A National Study of Outcomes among HIV-Infected Kidney Transplant Recipients

Jayme E. Locke,* Shikha Mehta,* Rhiannon D. Reed,* Paul MacLennan,* Allan Massie,† Anoma Nellore,* Christine Durand,‡ and Dorry L. Segev†

*Comprehensive Transplant Institute, University of Alabama at Birmingham, Birmingham, Alabama; †Departments of Surgery and Epidemiology, Johns Hopkins University, Baltimore, Maryland; and ‡Department of Medicine, Division of Infectious Diseases, Johns Hopkins University, Baltimore, Maryland

ABSTRACT

Kidney transplantation is a viable treatment for select patients with HIV and ESRD, but data are lacking regarding long-term outcomes and comparisons with appropriately matched HIV-negative patients. We analyzed data from the Scientific Registry of Transplant Recipients (SRTR; 2002–2011): 510 adult kidney transplant recipients with HIV (median follow-up, 3.8 years) matched 1:10 to HIV-negative controls. Compared with HIV-negative controls, HIV-infected recipients had significantly lower 5-year (75.3% versus 69.2%) and 10-year (54.4% versus 49.8%) post-transplant graft survival (GS) (hazard ratio [HR], 1.37; 95% confidence interval [95% CI], 1.15 to 1.64; $P<0.001$) that persisted when censoring for death (HR, 1.43; 95% CI, 1.12 to 1.84; $P=0.005$). However, compared with HIV-negative/hepatitis C virus (HCV)–negative controls, HIV monoinfected recipients had similar 5-year and 10-year GS, whereas HIV/HCV coinfected recipients had worse GS (5-year: 64.0% versus 52.0%, $P=0.02$; 10-year: 36.2% versus 27.0%, $P=0.004$ [HR, 1.38; 95% CI, 1.08 to 1.77; $P=0.01$]). Patient survival (PS) among HIV-infected recipients was 83.5% at 5 years and 51.6% at 10 years and was significantly lower than PS among HIV-negative controls (HR, 1.34; 95% CI, 1.08 to 1.68; $P<0.01$). However, PS was similar for HIV monoinfected recipients and HIV-negative/HCV-negative controls at both times. HIV/HCV coinfected recipients had worse PS compared with HIV-negative/HCV-infected controls (5-year: 67.0% versus 78.6%, $P=0.007$; 10-year: 29.3% versus 56.23%, $P=0.002$ [HR, 1.57; 95% CI, 1.11 to 2.22; $P=0.01$]). In conclusion, HIV-negative and HIV monoinfected kidney transplant recipients had similar GS and PS, whereas HIV/HCV coinfected recipients had worse outcomes. Although encouraging, these results suggest caution in transplanting coinfected patients.

J Am Soc Nephrol 26: 2222–2229, 2015. doi: 10.1681/ASN.2014070726

Since the introduction of highly active antiretroviral therapy (HAART) in the mid-1990s, HIV-related deaths have declined, and the number of individuals living with HIV has increased.[1–3] Chronic diseases, such as ESRD, have now surpassed opportunistic infections as the leading cause of death among HIV-positive (HIV^+) individuals, and HIV-associated nephropathy is the third leading cause of ESRD among African Americans.[4–10] Kidney transplantation is now offered as an acceptable treatment option for HIV^+ ESRD patients and has expanded beyond the scope of clinical trials. Although this marks a new era in the care of the HIV^+ ESRD patient, experience with HIV^+ kidney transplantation remains in its relative infancy.

Recently, the largest prospective clinical trial examining outcomes among 150 HIV^+ kidney transplant recipients reported 3-year patient and graft survival of 88.2% and 73.7%, respectively, which were similar to survival rates among a cohort of unmatched elderly (>65 years) HIV-negative (HIV^-)

Received July 31, 2014. Accepted November 24, 2014.

Published online ahead of print. Publication date available at www.jasn.org.

Correspondence: Dr. Jayme E. Locke, 701 19th Street South, LHRB 748, Birmingham, AL 35294. Email: jlocke@uabmc.edu

kidney recipients. The median length of follow-up among study participants was 1.7 years (interquartile range [IQR], 0.7–3), but <60 patients had 3 years of follow-up.[11] Although these findings are encouraging, concerns remain regarding the high incidence of acute rejection after HIV$^+$ kidney transplantation and its possible effect on long-term transplant outcomes.[12,13]

To date no study has examined long-term outcomes or compared HIV$^+$ recipients to their appropriately matched HIV$^-$ counterparts. Furthermore, current practice is on the basis of results from a highly scrutinized clinical protocol used within the prospective National Institutes of Health (NIH) trial. The trial was limited to high-volume centers and involved only 150 study participants, representing a small sample of the >500 HIV$^+$ kidney transplants that have been performed in the United States. Going beyond the confines of the NIH trial to study the entire United States experience with HIV$^+$ kidney transplantation is necessary to properly assess the generalizability of findings, to provide the power for risk factor estimation, and to allow for comparison with properly matched controls.

To better understand outcomes in this unique patient population, we examined long-term patient and graft survival among the United States HIV$^+$ kidney transplant population in its entirety and compared these outcomes with the outcomes of appropriately matched HIV$^-$ recipients.

