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Real-world Experiences in the Transplantation of Hepatitis C-NAAT–positive Organs

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Background. Hepatitis C virus (HCV) nucleic acid amplification test (NAAT)–positive donors have increased the organ pool. Direct-acting antivirals (DAAs) have led to high rates of treatment success and sustained virologic response (SVR) in recipients with donor-derived HCV infection without significant adverse effects, although variability remains in the timing and duration of antivirals. **Methods.** This retrospective study analyzed all adult HCV-NAAT–negative transplant recipients who received an organ from HCV-NAAT–positive donors from November 24, 2018, to March 31, 2022, at Duke University Medical Center with protocolized delay of DAA initiation until after hospital discharge, with at least 180-d follow-up on all patients. Transplant and HCV-related outcomes were analyzed. **Results.** Two hundred eleven transplants (111 kidneys, 41 livers, 34 hearts, and 25 lungs) were performed from HCV-NAAT–positive donors to HCV-NAAT–negative recipients. Ninety percent of recipients became viremic within 7 d posttransplant. Ninety-nine percent of recipients were initiated on pangenotypic DAAs in the outpatient setting a median of 52 d posttransplant, most commonly with 12-wk courses of sofosbuvir–velpatasvir (lungs) and glecaprevir–pibrentasvir (heart, kidney, and liver). Ninety-seven percent of recipients had SVR after a first-line DAA; all ultimately achieved SVR at 12 wk after subsequent treatment courses. The median peak HCV RNA for all organ systems was 2 436 512 IU/mL; the median time from antiviral to undetectable RNA was 48 d, although differences were noted between organ groups. No patient deaths or graft losses were directly attributable to HCV infection. **Conclusions.** One hundred percent of transplant recipients of HCV-NAAT–positive organs ultimately developed SVR without significant adverse effects when HCV antivirals were initiated in the outpatient setting after transplant hospitalization, suggesting that this real-world treatment pathway is a viable option.

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The need for life-saving organs has long exceeded organ availability in transplantation, with >100 000 candidates currently on transplant waitlists.[1] Many remain waiting for years, dependent on hemodialysis or other life-sustaining measures, significantly compromising their quality of life and longevity.

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The transplantation of organs from hepatitis C virus (HCV) nucleic acid amplification test (NAAT)–positive donors was previously not an option because of the absence of effective and tolerable antivirals safe for use in transplantation.[2] However, well-tolerated pangenotypic direct-acting antivirals (DAAs) are now available, curing disease in >95% of patients.[3-5] With this, the use of organs from HCV-NAAT–positive donors for HCV-negative recipients has become a common practice in transplant medicine.

However, significant interinstitutional differences remain regarding the timing and duration of DAAs in relation to transplantation, particularly whether DAAs are initiated during the index hospitalization (prophylactically/preemptively) or delayed until after the transplant hospitalization discharge.[6-9] Timing of therapy has important logistical and financial ramifications and has a conflicting impact on clinical outcomes depending on the clinical study.[8,10-12] We present data from a single major transplant center describing our real-world experience with HCV-NAAT–positive organ transplantation to HCV-negative recipients across multiple organ programs with protocolized delay in DAA initiation until after transplant hospitalization discharge.

MATERIALS AND METHODS

This retrospective study analyzed all adult HCV-NAAT–negative transplant recipients who received an organ from an HCV-NAAT–positive donor from November 24, 2018, to March 31, 2022, at Duke University Medical Center in Durham, NC. Patients were followed for a minimum of 180 d posttransplant. The study was reviewed by the institutional review board of Duke University (Pro00112835). Donor and recipient transplant demographics were collected, along with HCV treatment (including initiation timing, treatment response, insurance payers), and clinical outcomes (including mortality, cytomegalovirus [CMV] DNAemia, and allograft rejection).

