions on HIV-positive donor organs to HIV-positive organ transplant recipients. The study will then include a qualitative and quantitative analysis of the survey results.

### **Study population and sampling**

The study population is all transplant surgeons, transplant nephrologists, and transplant surgical physician assistants in the United States. There are 208 transplant surgeons<sup>60</sup> and 9651 nephrologists<sup>60</sup> in the United States, as well as 94,400 PAs in the United States<sup>11</sup>. Of the PAs, 27% practice in surgery or a surgical subspecialty<sup>1</sup> and 56 of 15,925 (0.35%) respondents to a national PA survey identify their specialty as transplant surgery<sup>1</sup>. The contact information for the intended study participants will be obtained via the American Society of Transplantation (AST), American Society of Transplant Surgeons (ASTS), and American Association of Surgical Physician Assistants (AASPA) mailing lists. Study inclusion criteria is participation in at least 15 transplant surgeries within the past 12 months. Exclusion criteria include self-identification as retired or inactive, unwilling to complete the survey, or more than 3 questions on the survey left unanswered.

Surveys will be sent to each identified person in order to maximize the number of results because health care providers typically have low response rates to surveys.

## **Intervention**

In the Winter of 2017, the American Society of Transplantation (AST), American Society of Transplant Surgeons (ASTS), and American Association of Surgical Physician Assistants (AASPA) mailing lists will be rented.

At the same time, the Presidents of these three associations will be contacted about the purpose of the study to see if they will be willing to forward the email with survey link to members of their associations

In the Spring of 2017, each of the identified transplant surgeons, transplant nephrologists, and surgical physician assistants will be sent a personalized pre-survey notification of the study. This email will be sent to them from the president of the association from which their contact information was obtained in order to increase participation rates. This pre-survey email will explain the purpose of the study on Boston University letterhead. A copy of the pre-survey email can be found in Appendix A.

Two weeks later an email with a link to the survey will be emailed to each identified subject from the president of the association. The body of the email will include the Boston University logo and the text will explain the purpose of the study. An example of the email text can be found in Appendix B and a copy of the survey can be found in Appendix C.

After 1, 2, and 3 weeks, if there is no response to the survey the reminder emails will be sent that include the link to the survey.

## **Study variables and measures**

The survey will include two sections- one on the respondent's demographics and one on their perceptions.

Demographics:

- Age (decade)
- Gender
- OPTN Region
- Professional Role
- Years in Practice
- Number of transplants they participated in within the last year
- Number of HIV-positive transplants they participated in within the past year

Perceptions:

- If they are aware that HIV-positive to HIV-positive organ transplants are legal
- If they think HIV-positive to HIV-positive transplants will be successful
- If they think HIV-positive patients will agree to receive HIV-positive organs
- Thoughts on HIV-positive living donors
- Concerns, limitations or obstacles
- Overall feelings

## **Recruitment**

The subjects will include all US transplant surgeons, transplant nephrologists, and transplant PAs in the mailing lists of the American Society of Transplant Surgeons, the

American Society of Transplantation, and American Association of Surgical Physician Assistants, as of January 1, 2017. The physicians and any PAs on the AST and ASTS lists will be contacted. Because there is no specific organization that targets PAs who participate in transplants, the AASPA list will ensure transplant PAs are reached, and the inclusion/exclusion criteria will omit PAs who are on the AASPA mailing list but are inappropriate for the study. It is expected that the AASPA list will generate many names that are excluded. If an email address appears on more than one organization mailing list, only one email will be sent. From these lists, everyone who has not participated in transplant surgeries within the past year or who self-identifies as retired or non-active will be excluded.

### **Data collection**

The data will be collected as electronic surveys using Qualtrics software. Perception questions will appear first, followed by demographic questions. Perception questions types will include ranking on a scale from 1-5, multiple choice with multiple responses allowed, and open-ended response. Demographic questions will be multiple choice responses. A copy of the survey can be found in Appendix C.

### **Data analysis**

The data obtained from the surveys will be reviewed and analyzed. Overall perceptions of transplant specialists will be determined. Questionnaire items that were in agree-disagree form will be converted into a numerical score for analysis using the Likert scale.

Question 1 is for consent and will not be analyzed. Any respondent that answers “no” will have all of their responses removed from the data pool.