RESULTS

Study Population

During the study period, there were 510 HIV$^+$ first-time kidney transplants performed (median follow-up: 3.8 years; IQR, 2.4–5.5) and 94,948 HIV$^-$ transplants (median follow-up: 4.7 years; IQR, 3.0–6.9). Between 2003 and 2009, there was a 10-fold increase in the number of HIV$^+$ kidney transplants performed, from 8 transplants in 2003 to 93 in 2009. More recently, however, the number performed annually has declined slightly to 82 (Figure 1). Compared with the general pool of HIV$^-$ recipients, HIV$^+$ recipients were younger (≤50 years old: 61.4% versus 41.2%, $P<0.001$), less likely to be obese (body mass index [BMI](kg/m^2)≥30: 18.1% versus 33.3%, $P<0.001$), and were more often men (79.6% versus 61.0%, $P<0.001$), African American (71.0% versus 26.5%, $P<0.001$), infected with hepatitis C virus (HCV) (24.2% versus 5.5%, $P<0.001$), and receiving maintenance steroids (75.1% versus 66.1%, $P<0.001$). Moreover, HIV$^+$ patients were less likely to receive a kidney from a living donor (27.7% versus 38.4%, $P<0.001$) and receive anti-thymocyte globulin (ATG) induction therapy (27.8% versus 42.6%, $P<0.001$) and were more likely to have developed acute rejection post-transplant (17.8% versus 8.8%, $P<0.001$) compared with the general HIV$^-$ population (Table 1). Among the matched cohort, HIV+ recipients were more likely to be men (79.1% versus 63.5%, $P<0.001$), receive maintenance steroids (77.2% versus 67.0%, $P<0.001$), and have acute rejection (17.4% versus 10.3%, $P<0.001$) and were less likely to be obese (BMI≥30: 17.1% versus 37.5%, $P<0.001$) and receive ATG induction (29.5% versus 47.1%, $P<0.001$) (Table 1).

Five- and 10-Year Graft Outcomes

Graft survival (GS) among all HIV$^+$ recipients was 68.9% at 5 years and 49.5% at 10 years. Overall, GS was highest among monoinfected HIV$^+$ recipients (HIV$^+$/hepatitis C virus negative [HCV$^-$]), with 75.0% at 5 years and 55.9% at 10 years. In comparison, GS was significantly lower among coinfected HIV$^+$ recipients (HIV$^+$/hepatitis C virus positive [HCV$^+$]) at 5 years (49.9%) and 10 years (25.9%) post-transplant (Table 2). These trends persisted after censoring for death [death-censored graft survival (DCGS)] (Table 2). Among HIV$^+$ recipients, risk for graft loss was higher among patients coinfected with HCV (hazard ratio [HR], 2.41; 95% confidence interval [CI], 1.73 to 3.38; $P<0.001$), those with peak PRA>80% (HR, 1.79; 95% CI, 1.01 to 3.16; $P=0.05$), those who developed acute rejection (HR, 1.56; 95% CI, 1.05 to 2.31; $P=0.03$), and those transplanted with >10 hours of cold ischemia time (CIT) (HR, 1.69; 95% CI, 1.01 to 2.82; $P=0.05$). In contrast, the risk of graft loss was lower with the use of kidneys from living donors (HR, 0.45; 95% CI, 0.30 to 0.68; $P<0.001$) and with the use of calcineurin-inhibitor (CNI)-maintenance immunosuppression (HR, 0.60; 95% CI, 0.37 to 0.96; $P=0.03$) (Table 3).

Five- and 10-Year Graft Outcomes Compared with HIV-Matched Cohort

Compared with appropriate matched HIV$^-$ controls, GS was statistically lower at 5 years (69.2% versus 75.3%, $P=0.003$) and 10 years (49.8% versus 54.4%, $P<0.001$) post-transplant (HR, 1.37; 95% CI, 1.15 to 1.64; $P<0.001$); this difference persisted even after censoring for death at 5 years (83.0% versus 87.2%, $P=0.01$) and 10 years (76.9% versus 79.9%, $P=0.01$; HR, 1.43; 95% CI, 1.12 to 1.84; $P=0.01$). When risk stratified by HCV infection status, monoinfected HIV$^+$ recipients had similar 5-year (75.0% versus 75.8%, $P=0.58$) and 10-year GS (55.9% versus 56.0%, $P=0.49$) compared with HIV$^-$/HCV$^-$ controls (HR, 1.06; 95% CI, 0.85 to 1.33; $P=0.61$) (Figure 2A). In contrast, coinfected HIV$^+$ patients (HIV$^+$/HCV$^+$) had worse 5-year (52.0% versus 64.0%, $P=0.02$) and 10-year (27.0% versus 36.2%, $P=0.004$) GS post-transplant compared with HIV$^-$/HCV$^+$ matched controls (HR, 1.38; 95% CI, 1.08 to 1.77; $P=0.01$) (Figure 2B). These findings persisted even after censoring for death (monoinfected HR, 0.96; 95% CI, 0.71 to 1.29; $P=0.79$; coinfected HR, 1.66; 95% CI, 1.05 to 2.63; $P=0.03$) (Figure 3).

Five- and 10-Year Patient Survival

Patient survival (PS) among all HIV$^+$ recipients was 83.3% at 5 years and 51.5% at 10 years. Overall, PS was highest among monoinfected HIV$^+$ recipients (HIV$^+$/HCV$^-$), with 88.7% at 5 years and 63.5% at 10 years. In comparison, PS was significantly lower among coinfected HIV$^+$ recipients (HIV$^+$/HCV$^+$) at 5 years (66.3%) and 10 years (29.3%) post-transplant (Table 2). Among HIV$^+$ recipients, risk for death was higher among

