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Kidney Transplantation From Hepatitis C Viremic Deceased Donors to Aviremic Recipients in a Real-world Setting

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Background. Transplantation of hepatitis C viremic (HCV+) deceased donor kidney transplants (DDKT) into aviremic (HCV–) recipients is a strategy to increase organ utilization. However, there are concerns around inferior recipient outcomes due to delayed initiation of direct-acting antiviral (DAA) therapy and sustained HCV replication when implemented outside of a research setting. **Methods.** This was a retrospective single-center matched cohort study of DDKT recipients of HCV+ donors (cases) who were matched 1:1 to recipients of HCV– donors (comparators) by age, gender, race, presence of diabetes, kidney donor profile index, and calculated panel-reactive antibody. Data were analyzed using summary statistics, t-tests, and chi-square tests for between-group comparisons, and linear mixed-effects models for longitudinal data. **Results.** Each group consisted of 50 recipients with no significant differences in baseline characteristics. The 6-mo longitudinal trajectory of serum creatinine and estimated glomerular filtration rate did not differ between groups. All recipients had similar rates of acute rejection and readmissions (all $P>0.05$). One case lost the allograft 151 d posttransplant because of acute rejection, and 1 comparator died on postoperative day 7 from cardiac arrest. HCV+ recipients initiated DAA on average 29 ± 11 d posttransplant. Ninety-eight percent achieved sustained virologic response at 4 and 12 wks with the first course of therapy; 1 patient had persistent HCV infection and was cured with a second course of DAA. **Conclusions.** Aviremic recipients of HCV+ DDKT with delayed DAA initiation posttransplant had similar short-term outcomes compared with matched recipient comparators of HCV– donors.

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INTRODUCTION

A critical organ shortage exists for those in need of and those awaiting kidney transplantation in the United States with the waitlist nearing 100 000 patients.[1] In 2019, the total number of kidney transplants in the United States was slightly over 23 000, which was a record year with 10% growth from 2018, largely driven by an increase in

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donors from the opioid epidemic.[1-3] The ongoing opioid crisis has caused increased deaths due to intravenous drug overdose resulting in an increase in available donor organs infected with the hepatitis C virus (HCV).[4] With the introduction of direct-acting antiviral agents (DAA) for the treatment of HCV, transplantation of kidneys from HCV viremic (nucleic acid test positive donors) into aviremic recipients (HCV D+/R–) have been occurring with promising outcomes.[5-8] Cure rates of DAA regimens are greater than 90% in the general population and have shown similarly high effectiveness in those receiving immunosuppression and those with kidney impairment.[8-15]

Transplant centers are using 2 approaches to HCV D+/R– organ transplantation: (1) preemptive, prophylactic, or early administration of DAA usually as a part of a clinical trial or research study,[9-12,16,17] or (2) delayed initiation of DAA therapy, usually within a few weeks after transplant and performed under a "real-world setting."[8,18-20] In the first approach, the cost of DAA is usually covered as part of the clinical trial, whereas in the second approach, an insurance approval route for DAA coverage is used and initiation of DAA therapy only occurs after insurance approval is obtained. This usually requires documentation of recipient HCV viremia and HCV genotype and may take several weeks.

Two single-center pilot studies, conducted in a clinical trial setting, enrolled a total of 30 patients and demonstrated 100% HCV cure rates and excellent posttransplant kidney function in uninfected HCV patients who received HCV–infected kidneys along with prophylactic/preemptive[11] or early DAA initiation[9,10] and a 12-wk treatment course. Two centers have also reported outcomes on a total of 129 patients who underwent HCV D+/R– kidney transplantation in a real-world setting with delayed DAA initiation.[18-20] The median times to DAA initiation at these centers were 76 and 72 d, respectively. In this real-world experience, HCV cure rates and posttransplant kidney outcomes were excellent. However, a total of 3 patients developed fibrosing cholestatic hepatitis. In addition, based on the outcomes reported by Molnar et al,[18] concerns have also been raised that immune activation by replicating HCV can lead to an increased risk of complications such as cytomegalovirus infection, BK virus infection, and allograft rejection.[21] Although Reese et al[9] performed a matched-comparator analysis of posttransplant kidney function in the THINKER trial, which used early DAA treatment initiation, there has not to date been a matched-comparator analysis of HCV D+/R– kidney transplantation performed with delayed DAA initiation.

Therefore, the aim of this study was to compare short-term posttransplant outcomes including kidney function and rates of acute rejection and readmissions between HCV D+/R– recipients (cases) and matched HCV D–/R– comparators. Our hypothesis was that outcomes of cases would not be different from those of the comparators.

MATERIALS AND METHODS

Study Setting

This study was conducted at Vanderbilt University Medical Center (VUMC) and included patients who received kidney transplants between January 1, 2008, and December 31, 2019; it was approved by the VUMC Institutional Review Board no. 191146.