Questions 2-9 measure respondents’ perceptions. Questions 2-6 are based on Likert Scales. For each question, the mean and standard deviation will be calculated, with 3.0 considered neutral. Question 7 has multiple choices in which the respondent may choose one, without write-in options. This question will be analyzed using proportions. Question 8 has multiple answer selections as well as fill-in-the-blank responses, and therefore will be analyzed by raw counts. Question 9 allows for a write in answer only. Qualtrics software will be utilized to determine themes.

Questions 10 – 17 gather demographic data and all will be analyzed as proportions. Questions 18 and 19 are follow ups to question 17, depending on whether yes or no is selected in question 17. If yes is selected in question 17, the respondent sees question 18. If no is selected in question 17, the respondent sees question 19. Question 18 is a fill-in question. Responses will be analyzed as raw counts and proportions. Question 19 has dichotomous data. It will be analyzed as both means and proportions.

After each question is analyzed individually, certain questions will be correlated. Questions 2-5 will be analyzed using demographic information. For each question, Mann-Whitney U test will be used to analyze the effect of gender on the response (Question 10) as well as the effect of participation on a HIV-positive case in the past year on response (Question 17). One-way analysis of variance (ANOVA) will be completed for age, professional role, years in practice, OPTN region, primary organs transplanted,

and transplants within the past year to determine if there are significant differences.

Questions 6-9 will also be examined with demographic data via ANOVA.

Additionally, all data would be read through looking for nascent themes and would be categorized based on themes.

### **Timeline and resources**

Fall 2016

- Create survey, pre-survey email
- Obtain contact information for participants
- IRB submission and approval

Spring 2017

- Send pre-survey email
- Send surveys via email
- Send survey reminders via email
- Obtain results

Summer and Fall 2017

- Analysis of results
- Manuscript submission

Additional resources needed:

- Qualtrics software
- Statistician
- Fees for Mailing Lists

### **Institutional Review Board**

This study will be submitted to the Boston University Medical Campus Institutional Review Board for expedited review. This survey meets criteria for expedited review for “research on individual or group characteristics or behavior or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance”. The pre-survey email and the text of the email will both include a consent statement to ask the participants’ approval to be involved in research. Furthermore, Qualtrics is an IRB approved software. The study invokes minimal risk to its participants, is not misleading or deceiving, does not involve sensitive populations, or involve intrusive or stressful procedures. If the IRB does not approve the study for expedited review, the study will be submitted for full review.

## CONCLUSION

### Discussion

HIV-positive donor to HIV-positive recipient transplants were made legal in 2013 in the United States when the HOPE Act was passed, and the first HIV-positive donor to HIV-positive recipient transplant was completed in March 2016. To date, there has been no study that has assessed at the attitudes of the medical community involved in these transplants. This study is unique in that it attempts to obtain the perceptions and concerns the transplant specialists have about HIV-positive donor organs to HIV-positive transplant recipients.

There are limitations to this study that should be pointed out. First, survey studies in the medical community traditionally have a very low response rate. If there are too few responses, the data will not have enough power to draw any significant conclusions. Attempts to increase the response rate include sending a pre-survey email, having the President of the organization forward the emails, and inclusion of the Boston University letterhead throughout study materials. Additionally, because the survey will be sent out via email it is likely that some intended participants will have not receive the survey due to their email settings or a changed their email address. Other limitations include that respondents may feel uncomfortable responding with their true perception, and therefore provide untruthful answers. Furthermore, people may not choose the extremes on the Likert scale even if that is where their perception lays.

As HIV-positive to HIV-positive organ transplants become legal in more countries, similar surveys can be conducted in those regions. While this study will be a

good representation for transplant professionals in the United States, it should not be generalized to other countries. It would be interesting to compare perceptions between United States transplant professionals and those from other countries. Furthermore, it will be interesting to repeat the study when HIV-positive to HIV-positive organ transplants are no longer in clinical trial phases to analyze how perceptions have changed over time in the United States.

### **Summary**

Kidney transplants have been proven to be the best choice of renal replacement therapy for most people with ESRD and appears to be similar for HIV-positive patients who have renal failure. Studies in South Africa show that using HIV-positive organ donors for HIV-positive recipients have high success rates. These transplants were made legal in the United States in 2013 when the HOPE Act was passed, and the first HIV-positive organ transplant was completed in March 2016 with good results. It is likely that transplant surgeons, nephrologists and transplant surgical physician assistants will welcome HIV-positive donor organs to HIV-positive transplants as an advancement in the field of transplant sciences, and expect these transplants to be a good treatment option for patients within the next five to ten years.

The proposed study will look to understand the opinions of transplant surgeons, transplant nephrologists and transplant physician assistants concerning HIV-positive to HIV-positive organ transplants. There has been no study to date that has gathered perceptions on this topic in the United States.