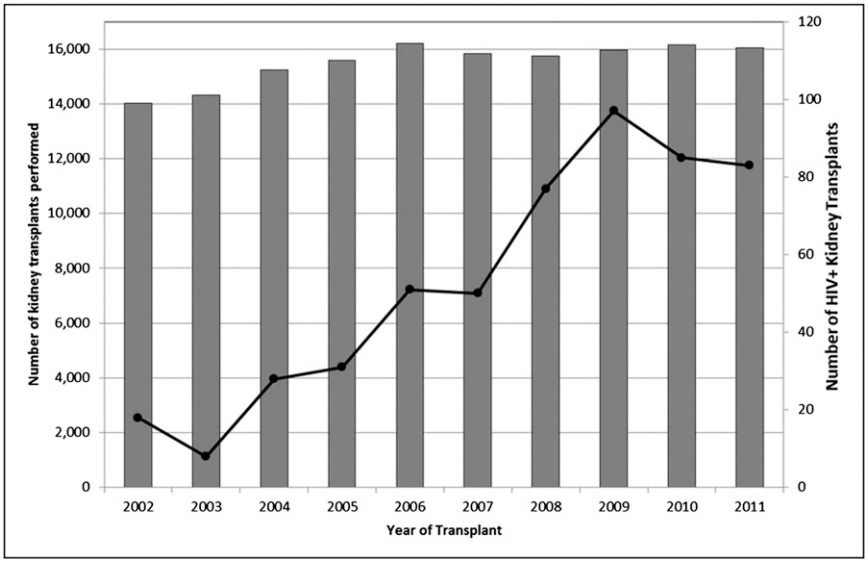

Figure 1. The number of kidney transplants performed among the general ESRD population and the number of kidney transplants performed among HIV$^+$ ESRD patients between 2002 and 2011. Since 2010 there has been a steady decline in the number of HIV$^+$ kidney transplants performed annually.

patients coinfected with HCV (HR, 2.85; 95% CI, 1.89 to 4.31; $P<0.001$) and among recipients >50 years of age (HR, 2.05; 95% CI, 1.36 to 3.09; $P<0.001$). In contrast, the risk of death was lower with the use of kidneys from living donors (HR, 0.49; 95% CI, 0.29 to 0.83; $P=0.01$) and among overweight recipients (HR, 0.56; 95% CI, 0.32 to 0.96; $P=0.04$) (Table 3).

Five- and 10-Year PS Compared with HIV- Matched Cohort

Compared with appropriate matched HIV$^-$ controls, PS among HIV$^+$ recipients was similar at 5 years (83.5% versus 86.2%, $P=0.06$) and significantly lower at 10 years (51.6% versus 72.1%, $P<0.01$) post-transplant (HR, 1.34; 95% CI, 1.08 to 1.68; $P=0.01$). When risk stratified by HCV infection status, monoinfected HIV$^+$ recipients had similar PS compared with HIV$^-$/HCV$^-$ controls at 5 years (88.7% versus 89.1%, $P=0.50$) and 10 years (63.5% versus 77.6%, $P=0.10$) post-transplant (HR, 1.26; 95% CI, 0.98 to 1.69; $P=0.13$) (Figure 4A). In contrast, HIV$^+$/HCV$^+$ recipients had worse PS compared with HIV$^-$/HCV$^+$ controls at 5 years (67.0% versus 78.6%, $P<0.01$) and 10 years (29.3% versus 56.23%, $P=0.002$) post-transplant (HR, 1.57; 95% CI, 1.11 to 2.23; $P=0.01$) (Figure 4B).

DISCUSSION

In this national study examining long-term outcomes among HIV$^+$ kidney transplant recipients, we found that when compared with the general HIV$^-$ population, long-term graft outcomes and PS were significantly lower among HIV$^+$ recipients, particularly among those recipients coinfected with HCV. In fact, 10 years post-transplant, only 49.8% of HIV$^+$ recipients had functioning grafts, and 51.6% were still living compared with 59.7% and 72.1%, respectively, among the general, unmatched population of HIV$^-$ recipients. However, significant differences in the baseline characteristics of HIV$^+$ recipients compared with the general population of HIV$^-$ recipients were identified, including factors known to be associated with increased risk of graft loss and death, such as coinfection with HCV, African American race, development of acute rejection within the first post-transplant year, and fewer living kidney donor transplants. These differences in demographics highlight potential confounding in using the general HIV$^-$ transplant population as a comparator group with study outcomes after kidney transplantation among HIV$^+$ recipients.

When compared with matched HIV$^-$ controls, HIV$^+$ kidney recipients had inferior graft outcomes and PS compared with their matched HIV$^-$ counterfactuals. However, after risk stratification by HCV infection status, it was clear that these worse outcomes were driven primarily by HCV coinfection because monoinfected HIV$^+$ recipients achieved similar 5- and 10-year post-transplant outcomes compared with HIV$^-$/HCV$^-$ matched controls, whereas HIV$^+$ recipients coinfected with HCV had significantly worse graft outcomes and PS compared with HIV$^-$/HCV$^+$ matched controls. These findings likely reflect the natural history of HCV coinfection among HIV$^+$ patients, and in particular, the increased mortality among this population. Although worrisome, these findings do motivate future studies aimed at examining the survival benefit of kidney transplantation over dialysis among HIV$^+$ patients coinfected with HCV. Moreover, efforts to improve long-term outcomes may require modifications of post-transplant processes of care for coinfected HIV$^+$ recipients, such as life-long follow-up at a transplant center, as opposed to the more traditional practice of transitioning care to the community. In addition to HCV coinfection, worse outcomes were also seen among HIV$^+$ recipients who received kidneys with >10 hours of CIT, whereas the use of kidneys from living donors was associated with improved outcomes.

