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Outcomes in Human Immunodeficiency Virus Infected Recipients of Heart and Lung Transplants

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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

HBc, hepatitis B core

HCV, hepatitis C virus

EBV, Epstein-Barr virus

CMV, cytomegalovirus

ATG, anti-thymocyte globulin

IL-2, interleukin-2

DCM, dilated cardiomyopathy

CAD, coronary artery disease

DRS, disease risk score

HTR, heart transplant recipient

LTR, lung transplant recipients

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3 IPF, idiopathic pulmonary fibrosis
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5 COPD, chronic obstructive pulmonary disease
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7 SD, standard deviation
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9 IQR, interquartile range
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11 XMATCH, histocompatibility cross match
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13 CI, confidence interval
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15 ISHLT, International Society for Heart Lung Transplantation
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CONFIDENTIAL

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 compared outcomes of heart and lung transplantations between HIV positive and HIV negative recipients from a large transplant registry.

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). Descriptive analysis was performed for HIV-positive lung transplant recipients (LTRs).

Results

In total 35 HTRs and 6 LTRs with HIV were identified. No significant difference was 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. Among 6 HIV positive LTRs, two patients died in their first and fourth year after transplantation respectively.

Conclusions

This study supports the use of heart and lung transplant procedures in selected HIV positive patients.

(Words count: 197)

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). The scarcity of donor organs forced practitioners to only consider patients with the best prognosis because success is dependent on a lifetime of adherence to a complex medication regimen (4). Furthermore, with continual immunosuppressant therapy as the mainstay in post-operative treatment, patients with immunocompromising conditions, such as HIV, may be more prone to adverse health outcomes (2, 5). Studies in early 1990s consistently showed shorter incubation periods for advanced disease and lower survival rates in transplant recipients infected with HIV (5-8). Additionally, some immunosuppressive therapies may inhibit the development of CD4+ T cells in patients after transplantation (9-11). However, with the introduction of combined antiretroviral therapy (cART) in 1996, survival and quality of life have improved markedly in HIV infected patients (12-14). The estimated 10-year survival rate in patients treated with cART exceeds 90%; denoting a shift in classifying HIV as an chronic infective process rather than an acute illness (15). In this new treatment era, studies supporting renal and hepatic transplantations in HIV infected patients have shown promising results (16-19). In contrast, limited instances of heart and lung transplants restricts the evidence to observational case studies (20, 21).

Even though transplantation may be the last chance of survival for patients with end-stage disease (22), many transplant centers remain reluctant to perform these procedures on patients infected with HIV (23). Despite recent reports suggesting that patients with HIV do not experience poorer health outcomes when compared to

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3 uninfected transplant recipients (24-26), many clinicians remain steadfast in the
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5 antiquated eligibility guidelines. The case series study by Uriel et al. reported a 100%
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7 survival rate over a 5-year period without development of AIDS-defining illnesses
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9 among 7 HIV positive patients who received heart transplants (26). Similarly, Kern et al.
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11 reviewed three case studies of lung transplantations among patients with HIV infection
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13 and suggested that it might be a promising option for patients with selected end-stage
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15 lung disease (27) However, in the defense of the reluctant clinicians, these case reports
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17 are not comprehensive enough to provide conclusive evidence for supporting heart and
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19 lung transplantations in HIV infected patients. Therefore, this study aims to provide
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21 some guidance by evaluating heart and lung transplant outcomes among HIV positive
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23 and HIV negative recipients using a large transplant registry in the United States.
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33 **Methods**

34 **Data Source**

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38 This study used data from the Scientific Registry of Transplant Recipients
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40 (SRTR). The SRTR data system includes data on all donor, wait-listed candidates, and
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42 transplant recipients in the US, submitted by the members of the Organ Procurement
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44 and Transplantation Network (OPTN), and has been described elsewhere (28). The
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46 Health Resources and Services Administration (HRSA), U.S. Department of Health and
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48 Human Services provides oversight to the activities of the OPTN and SRTR contractors.
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50 This study utilized longitudinal clinical and demographic data on each patient from
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52 2004-2016. It has been approved by the University of Rhode Island Institutional Review
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54 Board (IRB#955723-3).
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Study Design

Outcomes in HIV positive transplant recipients were compared to HIV negative recipients in this retrospective cohort study. All patients who received a heart and/or lung 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, and loss of SRTR follow-up. 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 means and standard deviations 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 adopted, 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.

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Multivariate Cox regression was used to adjust for confounders between HIV positive and HIV negative groups. Covariates investigated in this study included patient age, gender, race, recipient educational level, calendar year of transplantation, body mass index (BMI), receipt of induction therapy, baseline viral serology, primary cardiovascular diseases, number of human leukocyte antigen (HLA) recipient to donor mismatch, pre-transplant panel reactive antibody (PRA), histocompatibility cross match results, steroids regimen use, and ventricular assist device use. Besides HIV status, other pre-transplant viral antibody serology status were also examined, including hepatitis B core (HBc), hepatitis C virus (HCV), Epstein-Barr virus (EBV) and cytomegalovirus (CMV). The induction therapy utilized was classified as anti-thymocyte globulin (ATG), alemtuzumab, interleukin-2 (IL-2) inhibitors including basiliximab or daclizumab, other induction therapy and no induction. Primary diagnoses, defined as the reasons for receiving transplantation, were adjusted for and included dilated cardiomyopathy (DCM), coronary artery disease (CAD) and other diseases.