VUMC began utilizing HCV D+/R– kidney transplantation on October 18, 2018. To have data on sustained virologic response at 12 wks (SVR-12) for all patients receiving HCV D+/R– kidney transplants, we included only patients in this cohort from October 18, 2018, through December 31, 2019, of which there were 50. We then created a matched-comparator cohort of 50 patients who received HCV D–/R– transplants matched for age, gender, race, presence of diabetes, kidney donor profile index (KDPI), and calculated panel-reactive antibody (cPRA). All data were collected from the VUMC transplant dataset, the electronic medical record, and the United Network of Organ Sharing data files. Data were collected, stored, and managed in the Research Electronic Data Capture tool at Vanderbilt University.[22]

Clinical Protocol

This study included adult patients ≥18 y who were either the recipient of an HCV D+/R– kidney transplant or an HCV D–/R– transplant matched on age, gender, race, presence of diabetes, KDPI, and cPRAs. Patients who received multiorgan transplants or had a prior history of HCV were excluded. Our center offered waitlisted candidates the option to accept HCV D+/R– kidney transplants if they met the following criteria: age ≥18, body mass index ≤40, any blood group, and no living donor. Patients with clinically evident liver disease (abnormal liver function tests, evidence of underlying hepatic disease on imaging such as nodularity of the liver and steatosis, or diagnosis of cirrhosis) were not eligible.

HCV Consent Process

Every waitlisted candidate who met the inclusion criteria for HCV D+/R– kidney transplants was called by the transplant nurse coordinator to determine the candidate's interest in HCV+ offers. For interested candidates, risks and benefits of HCV D+/R– kidney transplants and an overview of HCV treatment including known cure rates and possible adverse events were discussed with each patient by a hepatology nurse practitioner (NP). Consent was then obtained for each patient interested in registering for an HCV D+/R– kidney transplant.

For those patients in the evaluation process, a brief educational slide deck was delivered with the option of listing for an HCV D+/R– kidney transplant. The evaluating physician then discussed the option during the medical or surgical evaluation. The nurse coordinator then discussed the option again and consented any patient who met inclusion criteria for and desired to accept offers for HCV D+/R– kidney transplants after again reviewing the risks, benefits, and known cure rates for HCV with DAAs.

At the time of HCV D+/R– kidney transplant organ offer, the coordinator again reviewed the risks, benefits, and known cure rates for HCV with DAAs before the patient reporting to the hospital. Once admitted for transplant work-up, the surgical and medical kidney transplant teams reviewed the risks, benefits, and known cure rates for HCV with DAAs, which was included on the surgical consent requiring patient signature.

Donor Acceptance Criteria

Our center protocol excluded acceptance of KDPI ≥85% for HCV D+/R– kidney transplants. Kidneys were not biopsied exclusively for having HCV, but biopsies were obtained if otherwise clinically indicated. A donor history of intravenous

drug abuse was not a contraindication to acceptance; patients were made aware of any applicable Public Health Service Increased Risk donor criteria. Donor genotyping for HCV+ donors was not available at time of organ acceptance.

Immunosuppression Protocol

Standard induction and maintenance immunosuppression protocols were utilized when we initiated HCV D+/R− kidney transplant in October 2018. Alemtuzumab was the standard induction agent with a high-dose steroid taper. Maintenance immunosuppression included: tacrolimus, mycophenolate mofetil, and prednisone; for our initial protocol, if cPRA was <20% with no other indications for steroids, patients received no additional prednisone after the intravenous taper. Patients who were both older age (≥65 y) and unsensitized received basiliximab for induction with tacrolimus, mycophenolate mofetil, and prednisone for maintenance. In April 2019, we transitioned to maintain all patients undergoing an HCV D+/R− kidney transplant on tacrolimus, mycophenolate mofetil, and prednisone after alemtuzumab induction.

Screening and Treatment Protocol

After the receipt of an HCV D+/R− kidney transplant, patients received counseling and education from the inpatient NP regarding virus transmission risk, laboratory testing schedule, and symptoms of acute HCV infection. HCV genotype and HCV polymerase chain reaction (PCR) quantitative labs were sent on postoperative day 3 and a hepatology NP clinic appointment was arranged for 1–2 wks after discharge. The hepatology NP was responsible for the posttransplant treatment and monitoring of HCV viremic recipients. Appropriate HCV treatment per the patient's genotype and posttransplant status were ordered. An HCV PCR quantitative laboratory was sent 4 wks into HCV therapy. If the HCV PCR quantitative level was undetectable, a 12-wk treatment course was planned. If the HCV remained detectable at 4 wks, the option to increase to 24 wks was evaluated. An HCV PCR quantitative level was obtained at the end of therapy and at 4 and 12 wks after the termination of therapy.

