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Factors Associated with Failure to List HIV-Positive Kidney Transplant Candidates

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Abstract

With improved survival in the antiretroviral era, data from ongoing studies suggest that HIV patients can be safely transplanted. The disproportionate burden of HIV-related end-stage renal disease in minority populations may impose additional obstacles to successful completion of the transplant evaluation. We retrospectively reviewed 309 potentially eligible HIV patients evaluated for kidney transplant at our institution since 2000. Only 20% of HIV patients have been listed, compared to 73% of HIV-negative patients evaluated over the same period ($p<0.00001$). Failure to provide documentation of CD4 and viral load (36% of candidates) was the most common reason for failure to progress beyond initial evaluation. Other factors independently associated with failure to complete the evaluation included CD4 < 200 at initial evaluation (OR 15.17; 95% CI 1.94-118.83), black race (OR 2.33; 95% CI 1.07-5.06), and history of drug use (OR 2.56; 95% CI 1.22-5.37). More efficient medical record sharing and an awareness of factors associated with failure to list HIV-positive transplant candidates may enable transplant centers to more effectively advocate for these patients.

Introduction

Since the introduction of combination antiretroviral therapy (ART), patient survival with HIV has improved dramatically, and end organ failure has replaced opportunistic infections (OI) as the major cause of morbidity and mortality in this population (1,2). Survival rates have also improved among HIV-infected end-stage renal disease (ESRD) patients, with 1-year survival exceeding 74% by 1999 (3). At the end of 2005, there were more than 2,700 individuals with ESRD attributed to HIV-associated nephropathy (HIVAN) in the United States (US), predominantly African-Americans (4). The prevalence of HIV-related ESRD is projected to increase with improved survival and growth of the HIV epidemic in minority populations (5). In addition, the number of individuals living with HIV and ESRD resulting from comorbid disease is unknown, but is also likely to increase with aging of the HIV population. The growing burden of ESRD and improved survival among HIV patients has increased interest in the feasibility of kidney transplantation in this population. Several studies have demonstrated acceptable short-term patient and allograft outcomes (6–9), and a recent single center study has suggested a survival benefit for kidney transplant over dialysis in HIV-positive patients (10).

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The current study was motivated by an observation of low completion rates for HIV positive patients referred to our institution for kidney transplant evaluation. From January 2000 through October 2007, 344 HIV positive patients and 4044 HIV negative patients were referred for evaluation, including 309 and 3353, respectively, who were potentially eligible for transplantation based on initial evaluation. While more than 70% of HIV negative candidates completed the transplant evaluation, only 20% of the HIV positive patients did so. In this study we sought to understand the factors associated with failure to list HIV-positive kidney transplant candidates.

Methods

This study was approved by the Institutional Review Board of the Mount Sinai School of Medicine. A list of adult HIV positive patients referred to our institution for kidney transplant evaluation between January 2000 and October 2007 was generated using an electronic Organ Transplant Tracking Record (OTTR). Self-reported demographic data were abstracted from a standardized intake questionnaire, including age, gender, self-reported race-ethnicity, employment, education, and marital status. Data on dialysis modality and vintage, history of illicit drug use, history of hepatitis virus co-infection, and current ART use were also abstracted from the questionnaire. CD4 lymphocyte count and HIV viral load were recorded for subjects with results documented within 3 months of initial evaluation. The Centers for Medicare and Medicaid Services (CMS) covers a limited number of viral load assays annually, and additional testing performed for transplant evaluation may interfere with clinical care or generate out-of-pocket costs. As a result, most US transplant centers request documentation of CD4 and viral load from the primary HIV provider. Patients provided written informed consent for the transfer of HIV-related data, which was reviewed by a co-investigator with specialty training in infectious diseases.

Patients were considered eligible if they fulfilled routine transplant criteria and study criteria for the NIH-sponsored HIV and Solid Organ Transplantation Multi-site Study (8). Briefly, the study criteria require a CD4 > 200 cells/m^3 for 6 months and an undetectable viral load for 3 months, based on at least 2 consecutive measurements. Patients whose CD4 or viral load deviated to a small extent from the study criteria were not declined initially if it was felt that modifications to ART or greater compliance would result in complete viral suppression. In these cases, the HIV provider was contacted to discuss the protocol and potential strategies to achieve viral suppression, and laboratory results were reviewed for eligibility at regular intervals for up to 2 years. Prior to April 2002, patients with a history of any AIDS-defining OI except Candida esophagitis were excluded. Subsequently, patients with previously treated OIs were considered eligible, unless there was a history of chronic cryptosporidiosis, progressive multifocal leucoencephalopathy, lymphoma, or visceral Kaposi's sarcoma.