Worse outcomes among coinfected recipients highlight the negative effect of HCV coinfection in the HIV$^+$ kidney transplant population. Our results are consistent with findings from prior studies, which have also demonstrated worse GS and PS among kidney transplant recipients infected with HCV.[11,14] Importantly, the burden of HCV infection appears to be much greater among HIV$^+$ recipients compared with

Table 1. Patient characteristics by HIV status

Demographics	HIV$^+$ (n=510)	HIV$^-$General Unmatched (n=94,948)	P Value	HIV$^+$ Matched Patients (n=467)	HIV- Matched Controls (n=4,670)	P Value
Follow-up time in years, median (IQR)	3.8 (2.4–5.5)	4.7 (3.0–6.9)	<0.001	3.8 (2.5–5.5)	4.1 (2.6–5.8)	0.02
Recipient characteristics (%)						
Age≥50 yr	38.6	58.8	<0.001	38.8	38.8	>0.99
Male	79.6	61.0	<0.001	79.2	61.8	<0.001
African American race	71.0	26.5	<0.001	70.9	70.9	>0.99
BMI (kg/m^2)						
<18.5	1.9	2.4	<0.001	2.1	2.5	<0.001
18.5–24.9	47.2	30.4		47.5	29.4	
25–29.9	32.8	33.9		33.2	32.1	
≥30	18.1	33.3		17.3	36.0	
Cause of renal failure						
Diabetes	10.4	25.4	<0.001	11.1	21.8	<0.001
Drug-related nephrotoxicity	1.0	1.3		1.1	1.1	
FSGS	4.5	6.4		4.9	9.1	
Glomerulonephritis	1.0	5.2		1.1	4.7	
Hypertension	32.4	23.1		32.1	32.6	
IgA nephropathy	1.6	4.6		1.1	2.6	
Polycystic kidney disease	2.2	9.8		2.4	5.3	
Systemic lupus	0.4	3.0		0.4	4.8	
Other	46.5	21.2		45.8	18.0	
Peak PRA>80%	6.3	6.2	0.9	5.1	5.1	>0.99
HCV infection	24.2	5.5	<0.001	22.5	22.5	>0.99
Antithymocyte globulin induction	27.8	42.6	<0.001	28.9	44.6	<0.001
CNI maintenance regimen	89.6	92.3	0.01	90.6	90.6	>0.99
Maintenance steroids	75.1	66.1	<0.001	76.9	67.0	<0.001
Acute rejection within 1 yr	17.8	8.8	<0.001	17.1	10.6	<0.001
Donor characteristics (%)						
Age≥50 yr	23.3	28.8	0.01	23.1	25.1	0.34
Race						
African American	24.1	14.0	0.25	24.8	26.5	0.44
Caucasian	60.2	68.9		59.5	59.9	
Other	15.7	17.0		15.6	13.6	
Living donor	27.7	38.4	<0.001	29.1	29.1	>0.99
Expanded criteria donor	8.8	11.7	0.04	8.6	10.5	0.18
Donor after cardiac death	7.5	7.0	0.70	7.1	8.4	0.31
CIT>10 h (among deceased donors)	80.6	80.4	0.94	80.2	80.2	>0.99

the general HIV$^-$ kidney transplant population. In fact, we found that >24% of HIV$^+$ recipients were coinfected with HCV compared with only 5.5% among the HIV$^-$ population. Traditionally, HCV infection was not thought to be a modifiable risk factor for graft loss because antiviral treatments lacked effectiveness. More recently, however, newer antiviral treatments for HCV genotype-1 have demonstrated sustained virologic responses >99%,[15,16] offering the promise of potential cure and attenuation of lower survival rates among HIV kidney transplant recipients coinfected with HCV.

Another potentially modifiable risk factor for outcomes among HIV$^+$ recipients was CIT. Our finding parallels results from studies within the general transplant population that have demonstrated an association between prolonged CIT and increased risks for the development of delayed graft function (DGF) and graft loss.[17–20] We have previously shown that the effect of CIT on outcomes after kidney transplantation is more pronounced among HIV$^+$ recipients compared with their HIV$^-$ counterparts.[21] These findings motivate a focus in clinical practice to reduce CIT in HIV$^+$ recipients. Additionally, it is possible that the mechanism for this relationship is the association between CIT and DGF. Management strategies aimed at reducing the effect of DGF on graft outcomes may be prudent. This increased susceptibility to the adverse effects of DGF may be in part explained by the increased risk for CNI nephrotoxic effects among HIV$^+$ patients on a ritonavir-boosted protease inhibitor based regimen.[22,23] Focused attention to transitioning HIV$^+$ candidates to integrase inhibitor-based HAART and off protease inhibitor-based HAART may

Table 2. Survival rates by HIV status and additional patient characteristics

Recipient Infection Status	*n*	Death-Censored GS (%)				GS (%)				PS (%)			
		1 yr	3 yr	5 yr	10 yr	1 yr	3 yr	5 yr	10 yr	1 yr	3 yr	5 yr	10 yr
Compared with general, unmatched HIV$^-$ population													
HIV$^+$/HCV$^-$	362	93.3	89.2	85.1	81.4	90.0	82.6	75.0	55.9	96.1	92.0	88.7	63.5
HIV$^-$/HCV$^-$	84,257	96.0[a]	92.5[a]	89.0[a]	82.7[a]	93.3[a]	86.4[a]	78.9[a]	60.8[a]	96.5	92.1	86.8	71.4
HIV$^+$/HCV$^+$	105	95.2	80.7	74.8	57.5	86.2	61.5	49.9	25.9	89.9	75.5	66.3	29.3
HIV$^-$/HCV$^+$	4,677	94.7	88.6[a]	83.1	74.5[a]	89.5	77.6[b]	66.1[b]	41.1[b]	93.1	85.2[a]	76.7[a]	53.3[a]
Compared with matched HIV$^-$ controls													
HIV$^+$/HCV$^-$	362	93.3	89.2	85.1	81.4	90.1	82.6	75.0	55.9	96.1	92.0	88.7	63.5
HIV$^-$/HCV$^-$	3,620	95.3	89.4	84.9	73.6	92.5	84.0	75.8	56.0	96.9	93.8	89.1	77.6
HIV$^+$/HCV$^+$	105	95.1	82.1	76.1	58.5	87.6	62.8	52.0	27.0	90.5	76.5	67.0	29.3
HIV$^-$/HCV$^+$	1,050	93.4	85.5	79.4	65.4	88.7	76.9[a]	64.0[a]	36.2[a]	93.9	86.2[a]	78.6[a]	56.2[a]

[a]Significant at an α level of 0.05.
[b]significant at an α level of 0.001.