Direct-acting Antiviral Application and Approval Process

Once the patient's genotype was known, the patient was referred for HCV therapy insurance approval through the institutional transplant specialty pharmacy where clinical and insurance factors were reviewed. An appeal process was completed if the desired antiviral medication was not on the patient's insurance formulary. To obtain DAA approval, the pharmacy team managed the following: a benefit investigation to identify formulary status of HCV medications, patient financial responsibility, network pharmacy restrictions, and prior authorization form. The pharmacy team also coordinated and completed all prior authorization appeal steps. Once the medication was approved, the provider was notified and ordered the prescription to the appropriate pharmacy. The specialty pharmacy team also obtained copay assistance, monitored for drug interactions, and documented DAA course completion.

Data Encoding and Comparator Cohort Formation

KDPI is calculated by 10 factors, one of which is hepatitis C positivity, and predicts organ quality and outcomes. Since many of the contemporary HCV+ donors are relatively young

with less chronic exposure to hepatitis, these organs likely are not as negatively impacted by the virus and therefore KDPI may be falsely higher than the actual quality of the kidney. Therefore, we adjusted the KDPI of these organs to reflect a negative HCV status for better alignment and comparison to the comparators, which is similar to the matched-comparator cohort used by Reese et al.[9] To form a comparator cohort that would be statistically comparable on a set of characteristics that would be expected to be associated with the outcomes of interest, 50 HCV D+/R− kidney transplant recipients were matched 1:1 to 50 HCV D−/R− comparator recipients on the collective basis of age at transplant (±5 y), gender, race (whether Black), whether diabetic, KDPI (±5 points), and the potential comparator having the closest cPRA value.

Outcomes

The outcomes of interest were patient and graft survival at 180 d posttransplant, the trajectories of serum creatinine (SCr) and estimated glomerular filtration rate (eGFR) through and values at 180 d posttransplant, readmissions within 90 d of transplant, and acute rejection episodes within 180 d of transplant.

Statistical Analysis

Summary statistics were computed. Between-group comparisons were performed using t-tests or chi-square tests of proportions, as appropriate. Longitudinal kidney function data were analyzed using linear mixed-effects models to evaluate the effects of: (a) time and (b) whether 6-mo temporal trajectories of SCr and eGFR differed between cases and comparators. Data were analyzed using the IBM SPSS statistical package (version 27, Armonk, NY).

RESULTS

Recipient and Donor Characteristics

The study included 50 HCV D+/R− cases and 50 HCV D−/R− comparators. There were no differences in baseline recipient characteristics between the 2 groups (Table 1). The mean age of the cohort was 56 ± 11 y, 48% were Black, and over a third of patients were diabetic. The majority of patients received alemtuzumab induction and all were maintained on tacrolimus and mycophenolate. There were significantly more cases compared with comparators who were maintained on prednisone, 88% versus 47%, respectively ($P < 0.001$). There was no difference in KDPI values or KDPI strata between the 2 recipient groups. More than half of patients received a kidney with a KDPI ≤20% and none had a KDPI >85% based on adjustment as described in the methods. There were 82 unique donors (32 HCV+ 50 HCV−). With the exception of HCV+ donors being, on average, 4 y older than HCV− donors, donors were comparable in terms of their age, percentage Black, terminal SCr, KDPI, and whether donation occurred after circulatory death (Table 1).

Short-term Outcomes

Patient and Graft Survival

Among cases, there was 100% patient survival at 180 d posttransplant. One case lost the allograft at 151 d posttransplant because of acute rejection. Among comparators, 1 patient died on postoperative day 7 of cardiac arrest. Of the remaining patients, none lost their graft or died within 180 d posttransplant.

Recipient and donor characteristics

Recipient characteristics		HCV+ donor (n = 50)	HCV− donor (n = 50)[a]	P
Age at transplant, y		56 (11)	56 (11)	0.946
Gender, male		34 (68%)	34 (68%)	1.000
Race, Black		24 (48%)	24 (48%)	1.000
Primary etiology of kidney disease	Diabetes	15 (30%)	13 (26%)	0.947
	Hypertension	16 (32%)	18 (36%)	
	Glomerulonephritis	11 (22%)	10 (20%)	
	Other	8 (16%)	9 (18%)	
Pretransplant dialysis		49 (98%)	45 (90%)	0.204
Comorbidities	Coronary disease	12 (24%)	7 (14%)	0.308
	Diabetes	18 (36%)	21 (42%)	0.682
EPTS		0.43 (0.04)	0.48 (0.29)	0.300
cPRA		17 (29)	21 (35)	0.559
cPRA categories	0 to <0.5	30 (60%)	31 (62%)	0.400
	≥0.5 to ≤20	4 (8%)	5 (10%)	
	>20 to ≤80	12 (24%)	7 (14%)	
	>80 to <97.5	3 (6%)	7 (14%)	
	≥97.5	1 (2%)	0 (0%)	
Induction immunosuppression	Alemtuzumab	47 (94%)	47 (94%)	1.000
	Basiliximab	3 (6%)	3 (6%)	
Maintenance immunosuppression	Tacrolimus	50 (100%)	49 (100%)	n/a
	Mycophenolate mofetil (or MPA)	50 (100%)	49 (100%)	n/a
	Prednisone	44 (88%)	23 (47%)	<0.001