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Transplantation in HIV infected recipients is relatively infrequent and could impact the validity of traditional multivariate regression with exposure propensity score (29-31). Disease risk score (DRS) is better suited for studies with rare exposures and was adopted as an alternative for the adjustment of confounders (30, 32). This method has been validated by previous simulated and observational studies (29, 33). To calculate DRS, each study outcome was regressed over the entire cohort on both the exposure variable and covariates (32). The score was compiled from the fitted values of the model for each study subject when setting the individual exposure variable to unexposed (32). The quintiles of the DRS were used for covariate adjustment within the

1
2
3 final Cox regression model to derive adjusted hazard ratios between HIV positive and
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5 negative patients with better precision (34).
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8 All analyses were performed using SAS software, version 9.4 (SAS Institute Inc,
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10 Cary, NC). Statistical significance was based on a P value less than 0.05 and all
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12 confidence intervals used a 95% threshold.
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17 Results

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20 Thirty-five HIV-positive adult heart transplant recipients (HTRs) and 6 HIV-
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22 positive lung transplant recipients (LTRs) were identified using SRTR data from 2004
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24 through 2016. The demographic and clinical characteristics of these 41 HIV-positive
25
26 cases were summarized in table 1 and table 2 respectively. Statistical analyses
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28 between HIV negative and HIV positive LTRs were not conducted due to the limited
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30 number of observed occurrences. The 35 HTRs with positive HIV consisted of 25 male
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32 (71.43%) and 10 female (28.57%) patients with an average age of 49 years (SD: 12.00).
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34 In comparison, HTRs with a negative HIV serology were mostly male (74.66%) with a
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36 mean age of 53 years (SD: 12.80). Almost half of the transplantations among HIV-
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38 positive patients (51.14%) occurred in 2014-2016, while only about one-fourth of HIV-
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40 negative patients (25.95%) received transplantation in this period. HIV-positive HTRs
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42 had a significantly higher rate of chronic viral infections including hepatitis B (31.43% vs
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44 4.51%, $p<0.001$), hepatitis C (8.56% vs 1.93%, $p=0.0491$), and cytomegalovirus
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46 (85.71% vs 59.35%, $p=0.0341$). Additionally, HIV-positive HTRs were less likely to have
47
48 received anti-thymocyte globulin (ATG) as induction therapy; although, this comparison
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50 is not statistically significant (8.57% vs 19.49%, $p=0.3438$). HIV-positive HTRs had a
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3 higher frequency of coronary arterial disease as a primary medical diagnosis when
4 compared to patients without HIV infection (11.43% vs 4.18%, $p = 0.0289$). There were
5 significantly more HIV-positive HTRs with a college level education (68.57% vs 48.93%,
6 $p=0.0461$).
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12 The median follow-up times were 2.00 years for HIV-positive HTRs and 3.00
13 years for HIV-negative HTRs. Among the 35 HIV-positive HTRs, two patients died at
14 2.78 and 2.93 years respectively and one patient did not receive a successful
15 transplant. The remaining patients survived the whole study period with a functioning
16 graft. Even though the results were inconclusive, HIV-positive HTRs appeared to have a
17 better patient survival (1-year: 100% vs 89%, 3-year: 88% vs 83%, 5-year: 88% vs 77%;
18 $p=0.1493$), overall graft survival (1-year: 97% vs 89%, 3-year: 85% vs 82%, 5-year: 85%
19 vs 76%; $p=0.2758$), and death-censored graft survival rates (1-year: 97% vs 96%, 3-
20 year: 91% vs 93%, 5-year: 91% vs 91%; $p=0.9871$) (Figure 1 a, b, and c). Adjusting for
21 demographic and clinical characteristics using a multivariate Cox regression or DRS
22 adjustment model did not alter the results (Figure 2).
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38 Among the 6 HIV-positive LTRs, all patients were white with ages varying
39 between 50 to 70 years old. Three patients had a BMI>30, one patient was female, and
40 only one did not have a college-level education. Two patients were infected with
41 Hepatitis B, all six patients were coinfecting with cytomegalovirus and Epstein Barr virus,
42 and none of the patients were infected with Hepatitis C. Four patients received
43 transplants due to idiopathic pulmonary fibrosis (IPF) and one due to chronic obstructive
44 pulmonary disease (COPD). Two patients were lost to follow-up immediately after
45 transplantation, one patient was censored at the fourth year, and another was censored
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3 at the fifth year. No graft failures were observed for these four patients. The remaining
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5 two patients died in 116 days and 1541 days after transplantation.
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10 **Discussions**