Table 3. Univariate HRs of graft loss and death among HIV$^+$ recipients

Demographics	Risk of Graft Loss		Risk of Death	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Recipient characteristics				
Age≥50 yr	1.16 (0.83 to 1.62)	0.38	2.05 (1.36 to 3.09)	<0.001
Male sex	0.91 (0.61 to 1.35)	0.64	0.88 (0.53 to 1.46)	0.62
African American race	1.34 (0.92 to 1.94)	0.13	0.78 (0.51 to 1.22)	0.28
BMI (kg/m^2)				
Normal weight	Reference		Reference	
Underweight	1.14 (0.36 to 3.62)	0.83	2.13 (0.66 to 6.92)	0.21
Overweight	0.73 (0.49 to 1.09)	0.12	0.56 (0.32 to 0.96)	0.04
Obese	0.79 (0.47 to 1.32)	0.37	0.60 (0.30 to 1.23)	0.31
Peak PRA>80%	1.79 (1.01 to 3.16)	0.05	1.62 (0.78 to 3.36)	0.19
HCV infection	2.41 (1.73 to 3.38)	<0.001	2.85 (1.89 to 4.31)	<0.001
Antithymocyte globulin induction	0.94 (0.64 to 1.37)	0.74	1.14 (0.71 to 1.82)	0.59
CNI maintenance regimen	0.60 (0.37 to 0.96)	0.03	0.61 (0.34 to 1.10)	0.10
Acute rejection within 1 yr	1.56 (1.05 to 2.31)	0.03	0.62 (0.33 to 1.16)	0.14
Maintenance steroids	1.15 (0.76 to 1.72)	0.51	1.14 (0.67 to 1.94)	0.63
Donor characteristics				
Age≥50 yr	1.02 (0.69 to 1.49)	0.93	1.09 (0.68 to 1.75)	0.73
Race				
Caucasian	Reference		Reference	
African American	0.89 (0.60 to 1.34)	0.59	0.60 (0.34 to 1.05)	0.07
Other	1.24 (0.80 to 1.91)	0.33	1.10 (0.64 to 1.88)	0.90
Living donor	0.45 (0.30 to 0.68)	<0.001	0.49 (0.29 to 0.83)	0.01
Expanded criteria donor	1.51 (0.90 to 2.54)	0.12	1.34 (0.73 to 2.57)	0.33
Donor after cardiac death	0.94 (0.51 to 1.73)	0.83	0.78 (0.34 to 1.79)	0.56
CIT>10 h[a]	1.69 (1.01 to 2.82)	0.05	1.59 (0.82 to 3.11)	0.17

[a]Among deceased donor transplants only.

lower the risk for the development of CNI nephrotoxic affects and as such limit the development of DGF related to drug-drug interactions. Identification of optimal management strategies aimed at lowering the risk for DGF among HIV$^+$ recipients, careful attempts to minimize CIT among HIV+ deceased donor recipients, and optimization of living kidney transplantation may serve to improve outcomes among this vulnerable population.

Inferences on the basis of our findings must take into account a number of important limitations. SRTR's data lack granularity with regard to CD4 count, viral loads, infections, and malignancies, factors that are known to influence long-term outcomes among HIV$^+$ patients. However, the NIH's protocol used relatively restricted criteria for HIV$^+$ ESRD patients to be considered candidates for transplantation, requiring undetectable viral loads and CD4 counts of ≥200. It is

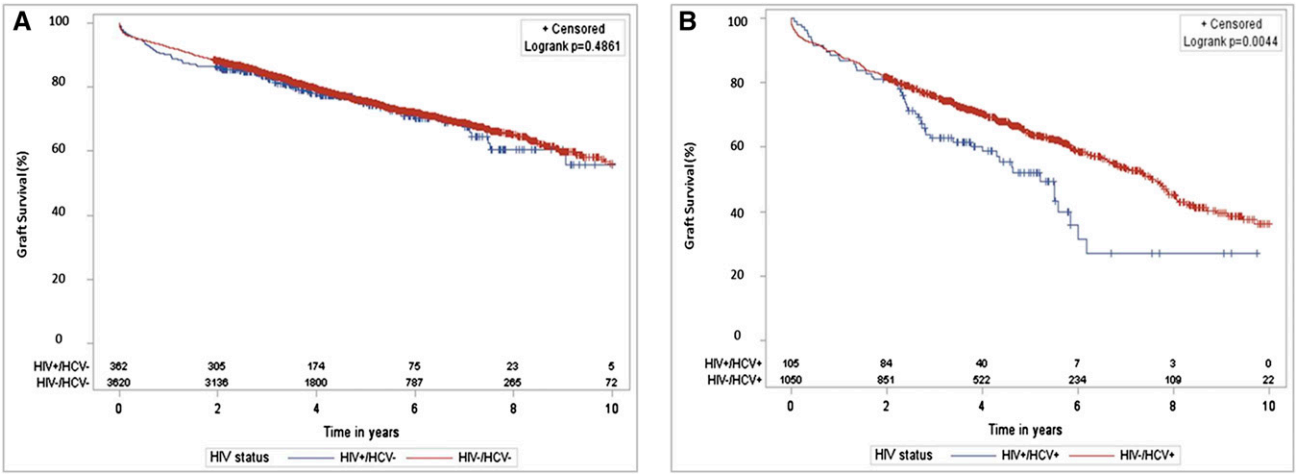

Figure 2. GS among a matched case-controlled cohort of HIV^+ and HIV^- kidney transplant recipients, stratified by HCV status. (A) Monoinfected HIV^+ recipients compared with HIV^-/HCV^- matched controls. (B) HIV^+ recipients coinfected with HCV compared with HIV^-/HCV^+ matched controls.

