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Barriers to listing for HIV-infected patients being evaluated for kidney transplantation

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Abstract

Background—Human immunodeficiency virus (HIV)-infected patients have excellent outcomes following kidney transplantation (KT) but still might face barriers in the evaluation and listing process. The aim of this study was to characterize the patient population, referral patterns, and outcomes of HIV-infected patients who present for KT evaluation.

Methods—We performed a single-center retrospective cohort study of HIV-infected patients who were evaluated for KT. The primary outcome was time to determination of eligibility for KT.

Results—Between 2011 and 2015, 105 HIV-infected patients were evaluated for KT. Of the 105 patients, 73 were listed for transplantation by the end of the study period. For those who were deemed ineligible, the most common reasons cited were active substance abuse (n = 7, 22%) and failure to complete the full transplant evaluation (n = 7, 22%).

Conclusion—Our cohort demonstrated a higher proportion of HIV-infected patients eligible for KT than in previous studies, likely secondary to advances in HIV management. Among those who were denied access to transplantation, we identified that many were unable to complete the evaluation process, and that active substance was common. Future prospective studies should examine reasons and potential interventions for the lack of follow-through and drug use we observed in this population.

Keywords

barrier; evaluation; HIV; kidney transplantation

1 INTRODUCTION

After the introduction of combination antiretroviral therapy (cART), the human immunodeficiency virus (HIV) epidemic in the United States has transformed from one of

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acute and devastatingly high mortality to one of a chronic disease.¹ Despite this advancement, many chronic comorbid conditions burden the lives of HIV-infected patients. Among these comorbid conditions, chronic kidney disease is quite prevalent.^{2–4} For those who progress to end-stage renal disease (ESRD), mortality is higher in HIV-infected patients than their uninfected counterparts.^{5,6} Kidney transplantation (KT) has emerged as an effective and preferred alternative to dialysis in HIV-infected patients with ESRD with outcomes that are similar to the uninfected population.^{7–10}

Given these excellent outcomes, KT for HIV-infected patients has increased 42-fold between 2000 and 2014.⁷ The HIV Organ Policy Equity (HOPE) Act recently legalized the use of HIV-infected organs for transplantation into HIV-infected patients to expand the donor pool for KT in the HIV-infected population as well as to mitigate organ shortages for the general population.^{11,12}

Despite advances in KT for HIV-infected patients, data are few on the KT evaluation and listing process, including how it might differ from that of the general population. Given the potential benefits of KT for HIV-infected patients with ESRD, and to facilitate centers to optimally take advantage of the expansion of the donor pool through the HOPE Act, in this study we examined potentially modifiable barriers to transplantation by assessing outcomes of the evaluation and listing process for HIV-infected patients referred to our transplant center.

2 METHODS

2.1 Study design

We performed a retrospective cohort study of HIV-infected patients referred for KT to Hahnemann University Hospital (Philadelphia, PA USA). Patients were included in the study if they were > 18 years of age, and were HIV positive when evaluated for KT at our center between January 1, 2011 and December 31, 2015. The Institutional Review Board of Drexel University approved this study.

Hahnemann University Hospital is a tertiary care center, which has performed 111 kidney transplants for HIV-infected patients between 2001 and 2015. At present, approximately 50 HIV-infected patients are listed for KT at the center, which is > 10% of the entire HIV-infected KT wait list. The evaluation process for HIV-infected patients is comprised of a full-day medical clinic visit. This visit includes patient-centered transplant education as well as individual clinical assessments by a transplant nephrologist, transplant surgeon, infectious disease physician, and social worker. A transplant pharmacist is available for assessment of complex drug-drug interactions and/or pre-transplant pharmacokinetic modeling. The infectious disease physician evaluates HIV-related history, including opportunistic infection (OI), route of infection, past ART and compliance, most recent HIV outpatient clinic records from the patients' HIV care provider were reviewed. CD4 counts and viral loads (VLs) are drawn during the transplant evaluation.