To safely facilitate HCV-NAAT–positive transplantation, we developed an institutional protocol, starting with institutional review board–approved consent of recipients pretransplant for use of organs from HCV-NAAT–positive donors (**Figure S1, SDC,** http://links.lww.com/TXD/A577). Induction and maintenance immunosuppression regimens were chosen based on standard institutional criteria and were not altered because of use of an HCV-NAAT–positive organ. The Transplant Infectious Diseases (kidney and lung recipients) or Transplant Hepatology (liver or heart recipients) team was consulted during the index transplant hospitalization, and regular liver function tests (LFTs) were performed on recipients. HCV quantitative ribonucleic acid (RNA) polymerase chain reaction (PCR) testing (Roche Taqman until September 15, 2022; transitioned to Abbott Alinity because of instrument discontinuation) was obtained on posttransplant days 5, 10, and 21, then every 2 wk until the end of posttransplant month 2 or until 2 consecutive HCV RNAs were documented >500 IU/mL. At our medical center, the HCV RNA upper limit of quantification (LOQ) is >100 000 000 IU/mL. For analysis in this article, all values ≥100 000 000 IU/mL were recorded as 100 000 000 IU/mL. HCV genotype was ordered before index hospital discharge to ensure results were available by the first outpatient visit. After transplant hospitalization discharge, recipients followed up in Transplant Hepatology or Transplant Infectious Diseases clinic. A dedicated pharmacy team was created for DAA medication review and approval—patients received initiation counseling and biweekly phone calls with a pharmacist while on antivirals. If insurance declined to cover the required DAA, the hospital transplant center administration was appealed to cover the cost.

Descriptive statistical analyses and figure generation were performed by RStudio version 1.2.5019 and GraphPad Prism version 9.5.1, using the Mann-Whitney *U* test for continuous data and the chi-square test for categorical data. The Kruskal-Wallis test was used to assess for significant differences between a continuous dependent variable and a categorical independent variable. Peak HCV RNA and time to virologic suppression were compared using Spearman correlation. A 2-sided *P* value of <0.05 was considered statistically significant.

RESULTS

HCV Kinetics and Outcomes

Two hundred eleven solid organ transplants were performed from HCV-NAAT–positive donors to HCV-NAAT–negative recipients during the study period (111 kidneys, 41 livers, 34 hearts, and 25 lungs). Full transplant demographics are listed in Table 1. Almost all recipients (90%) became viremic within 7 d posttransplant (Figure 1). Among all organs, the median peak RNA was 2 436 512 IU/mL (interquartile range [IQR], 535 690–18 502 354; Figure 2), and the median time from transplant to antiviral initiation was 52 d (IQR, 35–78). The overall median time from DAA prior authorization initiation to approval was 1 d (IQR, 0–4) with a median of 9 d (IQR, 5–15) between prior authorization approval and medication start. Twelve recipients required further appeal for financial coverage. Eight recipients started DAAs through the Veterans Affairs Medical System, in which additional prior authorization was not required.

Only 3 organ recipients were started on HCV therapy as an inpatient: 1 lung recipient at 137 d posttransplant owing to a prolonged transplant admission, 1 lung recipient at 27 d posttransplant due to concerns that acute HCV was contributing to severe refractory immune thrombocytopenic purpura, and 1 heart-lung recipient at 27 d posttransplant due to persistently elevated alanine aminotransferase/aspartate aminotransferase and alkaline phosphatase (although <3 times the upper limit of normal). The median time from antiviral initiation to undetectable HCV RNA was 48 d across all organs (IQR, 33–78), noting some provider variability in testing. Full HCV data are outlined in Table 2. Notably, 11 patients (5 kidney and 6 heart recipients) had peak RNA levels above the upper LOQ; there was a significant positive correlation between peak HCV RNA and time to virologic suppression in kidney recipients ($\rho = 0.348$, $P = 0.0002$; Figure 3A) but not in heart recipients ($\rho = 0.142$, $P = 0.43$; Figure 3B).

HCV genotype 1a was the most common in all transplant groups (123; 58%), followed by genotypes 3 (53; 25%), 2 (22; 10%), 1b (7; 3%), and 4 (3; 1%). One kidney, 1 lung, and 1 heart transplant recipient never developed detectable HCV RNA, despite receiving organs from donors who were both HCV antibody positive and NAAT positive; these patients were never started on antiviral therapy. The heart recipient was newly HCV antibody reactive at 2 and 10 d posttransplant, although remained PCR negative, and was HCV

TABLE 1.

