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Outcomes in Human Immunodeficiency Virus Infected Recipients of Heart Transplants

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Abstract

Background—With the advent of combined antiretroviral therapy (cART), growing evidence has shown Human Immunodeficiency Virus (HIV) may no longer be an absolute contraindication for solid organ transplantation. This study compares outcomes of heart transplantations between HIV positive and HIV negative recipients using SRTR transplant registry data.

Methods—Patient survival, overall graft survival and death-censored graft survival were compared between HIV positive and HIV negative recipients. Multivariate Cox regression and Cox regression with a disease risk score (DRS) methodology were used to estimate the adjusted hazard ratios among heart transplant recipients (HTRs).

Results—In total 35 HTRs with HIV+ status were identified. No significant differences were found in patient survival (88% vs 77%; $p=0.1493$), overall graft survival (85% vs 76%; $p=0.2758$) and death-censored graft survival (91% vs 91%; $p=0.9871$) between HIV positive and HIV negative HTRs in 5-year follow-up. No significant differences were found after adjusting for confounders.

Conclusions—This study supports the use of heart transplant procedures in selected HIV positive patients. This study suggests that HIV positive status is not a contraindication for life saving heart transplant as there were no differences in graft, patient survival.

Introduction

Traditionally, transplantation eligibility hinged on a strict set of patient specific criteria. Patients infected with Human Immunodeficiency Virus (HIV) were generally excluded [1–3]. However, with the introduction of more effective treatment options for HIV in 1996, such as protease inhibitors and antiretroviral therapy, survival and quality of life have improved markedly in HIV infected patients [4–6]. Currently, more than one million Americans are infected with human immunodeficiency virus (HIV) [7]. The estimated 10-year survival rate in patients treated with cART exceeds 90%; denoting a shift in classifying HIV as a chronic medical condition rather than an acute illness which was life threatening [8]. Consequently,

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an increasing number of HIV-positive patients with other co-morbid conditions are presenting with manifestations of end-stage organ dysfunction from chronic HIV infection including chronic liver disease, chronic kidney disease, cardiomyopathy and end stage lung disease [9–11]. Co-infection with hepatitis B/C is common as they share the same routes of infection. Prior to the advent of cART, HIV patients were usually not considered for transplantation because of the poor prognosis of their underlying disease and concerns regarding potential detrimental effects of immunosuppression on viral load and immune status [1–3, 12, 13]. In this new treatment era, studies supporting renal and hepatic transplantations in HIV infected patients have shown promising results [12, 14–16]. South Africa pioneered many successful kidney transplants in HIV positive patients using HIV positive donor [17]. Survivors in the study with kidney transplant in HIV positive patients were followed for a median of 2.4 years. The rate of patient survival was 84% at year 1 and 74% at year 5. The corresponding graft survival rate, defined as the percentage of functioning graft regardless of patient death, was 93% and 84% [17]. Kidney transplantations hence have been performed successfully in HIV- positive patients; graft and patient survival appears to be similar to that of HIV-negative recipients [18]. In contrast, insufficient data is available for heart transplantation in HIV positive patients and is limited to a few observational case studies [19, 20].

Even though transplantation may be the last chance of survival for patients with end-stage organ failure [21], many transplant centers remain reluctant to perform these procedures on HIV positive patients [22]. Despite recent reports suggesting that patients with HIV do not experience poorer health outcomes when compared to HIV negative transplant recipients [23–26], many transplant centers remain steadfast in the outdated eligibility guidelines. The case series by Uriel et al. reported a 100% survival rate over a 5-year period without development of AIDS-defining illnesses among 7 HIV positive patients who received heart transplants [25]. However, these case reports are not comprehensive enough to provide conclusive evidence for supporting heart transplantations in HIV positive patients. Therefore, this study aims to fill this gap by evaluating heart transplant outcomes among HIV positive and HIV negative recipients using SRTR transplant registry in the United States.