2.2 Outcomes

The primary outcome for this study was listing for KT (either active or inactive status). Secondary outcomes included the active vs inactive listing status, median time to listing, and receipt of a kidney transplant. For those who were deemed ineligible for listing, we abstracted the reason for ineligibility from the medical record and categorized reasons as one of the following: unable to complete the evaluation process requirements; medically unfit; concomitant psychiatric illness; active drug abuse; obesity; recovery of glomerular filtration rate; patient withdrawal of consent for KT; uncontrolled HIV (HIV VL > 200 copies/mL); and death. If the reason for ineligibility could not be ascertained, it was categorized as “unknown.” The duration of evaluation was defined as the time between the date of initial KT evaluation and the date of listing with active status. If a patient had a status change after the date of active listing (eg, changing from active to inactive status), the initial date of active listing was used to calculate the evaluation duration. Delayed time to listing was defined as > 90 days from initial evaluation, based on our center averages.

2.3 Covariates

We used the electronic medical record to assess baseline demographic information (ie, age, gender, race/ethnicity, employment status) and medical history. Medical history included common comorbidities (eg, hypertension, diabetes, chronic hepatitis B and C infection), cause of kidney disease, receipt and modality of dialysis, and history of alcohol or drug abuse. HIV history was abstracted from the HIV treatment providers’ records, and included cART regimen, history of OI infections, mode of HIV transmission, CD4 count (cells/ml), VL (copies/ml), and presence of resistance mutations.

To ascertain referral mechanisms, we reviewed the self-documented intake form from the initial transplant evaluation. Referral sources were divided into six categories: (i) nephrologist, (ii) dialysis center, (iii) HIV provider, (iv) primary care provider, (v) self-referral, or (vi) social worker. Time to transplant referral was defined as the time between the date of dialysis initiation and the date of KT evaluation.

2.4 Statistical analysis

We summarized continuous variables with medians and categorical variables with proportions. We used Student’s t-test or Wilcoxon rank-sum test as appropriate to compare continuous variables and the chi-square test to compare categorical variables across groups. Data analysis was completed using the Statistical Package for the Social Sciences, SPSS (version 24; Chicago, IL USA).

3 RESULTS

3.1 Patient characteristics

During the study period, 105 HIV-infected patients were evaluated for KT at our center and included in our analysis (Figure 1). Table 1 depicts demographics and characteristics. The median age was 49 years (interquartile range [IQR] 43.5–55.5 years). The majority of the cohort was male (73%) and black (86%). The underlying causes of kidney disease included hypertension (46%), HIV (23%), and graft failure (12.4%). Most patients (n = 93, [88.6%])

were receiving dialysis at the time of evaluation. Of the patients, 24% (n = 25) had chronic hepatitis C infection and 23% used cocaine in the past (n = 24).

Median duration of HIV infection was 14.5 years (IQR 10.0–20.8) and 16.5% (n = 17) had history of documented OI infection. Median CD4 counts were high (CD4 = 498 cells/mm³; IQR 315–723) with controlled viremia (VL <200 copies/mm³) (n = 98 [93.3%]). About a half were taking integrase inhibitors (n = 45, 45%), 52% (n = 52) were on protease inhibitor-based cART, and 32% (n = 32) were on non-nucleoside reverse transcriptase inhibitor (NNRTI)-based cART.

3.2 Transplant evaluation referral patterns

More than half the cohort of HIV patients were referred by nephrologists or dialysis centers (n = 51, 57.3%), compared to only a small portion that were referred by either primary care or an HIV physician (n = 5, 5.6%). The median time from start of dialysis date to evaluation at the transplant center was 24.6 months (IQR 4 to 63.8 months) (Figure 2).

3.3 Transplant evaluation outcomes

Of the 105 HIV-infected patients evaluated for KT at our center over 4 years, 70% (n = 73) were ultimately deemed eligible for KT. Of the patients who were deemed ineligible for KT, the most common reasons were active substance abuse (n = 7, 23%) and inability to complete the requirements of the transplant evaluation, which might include subspecialty evaluations, such as cardiology and hepatology (n = 7, 22.6%) (Figure 3). Eligible and ineligible patients were similar with respect to most baseline characteristics. Exceptions included the incidence of hypertension (eligible, 71 [97%]; ineligible, 27 [84%], *P*-value .02), NNRTI use (eligible, 15 [21.1%]; ineligible, 17 [58.6%], and availability of the primary HIV care provider's medical notes to the transplant evaluation team (eligible, 19 [70.4%]; ineligible, 10 [34.5%]).