**Public health significance**

Gathering the opinions of transplant surgeons, transplant nephrologists and surgical PAs regarding HIV-positive to HIV-positive organ transplants at the beginning of this era has substantial public health applications. First, understanding these perceptions at a time when very few of these transplants have been completed in the United States sets a foundation for future researchers in which to compare. Additionally, determining if there are variations in opinions based on the demographic stratification will assist in our analysis of any potential demographical differences that can affect care for HIV-positive organ recipient failure or survival. For example, the survey can reveal regional differences in HIV-positive patient access to surgical teams willing to transplant HIV-positive organs. Furthermore, understanding the concerns of the transplant specialists can help determine where funding for further studies can be allocated. Therefore, the public health implications of this survey study may be significant.

## APPENDIX A

Pre-survey email

Dear \_\_\_\_\_,

As the transplant community continues to expand our collective knowledge, it's important to collect information on what our colleagues perceive about these advancements. On February 1<sup>st</sup>, 2017, you will receive an email with a survey link giving you the opportunity to share your perspective on one of the newest advancements in our field: HIV-positive organ donations to HIV-positive recipient transplants.

The purpose of this survey is to obtain your opinions on HIV-positive to HIV-positive transplants at the beginning of this era. The survey measures opinions and perceptions, there are no right or wrong answers. We will also be asking questions about your demographics. There are no mandatory questions and feel free to leave any questions unanswered that you wish to. All of your responses will be kept confidential.

This is a research study conducted by Boston University researchers. We anticipate it taking less than 15 minutes to complete. The survey is completely voluntary and a decision to not participate will not affect you in any way. If you would prefer to not receive the survey, please contact us and we would be happy to take your email off of our mailing list. If you have questions about your rights as a research subject, please contact Boston University IRB at 617-638-7207 or [medirb@bu.edu](mailto:medirb@bu.edu).

Thank you in advance for your time in February when you receive the survey.

## Appendix B

Survey Email, email body text

Dear \_\_\_\_\_,



A few weeks ago, you were sent a pre-notification of a survey about HIV-positive organ donations to HIV-positive transplant recipient. Please click the link below or copy and paste into your browser to complete the survey. By clicking the link and taking the survey, you are consenting to being a research subject in this study.

[https://bostonu.qualtrics.com/SE/?SID=SV\\_2cceHafj4ZLPtMF](https://bostonu.qualtrics.com/SE/?SID=SV_2cceHafj4ZLPtMF)

The purpose of this survey is to obtain your opinions on HIV-positive to HIV-positive transplants at the beginning of this era. The survey measures opinions and perceptions, there are no right or wrong answers. We will also be asking questions about your demographics. There are no mandatory questions and feel free to leave any questions unanswered that you wish to. All of your responses will be kept confidential.

This is a research study conducted by Boston University researchers. We anticipate it taking less than 15 minutes to complete. The survey is completely voluntary and a decision to not participate will not affect you in any way. If you would prefer to not take the survey, please contact us and we would be happy to take your email off of our list so you will not receive any reminder emails. If you have questions about your rights as a research subject, please contact Boston University IRB at 617-638-7207 or [medirb@bu.edu](mailto:medirb@bu.edu).

Thank you in advance for your time.

## Appendix C

### Survey for Transplant Professionals

Q1) You are invited to take part in a research survey about HIV-positive donor to HIV-positive recipient organ transplants. Your participation will require approximately 15 minutes and is completed online at your computer. There are no known risks or discomforts associated with this survey. Taking part in this study is completely voluntary. If you choose to be in the study you can withdraw at any time without adversely affecting your relationship with anyone at Boston University. Your responses will be kept strictly confidential, and digital data will be stored in secure computer files. Any report of this research that is made available to the public will not include your name or any other individual information by which you could be identified. Please feel free to print a copy of this consent page to keep for your records. Clicking the “Next” button below indicates that you are 18 years of age or older, and indicates your consent to participate in this survey. Clicking the "Close" button will close the survey.

- Next
- Close

Q2) Are you aware that HIV-positive organs are now able to be transplanted into HIV-positive patients in the United States as part of clinical research trials?

- Yes
- No

Q3) To what extent do you agree/disagree with the following statement: Within the next 5-10 years, HIV-positive to HIV-positive organ transplants will be a safe and effective treatment option, with success rates similar to non-HIV infected donor organs.