Statistical analyses were performed using STATA version 9 (College Station, Texas). Comparisons were performed by chi-square or Fisher's exact test for categorical variables and t-tests or Wilcoxon rank-sum for continuous variables. Multivariate logistic regression was used to identify factors independently associated with failure to complete the transplant evaluation. Factors considered for inclusion in the model included demographics, employment, education, marital status, dialysis modality and vintage, CD4, viral load, ART use, hepatitis co-infection, and history of illicit drug use (Table 1). Factors that approached significance in univariate analysis ($p < 0.1$) were tested for inclusion in the multivariate model, and covariates and potential interaction terms were maintained in the model at a significance level of 0.2. Model fit was tested using the Hosmer-Lemeshow goodness of fit test.

Results

At the time of this analysis, 344 HIV-positive patients had completed an initial kidney transplant evaluation at our institution, including 5 patients referred for combined liver-kidney transplantation. Thirty-three patients were declined for medical reasons, including active or recent malignancy (n=9), persistent or anticipated failure to achieve viral suppression (n=6), no ART (n=5), recent OI or tuberculosis (n=4), severe comorbidity (n=4), active substance abuse (n=3), and history of noncompliance (n=2). Patients who were declined for medical reasons and 2 additional patients who declined further evaluation were excluded from this analysis. Excluded patients were similar to those referred for further evaluation with respect to age (median 46 years in both), gender (77% versus 72% male, p 0.5), and race (77% versus 75% black, p 0.8).

Demographic and clinical characteristics of 309 patients deemed eligible for further evaluation are summarized in Table 1. Consistent with the epidemiology of HIV-related ESRD, (4,11,12) black males comprised more than half of the cohort. Among patients who reported socioeconomic and marital status, 25% were working at least part-time and 20% were married at the time of initial evaluation. The majority of patients who reported their educational status held a high school or equivalent degree, with less than 20% reporting a college or graduate education. Most patients were dialysis-dependent, with only 5% referred for pre-emptive evaluation. Overall, one-third of the cohort was evaluated within the first year of initiating dialysis. Among 50 patients with a biopsy-proven diagnosis, the etiology of ESRD was most commonly attributed to HIVAN (40%), hypertension (30%), or diabetes (10%). Documentation of CD4 and viral load was provided within 3 months of the initial visit for only 64% of patients. The median CD4 was 379 cells/mm^3, and nearly 85% of documented results were above 200 cells/mm^3. The viral load was undetectable in nearly three-quarters of patients with documented results, and 90% were on ART. Co-infection with hepatitis B or C was documented in 43% of patients with available data, and 46% reported a history of illicit drug use. Only 22 patients (7%) received their primary HIV or nephrology care at our institution.

At the time of this analysis, 63 of 309 patients (20%) had completed the full evaluation and were either listed or transplanted (Table 1), compared to 2440 of 3353 (73%) HIV-negative patients evaluated at our institution during the same period ($p<0.0001$). The median time from initial evaluation to listing was 414 days (IQR 199–650 days). Patients who failed to complete the evaluation had lower CD4 at initial evaluation (median 343 versus 461, p 0.004), and were less likely to have achieved viral load suppression prior to referral (60% versus 72%, p 0.02). In addition, patients who failed to complete the evaluation were less likely to have documentation of CD4 and viral load available within 3 months of the initial visit (57% versus 91%, $p<0.0001$). Patients who did not meet HIV disease-specific criteria at the initial evaluation were not excluded, but were encouraged to re-evaluate their ART regimen with the referring HIV provider and/ or to submit documentation of CD4 and viral load. If these patients were excluded from the current analysis, the proportion of HIV-positive patients who successfully completed the evaluation was still significantly lower than that observed among HIV-negative candidates (38% versus 62%, $p<0.0001$). In addition to HIV disease-specific characteristics, black race and history of illicit drug were also marginally more common among patients who failed to complete the evaluation.

In multivariate analysis, factors independently associated with failure to complete the transplant evaluation included CD4 < 200 cells/mm^3 at initial evaluation (OR 15.17; 95% CI 1.94–118.83), black race (OR 2.33; 95%CI 1.07–5.06), and history of illicit drug use (OR 2.56; 95% CI 1.22–5.37; Table 2). Viral load was no longer significantly associated with completion after adjustment for CD4. There were no significant interactions. Substitution of

log-transformed CD4 for the dichotomous variable produced qualitatively similar results. Model estimates were also similar if patients without documentation of CD4 or viral load at the initial visit were considered to have unacceptable results. A final sensitivity analysis was performed to account for the timing of initial evaluation. Unlisted patients were evaluated a median of 871 days prior to the close of data collection, compared to 414 days from initial evaluation to listing for those who completed the evaluation ($p<0.0001$). Results of the adjusted analysis were similar after excluding 71 unlisted patients with an initial evaluation less than 414 days prior to the close of data collection.