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12 Throughout the 12-year study period, 35 HTRs and 6 LTRs were infected with
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14 HIV; which, to our knowledge is the largest study conducted on heart and lung
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16 transplantations among HIV patients. When comparing transplantation outcomes within
17
18 the total cohort (N=21,435), there was no significant difference in the rates of patient
19
20 survival or graft failure. Consistent with previous reports, these findings suggest that
21
22 both heart and lung transplantations may be viable options for selected HIV infected
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24 patients (20, 26, 27).
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29 While Agüero et al. summarized previous studies showing the 1-, 2-, and 5-year
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31 survival rates for HIV-positive HTRs of 90-100%, 90-100%, and 63% (20), the survival
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33 rates in this study exhibited a more encouraging 5-year survival rate of 88%. Compared
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35 to Kern et al. study, in which all three LTRs remained alive during the study period with
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37 the longest follow-up time surpassing 4 years (27), our study observed two LTRs who
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39 died in their first and fourth year after transplantation, two who were lost to follow-up
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41 immediately after transplantation, and two who remained alive for more than four years
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43 post-transplant. HIV-positive LTRs had acceptable outcomes with wide variability but
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45 displayed a higher risk of poorer outcomes when compared to HIV-positive HTRs. The
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47 selection of transplant candidates should be cautious, as many factors may affect the
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49 transplant outcomes, for example, HCV positivity will put HIV patients at greater risk
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3 than non-HIV patients after liver transplantation (16). Therefore more cases are required
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5 to examine the factors that impact health outcomes between these groups.
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8 Overall, the knowledge of heart and lung transplant outcomes among HIV
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10 recipients remains limited, despite the developing evidence on the safety and efficacy of
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12 kidney and liver transplants (35, 36). Similar to arguments of these kidney and liver
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14 transplant studies, this analysis suggests that HIV positivity in heart and lung transplant
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16 candidates should not signify automatic exclusion.
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20 HIV-infected patients are more likely to develop cardiovascular diseases
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22 including cardiomyopathy, coronary arterial disease, myocarditis, cardiomegaly, and
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24 malignancy (37-39). Similarly, HIV is associated with an increased risk of chronic
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26 obstructive pulmonary disease, pulmonary fibrosis, pulmonary arterial hypertension, and
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28 lung cancer (40-42). It would be advantageous to develop a clear understanding of the
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30 outcomes and risks of heart transplantations and lung transplantations in this patient
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32 group. Furthermore, HIV infection is no longer considered an absolute contraindication
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34 in the updated consensus guidelines developed by the International Society for Heart
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36 Lung Transplantation (ISHLT) (43, 44). However, most transplant centers still remain
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38 reluctant to perform heart or lung transplants within this population because of the
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40 concerns for infection, HIV reactivation by immunosuppressants, and drug-drug
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42 interactions (23). Even though the published literature on this topic is in its adolescent
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44 stages, this study indicates that the stigma associated with HIV on heart and lung
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46 transplant outcomes should be revisited.
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53 While these findings provide promising results derived from the largest known
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55 cohort of HIV positive heart and lung transplant recipients, the conclusions remain
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3 vulnerable to several study limitations. The most prominent of which, is the lack of HIV-
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5 positive heart and lung transplant cases observed within the registry. We suspect that
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7 as time progresses more cases will be captured. However, because this study can only
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9 make inferences about the observations included within the registry, the validity of the
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11 derived estimates remains inconclusive.
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15 Additionally, the SRTR provides limited information about the baseline, pre-
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17 operative, and post-operative clinical depiction of each patient. For example, information
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19 regarding the viral load, CD4 count, or instances of AIDS opportunistic infection are
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21 absent. This can introduce uncertainty when comparing outcomes across transplant
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23 recipients; who, may be suffering from varying levels of HIV severity. In contrast, HIV
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25 infected individuals who progress to the solid organ waiting-list may be healthier than
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27 the average HIV patient. In many reports, the HIV-infected patients selected exhibited
28
29 undetectable viral loads, moderate CD4 counts, and a lack of AIDS-related infections.
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31 This limits the generalizability of results to a healthier HIV subpopulation and
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33 introduces an unavoidable, systemic selection bias.
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39 Along with the lack of markers depicting the clinical health of each patient, this
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41 dataset is incapable of evaluating medication adherence. The complicated home-
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43 medication regimen that the average transplant recipient receives can increase in
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45 complexity when the common drug-drug interactions between antiretroviral therapies
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47 and immunosuppressive therapies are introduced. If patients with superb medication
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49 adherence experienced better health outcomes than those with moderate or suboptimal
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51 adherence, this effect would never be identified.
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3 While these limitations are not all-inclusive or completely avoidable, the results
4 still indicate that HIV status should not trigger automatic exclusion from transplant
5 eligibility. Instead, clinicians should review HIV-positive transplant candidates under
6 updated criteria. Further research is required to develop a clearer understanding of the
7 variables that impact health outcomes in HIV-positive heart and lung transplant
8 recipients as these procedures could improve prognosis by many years.
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20 **Acknowledgement:**

21 The data reported here have been supplied by the Minneapolis Medical
22 Research Foundation (MMRF) as the contractor for the Scientific Registry of Transplant
23 Recipients (SRTR). The interpretation and reporting of these data are the responsibility
24 of the author(s) and in no way should be seen as an official policy of or interpretation by
25 the SRTR or the U.S. Government.
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40 **References:**