Transplant demographics

Demographics	Total (N = 211)	Kidney (N = 111)	Liver (N = 41)	Heart (N = 34)	Lung (N = 25)
Recipient age (at transplant), y, median (IQR)	57 (48–65)	57 (48–66)	58 (48–64)	57 (50–62)	52 (43–59)
Recipient male sex, n (%)	123 (58)	70 (63)	22 (54)	22 (65)	9 (36)
Donor age, y, median (IQR)	36 (30–43)	36 (30–46)	36 (31–43)	34 (30–38)	32 (29–36)
Donor male sex, n (%)	131 (62)	68 (72)	24 (59)	26 (76)	13 (52)
Donor PWID, n (%)	167 (79)	78 (83)	36 (88)	32 (94)	21 (84)
Prior transplant, n (%)	16 (8)	13 (12)	1 (2)	0 (0)	2 (8)
Dual transplant, n (%)	30 (14)	10 (9)	10 (24)	6 (18)	4 (16)
Heart + kidney		2	NA	2	NA
Lung + kidney		1	NA	NA	1
Liver + kidney		7	7	NA	NA
Heart + liver		NA	2	2	NA
Liver + lung		NA	1	NA	1
Heart + lung		NA	NA	2	2
Time on waitlist, d, median (IQR)	160 (27–530)	1079 (713–1580)	91 (19–196)	51 (13–142)	20 (11–38)
Induction immunosuppression, n (%)					
Alemtuzumab	6 (3)	6 (6)	0 (0)	0 (0)	0 (0)
Basiliximab	59 (28)	3 (1)	0 (0)	32 (94)	24 (96)
Steroids only	98 (46)	57 (51)	41 (100)	0 (0)	0 (0)
Thymoglobulin	44 (21)	44 (28)	0 (0)	0 (0)	0 (0)
Other[a]	2 (1)	1 (1)	0 (0)	0 (0)	1 (4)
None	2	0 (0)	0 (0)	2 (6)	0 (0)
Cold ischemic time, min, median (IQR)	600 (307–1355)	1303 (1268–1688)	310 (251–369)	179 (143–222)	387 (326–485)
Time from transplant to index hospital discharge, d, median (IQR)	8 (5–16)	5 (4–7)	11 (7–14)	20 (11–31)	26 (17–56)
Insurance type, n (%)					
Commercial	83 (39)	39 (35)	20 (49)	10 (29)	14 (56)
Medicaid	27 (13)	10 (9)	8 (20)	8 (24)	1 (4)
Medicare	76 (36)	41 (37)	12 (29)	15 (44)	8 (32)
Other	25 (12)	21 (19)	1 (2)	1 (3)	2 (8)

[a]Other immunosuppression: thymoglobulin, belatacept, and carfilzomib (lung) or basiliximab, steroids, and thymoglobulin (kidney).
IQR, interquartile range; NA, not available; PWID, person who injects drugs.

antibody negative again at 1 y posttransplant. This could suggest false positive recipient antibody testing, potentially due to the left ventricular device in place before transplant.[13,14] However, published literature also reports that early posttransplant anti-HCV antibodies in similar circumstances may be donor-derived, although can resolve over time.[15] The lung and kidney recipients did not have HCV antibody testing performed posttransplant.

Antiviral regimens were well tolerated; no patients required a change or cessation of antiviral therapy because of adverse medication effects. In heart, kidney, and liver recipients, the most regularly chosen antiviral was glecaprevir–pibrentasvir, followed by sofosbuvir–velpatasvir, then ledipasvir–sofosbuvir. Lung transplant recipients were most frequently treated with sofosbuvir–velpatasvir because of concerns about pill burden in the setting of difficulty swallowing and azole medication interactions (more common in this organ population). All recipients were initially treated with a 12-wk antiviral course, irrespective of DAA, except 5 heart recipients who were initially treated with 8 wk of glecaprevir–pibrentasvir.