Among eligible transplant candidates, 36% (n = 26) were activated on the waiting list. For those who achieved active status, the median time to activation was 136 days (IQR 72–399). In comparison, our center evaluated 110 HIV-uninfected patients in the 2013 calendar year and 101 in the 2014 calendar year. Of these, 48 (40%) and 51 (60%) patients obtained active status within their respective calendar years, with median times to active listing of 95 days (IQR 79.5–151) and 96 days (IQR 63–142), respectively.

We observed that 50% of the HIV-infected patients deemed eligible for transplant (n = 35) experienced delayed time to listing (defined as > 90 days). Reasons cited for delay were evaluation of non-compliance (n = 8; 27%); cardiac evaluation (n = 6; 20%); and insurance-related issues (n = 5; 17%) (Figure 3). Ultimately, of the 105 patients evaluated, 10 patients received KT within the 4 years of the study (Figure 1).

4 DISCUSSION

In this single-center cohort study of 105 HIV-infected patients who were evaluated for KT from 2011–2015, we demonstrated that many HIV-infected patients with ESRD endure years of dialysis prior to referral to KT, and that 30% of referred patients were deemed

ineligible for KT and never waitlisted. Further, among the 70% of referred patients who completed the evaluation process and were ultimately listed for KT, nearly half had significant delays in completing the requirements for listing. Among patients who were ineligible, the most common reasons were active substance abuse and failure to complete the required clinical work-up for listing.

For HIV-infected patients with ESRD, KT provides superior morbidity and mortality outcomes compared to remaining on dialysis.^{6,13} To our knowledge, our study is one of few to ever document barriers to transplant access among HIV-infected candidates in the current era of HIV management. Sawinski et al¹⁴ performed a similar study of patients evaluated between 2000 and 2007 at a large-volume center in New York City. Of the 309 HIV-infected patients evaluated for KT, only 20% met eligibility.¹⁴ Of those who did not meet eligibility, the primary disqualifying factor was lack of CD4 and VL data at time of evaluation or evidence of uncontrolled HIV.¹⁴ Interestingly, our study demonstrated a much higher rate of eligibility and fewer had uncontrolled HIV as a reason for ineligibility. This difference probably reflects many factors. First, dialysis providers may be more aware of listing criteria for KT than they were in the historical cohort, limiting the number of patients referred with detectable VLs. Also, the success we have had in listing HIV-infected patients might largely be driven by our on-site assessment by an infectious disease physician, who reviewed outpatient HIV management records during the initial visit. Other factors could be acquisition of CD4/VL on-site and improved HIV management owing to more effective and widely available ART. Our study was performed over a 4-year period, providing opportunities for persons who were initially not appropriate, which would also account for the higher rate of listing.

Our study and that of Sawinski et al¹⁴ had similar observations with respect to the significant proportion of patients who were ineligible for listing because of failure to complete the requisite work-up, including cardiology and hepatology evaluations. This suggests that the complexity of the evaluation process is still significantly burdensome for many HIV-infected patients despite advances in overall HIV management. The complexity of the evaluation process might also contribute to the relatively high proportion of delayed listings observed in both studies. While our study had a markedly shorter median time to listing compared to that reported by Sawinski et al.¹⁴ (136 days vs 414 days), nearly half of the patients in our study still required > 90 days to be listed and had a longer median listing time than a cohort of HIV-uninfected patients evaluated at our center (95 days in 2013; 96 days in 2014). Few significant differences were seen in measured covariates between the baseline characteristics of patients who were ultimately considered eligible vs ineligible. This finding might lead us to conclude that less tangible factors, such as individual social circumstances, might be the primary driver for KT eligibility. Future studies will be needed to better discern what these specific circumstances might include, with attention to streamlining what may be an overly burdensome evaluation process for some HIV-infected patients.