- 41 1. Cooper CL, DeForest J, Gill J, Lalonde R, Group CHTNC-IC. Barriers preventing liver
42 transplantation in Canadians with HIV infection—Perceptions of HIV specialists. *Canadian Journal of*
43 *Gastroenterology and Hepatology* 2007;21(3):179-182.
- 44 2. Rubin RH, Jenkins RL, Shaw JR BW, Shaffer D, Pearl RH, Erb S et al. The acquired
45 immunodeficiency syndrome and transplantation. *Transplantation* 1987;44(1):1-4.
- 46 3. Spital A. Should all human immunodeficiency virus-infected patients with end-stage renal
47 disease be excluded from transplantation?: the views of US transplant centers. *Transplantation*
48 1998;65(9):1187-1191.
- 49 4. Mullen MA, Kohut N, Sam M, Blendis L, Singer PA. Access to adult liver transplantation in
50 Canada: a survey and ethical analysis. *CMAJ: Canadian Medical Association Journal* 1996;154(3):337.
- 51 5. Tzakis AG, Cooper MH, Dummer JS, Ragni M, Ward JW, Starzl TE. Transplantation in HIV+
52 patients. *Transplantation* 1990;49(2):354.
- 53 6. Bouscarat F, Samuel D, Simon F, Debat P, Bismuth H, Saimot A. An observational study of 11
54 French liver transplant recipients infected with human immunodeficiency virus type 1. *Clinical infectious*
55 *diseases* 1994;19(5):854-859.
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7. Gordon F, Mistry P, Sabin C, Lee C. Outcome of orthotopic liver transplantation in patients with haemophilia. *Gut* 1998;42(5):744-749.
8. Swanson S, Kirk A, Ko C, Jones C, Agodoa L, Abbott K. Impact of HIV seropositivity on graft and patient survival after cadaveric renal transplantation in the United States in the pre highly active antiretroviral therapy (HAART) era: an historical cohort analysis of the United States Renal Data System. *Transplant infectious disease* 2002;4(3):144-147.
9. Korczak-Kowalska G, Wierzbicki P, Bocian K, Klosowska D, Niemczyk M, Wyzgal J et al. The influence of immunosuppressive therapy on the development of CD4+ CD25+ T cells after renal transplantation. In: *Transplantation proceedings; 2007: Elsevier; 2007. p. 2721-2723.*
10. Chu Z, Zhang J, Zhao Y, Ji Q, Zhong J, Zhang C et al. Influence of Immunosuppressive Drugs on the Development of CD4+ CD25 high Foxp3+ T Cells in Liver Transplant Recipients. In: *Transplantation proceedings; 2010: Elsevier; 2010. p. 2599-2601.*
11. Carter J, Melcher M, Carlson L, Roland M, Stock P. Thymoglobulin-Associated Cd4+ T-Cell Depletion and Infection Risk in HIV-Infected Renal Transplant Recipients. *American journal of transplantation* 2006;6(4):753-760.
12. Palella Jr FJ, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. *New England Journal of Medicine* 1998;338(13):853-860.
13. Kaplan JE, Hanson D, Dworkin MS, Frederick T, Bertolli J, Lindegren ML et al. Epidemiology of human immunodeficiency virus-associated opportunistic infections in the United States in the era of highly active antiretroviral therapy. *Clinical infectious diseases* 2000;30(Supplement 1):S5-S14.
14. Detels R, Munoz A, McFarlane G, Kingsley LA, Margolick JB, Giorgi J et al. Effectiveness of potent antiretroviral therapy on time to AIDS and death in men with known HIV infection duration. *Jama* 1998;280(17):1497-1503.
15. Collaboration C. Determinants of survival following HIV-1 seroconversion after the introduction of HAART. *The Lancet* 2003;362(9392):1267-1274.
16. Terrault NA, Roland ME, Schiano T, Dove L, Wong MT, Poordad F et al. Outcomes of liver transplant recipients with hepatitis C and human immunodeficiency virus coinfection. *Liver Transplantation* 2012;18(6):716-726.
17. Sawinski D. Kidney transplantation for HIV-positive patients. *Transplantation Reviews* 2016.
18. Stock PG, Barin B, Murphy B, Hanto D, Diego JM, Light J et al. Outcomes of kidney transplantation in HIV-infected recipients. *New England Journal of Medicine* 2010;363(21):2004-2014.
19. Roland M, Barin B, Carlson L, Frassetto L, Terrault N, Hirose R et al. HIV-Infected Liver and Kidney Transplant Recipients: 1-and 3-Year Outcomes. *American Journal of Transplantation* 2008;8(2):355-365.
20. Agüero F, Castel M, Cocchi S, Moreno A, Mestres C, Cervera C et al. An Update on Heart Transplantation in Human Immunodeficiency Virus–Infected Patients. *American Journal of Transplantation* 2016;16(1):21-28.
21. George MP. Time to reconsider transplant criteria for candidacy? Lung transplantation feasibility in HIV-infected patients. In.: *Am Thoracic Soc, 2014.*