- Strongly agree
- Somewhat agree
- Neither agree nor disagree
- Somewhat disagree
- Strongly disagree

Q4) To what extent do you agree/disagree with the following statement: After appropriate counseling, most of my HIV-positive patients will agree to accept an HIV-positive organ if one became available instead of remaining on the organ donor waiting list.

- Strongly agree
- Somewhat agree
- Neither agree nor disagree
- Somewhat disagree
- Strongly disagree

Q5) I believe that there are ethical considerations concerning HIV-positive to HIV-positive organ transplants that the community needs to address.

- Strongly agree
- Somewhat agree
- Neither agree nor disagree
- Somewhat disagree
- Strongly disagree

Q6) I am willing to participate in HIV-positive to HIV-positive organ transplants in my professional role.

- Strongly agree
- Somewhat agree
- Neither agree nor disagree
- Somewhat disagree
- Strongly disagree

Q7) I believe that clinical research trials using HIV-positive organs should continue

- Yes, using deceased donors only
- Yes, using living donors only
- Yes, using both deceased and living donors
- No, I do not think HIV-positive organs should be used in transplants, even in clinical trials.

Q8) My concerns about HIV-positive to HIV-positive organ transplants include:

- Lack of demonstrated success
- Interactions of immunosuppressant therapy and HAART therapy
- Risk of superinfection
- Increased harm to patient
- Increased need for re-transplant
- Increased complexity of transplant surgery itself
- Safety of my transplant staff
- Other: \_\_\_\_\_
- None of the above

Q9) Overall, my feelings about HIV-positive to HIV-positive organ transplants can be summarized as:

Q10) Sex:

- Male
- Female
- Other
- Prefer not to say

Q11) Age:

- 20-30
- 31-40

- 41-50
- 51-60
- 61-70
- 71-80
- 81+

Q12) What is your professional role?

- Transplant surgeon
- Transplant Nephrologist
- Transplant Coordinator
- Transplant physician assistant/nurse practitioner
- Other \_\_\_\_\_

Q13) How many years have you been in practice?

- Less than 5
- 6-10
- 11-15
- 16-20
- 21-25
- >25

Q14) What OPTN region do you practice in?

Q15) What organ(s) do you primarily transplant?

Q16) Approximately how many transplants did you participate in within the past 12 months?

- <10
- 10-25
- 25-50
- 50-75
- 75-100
- >100

Q17) Did you participate in the transplantation of any organ into any HIV-positive patients within the past 12 months?

- Yes
- No
- I don't remember

Answer) If, Did you participate in the transplanting an organ into any HIV-positive patients within the past 12 months? Yes Is Selected

Q18 Approximately how many HIV-positive organ transplants did you participate in within the past 12 months?

Answer) If, Did you participate in the transplanting an organ into any HIV-positive patients within the past 12 months? Yes Is Not Selected

Q19 Are HIV-positive patients considered contraindicated to transplantation at your center?

- Yes
- No

## LIST OF JOURNAL ABBREVIATIONS

Am J Kidney Dis	American Journal of Kidney Diseases
Am J Transplant	American Journal of Transplantation
Ann Intern Med	Annals of Internal Medicine
Ann Surg	Annals of Surgery
Br J Clin Pharmacol	British Journal of Clinical Pharmacology
CA Cancer J Clin	CA: A Cancer Journal for Clinicians
Clin Pharm	Clinical Pharmacy
Clin Transplant	Clinical Transplantation
Curr Infect Dis Rep	Current Infectious Disease Reports
Eur Rev Med Pharmacol Sci	European Review for Medical and Pharmacological Sciences
Expert Opin Investig Drugs	Expert Opinion on Investigational Drugs
Fed Regist	Federal Register
Int J STD AIDS	International Journal of STD & AIDS
J Health Care Poor Underserved	Journal of Health Care for the Poor and Underserved
JAMA	JAMA: The Journal of the American Medical Association
JAMA Intern Med	JAMA Internal Medicine
Kidney Int	Kidney International
MMWR Morb Mortal Wkly Rep	MMWR: Morbidity and Mortality Weekly Report
N Engl J Med	New England Journal of Medicine
Nat Med	Nature Medicine

Nat Rev Nephrol	Nature Reviews. Nephrology
Rev Investig Clin	Revista de Investigación Clínica
Trans Am Clin Climatol Assoc	Transactions of the American Clinical and Climatological Association
Transpl Int	Transplant International
Transplant Infect Dis	Transplant Infectious Disease
World J Surg	World Journal of Surgery

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**CURRICULUM VITAE**