Donor characteristics		HCV+ donor (n = 32)	HCV− donor (n = 50)	P
Age, y		34 (8)	30 (12)	0.044
Sex, male		22 (69%)	35 (70%)	1.000
Race, Black		1 (3%)	3 (6%)	1.000
DCD		3 (9%)	12 (24%)	0.143
Terminal SCr, mg/dl		0.85 (0.41)	0.91 (0.29)	0.533
KDPI,[b] %		23 (16)	25 (19)	0.542
KDPI[b]	≤20%	17 (53%)	26 (52%)	0.934
	>20% to <35%	9 (28%)	13 (26%)	
	≥35% to ≤85%	6 (19%)	11 (22%)	
	>85%	0 (0%)	0 (0%)	
KDPI,[c] %		24 (16)	25 (19)	0.608
KDPI[c]	≤20%	25 (50%)	26 (52%)	0.900
	>20% to <35%	15 (30%)	13 (26%)	
	≥35 to% ≤85%	10 (20%)	11 (22%)	
	>85%	0 (0%)	0 (0%)	

Table entries are mean (SD) or frequency (%).

[a]Baseline characteristics include 50 HCV− recipients. However, 1 mortality at a week posttransplant reduced the group size to 49 for analysis of maintenance immunosuppression.

[b]Kidney donor profile index (among 32 HCV+ and 50 HCV− unique donors).

[c]Kidney donor profile index (among 50 HCV+ and 50 HCV− donor recipients).

cPRA, calculated panel-reactive antibodies; DCD, donation after circulatory death; EPTS, estimated posttransplant survival; HCV, hepatitis C virus; HCV+, hepatitis C viremic; HCV−, hepatitis C aviremic; KDPI, kidney donor profile index; MPA, mycophenolic acid; SCr, serum creatinine.

Kidney Function

A minority of patients experienced delayed graft function, specifically 2 (4%) cases and 6 (12%) comparators (Table 2). Overall, SCr and eGFR were stable over time (both main effects of time, $P > 0.60$), and their trajectories did not differ between cases and comparators (both time by group interaction effects, $P > 0.41$) (Figure 1). Posttransplant kidney function did not differ significantly between cases and comparators at 180 d posttransplant (mean eGFR of 58.9 ± 16.5 mL/min/1.73m2 in cases

Key short-term outcomes

		HCV+ donor (n = 50)	HCV− donor (n = 49)	P
Delayed graft function[a]		2 (4%)	6 (12%)	0.269
Serum creatinine at 180 d (mg/dl)		1.37 (0.44)	1.36 (0.50)	0.920
Estimated GFR at 180 d (mL/min/1.73m²)		58.92 (16.50)	61.88 (23.46)	0.472
Readmissions within 90 d (number of persons)	Any reason	25 (50%)	22 (45%)	0.689
	Due to infection	16 (32%)	10 (20%)	0.254
Acute rejection episodes within 180 d (number of persons)		5 (10%)	4 (8%)	1.000

Table entries are mean (SD) or frequency (%).

Baseline characteristics include 50 HCV− recipients. However, 1 mortality at a week posttransplant reduced the group size to 49 for analysis of posttransplant outcomes.

[a]Defined as dialysis within 7 d after transplant.

GFR, glomerular filtration rate; HCV, hepatitis C virus; HCV+, hepatitis C viremic; HCV−, hepatitis C aviremic.

versus 61.8 ± 23.5 mL/min/1.73m2 in comparators, $P = 0.46$) (Table 2).

Readmission

There were 25 (50%) cases and 22 (45%) comparators who required a readmission within 90 d of transplant (Tables 2 and 3). Sixteen cases and 10 comparators were readmitted because of an infectious cause. Among the cases, 6 patients had multiple readmissions. The mean length of stay per readmission was 5.9 ± 4.6 d. Six cases were readmitted because of a genitourinary infection, 3 because of pneumonia, and 3 because of *Clostridium difficile* infection.