22. Sackoff JE, Hanna DB, Pfeiffer MR, Torian LV. Causes of death among persons with AIDS in the era of highly active antiretroviral therapy: New York City. *Annals of Internal Medicine* 2006;145(6):397-406.
23. Uriel N, Nahumi N, Colombo PC, Yuzefpolskaya M, Restaino SW, Han J et al. Advanced heart failure in patients infected with human immunodeficiency virus: is there equal access to care? *The Journal of Heart and Lung Transplantation* 2014;33(9):924-930.
24. Calabrese LH, Albrecht M, Young J, McCarthy P, Haug M, Jarcho J et al. Successful cardiac transplantation in an HIV-1–infected patient with advanced disease. *New England Journal of Medicine* 2003;348(23):2323-2328.

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25. Gupta S, Markham D, Mammen P, Kaiser P, Patel P, Ring W et al. Long-Term Follow-up of a Heart Transplant Recipient with Documented Seroconversion to HIV-Positive Status 1 Year After Transplant. *American Journal of Transplantation* 2008;8(4):893-896.
26. Uriel N, Jorde UP, Cotarlan V, Colombo PC, Farr M, Restaino SW et al. Heart transplantation in human immunodeficiency virus–positive patients. *The Journal of Heart and Lung Transplantation* 2009;28(7):667-669.
27. Kern RM, Seethamraju H, Blanc PD, Sinha N, Loebe M, Golden J et al. The feasibility of lung transplantation in HIV-seropositive patients. *Annals of the American Thoracic Society* 2014;11(6):882-889.
28. Leppke S, Leighton T, Zaun D, Chen S-C, Skeans M, Israni AK et al. Scientific Registry of Transplant Recipients: collecting, analyzing, and reporting data on transplantation in the United States. *Transplantation Reviews* 2013;27(2):50-56.
29. Arbogast PG, Ray WA. Performance of disease risk scores, propensity scores, and traditional multivariable outcome regression in the presence of multiple confounders. *American journal of epidemiology* 2011;174(5):613-620.
30. Glynn RJ, Gagne JJ, Schneeweiss S. Role of disease risk scores in comparative effectiveness research with emerging therapies. *Pharmacoepidemiology and drug safety* 2012;21(S2):138-147.
31. Tadrous M, Gagne JJ, Stürmer T, Cadarette SM. Disease risk score as a confounder summary method: systematic review and recommendations. *Pharmacoepidemiology and drug safety* 2013;22(2):122-129.
32. Miettinen OS. Stratification by a multivariate confounder score. *American journal of epidemiology* 1976;104(6):609-620.
33. Stürmer T, Schneeweiss S, Brookhart MA, Rothman KJ, Avorn J, Glynn RJ. Analytic strategies to adjust confounding using exposure propensity scores and disease risk scores: nonsteroidal antiinflammatory drugs and short-term mortality in the elderly. *American Journal of Epidemiology* 2005;161(9):891-898.
34. Arbogast P, Seeger J, Group DMCSVW. Summary variables in observational research: propensity scores and disease risk scores. *Effective health care program research report* 2012(33).
35. Pelletier S, Norman S, Christensen L, Stock P, Port F, Merion R. Review of transplantation in HIV patients during the HAART era. *Clinical transplants* 2004:63.
36. Joshi D, Agarwal K. Role of liver transplantation in human immunodeficiency virus positive patients. *World journal of gastroenterology* 2015;21(43):12311-12321.
37. Kaul S, Fishbein MC, Siegel RJ. Cardiac manifestations of acquired immune deficiency syndrome: a 1991 update. *American heart journal* 1991;122(2):535-544.
38. Zareba KM, Lipshultz SE. Cardiovascular complications in patients with HIV infection. *Current infectious disease reports* 2003;5(6):513-520.
39. Currier J. Update on cardiovascular complications in HIV infection. *Topics in HIV medicine: a publication of the International AIDS Society, USA* 2008;17(3):98-103.
40. Crothers K, Huang L, Goulet JL, Goetz MB, Brown ST, Rodriguez-Barradas MC et al. HIV infection and risk for incident pulmonary diseases in the combination antiretroviral therapy era. *American journal of respiratory and critical care medicine* 2011;183(3):388-395.
41. Gingo MR, Morris A. Pathogenesis of HIV and the lung. *Current HIV/AIDS Reports* 2013;10(1):42-50.
42. Gingo MR, Balasubramani G, Kingsley L, Rinaldo Jr CR, Alden CB, Detels R et al. The impact of HAART on the respiratory complications of HIV infection: longitudinal trends in the MACS and WIHS cohorts. *PLoS One* 2013;8(3):e58812.