Methods

Data Source

This study used data from the Scientific Registry of Transplant Recipients (SRTR). The SRTR data system includes data on all donor, wait-listed candidates, and transplant recipients in the US, submitted by the members of the Organ Procurement and Transplantation Network (OPTN), and has been described elsewhere [27]. The Health Resources and Services Administration (HRSA), U.S. Department of Health and Human Services provides oversight to the activities of the OPTN and SRTR contractors. This study utilized longitudinal clinical and demographic data on each patient from 2004–2016. It has been approved by the University of Rhode Island Institutional Review Board (IRB#955723–3).

Study Design

Outcomes in HIV positive heart transplant recipients were compared to HIV negative recipients in this retrospective cohort study. All patients who received a heart transplant over the age of 18 were included. Any patients who received other organ transplants or who did not have a conclusive HIV serology at the time of transplantation were excluded from the study.

Patients were followed from the date of transplantation until the first occurrence of any of the following: end of the fifth transplant year, re-transplantation, death, graft failure of any cause, and loss of follow-up in SRTR data. The endpoints were defined as patient survival, overall graft survival, and death-censored graft survival. Death with functioning graft was censored in death-censored graft survival analysis, but treated as an event in overall graft survival.

Statistical Analysis

Baseline cohort characteristics were summarized by calculated group median and interquartile for continuous variables and proportional frequencies and percentages for categorical variables. Student t-tests and chi-square tests were used to quantify statistically significant differences in baseline characteristics between the HIV positive and negative groups. The Fischer's exact test was used, instead of Chi-square test, where any cell had an observed count less than five. The Kaplan–Meier analysis and log-rank test were used to compare the crude risk of transplantation outcomes between HIV positive and HIV negative recipients.

Multivariate Cox regression was used to adjust for confounders between HIV positive and HIV negative patients. Covariates investigated in this study included patient age, gender, race, calendar year of transplantation, body mass index (BMI), baseline viral serology, primary cardiovascular diseases, number of human leukocyte antigen (HLA) mismatch, pre-transplant calculated panel reactive antibody (cPRA), histocompatibility cross match results, steroids regimen use, and ventricular assist device use. Besides HIV status, co-infection with hepatitis B and C were also examined. Primary diagnoses, defined as the reasons for receiving transplantation, were also adjusted, including dilated cardiomyopathy (DCM), coronary artery disease (CAD) and other diseases.

Transplantation in HIV positive recipients is relatively infrequent and could impact the validity of traditional multivariate regression with exposure propensity score [28–30]. With the concern that the exposure is too rare to obtain sufficient power for covariate adjustment, a disease risk score (DRS) method was used to combine covariates into a summary score. This method is better suited for studies with rare exposures and was adopted as an alternative for the adjustment of multiple confounders [29, 31]. This method has been validated by previous simulated and observational studies [28, 32]. To calculate DRS, each study outcome was regressed over the entire cohort on both the exposure variable and covariates [31]. The score was compiled from the fitted values of the model for each study subject when setting the individual exposure variable to unexposed [31]. The quintiles of the

DRS were used for covariate adjustment within the final Cox regression model to derive adjusted hazard ratios between HIV positive and negative patients with better precision [33].

All analyses were performed using SAS software, version 9.4 (SAS Institute Inc, Cary, NC). Statistical significance was based on a p value 0.05 and all confidence intervals used a 95% threshold.

Results

Thirty-five HIV-positive heart transplant recipients (HTRs) aged 18 or above, were identified using SRTR registry data from 2004 through 2016. The demographic and clinical characteristics of these 35 HIV-positive cases were summarized in table 1. The 35 HIV positive HTRs consisted of 25 males (71%) with a median age of 54 years (interquartile range (IQR): 43–61). In comparison, among total 21400 HIV negative HTRs, majority were male (75%) with a median age of 56 years (IQR: 46–62). More than half of the HIV positive HTRs were African Americans (57%) while only 20% of HIV negative HTRs were African Americans.