Acute Rejection

All allograft biopsies were performed for-cause, and all acute rejection episodes were biopsy-proven. Acute rejection episodes at 180 d posttransplant were similar among cases and comparators, specifically 5 (10%) cases versus 4 (8%) comparators (Table 2). There was no history of nonadherence to immunosuppressive therapy and all patients had therapeutic tacrolimus levels before the rejection episodes. Two cases experienced 2 episodes of acute rejection each. One of the cases (patient ID 2) had findings of severe microcirculation inflammation with associated acute tubular injury on biopsy but no detectable donor specific antibody. This patient received treatment for presumed nonhuman leukocyte antigen antibody-mediated rejection with plasmapheresis, intravenous immunoglobulin, and rituximab. However, the patient did not respond to therapy and lost the allograft at 151 d posttransplant. Table 4 summarizes the types of rejection among cases and the treatment administered. Among the 4 cases who developed acute rejection and did not lose the allograft, the eGFR at 180 d posttransplant ranged from 29 to 84 mL/min/1.73m2 (SCr range of 0.9 to 2.4 mg/dl).

Among the 4 comparators who developed acute rejection, all had acute cellular rejection, 3 of whom had acute vascular rejection. There was no antibody-mediated rejection. The patient without acute vascular rejection was treated with steroids alone, whereas the remaining 3 patients were treated with rabbit antithymocyte globulin. One patient did not respond to therapy and died of cardiovascular causes 21 d after the diagnosis of acute rejection (posttransplant month 7). The remainder responded to therapy.
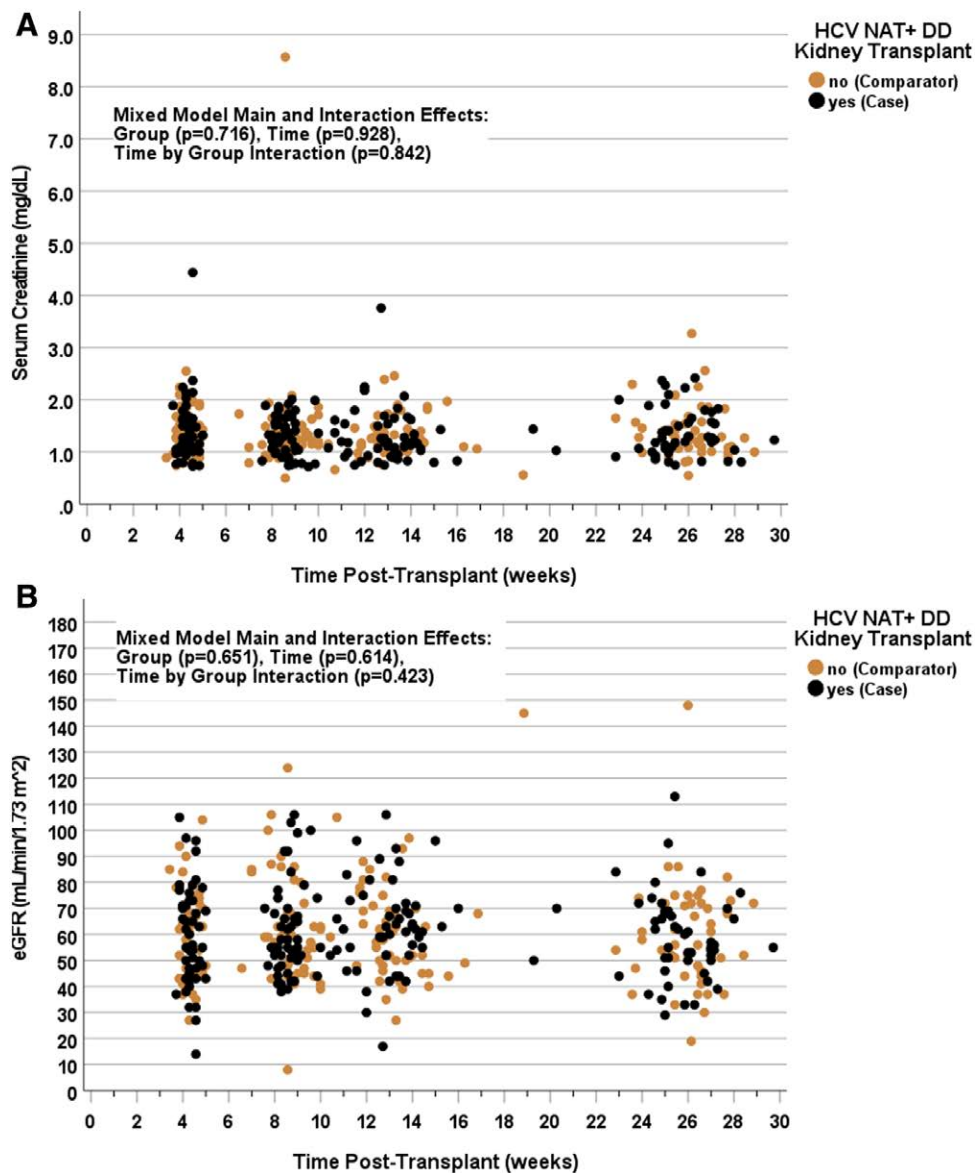
FIGURE 1. Linear mixed-effects models of longitudinal serum creatinine (A) and eGFR (B). DD, deceased donor; eGFR, estimated glomerular filtration rate; HCV, hepatitis C virus; NAT+, nucleic acid test positive.