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3 43. Weill D, Benden C, Corris PA, Dark JH, Davis RD, Keshavjee S et al. A consensus document for the
4 selection of lung transplant candidates: 2014—an update from the Pulmonary Transplantation Council
5 of the International Society for Heart and Lung Transplantation. In.: Elsevier, 2015.
6
7 44. Mehra MR, Canter CE, Hannan MM, Semigran MJ, Uber PA, Baran DA et al. The 2016
8 International Society for Heart Lung Transplantation listing criteria for heart transplantation: a 10-year
9 update. J Heart Lung Transplant 2016;35(1):1-23.
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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	<i>p</i>
Year of transplant			0.0027
2004-2006	1 (2.86)	3772 (17.63)	
2007-2009	5 (14.29)	4839 (22.61)	
2010-2013	11 (31.43)	7236 (33.81)	
2014-2016	18 (51.43)	5553 (25.95)	
Pretransplant viral serology			
Hepatitis B antibody+	11 (31.43)	965 (4.51)	<0.001
Hepatitis C antibody+	3 (8.57)	413 (1.93)	0.0491
Epstein Barr virus+	27 (77.14)	16116 (75.31)	0.8100
Cytomegalovirus+	30 (85.71)	12700 (59.35)	0.0341
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)	
Mean age (SD)	48.69 (12.00)	52.64 (12.80)	0.0678
Age categories:			0.1953
18-45	13 (37.14)	5246 (24.51)	
46-60	14 (40.00)	9336 (43.63)	
Over 60	8 (22.86)	6818 (31.66)	
Median follow-up years (IQR)	2.00 (0.5, 4.98)	3.00 (1.00, 4.99)	0.1606
Recipient race:			<0.001
White	12 (34.29)	14549 (67.99)	
Black	20 (57.14)	4214 (19.69)	
Hispanic	2 (5.71)	1717 (8.02)	
Others	1 (2.86)	9420 (4.30)	
Recipient sex			0.6607
Male	25 (71.43)	15977 (74.66)	
Female	10 (28.57)	5423 (25.34)	
Education level			0.0461
College	24 (68.57)	10470 (48.93)	
Non-college	7 (20.00)	8479 (39.62)	
Unknown	4 (11.43)	2451 (11.45)	
Previous transplant	1 (2.86)	612 (2.86)	1.0000
Recipient BMI:			0.7779
0-20	4 (11.43)	1387 (6.48)	
20-25	10 (28.57)	6244 (29.18)	
25-30	13 (37.14)	7873 (36.79)	
Above 30	8 (22.86)	5751 (26.87)	
HLA mismatch >3	28 (80.00)	16234 (75.86)	0.2336
Steroids use	33 (94.29)	20453 (95.57)	0.6676
Ventricular assist device	15 (42.86)	6409 (29.95)	0.0958
Left ventricular assist device	6 (17.14)	3725 (17.41)	0.9672

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Histocompatibility cross match			
Negative	22 (62.86)	14618 (68.31)	0.6045
Positive	1 (2.86)	816 (3.81)	
Weak positive	1 (2.86)	202(0.94)	
Unknown	11 (31.43)	5764 (26.93)	
Primary diagnoses:			0.0333
DCM	30 (85.71)	17783 (83.10)	
CAD	4 (11.43)	894 (4.18)	
Others	1 (2.86)	2723 (12.72)	

Abbreviation: HIV, Human Immunodeficiency Virus; ATG, anti-thymocyte globulin; IL-2, interleukin-2; SD, standard deviation; IQR, interquartile range; BMI, body mass index; HLA, human leukocyte antigen; DCM, dilated cardiomyopathy; CAD, coronary artery disease

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Table 2. Demographic and clinical characteristics of lung transplant HIV-positive recipients from 2004 through 2016