Overall, 108 of 309 potential candidates (35%) failed to proceed to full evaluation because CD4 and viral load data were not provided, and 66 candidates (21%) failed to proceed because these parameters did not meet eligibility criteria. Patients with documentation of acceptable HIV disease control were referred for full evaluation, including cardiology evaluation in all candidates and hepatology evaluation and liver biopsy in those with hepatitis co-infection. These evaluations could be performed at the referring institution or at Mount Sinai, based on patient preference and available expertise. Only 78 of the 135 candidates (58%) who were eligible for full evaluation completed cardiology clearance. Among the 54 candidates with hepatitis co-infection who were referred for full evaluation, 31 (57%) completed the hepatology clearance, including 27 who were subsequently listed.

Among the 63 HIV-positive candidates who were listed for kidney transplantation, 24 identified a potential living donor. Twenty-two HIV-positive patients received a kidney transplant during the study period, including 2 combined liver-kidney recipients. Transplant recipients were similar to the overall HIV-positive referral population with respect to age (median 43 versus 46 years, p 0.2) and gender (68% versus 73% male, p 0.7). Only 55% of the recipients were black, compared to 76% of those evaluated (p 0.06). Six patients ultimately received a kidney transplant in geographic regions with shorter waiting times. Among 16 patients transplanted at our institution, there were 7 living donor and 9 cadaveric donor transplants.

Discussion

Over the past decade the attitude towards kidney transplantation in HIV-positive individuals has changed significantly. A survey of US transplant centers published in 1998 demonstrated that only 9% of centers would consider an HIV-positive ESRD patient for kidney transplant(13). With encouraging early results from prospective studies of transplantation in recipients with HIV (6,7,8), there has been an increase in the number of transplant centers accepting HIV-positive candidates and in the number of transplants performed in HIV-positive recipients (14). At the same time, there has been an increase in awareness among nephrologists, hepatologists, and HIV providers that patients with well-controlled HIV and end stage organ disease may be candidates for transplantation. Since our center began accepting HIV-positive patients for transplant evaluation in 2000, we had evaluated 344 HIV-positive patients for kidney transplantation. Despite this large number, we were struck by the failure of patients to complete the evaluation, with only 20% of HIV-positive candidates being listed or transplanted, and with an average time from evaluation to listing of more than 16 months. This analysis was conducted to understand factors associated with failure to complete the transplant evaluation in HIV- positive candidates.

In contrast to the general transplant referral population, HIV-positive candidates do not start the full evaluation at the initial visit. The initial evaluation focuses on confirming adequate control of HIV and eligibility for transplantation, as described in the methods. Thirty-three patients were declined for medical reasons at this stage, and 2 additional patients declined to proceed with the evaluation. We did not receive documentation of CD4 and viral load for

35% of potential candidates, amounting to the most common reason for failure to be listed or transplanted. More efficient use of electronic medical records, as mandated by CMS, may result in more timely transfer of medical records. The failure of HIV providers to transfer information may also reflect provider concerns about transplantation in HIV-positive recipients, and improved communication regarding the transplant evaluation and the success of transplantation in HIV-positive recipients may facilitate the evaluation process.

Consistent with the epidemiology of HIV-related ESRD (4,11,12), three-quarters of the HIV- positive patients referred to our center for kidney transplant evaluation were black. In contrast, approximately half of the HIV-positive transplant recipients in the US are white (9,14). While this discrepancy may reflect differences in the demographics of our referral population, disparities in access to transplantation may result from multiple factors, including decreased referral of minority patients (15). While our study did not address referral patterns, our data suggest that black patients are also less likely to complete the transplant evaluation, a pattern that has been observed in the general transplant population (15).

The current study was not designed to compare HIV-positive transplant candidates to the general transplant referral population; however, it is notable that the prevalence of black race was significantly higher among HIV-positive compared to HIV-negative kidney transplant candidates referred to our center (74% versus 37%). A lower proportion of HIV-positive patients reported education beyond high school (18% versus 45%), while a similar proportion were employed at the time of initial evaluation (25% versus 30%). HIV-positive candidates also had a significantly higher prevalence of hepatitis virus infection compared to our institution’s general kidney transplant population (43% versus 14%). Kidney transplant candidates with hepatitis are required to undergo hepatology evaluation, including liver biopsy. Only 57% of potential candidates with hepatitis co-infection completed the hepatology evaluation, although hepatitis co-infection was not independently associated with failure to complete the evaluation among HIV-positive candidates. Future studies should investigate whether differences in demographics and comorbidity contribute to the disparity in completion rates observed between HIV-positive and HIV-negative kidney transplant candidates.