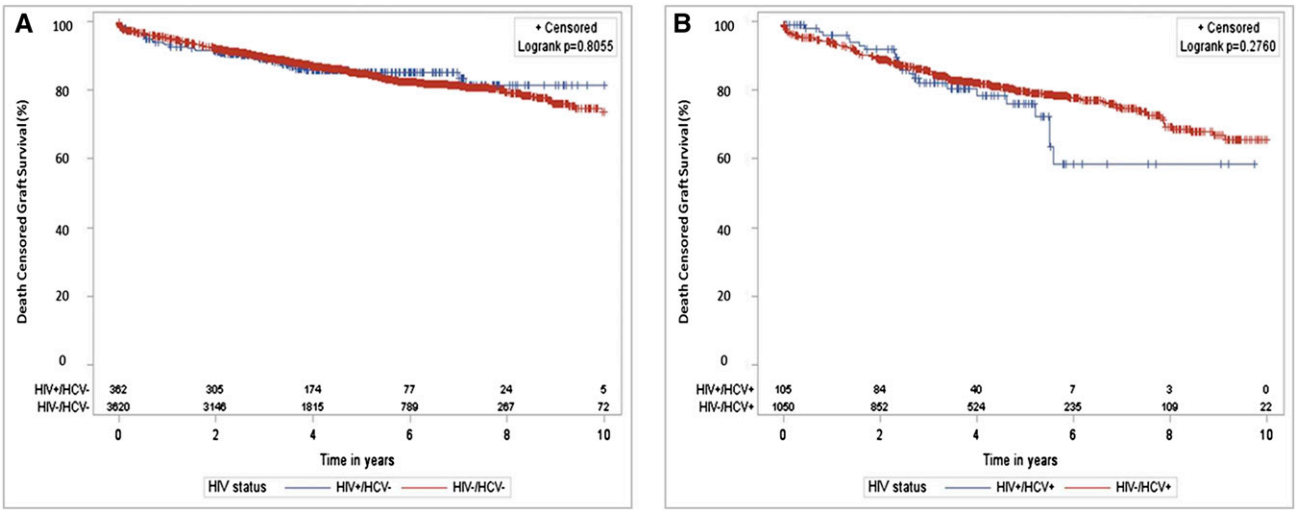

Figure 3. Death censored GS among a matched case-controlled cohort of HIV^+ and HIV^- kidney transplant recipients, stratified by HCV status. (A) Monoinfected HIV^+ recipients compared with HIV^-/HCV^- matched controls. (B) HIV^+ recipients coinfected with HCV compared with HIV^-/HCV^+ matched controls.

unlikely that there would be major deviations from this protocol in the national data. Moreover, immunosuppressant levels and antiviral regimens are not captured by SRTR data, and as such, it is impossible to determine whether drug interactions between HAART therapy and immunosuppressants led to subtherapeutic drug levels and higher rates of acute rejection and graft loss. Although understanding these interactions would help inform the mechanism of our long-term findings, the absence of these data do not bias our findings in any manner. Finally, the sample sizes available for our subgroup analyses were relatively small and may directly affect the accuracy of our estimates. However, these data represent the HIV^+ kidney transplant population in the United States in its totality and therefore contribute new and important information about long-term outcomes after kidney transplantation in this unique population.

To date, this is the first national study examining outcomes among the entire United States cohort of HIV^+ kidney transplant recipients and comparing their outcomes to appropriately matched HIV^- counterfactuals. In comparison with appropriately matched HIV^- controls, we found similar 5- and 10-year GS and PS among monoinfected HIV^+ recipients and significantly worse outcomes among HIV^+ recipients coinfected with HCV. These results are encouraging, but they do