Variables	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Year of Transplant	2004	2010	2012	2014	2016	2016
Pretransplant viral serology						
Hepatitis B antibody	+	-	+	-	-	-
Hepatitis C antibody	-	-	-	-	-	-
Epstein Barr virus	+	+	+	+	+	+
Cytomegalovirus	+	+	+	+	-	+
Induction therapy	Others	Others	Others	IL-2 inhibitors	IL-2 inhibitors	IL-2 inhibitors
Recipient age	56	63	60	70	53	57
Recipient race	White	White	White	White	White	White
Recipient sex	Male	Male	Male	Male	Female	Male
Education level	Non-college	College	College	College	College	College
Recipient BMI	Above 30	Above 30	25-30	25-30	20-25	Above 30
HLA mismatch >3	>3	>3	<=3	>3	>3	>3
Steroids use	Yes	Yes	Yes	Yes	Yes	Yes
Ventricular assist device	No	No	No	No	No	No
Left ventricular assist device	No	No	No	No	No	No
Histocompatibility cross match	Negative	Negative	Negative	Negative	Unknown	Unknown
Primary diagnoses	IPF	IPF	IPF	IPF	Others	COPD
Survival days	1826	1541	1462	116	0	0
Death	No	Yes	No	Yes	No	No
Overall graft failure	No	Yes	No	Yes	No	No

Abbreviation: HIV, Human Immunodeficiency Virus; IL-2, interleukin-2; BMI, body mass index; HLA, human leukocyte antigen; IPF, idiopathic pulmonary fibrosis; COPD, chronic obstructive pulmonary disease

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

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

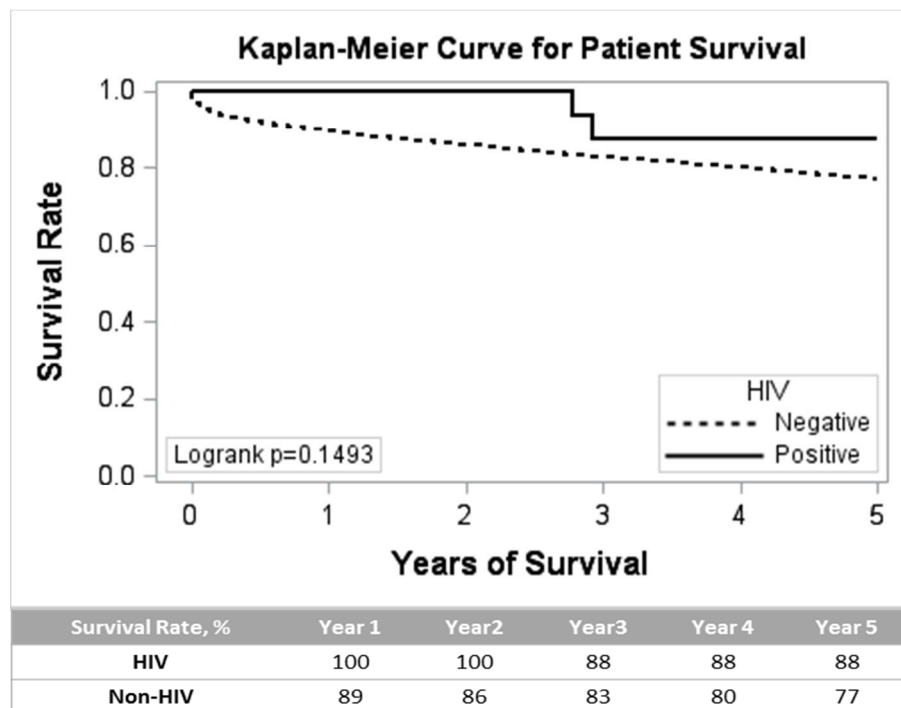


Figure 1.b Overall Graft Survival ($P= 0.2758$)

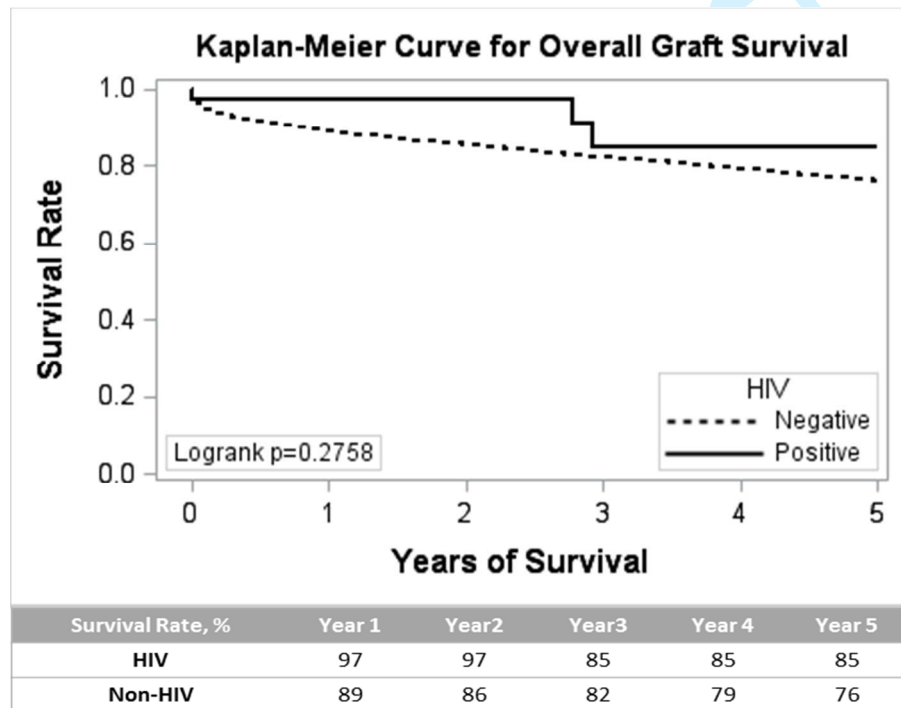
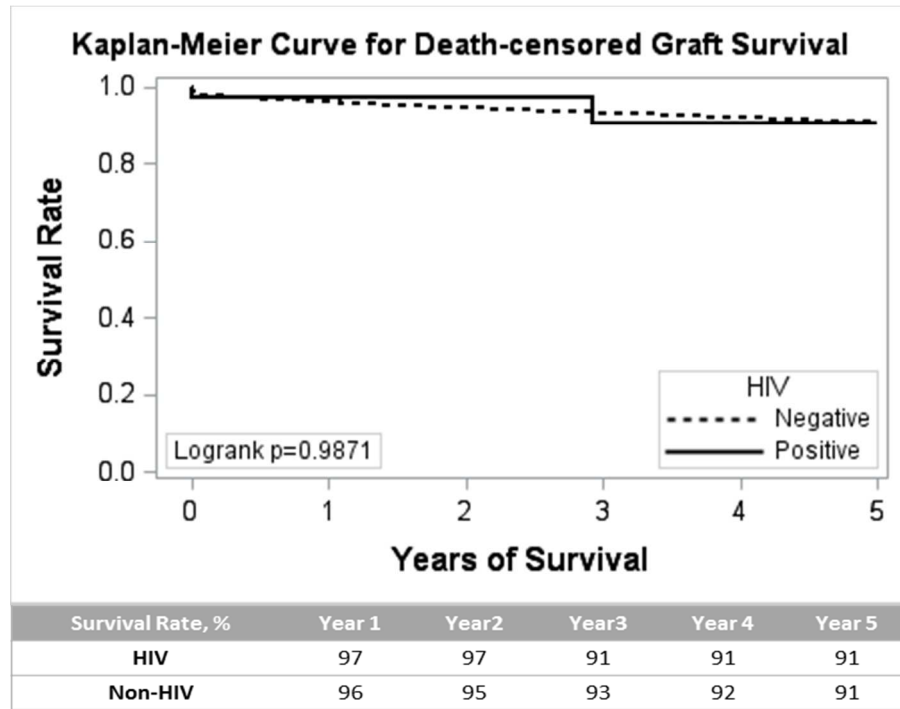