HCV+ Characteristics and Treatment

All cases developed HCV viremia after receiving an HCV+ kidney. Thirty-four (68%) were genotypes 1a, 1b, or 1a/1b, and 10 (20%) were genotype 3 (Table 5). All cases were able to access DAA posttransplant. HCV genotype and insurance approval dictated the choice of DAA prescribed. The mean time from transplant to DAA initiation (first dose) was 29 ± 11 d. All cases were prescribed and completed a 12-wk course of DAA, and 30 (60%) received glecaprevir/pibrentasvir. The HCV viral load measurements before and after initiation of DAA treatment are shown in Figure 2. The sustained virologic response rate at 4 wks (SVR-4) and SVR-12 among cases after the first course of DAA was 98%. One patient who was infected with HCV genotype 1a and was initially treated with ledipasvir/sofosbuvir did not achieve SVR-4 nor SVR-12 and was retreated with a 12-wk course of sofosbuvir/velpatasvir/voxilaprevir with subsequent SVR-12. Viral resistance testing was not performed in this patient, and there was no suspicion for medication nonadherence or drug interactions that could

have led to subtherapeutic DAA levels. There were no adverse events among the cohort that required cessation of DAA therapy. There were no cases of fibrosing cholestatic hepatitis.

DISCUSSION

In this study, we report excellent short-term outcomes of HCV D+/R− kidney transplantation performed with delayed DAA initiation at a single center. The rates of acute rejection, infectious complications, and readmissions among HCV D+/R− recipients were not different compared with well-matched HCV D−/R− comparators. There was also no difference in the longitudinal trajectory of kidney function up to 180 d posttransplant between the 2 groups. Mean SCr at 180 d posttransplant in the HCV D+/R− group was 1.4 mg/dl (eGFR of 58 mL/min/1.73m2), although 1 patient lost the graft because of a severe acute rejection unresponsive to therapy at 151 d posttransplant. Ninety-eight percent of HCV D+/R− recipients were cured of HCV with the

Readmissions among hepatitis C virus positive recipients within 90 d posttransplant

Readmission characteristics	Frequency, median, or mean	
Number of readmissions per recipient		
0	25 (50%)	
1	19 (38%)	
2	4 (8%)	
3	1 (2%)	
4	1 (2%)	
Mean total length of stay per patient across all readmissions, d (N = 25 patients)	8.20 (7.73)	
Median total length of stay per patient across all readmissions, d (N = 25 patients)	6.00 (2.50, 10.00)	
Mean length of stay per readmission per patient, d (N = 25 patients)	5.90 (4.58)	
Median length of stay per readmission per patient, d (N = 25 patients)	6.00 (2.50, 7.54)	
Noninfectious causes[a]	No. of readmissions	No. of patients
• Acute rejection	3	3
• Surgical	3	3
• Other	16	12
Infectious causes[a]	No. of readmissions (n = 17)	No. of patients (n = 15)
• Genitourinary (urinary tract infection, pyelonephritis, urosepsis)	6	6
• Pneumonia	3	3
• Clostridium difficile	3	3
• Bacteremia/sepsis (nongenitourinary)	2	2
• Wound infection/complication	2	2
• Cytomegalovirus viremia	1	1
• Herpes simplex virus esophagitis	1	1
• Viral gastroenteritis	1	1
• Diverticulitis	1	1
• Mycobacterium tuberculosis	1	1
• Septic arthritis	1	1

Table entries are mean (SD), median (lower quartile, upper quartile), or frequency (%).
[a]Not mutually exclusive.

first 12-wk course of DAA therapy initiated approximately a month after transplant.

Excellent HCV cure rates of 98%–100% have similarly been reported in previously published studies of HCV ± kidney transplantation utilizing various DAA regimens, regardless of timing of DAA initiation.[9-11,18-20] In our study, the 1 patient who did not achieve SVR-12 was retreated with a

second course of DAA and ultimately achieved SVR-12. The reason for failure to achieve SVR-12 in this patient with the first course of DAA is unclear, although no resistance testing was performed.

Compared with the experience of Molnar et al[18,20] and Kapila et al,[19] which utilized a similar practice to ours in that insurance approval was required before the initiation of DAA therapy, our recipients initiated DAA therapy earlier (median of 26 d versus 76 d and 72 d, respectively). This difference may be reflective of the extensive experience of our center's specialty pharmacy team in navigating the insurance approval process for DAA therapy. This hypothesis is supported by the report of Molnar et al[20] wherein their time to DAA initiation decreased significantly over the course of calendar year 2018 and is at 3–4 wks currently, suggesting that greater experience with the DAA approval process can reduce delays.