Three kidney transplant recipients experienced recurrent detectable HCV RNA after a 12-wk first-line antiviral course and documented undetectable RNA at the end of therapy—1 after initial treatment with glecaprevir–pibrentasvir and 2 after sofosbuvir–velpatasvir. Two of these required second-line treatment with sofosbuvir–velpatasvir–voxilaprevir for 12 wk, and 1 was treated with sofosbuvir–velpatasvir–voxilaprevir with ribavirin for 24 wk. After a 12-wk sofosbuvir–velpatasvir–voxilaprevir course, 1 patient required third-line therapy with sofosbuvir, glecaprevir–pibrentasvir, and ribavirin for 24 mo. One kidney recipient with an initial HCV RNA of >100 000 000 IU/mL did not have a significant response to the first 4 wk of glecaprevir–pibrentasvir—this patient was transitioned to sofosbuvir–velpatasvir–voxilaprevir for a 24-wk course with good treatment response. The details of these treatment failures are outlined in a separate article, with potential contributions from bariatric surgery impacting absorption, and DAA medication interaction.[16] One lung transplant recipient with questionable medication adherence experienced recurrent detectable HCV RNA after a 12-wk course of sofosbuvir–velpatasvir, possibly due to a DAA drug interaction (acid suppressant), treated with 12 wk of sofosbuvir–velpatasvir–voxilaprevir. One heart transplant recipient had persistently detectable HCV RNA (less than the lower LOQ) after 8 wk of glecaprevir–pibrentasvir and treatment was extended for 6 more weeks for a total of 14 wk. All initial treatment failures eventually achieved sustained virologic response (SVR) at 12 wk (SVR12).

All organ systems saw some degree of liver injury during the interval between transplant and DAA initiation, although no long-term hepatic complications were observed. Although many transplant recipients experienced LFT elevation acutely posttransplant, most of these patients had LFT normalization before DAA initiation (Table 2). In one example, 98% of liver transplant recipients had evidence of alanine aminotransferase/aspartate aminotransferase elevation 3 times the upper