Figure 1.c Death-censored graft Survival ($P=0.9871$)

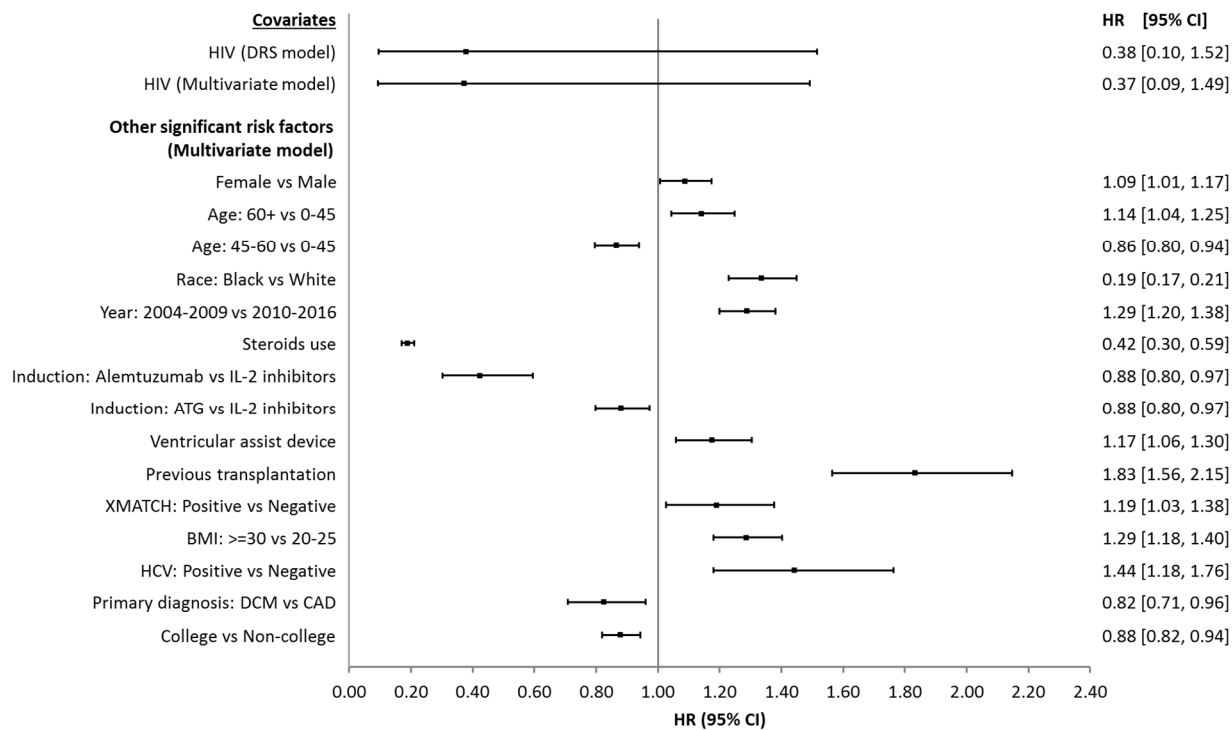


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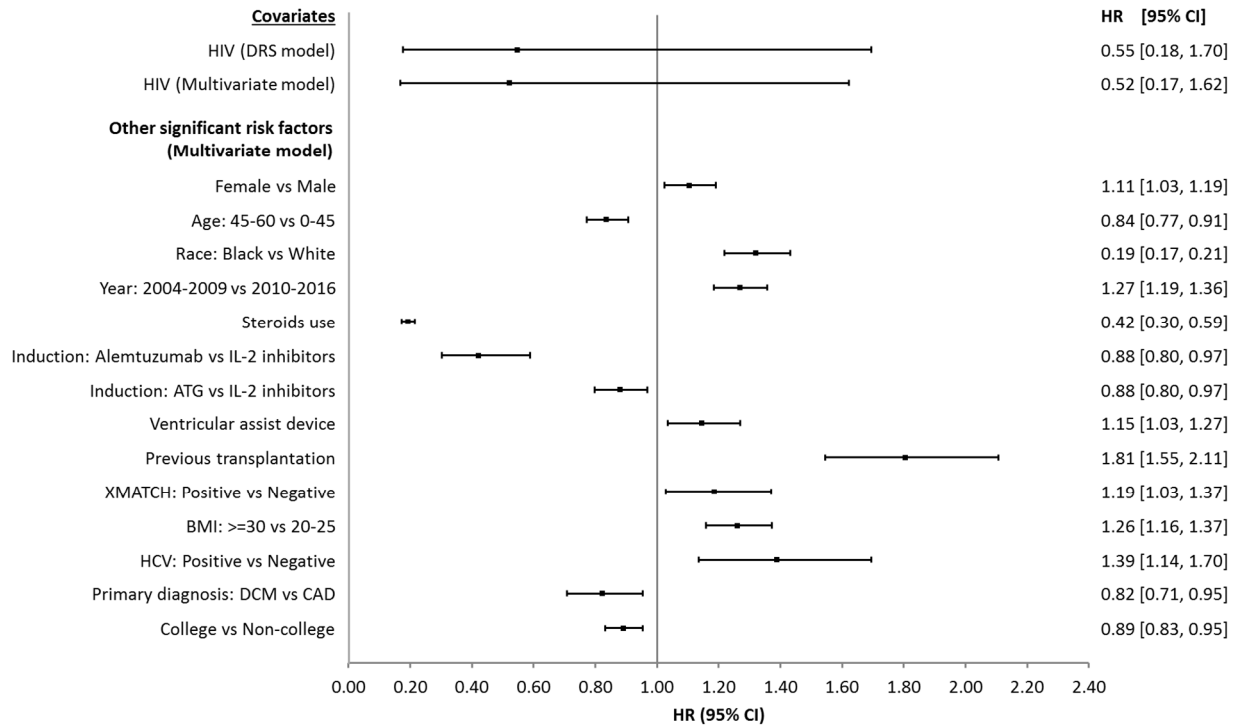
Figure 2 Forest plot of adjusted hazard ratios of HIV status and other significant risk factors for patient survival, overall graft survival and death-censored graft survival among heart transplant recipients

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



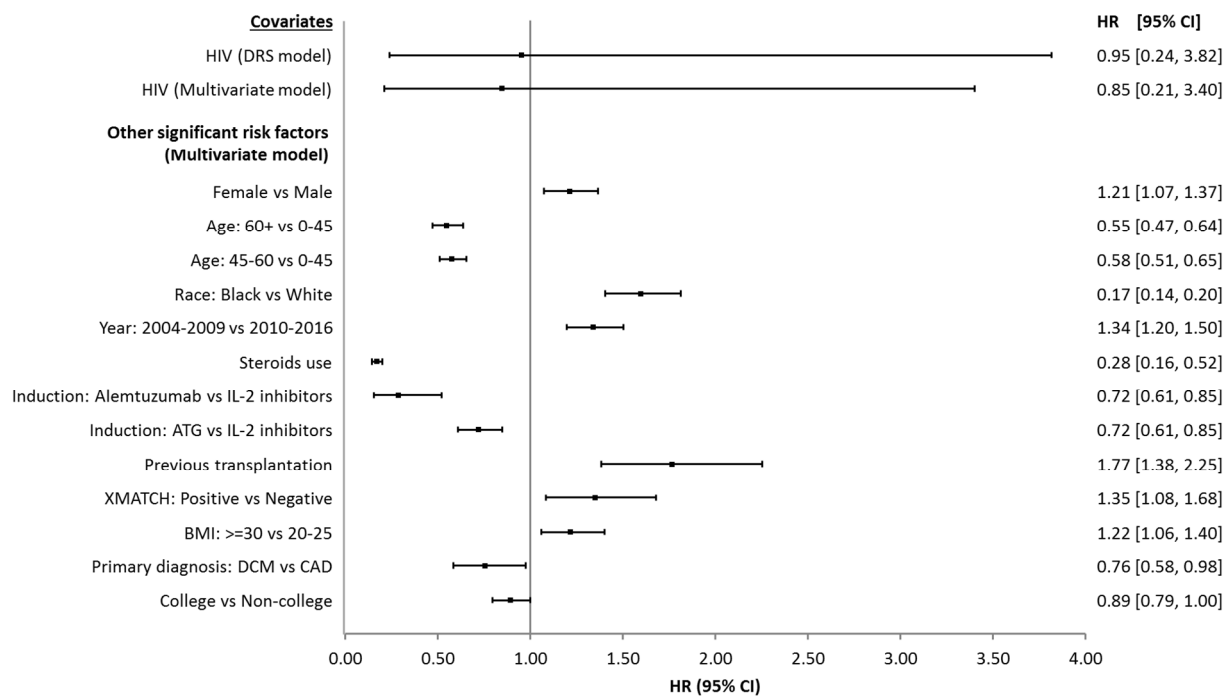
Abbreviation: HIV, Human Immunodeficiency Virus; DRS, disease risk score; XMATCH, histocompatibility cross match; CI, confidence interval; ATG, anti-thymocyte globulin; IL-2, interleukin-2; BMI, body mass index; DCM, dilated cardiomyopathy; CAD, coronary artery disease

Figure 2b. 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; ATG, anti-thymocyte globulin; IL-2, interleukin-2; BMI, body mass index; DCM, dilated cardiomyopathy; CAD, coronary artery disease

Figure 2c. 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; ATG, anti-thymocyte globulin; IL-2, interleukin-2; BMI, body mass index; DCM, dilated cardiomyopathy; CAD, coronary artery disease