In comparing posttransplant kidney function to previously published studies, the eGFR at 6-mo posttransplant in our HCV cohort is similar to that reported in the MYTHIC trial[16] wherein median eGFR was 57 mL/min at 6 mo posttransplant. However, this is slightly lower than what was reported in the THINKER trial[9] wherein median eGFR was 67.5 mL/min/1.73m2 at 6 mo posttransplant and in the study by Molnar et al[18] wherein mean eGFR was 67 mL/min/1.73m2 12 wks after completion of DAA treatment. The published data on 12-mo kidney function after HCV D+/R− transplantation remain reassuring. Molnar et al reported a 12-mo posttransplant mean eGFR of 64 mL/min/1.73m2 in their cohort and this was not statistically different from recipients at their center who received kidneys from HCV− donors in the same calendar year.[20] Similarly, a study by Potluri et al[23] of US registry data from 2015 to 2019 found that 1-y eGFR of aviremic recipients of HCV viremic kidneys was similar to matched recipients of HCV aviremic kidneys (66 versus 67 mL/min/1.73m2).

It has been postulated that sustained HCV viremia results in an inflammatory milieu and could increase the risk of acute rejection.[21] Similar to Molnar et al in which HCV D+/R− transplantation was performed with delayed DAA initiation, we observed a 10% acute rejection rate at 180 d posttransplant (5 acute rejection episodes) in our HCV cohort including 1 recipient who lost the allograft. Molnar et al reported a 7.5% acute rejection rate (4 acute rejection episodes).[18] The 12-mo follow-up data on their cohort did not find any difference in acute rejection rates or development of de novo donor specific antibodies between recipients of kidneys from HCV+ donors and recipients of HCV− donors who were transplanted during

Acute rejection among HCV+ recipients within 180 d posttransplant

Patient ID	Posttransplant d	Pretransplant cPRA (%)	Type(s) of rejection	C4d	DSA	Treatment(s)	SCr (eGFR) at 180 d posttransplant
1	47	0	Acute cellular and acute humoral	Yes	No	Steroids, rituximab, IVIG	2.3 (29)
2	89	3	Acute vascular and acute humoral	No	No	rATG, steroids, PLEX, rituximab, IVIG	Allograft loss
3	12	0	Acute humoral and chronic active AMR	No	Yes	Rituximab, IVIG	0.9 (84)
4	75	27	Acute cellular and acute humoral	Yes	Yes	Steroids, PLEX, rituximab, IVIG	2.4 (35)
5	154	0	Acute cellular and acute vascular	Yes	No	rATG, steroids	1.8 (50)
1	127	0	Acute cellular	No	No	Steroids	2.3 (29)
2	118	3	Acute humoral and chronic active AMR	Yes	No	Steroids, PLEX, IVIG	Allograft loss

AMR, antibody-mediated rejection; cPRA, calculated panel-reactive antibody; DSA, donor specific antibody; eGFR, estimated glomerular filtration rate; HCV+, hepatitis C viremic; IVIG, intravenous immunoglobin; PLEX, plasma exchange; rATG, rabbit antithymocyte globulin; SCr, serum creatinine.
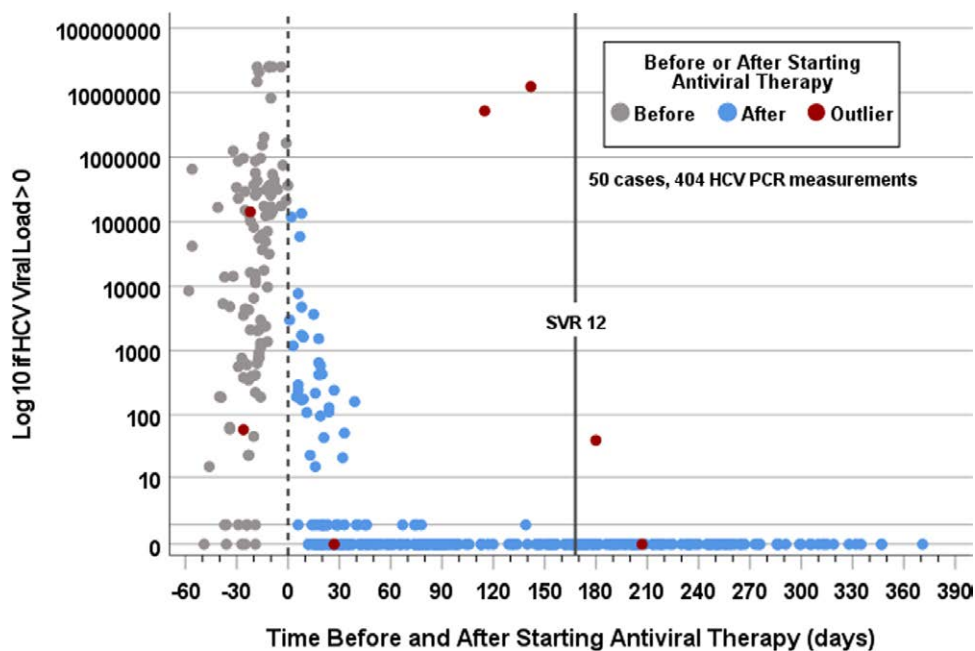
FIGURE 2. Scatter plot of HCV PCR measurements. HCV, hepatitis C virus; PCR, polymerase chain reaction; SVR-12, sustained virologic response at 12 wks.