Almost half of the transplantations among HIV-positive patients (51%) occurred in 2014–2016, which may be a result of the HIV Organ Policy Equity (HOPE) Act. HIV-positive HTRs were more likely to be co-infected with hepatitis B virus (31% vs 5%, $p<0.001$) and hepatitis C virus (9% vs 2%, $p=0.0491$) compared to HIV negative HTRs. Among 35 HIV-positive HTRs, three patients had hepatitis C antibody positive status. HIV-positive HTRs had a higher frequency of coronary arterial disease as a primary medical diagnosis when compared to patients without HIV infection (11.4% vs 4.2%, $p = 0.0289$).

The median follow-up times were 2 years for HIV-positive HTRs. Among the 35 HIV-positive HTRs, two patients died at 2.8 and 2.9 years respectively and one patient had graft failure immediate post transplantation. The remaining patients survived the whole study period with a functioning graft. Notably, no death or graft failure was observed among three patients who were both HCV and HIV positive.

HIV-positive HTRs appeared to have a non-inferior patient survival compared to HIV negative HTRs (1-year: 100% vs 89%, 3-year: 88% vs 83%, 5-year: 88% vs 77%; $p=0.1493$), overall graft survival (1-year: 97% vs 89%, 3-year: 85% vs 82%, 5-year: 85% vs 76%; $p=0.2758$), and death-censored graft survival rates (1-year: 97% vs 96%, 3-year: 91% vs 93%, 5-year: 91% vs 91%; $p=0.9871$) (Figure 1 a, b, and c). None of these differences were statistically significant. This did not change when adjusted for demographic and clinical characteristics using a multivariate Cox regression or DRS adjustment model (Figure 2 a, b, and c).

Discussions

This is the largest study so far examining 35 HIV positive HTRs performed over 12 years duration. When comparing transplantation outcomes within the total cohort ($N=21,435$), there were no significant differences in the rates of patient or graft survival. Consistent with

previous reports, these findings suggest that heart transplantations may be viable options for selected HIV positive patients [19, 25, 34].

While Aguero et al. summarized previous studies showing the 1-, 2-, and 5-year survival rates for HIV-positive HTRs of 90–100%, 90–100%, and 63% [19], the survival rates in this study exhibited a more encouraging 3-year survival rate of 88%. The selection of transplant candidates should be meticulous, as many factors may affect the transplant outcomes, for example, hepatitis C coinfection will put HIV patients at greater risk than HIV negative patients after liver transplantation [14]. However, advent of direct-acting antiviral (DAA) therapy in recent years is changing this scenario albeit slowly. Therefore more cases are required to examine the factors that impact health outcomes between these groups.

Overall, the knowledge of heart transplantation outcomes among HIV positive recipients remains limited, despite the developing evidence on the safety and efficacy of kidney and liver transplantations [35, 36]. In light of the positive results in kidney and liver transplantations, Congress passed the HIV Organ Policy Equity (HOPE) Act in 2013, which permits research in the area of HIV-infected to HIV-infected transplantation. It allows use of organs from HIV positive donors for transplantation into HIV-positive candidates under approved research protocols designed to evaluate the feasibility, effectiveness and safety of such organ transplants. The goal is to bridge the difference between demand and available organs. HIV-infected, living donation is permitted under the HOPE Act. Similar to the arguments presented in the kidney and liver transplant studies of HIV positive recipients, this analysis suggests that HIV status in heart transplantations should not indicate an automatic exclusion.

Compared to general population, HIV-positive patients are more likely to develop cardiovascular diseases including cardiomyopathy, coronary arterial disease, myocarditis, cardiomegaly, and malignancy [37–39]. Similarly, HIV is associated with an increased risk of chronic obstructive pulmonary disease, pulmonary fibrosis, pulmonary arterial hypertension, and lung cancer [40–42]. It is imperative to develop a clear understanding of the outcomes of heart transplantations in this patient group. Furthermore, HIV infection is no longer considered an absolute contraindication in the updated consensus guidelines developed by the International Society for Heart Lung Transplantation (ISHLT) [43, 44]. However, most transplant centers still remain reluctant to perform heart transplantations with this population because of the concerns for increased risk of rejection, infections, HIV reactivation by immunosuppressants, and significant drug-drug interactions [22]. The published literature on this topic is sparse. This study highlights the need to revisit the biases associated with HIV positive status in heart transplantation.