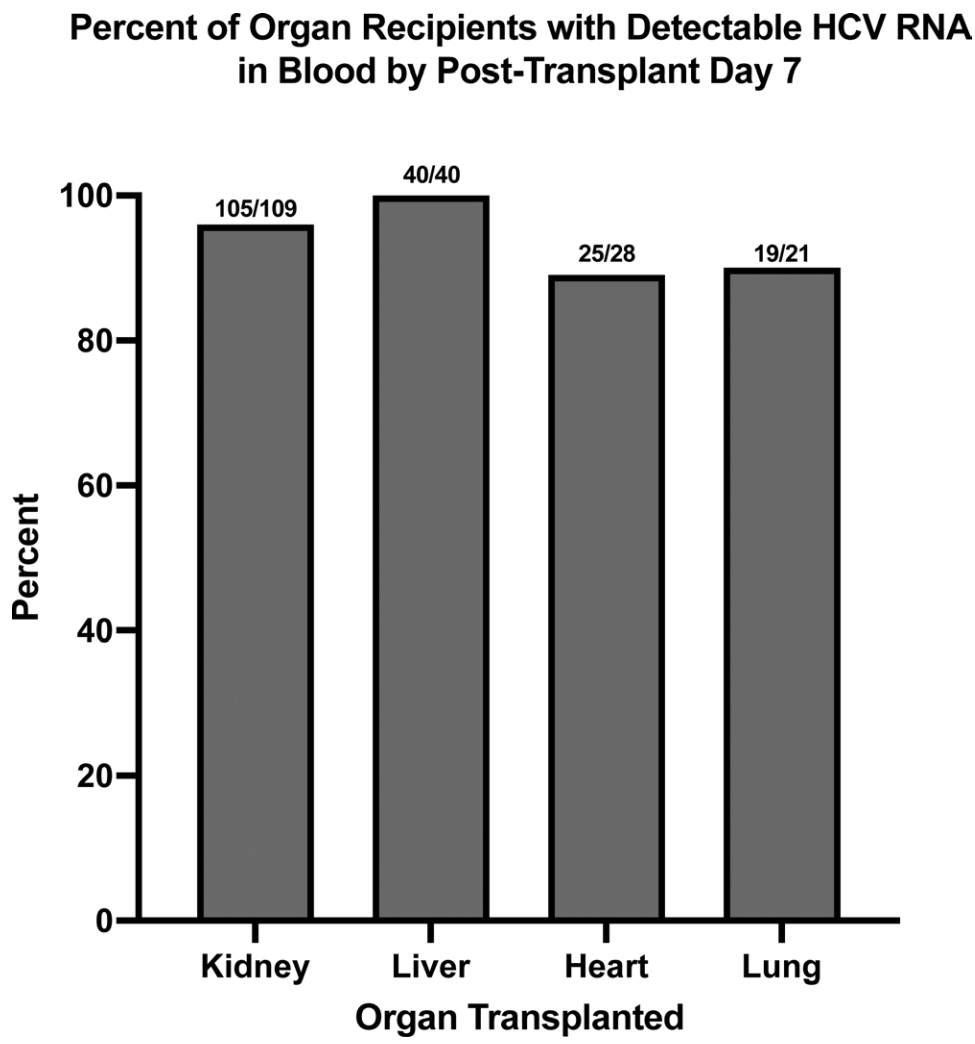

FIGURE 1. The percent of transplant recipients of each organ system that had a detectable HCV RNA within the first 7 d from transplantation. HCV, hepatitis C virus; RNA, ribonucleic acid.

limit of normal in the acute posttransplant period, but only 17% of total recipients had abnormal LFTs that persisted until DAA initiation, suggesting the potential role of HCV infection impacting the liver injury only in this subset of recipients.

Organ-specific Outcomes

Kidney

During the 3.5-y study period, 111 kidney transplants were performed on HCV-NAAT–negative recipients from 94 HCV-NAAT–positive donors. End-stage renal disease was due to a variety of etiologies, most commonly diabetes, hypertension, and polycystic kidney disease. Kidney transplant recipients spent a median of 1079 d on the transplant waitlist (IQR, 714–1580). This was comparative to the waitlist time for recipients from HCV-negative donors at 1107 d (IQR, 484–1934; $P=0.46$) for the same period. HCV-NAAT–positive donors were predominantly male with a median age of 36 y (IQR, 30–43)—not significantly different from the median age of HCV-NAAT–negative kidney donors at our center during this period (38 y; IQR, 28–49; $P=0.88$). The most common cause of donor death was anoxia from opioid overdose (60%; 56 of 94); 83% of donors were identified as a person who injects drugs (PWID). Three donors were both HCV- and HIV-NAAT positive, transplanted to HIV-infected recipients. The median Kidney Donor Profile Index in HCV-NAAT–positive donors was 65% (IQR, 50–76), higher than in HCV-NAAT–negative donors (median 46%; IQR, 25–66; $P<0.0001$), acknowledging that donor HCV status is included in Kidney Donor Profile Index calculations. Induction immunosuppression varied on the basis of recipient and transplant characteristics; steroid induction was most common (51%). Maintenance immunosuppression typically consisted of a calcineurin inhibitor, antimetabolite, and steroid. The exceptions to this were 6 recipients (6%) who received alemtuzumab induction and for whom maintenance immunosuppression consisted of sirolimus and belatacept. There was no significant difference in peak HCV RNA ($P=0.50$) or time to HCV clearance ($P=0.47$) based on the type of induction immunosuppression in kidney transplant recipients.

Kidney recipients reached a median peak HCV RNA of 826 993 IU/mL (IQR, 226 100–5 847 256). DAAs were initiated at a median of 37 d (IQR, 29–50) posttransplant, and HCV RNA was first undetectable at a median of 40 d (IQR, 27–66) postantiviral initiation.