the same calendar year.[20] Interestingly, despite initiation of DAA on posttransplant days 2–5 in the MYTHIC trial, a similar 10% acute rejection rate was observed.[16] Importantly, in comparing the acute rejection rate of our HCV cohort to our matched-comparator group, we did not detect any difference. We thus believe that our findings with regard to the risk of acute rejection are reassuring.

Overall, we believe that our study's findings provide additional data to inform transplant providers and patients as they weigh the risks and benefits of HCV D+/R– kidney transplantation with delayed DAA initiation. Until a more ideal scenario is achieved wherein preemptive or early initiation of DAA is covered by insurance, we believe that the risks of adverse outcomes such as those we examined here must be weighed against the potential benefits of increasing organ utilization and access to transplantation, shortening patient waiting times for a deceased donor transplant, and

ultimately improving patient survival. Although the probability of discard of HCV viremic kidneys in the United States has decreased over time,[23,24] Chang et al showed that in 2019, HCV viremic kidneys still had 48% higher odds of discard compared with aviremic kidneys.[24]

Our study's findings can also provide reassurance to transplant programs and providers with regard to concerns regarding difficulty in obtaining DAA therapy approval from insurance and the risk of transmitting resistant infection. In a 2020 survey of US kidney transplant programs by Lentine et al explored transplant practices related to the use of HCV-infected donors.[25] One hundred twelve responded, representing 54% of programs in the United States, and the study found that 58% of programs offer HCV D+/R– kidney transplantation: 35% under clinical protocols, 14% as standard of care, and 9% under research protocols. Fifty-three percent of respondents start DAA after discharge and documented viremia. Notably, 72% of respondents expressed concern regarding insurance coverage, whereas 44% were concerned about transmitting resistant infection. In our study, all patients were able to access DAA and although 1 patient did not achieve SVR-12 with the first course of DAA therapy, he was cured with a second DAA course.

The strength of our study is that it is the first real-world setting study to use matched comparators to assess important outcomes with granular data provided. Our experience is an important addition to the literature due to the limited data[18-20] on the outcomes of this practice that is currently available. The limitations of the study are the relatively short follow-up period and assessment limited to short-term outcomes. Although our study had a relatively large sample size compared with other published cohorts, the number of patients remains small. Our study did not examine BK virus and cytomegalovirus outcomes as these are being reported as part of a multicenter study. We did not elaborate on outcomes related to access to DAA therapy and associated costs as it was beyond the scope of our study.

TABLE 5.

HCV+ characteristics and treatment

HCV characteristics and treatment		N = 50
HCV genotype	1a	30 (60%)
	1a/1b	2 (4%)
	1b	2 (4%)
	2	6 (12%)
	3	10 (20%)
Mean time to initiation of DAA, d		29 (11)
Median time to initiation of DAA, d		26 (21, 37)
DAA treatment regimen[a]	Glecaprevir/pibrentasvir	30 (60%)
	Ledipasvir/sofosbuvir	13 (26%)
	Sofosbuvir/velpatasvir	7 (14%)
SVR	4 wks (SVR-4)	49 (98%)
	12 wks (SVR-12)	49 (98%)

Table entries are mean (SD), median (lower quartile, upper quartile), or frequency (%).
[a]12-wk treatment regimen (first course).
DAA, direct-acting antiviral; HCV, hepatitis C virus; SVR, sustained virologic response.

Future multicenter prospective studies with larger numbers of participants are needed to examine longer-term outcomes, to compare outcomes among the different approaches to DAA initiation (preemptive versus early versus delayed), and to examine other potential approaches to the real-world practice of HCV D+/R− transplantation, such as the use of short-term prophylaxis to prevent HCV transmission.[12,26] Finally, as stated earlier, we recognize that a vastly improved real-world scenario would be for third-party payers to approve DAA therapy pretransplant especially since HCV D+/R− kidney transplantation has already been demonstrated to be a cost-effective approach.[27-29] However, until this scenario becomes common practice, our experience and the findings of this study remain relevant.

In conclusion, aviremic recipients of HCV+ kidneys with delayed DAA initiation had comparable short-term outcomes compared with HCV− matched comparators. Our data suggest that this practice is reasonable, at least until a more ideal scenario is achieved in the real world.

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