While these findings provide important results derived from the largest known cohort of HIV positive heart transplantation recipients, the conclusions remain vulnerable to several study limitations. The most prominent of which, is the lack of HIV-positive heart transplant cases observed within the registry. HIV positive HRTs had relatively short follow-up as more than half these patients had transplant during 2014–2016. Although by using survival analysis we only compared HIV positive patients with HIV negative patients who had the same follow-up duration, future research is warranted to examine the long-term outcomes for these

patients when more data becomes available. Besides, this study was only based on the observations included within the registry, hence further studies using other data resources will be needed.

Additionally, the SRTR does not collect detailed HIV specific laboratory studies. For example, information regarding the viral load, CD4 count, or incidence of AIDS defining illnesses or incidence of other infections is absent. This can introduce uncertainty when comparing outcomes across transplant recipients. It is likely that patients with detectable viral loads and history of an AIDS defining illness were not transplanted. It is possible that HIV positive patients who get listed for the solid organ transplants may be healthier than the average HIV positive patients (with CD4 counts >200, undetectable viral load and no history of opportunistic infection) and could skew the data. In many reports, the HIV-positive patients who received transplants exhibited undetectable viral loads, moderate CD4 counts, and a lack of AIDS-related infections. This may limit the generalizability of results to a healthier HIV subpopulation and introduce an unavoidable, systematic selection bias. However, our data suggested that HIV-positive recipients were not healthier, but had a higher rate hepatitis C patients and more African Americans who have been associated with worse outcomes. Hep B serology status wasn't clear in dataset either. It should also be noted that the dataset did not provide details on nucleic acid testing to confirm the HCV and HBV status.

While these limitations are not all-inclusive or completely avoidable, the results still indicate that HIV-positive status should not trigger automatic exclusion from transplant eligibility for heart transplantation. Instead, clinicians should review HIV-positive transplant candidates case by case basis to decide their transplant candidacy. Further studies are required to develop a clearer understanding of the variables that impact graft survival and patient outcomes in HIV-positive heart transplant recipients as these procedures could improve quality and longevity of life.

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Abbreviations

HIV	Human Immunodeficiency Virus
cART	combined antiretroviral therapy
SRTR	Scientific Registry of Transplant Recipients
BMI	body mass index
HLA	human leukocyte antigen
PRA	panel reactive antibody

ATG	anti-thymocyte globulin
IL-2	interleukin-2
DCM	dilated cardiomyopathy
CAD	coronary artery disease
DRS	disease risk score
HTR	heart transplant recipient
IPF	idiopathic pulmonary fibrosis
COPD	chronic obstructive pulmonary disease
SD	standard deviation
IQR	interquartile range
XMATCH	histocompatibility cross match
CI	confidence interval
ISHLT	International Society for Heart Lung Transplantation

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Figure 1. Kaplan-Meier curve for patient outcomes among heart recipients (HIV-positive vs. HIV-negative)

Figure 1.a Patient Survival ($P=0.1493$)

Figure 1.b Overall Graft Survival ($P= 0.2758$)

Figure 1.c Death-censored graft Survival ($P=0.9871$)

Figure 2.

a. Forest plot of adjusted hazard ratios of HIV status and other significant risk factors for patient survival among heart transplant recipients

Abbreviation: HIV, Human Immunodeficiency Virus; DRS, disease risk score; XMATCH, histocompatibility cross match; CI, confidence interval; BMI, body mass index; HCV, hepatitis C virus

Figure 2.b. Forest plot of adjusted hazard ratios of HIV status and other significant risk factors for overall graft survival among heart transplant recipients