Liver

During the study period, 41 liver transplants were performed from HCV-NAAT–positive donors. End-stage liver disease

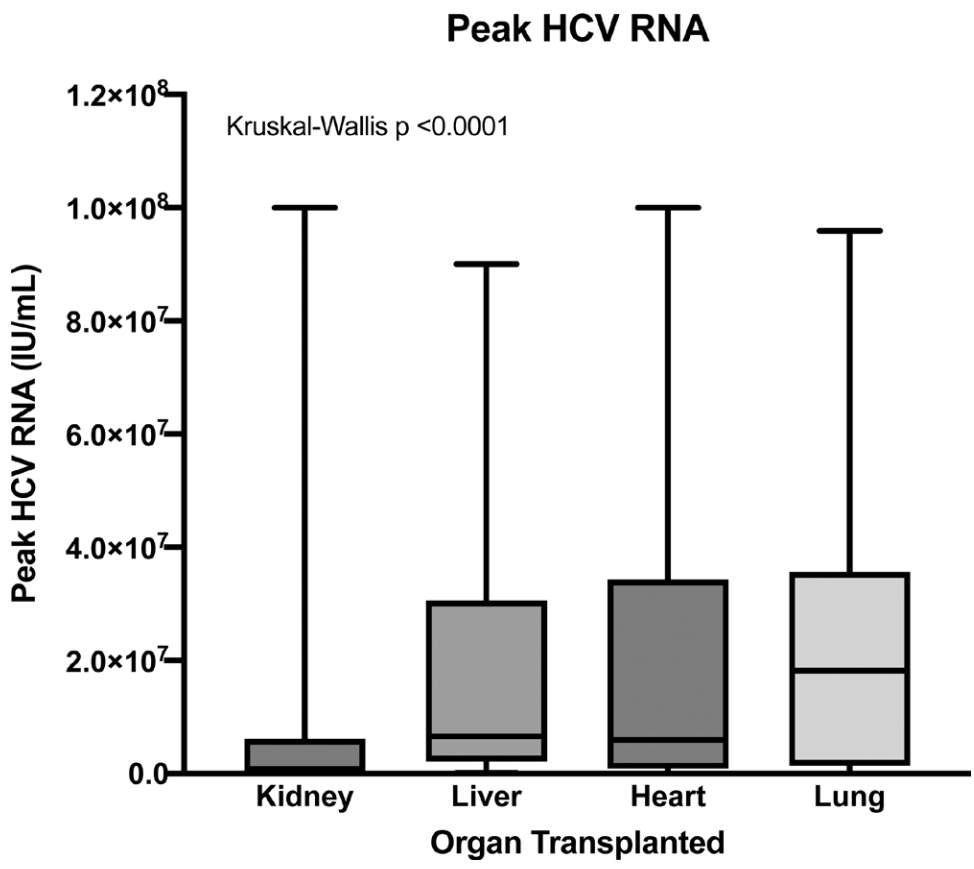

FIGURE 2. The peak HCV RNA (in IU/mL) of transplant recipients for each organ system. The upper and lower borders of the boxes represent to the third quartile and the first quartile, respectively. The lines through the boxes represent to the median. The top and bottom whiskers represent to the maximum and minimum values in the data set. HCV, hepatitis C virus; RNA, ribonucleic acid.

was most commonly due to hepatosteatosis or alcohol. HCV-NAAT–positive donors were predominantly male with a median age of 36 y (IQR, 31–43)—not significantly different from the median age of HCV-NAAT–negative liver donors at our center during this period (41 y; IQR, 27–52; $P = 0.11$). The most common cause of donor death was anoxia from an opioid overdose (73%; 30 of 41); 88% of donors were identified as PWIDs. All liver transplantations were performed with methylprednisolone induction. Maintenance immunosuppression typically consisted of tacrolimus, mycophenolate mofetil, and prednisone.

Liver transplant recipients spent a median of 91 d on the transplant waitlist (IQR, 19–196). This was comparative to the waitlist time for recipients from HCV-negative donors at 75 d (IQR, 18–192; $P = 0.61$) for the same period. The median of the model for end-stage liver disease score at the time of transplant was 24 (IQR, 21–27). This is higher than the model for end-stage liver disease score of non-HCV liver transplant recipients during this period at our center (median 17; IQR, 13–23)—this difference was statistically significant ($P < 0.0001$). Transplant recipients reached a median peak HCV RNA of 6 622 720 IU/mL (IQR, 2 436 512–30 545 497). DAAs were initiated at a median of 76 d (IQR, 63–98) post-transplant, and HCV RNA was first undetectable at a median of 55 d (IQR, 33–89) postantiviral initiation.