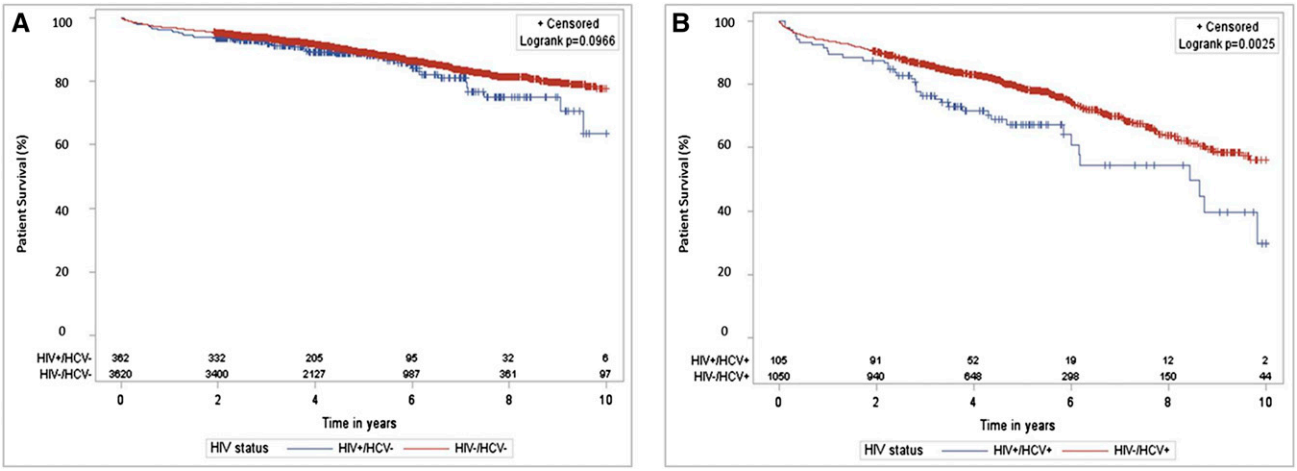

Figure 4. PS among a matched case-controlled cohort of HIV$^+$ and HIV$^-$ kidney transplant recipients, stratified by HCV status. (A) Monoinfected HIV$^+$ recipients compared with HIV$^-$/HCV$^-$ matched controls. (B) HIV$^+$ recipients coinfected with HCV compared with HIV$^-$/HCV$^+$ matched controls.

suggest caution in transplanting HIV$^+$ recipients coinfected with HCV, motivating future studies of survival benefit.

CONCISE METHODS

Data Source

This study used data from the SRTR. The SRTR data system includes data, submitted by the members of the Organ Procurement and Transplantation Network, on all donors, waitlisted candidates, and transplant recipients in the United States. The Health Resources and Services Administration of the US Department of Health and Human Services provides the oversight to the activities of the Organ Procurement and Transplantation Network and SRTR contractors.

Study Population

All adult, kidney-only, first-time transplants between January 1, 2002, and December 31, 2011, were identified (HIV$^+$: n=510; HIV$^-$: n=94,948). Deceased donor recipients missing information on CIT (n=25) and recipients missing information on HCV infection (n=14) were excluded from analysis, leaving a total of 471 HIV$^+$ patients eligible for matching (of whom 467 were successfully matched to HIV$^-$ controls). The entire HIV$^-$ cohort was classified as the general, unmatched HIV$^-$ population, and the HIV- cohort used in matched analyses was classified as the matched HIV$^-$ controls.

Outcome Ascertainment

The primary outcome measures were DCGS, GS, and PS. DCGS was defined as the time from transplantation to graft loss, return to dialysis, or last follow-up with a functioning graft, censored for death. GS was defined as the time from transplantation to graft loss, return to dialysis, last follow-up with a functioning graft, or death. PS was defined as the time from transplantation to death or last follow-up. Death indicators were supplemented by linkage to the Social Security Death Master File; death and graft loss were supplemented by linkage to data from the Centers for Medicare and Medicaid Services. All outcome measures were censored for administrative end of study.

Statistical Analyses

Exploratory Data Analyses

Donor and recipient characteristics were compared by HIV status. Continuous variables were analyzed using t tests or Wilcoxon rank–sum tests (on the basis of distribution), and categorical variables were examined using chi-squared or Fisher's exact tests of independence (on the basis of sample size).

Survival Analyses

DCGS, GS, and PS were estimated among HIV$^+$ recipients using Kaplan–Meier methods, log-rank tests, and Cox proportional hazards models. Risk factors for graft loss and patient death within the HIV$^+$ cohort were identified using univariate Cox proportional hazards with statistical significance set at 0.1. The proportional hazards assumption was assessed and verified using time-dependent variables.

DCGS, GS, and PS among HIV$^+$ recipients were compared with the general, unmatched HIV$^-$ population and to appropriately matched HIV$^-$ controls using Kaplan–Meier methods, log-rank tests, and Cox proportional hazards models. HIV$^+$ recipients were matched to appropriate HIV$^-$ counterfactuals 1:10 using iterative, expanded radius matching without replacement and were matched on factors found to be significantly associated with each outcome. The matching algorithm for GS included recipient age and race, HCV infection, CNI-based maintenance immunosuppression, PRA, CIT (for deceased donors only), and transplant year. The matching algorithm for PS included HCV infection, CNI-based maintenance, recipient age and race, and transplant year. Additional covariates were adjusted for as part of sensitivity analyses, and inferences did not change. For simplicity, results from the matched analyses without additional adjustment are reported.

Sensitivity Analyses

Covariates determined to be significant on exploratory analyses (Table 1) were used to build full multivariate models. Results from these models confirmed inferences reported from the matched (1:10) analyses. Matched control analyses must balance introduction of bias with reduction in variability (*i.e.*, with increasing numbers of controls per patient, more bias is potentially introduced; however, variability is theoretically reduced). Given this, the analyses were performed among four distinct matched cohorts (1:1, 1:3, 1:5, and 1:10); inferences did not change. For the purposes of simplicity, results comparing outcomes among HIV^+ and HIV^- kidney transplant recipients are from the 1:10 matched cohort. Finally, multivariate models, adjusting for additional covariates, were built in the 1:10 matched cohort: 1) GS and DCGS models adjusted for recipient age, race, sex, BMI, ATG induction, maintenance steroids, and donor age; and 2) PS model adjusted for recipient sex, BMI, PRA, ATG induction, maintenance steroids, and donor age and CIT; inferences did not change.

ACKNOWLEDGMENTS

This research was supported in part by the NIH (no. K24-DK101828) (principal investigator: Segev).

This research was presented in preliminary forms as abstracts at the 2014 American Society of Transplant Surgeons State of the Art Winter Symposium and the 2014 World Transplant Congress.

These analyses were performed by the University of Alabama at Birmingham's Comprehensive Transplant Institute Outcomes Research Center analytic team.

The data reported here have been supplied by the Minneapolis Medical Research Foundation as the contractor for the SRTR. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy of or interpretation by the SRTR or the US Government.