Abbreviation: HIV, Human Immunodeficiency Virus; DRS, disease risk score; XMATCH, histocompatibility cross match; CI, confidence interval; BMI, body mass index; HCV, hepatitis C virus

Figure 2.c. Forest plot of adjusted hazard ratios of HIV status and other significant risk factors for death-censored graft survival among heart transplant recipients

Abbreviation: HIV, Human Immunodeficiency Virus; DRS, disease risk score; XMATCH, histocompatibility cross match; CI, confidence interval; BMI, body mass index

Table 1.

Demographic and clinical characteristics of US heart transplant recipients (HIV-positive vs. HIV-negative) from 2004 through 2016

Variables	HIV positive N=35	HIV negative N=21400	p
Year of transplant			0.0027
2004–2006	1 (29.0)	3772 (17)	
2007–2009	5 (14.3)	4839 (23)	
2010–2013	11 (31.4)	7236 (34)	
2014–2016	18 (51.4)	5553 (26)	
Pretransplant viral serology			
Hepatitis B Core antibody+	11 (31.4)	965 (5)	<0.001
Hepatitis C antibody +	3 (8.6)	413 (2)	0.0491
Induction therapy			0.3438
ATG	3 (8.57)	4147 (19.49)	
Alemtuzumab	0 (0.00)	219 (1.02)	
IL-2 inhibitors	10 (28.57)	5918 (27.65)	
Others	22 (62.86)	11092 (51.83)	
Median age (IQR)	54 (43, 6)	56 (46, 62)	0.0678
Age categories:			0.1953
18–45	13 (37.1)	5246 (25)	
46–60	14 (40.0)	9336 (44)	
Over 60	8 (22.9)	6818 (32)	
Median follow-up years (IQR)	2.00 (1, 5)	3.0 (1, 5)	0.1606
Recipient race:			<0.001
White	12 (34)	14549 (68)	
Black	20 (57)	4214 (20)	
Hispanic	2 (6)	1717 (8)	
Others	1 (3)	9420 (4)	
Recipient sex			0.6607
Male	25 (71)	15977 (75)	
Female	10 (29)	5423 (25)	
Previous transplant	1 (3)	612 (3)	1.0000
Recipient BMI:			0.7779
0–20	4 (11)	1387 (7)	
20–25	10 (29)	6244 (29)	
25–30	13 (37)	7873 (37)	
Above 30	8 (23)	5751 (27)	
HLA mismatch			0.6407
0	0 (0)	30 (0)	
1–2	1 (3)	649 (3)	
3–4	13 (37)	7064 (33)	
5–6	20 (57)	11272 (53)	

Variables	HIV positive N=35	HIV negative N=21400	<i>p</i>
Ventricular assist device	15 (43)	6409 (30)	0.0958
Histocompatibility cross match			
Negative	22 (63)	14618 (68)	0.6045
Positive	1 (3)	816 (4)	
Weak positive	1 (3)	202(1)	
Unknown	11 (31)	5764 (27)	
Primary diagnoses:			0.0333
DCM	30 (86)	17783 (83)	
CAD	4 (11)	894 (4)	
Others	1 (3)	2723 (13)	

Abbreviation: HIV, Human Immunodeficiency Virus; SD, standard deviation; IQR, interquartile range; BMI, body mass index; HLA, human leukocyte antigen; DCM, dilated cardiomyopathy; CAD, coronary artery disease

Table 2.

Other clinical outcomes in US heart transplant recipients (HIV-positive vs. HIV-negative) from 2004 through 2016

Outcomes	HIV positive N=35	HIV negative N=21400	<i>p</i> -value
Biopsy proven rejection	10 (29%)	4864 (23%)	0.4100
Infection	6 (17%)	4717 (22%)	0.4859
Malignancy	3 (9%)	1841 (9%)	0.9947
Renal dysfunction	4 (11%)	5062 (24%)	0.0889