Heart

During the study period, 34 heart transplants were performed from HCV-NAAT–positive donors. Advanced heart failure was due to a variety of causess, most commonly ischemic or idiopathic cardiomyopathy. HCV-NAAT–positive donors were predominantly male with a median age of 34 y (IQR, 30–38)—older than the median age of HCV-negative heart donors at our center during this period (30 y; IQR, 25–36; $P = 0.01$). The most common cause of donor death was anoxia from opioid overdose (74%; 25 of 34); 94% of donors were identified as PWIDs. The majority of cardiac transplantations were performed with basiliximab induction. Maintenance immunosuppression typically consisted of tacrolimus, mycophenolate mofetil, and prednisone.

Heart transplant recipients spent a median of 51 d (IQR, 13–142) on the transplant waitlist. This was longer than the waitlist time for recipients from HCV-negative donors at 17 d (IQR, 6–75; $P = 0.009$) for the same period. The median heart status at the time of transplant was 3 (mean 2.92; IQR, 2–4). This is similar to that of non-HCV heart transplants during this same period at our center (median 3; mean 3.18; IQR, 2–4; $P = 0.51$). Transplant recipients reached a median peak HCV RNA of 5 800 000 IU/mL (IQR, 944 360–35 391 815). DAAs were initiated at a median of 97 d (IQR, 71–155) post-transplant, and HCV RNA was first undetectable at a median of 59 d (IQR, 38–86) postantiviral initiation.

Lung

During the study period, 25 lung transplants were performed from 25 HCV-NAAT–positive donors. End-stage pulmonary disease was most commonly due to interstitial lung disease or chronic obstructive pulmonary disease. HCV-NAAT–positive donors were predominantly male with a median age of 32 y

TABLE 2.

HCV transplant data

HCV clinical outcomes	Total (N = 211)	Kidney (N = 111)	Liver (N = 41)	Heart (N = 34)	Lung (N = 25)	P[a]
HCV RNA detectable by POD 7, n (%)						
Yes	189 (90)	105 (95)	40 (98)	25 (74)	19 (76)	0.0002
No	9 (4)	4 (4)	0 (0)	3 (9)	2 (8)	0.45
Not checked	13 (6)	2 (2)	1 (2)	6 (18)	4 (16)	0.0002
Peak HCV RNA, IU/mL, median (IQR)	2 436 512 (535 690–18 502 354)	826 993 (226 100–5 847 256)	6 622 720 (2 436 512–30 545 497)	5 800 000 (944 360–35 391 815)	18 175 141 (1 536 673–34 064 003)	<0.0001
Time from transplant to DAA initiation, d, median (IQR)	52 (35–78)	37 (29–50)	76 (63–98)	97 (71–155)	60 (48–77)	<0.0001
Time from DAA initiation to undetectable HCV RNA, d, median (IQR)	48 (33–78)	40 (27–66)	55 (33–89)	59 (38–86)	79 (51–98)	0.0001
Never HCV viremic, n (%)	3 (1)	1 (1)	0 (0)	1 (3)	1 (4)	0.47
Genotypes, n (%)						
1a	123 (58)	63 (57)	23 (56)	20 (59)	17 (71)	0.64
1b	7 (3)	6 (5)	0 (0)	1 (3)	0 (0)	0.29
2	22 (10)	9 (8)	4 (10)	6 (18)	3 (12)	0.42
3	53 (25)	30 (27)	14 (34)	5 (15)	4 (16)	0.20
4	3 (1)	2 (2)	0 (0)	1 (3)	0 (0)	0.65
Time from prior authorization request to approval, d, median (IQR)	1 (0–4)	1 (0–3)	1 (1–5)	4 (0–9)	1 (0–4)	0.12
Time from prior authorization approval to DAA start, d, median (IQR)	9 (5–15)	8 (5–13)	10 (6–17)	13 (7–21)	9 (6–14)	0.03
First-line DAA regimen, n (%)						
Glecaprevir–pibrentasvir	136 (64)	73 (66)	31 (76)	24 (71)	8 (32)	0.003
Ledipasvir–sofosbuvir	17 (8)	10 (9)	4 (10)	1 (3)	2 (8)	0.68
Sofosbuvir–velpatasvir	54 (26)	27 (24)	6 (15)	7 (21)	14 (56)	0.002
None	3 (1)	1 (1)	0 (0)	1 (3)	1 (4)	0.47
Unknown[b]	1 (1)	0 (0)	0 (0)	1 (3)	0 (0)	0.16
DAA duration, n (%)						
0 wk[c]	3 (1)	1 (1)	0 (0)	1 (3)	1 (4)	0.47
8 wk	5 (2)	0 (0)	0 (100)	5 (15)	0 (0)	<0.0001
12 wk	203 (96)	110 (99)	41 (100)	27 (79)	24 (96)	<0.0001
Unknown[b]	1 (1)	0 (0)	0 (0)	1 (3)	0 (0)	0.15
Treatment failure after first-line DAA, n (%)	6 (3)	4 (4)	0 (0)	1 (3)	1 (4)	0.67
Second-line DAA regimen, N			NA			
Glecaprevir–pibrentasvir	1	0		1	0	
Sofosbuvir–velpatasvir–voxilaprevir	4	3		0	1	
Sofosbuvir–velpatasvir–voxilaprevir–ribavirin	1	1		0	0	
AST/ALT elevation to 3 times the ULN before DAA initiation, n (%)	78 (37)	12 (11)	40 (98)[d]	16 (47)	10 (40)	
Time to LFT normalization after DAA initiation, d, median (IQR)	–26 (–53 to –69)	2 (–20 to –11)	–64 (–45 to –90)	–72 (–136 to –7)	–20 (–65 to –9)	