The low completion rate observed among HIV-positive candidates is particularly concerning in the setting of a clinical trial, with a dedicated study coordinator to facilitate the transfer of HIV-related information, and both a study coordinator and a clinical coordinator assigned at the time of full evaluation. Given the preliminary success of the protocol (8), kidney transplantation is likely to become standard of care in HIV-positive ESRD patients, and fewer resources will be available to help these patients navigate the evaluation process. Understanding the factors associated with failure of HIV-positive candidates to complete the transplant evaluation may help to guide the allocation of personnel and resources to ensure that these patients have access to transplantation.

Although this is the first large study to evaluate factors associated with failure to list HIV-positive kidney transplant candidates, several limitations must be acknowledged. Most importantly, this was a retrospective analysis, and data on HIV disease control were limited to the information provided by patients and their providers. Failure to provide documentation of CD4 and viral load prevented more than one-third of potential candidates from progressing beyond the initial evaluation; however, it is possible that informed HIV providers chose not to submit documentation for patients who did not meet HIV disease-specific eligibility criteria. This may be particularly true for self-referrals, who did not always consult their HIV provider prior to the initial evaluation. Potential transplant candidates provided contact information for both their primary nephrologist and their

primary HIV provider, and in many cases, they did not specify who referred them for evaluation. In addition, data on the availability of potential living donors were not rigorously collected for patients who did not proceed to full evaluation, so we are unable to estimate the effect of this variable on completion of the transplant evaluation. Finally, the current study did not address barriers to referral of potential transplant candidates, which are likely to be of unique importance in the HIV-positive ESRD population because of disparities in the referral of minority patients (15).

In conclusion, more efficient medical record sharing and an awareness of factors associated with failure to list HIV-positive transplant candidates may enable transplant centers and referring providers to more effectively advocate for these patients. Our data also suggest that given the complex nature of these patients' medical conditions, increased resources may be required to ensure that they benefit from transplantation.

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Table 1

Baseline characteristics of HIV-positive adult kidney transplant candidates at initial evaluation, Recanti-Miller Transplant Institute

	Not listed (n=246)	**Listed or Transplanted (n=63)**	**p-value**
Age, years	46 +/− 9.2	44.2 +/− 8.8	0.2
Male gender	175 (71.1%)	47 (74.6%)	0.6
Race Black White Other	162/210 (77.1%) 47/210 (22.4%) 1/210 (0.5%)	38/58 (65.5%) 18/58 (31.0%) 2/58 (3.5%)	0.06
Hispanic ethnicity	36/198 (18.2%)	11/52 (21.2%)	0.6
Currently employed	55/216 (25.5%)	13/55 (23.6%)	0.8
Education beyond high school	27/166 (16.3%)	12/45 (26.7%)	0.1
Married	38/209 (18.2%)	16/58 (27.6%)	0.1
Dialysis modality Hemodialysis Peritoneal dialysis Pre-emptive evaluation	183/209 (87.6%) 16/209 (7.7%) 10/209 (4.8%)	49/54 (90.7%) 2/54 (3.7%) 3/54 (5.6%)	0.6
Time on dialysis < 1 year 1–5 years > 5 years	66/195 (33.9%) 86/195 (44.1%) 43/195 (22.1%)	15/48 (31.3%) 21/48 (43.8%) 12/48 (25.0%)	0.9
CD4, cells/dL	Median 343 (IQR 291)	Median 461 (IQR 219)	0.004
CD4 < 200 cells/dL	32/141 (22.7%)	1/57 (1.75%)	<0.0001
Detectable HIV viral load*	44/145 (30.3%)	8/57 (14.0%)	0.02
Current antiretroviral therapy	175/196 (89.3%)	48/53 (90.6%)	0.8
Hepatitis B or C co-infection	90/213 (42.3%)	27/60 (45.0%)	0.7
History of illicit drug use	102/205 (49.8%)	18/52 (34.6%)	0.05
Referring provider at same institution	15/246 (6.1%)	7/63 (12.5%)	0.2

*Based on the assay available at the time of evaluation.

Table 2

Factors associated with failure to complete the full evaluation among HIV-positive kidney transplant candidates

	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Race, black versus non-black	1.83 (0.98–3.40)	2.33 (1.07–5.06)
History of illicit drug use	1.87 (0.99–3.53)	2.56 (1.22–5.37)
CD4 < 200 cells/mm3 at initial evaluation	16.91 (2.19–123.47)	15.17 (1.94–118.83)
Detectable HIV RNA at initial evaluation	2.67 (1.17–6.10)	**

** No longer significantly associated with failure to complete the full evaluation after adjusting for CD4