These findings highlight the last decade's advancements in overall HIV care, as well as the increased access to KT for HIV-infected ESRD patients. However, they also illustrate several areas in the KT evaluation process that require continued improvement. Failure to complete

the requisite clinical work-up is a recurrent barrier to listing for KT. We propose that restructuring the evaluation system is a potential way to mitigate this barrier. This restructuring might be accomplished by having more subspecialty consultants on-site during the evaluation of comorbid conditions (eg, cardiology and hepatology), like how we have incorporated on-site infectious disease consultation. This change could be of particular value for hepatitis C virus co-infected patients, who had an even lower incidence of listing than mono-infected patients with only HIV. Co-infected patients often need a liver biopsy prior to listing and on-site hepatology consultation could streamline this process. Restructuring the evaluation system could also offer the potential to decrease the proportion of delayed listings.

It is well-documented that a direct relationship exists between dialysis vintage and mortality in ESRD patients, and this association may be exacerbated by the presence of HIV, with its related higher risks of infection and mortality from cardiovascular disease.^{6,13} Thus, it is imperative to promote timely referral for HIV-infected patients with ESRD for KT evaluation, and ideally before dialysis onset to maximize waiting time accrual. In our study population, HIV-positive kidney candidates were on dialysis for a median of 2 years before transplant referral. This finding is similar to an observation from a prior national study, where dialysis vintage was longer in HIV-infected patients than non-infected patients (2.5 years vs 0.8 years; $P < .001$).¹⁵ Further, the majority of referrals in the study were generated from dialysis providers, with a minority from other providers, such as HIV care providers. This fact may highlight a need to educate HIV care providers and primary care physicians on the benefits of early referral for KT in HIV patients. We observed a significant difference between patients who were eligible for listing vs those who were not, based on access to their HIV care provider records (70.4% for listed patients vs 34.5% for unlisted patients; P -value .007). This finding implies that consistent follow-up with a trained HIV care provider may be associated with higher rates of successful transplant listing. This finding also underlies our assertion that an urgent need exists for greater awareness of the implications of CKD and the process of KT referral amongst HIV care providers.

Although this study is one of few to describe the KT evaluation process in HIV-infected patients at a high-volume center, it has important limitations. First, it is a single-center study in an urban environment with a predominantly black, male population. Also, it is one of the highest-volume centers for HIV-infected KT in the United States. These facts limit its generalizability to other centers and referral networks. In addition, this study was unable to capture data on patients who were referred, but did not present for evaluation, thus limiting our ability to comprehensively observe referral practices. We also only had access to the medical charts of HIV care providers for approximately 50% of the cohort ($n = 56$).

In conclusion, our single-center, retrospective cohort study of HIV-infected patients referred for KT evaluation demonstrated that a higher proportion of HIV-infected patients may be eligible for transplant compared to past studies. This increase is likely a result of advancements in HIV care over the last decade. However, barriers remain to KT eligibility in the HIV-infected population that are potentially modifiable. Strategies for modification include implementation of programs to lessen the incidence of failure to complete the entire

evaluation process, and education of non-nephrology providers in order enhance early evaluation referral.

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Abbreviations

cART	combination antiretroviral therapy
ESRD	end-stage renal disease
HIV	human immunodeficiency virus
HOPE Act	HIV Organ Policy Equity Act
IQR	interquartile range
KT	kidney transplantation
NNRTI	non-nucleoside reverse transcriptase inhibitor
OI	opportunistic infection
VL	viral load

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FIGURE 1.
Listing outcomes for 105 patients evaluated for kidney transplantation

FIGURE 2.

Time frame of transplant referral. IQR, interquartile range; HOPE, HIV Organ Policy Equity; Tx, transplant; HIV, human immunodeficiency virus

FIGURE 3.