DISCLOSURES

None

REFERENCES

1. Centers for Disease Control and Prevention: HIV in the United States: At a glance, 2013; http://www.cdc.gov/hiv/statistics/basics/ataglance.html. Accessed June 9, 2014
2. Palella FJ Jr, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, Aschman DJ, Holmberg SD; HIV Outpatient Study Investigators: Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. *N Engl J Med* 338: 853–860, 1998
3. Rao TK: Human immunodeficiency virus infection in end-stage renal disease patients. *Semin Dial* 16: 233–244, 2003
4. Ando M, Tsuchiya K, Nitta K: How to manage HIV-infected patients with chronic kidney disease in the HAART era. *Clin Exp Nephrol* 16: 363–372, 2012
5. Blumberg EA, Stock P; AST Infectious Diseases Community of Practice: Solid organ transplantation in the HIV-infected patient. *Am J Transplant* 9[Suppl 4]: S131–S135, 2009
6. Wyatt CM, Murphy B: Kidney transplantation in HIV-infected patients. *Semin Dial* 18: 495–498, 2005
7. Kopp JB, Winkler C: HIV-associated nephropathy in African Americans. *Kidney Int Suppl* (83): S43–S49, 2003
8. Herman ES, Klotman PE: HIV-associated nephropathy: Epidemiology, pathogenesis, and treatment. *Semin Nephrol* 23: 200–208, 2003
9. US Renal Data System: *USRDS 2009 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States (Volume 2)*, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2009
10. Winston JA, Klotman PE: Are we missing an epidemic of HIV-associated nephropathy? *J Am Soc Nephrol* 7: 1–7, 1996
11. Stock PG, Barin B, Murphy B, Hanto D, Diego JM, Light J, Davis C, Blumberg E, Simon D, Subramanian A, Millis JM, Lyon GM, Brayman K, Slakey D, Shapiro R, Melancon J, Jacobson JM, Stosor V, Olson JL, Stablein DM, Roland ME: Outcomes of kidney transplantation in HIV-infected recipients. *N Engl J Med* 363: 2004–2014, 2010
12. Gathogo EN, Hamzah L, Hilton R, Marshall N, Ashley C, Harber M, Levy JB, Jones R, Boffito M, Khoo SH, Drage M, Bhagani S, Post FA; UK HIV/Kidney Transplantation Study Group (see appendix): Kidney transplantation in HIV-positive adults: The UK experience. *Int J STD AIDS* 25: 57–66, 2014
13. Malat GE, Ranganna KM, Sikalas N, Liu L, Jindal RM, Doyle A: High frequency of rejections in HIV-positive recipients of kidney transplantation: A single center prospective trial. *Transplantation* 94: 1020–1024, 2012
14. Mazuecos A, Fernandez A, Andres A, Gomez E, Zarraga S, Burgos D, Jimenez C, Paul J, Rodriguez-Benot A, Fernandez C: HIV infection and renal transplantation. *Nephrol Dial Transplant* 26: 1401–1407, 2011
15. Afdhal N, Zeuzem S, Kwo P, Chojkier M, Gitlin N, Puoti M, Romero-Gomez M, Zarski JP, Agarwal K, Buggisch P, Foster GR, Brau N, Buti M, Jacobson IM, Subramanian GM, Ding X, Mo H, Yang JC, Pang PS, Symonds WT, McHutchison JG, Muir AJ, Mangia A, Marcellin P; ION-1 Investigators: Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. *N Engl J Med* 370: 1889–1898, 2014
16. Sulkowski MS: Interferon-containing and interferon-free HCV therapy for HIV-infected patients. *Semin Liver Dis* 34: 72–78, 2014
17. Mikhalski D, Wissing KM, Ghisdal L, Broeders N, Touly M, Hoang AD, Loi P, Mboti F, Donckier V, Vereerstraeten P, Abramowicz D: Cold ischemia is a major determinant of acute rejection and renal graft survival in the modern era of immunosuppression. *Transplantation* 85[Suppl]: S3–S9, 2008
18. Shoskes DA, Cecka JM: Deleterious effects of delayed graft function in cadaveric renal transplant recipients independent of acute rejection. *Transplantation* 66: 1697–1701, 1998
19. Kalble T, Alcaraz A, Budde K, Humke U, Karam G, Lucan M, Nicita G, Susal C: Guidelines on renal transplantation 10: 85, 2009
20. Troppmann C, Gillingham KJ, Benedetti E, Almond PS, Gruessner RW, Najarian JS, Matas AJ: Delayed graft function, acute rejection, and outcome after cadaver renal transplantation. The multivariate analysis. *Transplantation* 59: 962–968, 1995
21. Locke JE, Montgomery RA, Warren DS, Subramanian A, Segev DL: Renal transplant in HIV-positive patients: Long-term outcomes and risk factors for graft loss. *Arch Surg* 144: 83–86, 2009
22. Kumar MS, Sierka DR, Damask AM, Fyfe B, McAlack RF, Heifets M, Moritz MJ, Alvarez D, Kumar A: Safety and success of kidney transplantation and concomitant immunosuppression in HIV-positive patients. *Kidney Int* 67: 1622–1629, 2005
23. Granville DJ, Tashakkor B, Takeuchi C, Gustafsson AB, Huang C, Sayen MR, Wentworth P Jr, Yeager M, Gottlieb RA: Reduction of ischemia and reperfusion-induced myocardial damage by cytochrome P450 inhibitors. *Proc Natl Acad Sci U S A* 101: 1321–1326, 2004

See related editorial, "Kidney Transplantation in HIV-Infected Recipients: Encouraging Outcomes, but Registry Data Are No Longer Enough," on pages 2070–2071.