Reasons for not eligible for listing and delay. Pt, patient; HIV, human immunodeficiency virus; GFR, glomerular filtration rate

TABLE 1

Baseline demographics

	Total (n=105)	Eligible (n=73)	Not eligible (n=32)	P-values
Age at evaluation (years)				
Median, IQR	49 (43.5, 55.5)	49.0 (43.0, 54.0)	50.5 (45.5, 57.0)	.256
Gender				
Male	77 (73.3%)	56 (76.7%)	21 (65.6%)	.242
Race/Ethnicity				.560
Black	90 (85.7%)	61 (83.6%)	29 (90.6%)	
White	7 (6.7%)	6 (8.2%)	1 (3.1%)	
Hispanic	6 (5.7%)	5 (6.8%)	1 (3.1%)	
Asian	2 (1.9%)	1 (1.4%)	1 (3.1%)	
Current employment				
Yes	20 (19.0%)	16 (21.9%)	4 (12.5%)	.295
BMI				
Median, IQR	25.7 (23.6, 29.9)	25.8 (23.6, 29.5)	25.1 (23.1, 30.7)	.969
Comorbid condition				
HTN	98 (93.3%)	71 (97.3%)	27 (84.4%)	.026*
DM	34 (32.4%)	22 (30.1%)	12 (37.5%)	.501
Chronic HCV	25 (23.8%)	15 (20.5%)	10 (31.3%)	.319
CHF	12 (11.4%)	9 (12.3%)	3 (9.4%)	.752
Chronic HBV	11 (10.5%)	8 (11.0%)	3 (9.4%)	1.000
PVD	6 (5.7%)	5 (6.8%)	1 (3.1%)	.665
CAD	9 (8.6%)	6 (8.2%)	3 (9.4%)	1.000
History of Drug Abuse				
IVDA	13 (12.4%)	10 (13.7%)	3 (9.4%)	.750
Cocaine	24 (22.9%)	16 (21.9%)	8 (25.0%)	.802
Alcohol	11 (10.5%)	9 (12.3%)	2 (6.3%)	.497
Mode of transmission				.529
MSM	35 (33.7%)	25 (34.7%)	10 (31.3%)	
Heterosexual	51 (49.0%)	34 (47.2%)	17 (53.1%)	
IVDA	4 (3.8%)	2 (2.8%)	2 (6.3%)	
Unknown	14 (13.5%)	11 (15.3%)	3 (9.4%)	
History of OI				
Yes	17 (16.5%)	11 (15.5%)	6 (18.8%)	.854
cART				
Yes	100 (95.2%)	71 (97.3%)	29 (90.6%)	.164
cART details, n=100				
NRTI	94 (94%)	69 (97.2%)	25 (86.2%)	.057
Integrase	45 (45.0%)	36 (50.7%)	9 (31.1%)	.073

	Total (n=105)	Eligible (n=73)	Not eligible (n=32)	P-values
NNRTI	32 (32.0%)	15 (21.1%)	17 (58.6%)	.000*
Protease	52 (52.0%)	38 (53.5%)	14 (48.3%)	.634
Access to HIV provider notes, n=56				
Yes	29 (51.8%)	19 (70.4%)	10 (34.5%)	.007*
Documented resistance				
Yes	15 (15.6%)	11 (17.2%)	4 (12.5%)	.767
CD4 (cells/mm3)				
Median	498 (315.5, 723)	498 (338, 729)	460.5 (244.3, 663.3)	.411
VL (IU/mL) < 200 copies	12 (11.4%)	5 (15.6%)	7 (9.6%)	
Dialysis				.886
Hemodialysis	86 (81.9%)	60(82.2%)	26 (81.3%)	
Peritoneal dialysis	7 (6.7%)	4 (5.5%)	3 (9.4%)	
No dialysis	12 (11.4%)	9 (12.3%)	3 (9.4%)	
Cause of renal failure				.633
HTN	48 (45.7%)	34 (46.6%)	14 (43.8%)	
HIV	24 (22.9%)	15 (20.5%)	9 (28.1%)	
Graft failures	13 (12.4%)	9 (11.0%)	5 (15.6%)	
DM	12 (11.4%)	9 (12.3%)	3 (9.3%)	
Other	8 (7.6%)	7 (9.6%)	1 (3.1%)	

IQR, interquartile range; BMI, body mass index; HTN, hypertension; DM, diabetes mellitus; HCV, hepatitis C virus; CHF, congestive heart failure; HBV, hepatitis B virus; PVD, peripheral vascular disease; CAD, coronary artery disease; IVDA, intravenous drug abuser; MSM, male having sex with male; OI, opportunistic infection; cART, combination anti-retroviral therapy; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; HIV, human immunodeficiency virus; VL, viral load.