[a]*P* value determined by comparison between the 4 organ systems (kidney, liver, heart, and lung).
[b]HCV managed locally (not at Duke); HCV regimen unclear.
[c]Not started on DAA as the recipient never became viremic.
[d]AST/ALT in all but 7 of these recipients (83%) resolved to standard range before DAA initiation. Of those liver transplant recipients in which AST/ALT elevation persisted, LFTs resolved a median of 17 d after DAA initiation.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; DAA, direct-acting antiviral; HCV, hepatitis C virus; IQR, interquartile range; LFT, liver function test; POD, postoperative day; RNA, ribonucleic acid; ULN, upper limit of normal.

(IQR, 29–36)—not significantly different from the median age of HCV-NAAT–negative lung donors at our center during this period (33 y; IQR, 25–45; $P = 0.68$). The most common cause of donor death was anoxia from opioid overdose (76%; 19 of 25); 84% of donors were identified as PWID. Most lung transplantations were performed with basiliximab and methylprednisolone induction, aside from 1 recipient who also required thymoglobulin, belatacept, and carfilzomib for HLA allosensitization. Maintenance immunosuppression typically consisted of tacrolimus, mycophenolate mofetil, and prednisone.

Lung transplant recipients spent a median of 20 d on the transplant waitlist (IQR, 11–38). This was longer than the waitlist time for recipients from HCV-negative donors at 12 d (IQR, 5–22; $P = 0.02$) during the same period. The median lung allocation score at the time of transplant was 38.3 (IQR, 35.3–54.5). This is lower than the median lung allocation score of non-HCV lung transplants during this same period at our center (median 42.7; IQR, 37.6–50.9; $P = 0.29$). Transplant recipients reached a median peak HCV RNA of 18 175 141 IU/mL (IQR, 1 536 673–34 064 003). DAAs were initiated at a median of 60 d (IQR, 48–77) posttransplant, and HCV RNA was first undetectable at a median of 79 d (IQR, 51–98) postantiviral initiation.

Other Outcomes: Mortality, Rejection, CMV, Graft Loss

Transplant outcomes are listed in Table 3. Six of 211 (3%) organ transplant recipients, including 1 kidney, 1 lung, 1 liver, and 3 heart transplant recipients, died within 1 y of transplantation. No deaths were directly attributable to HCV infection.

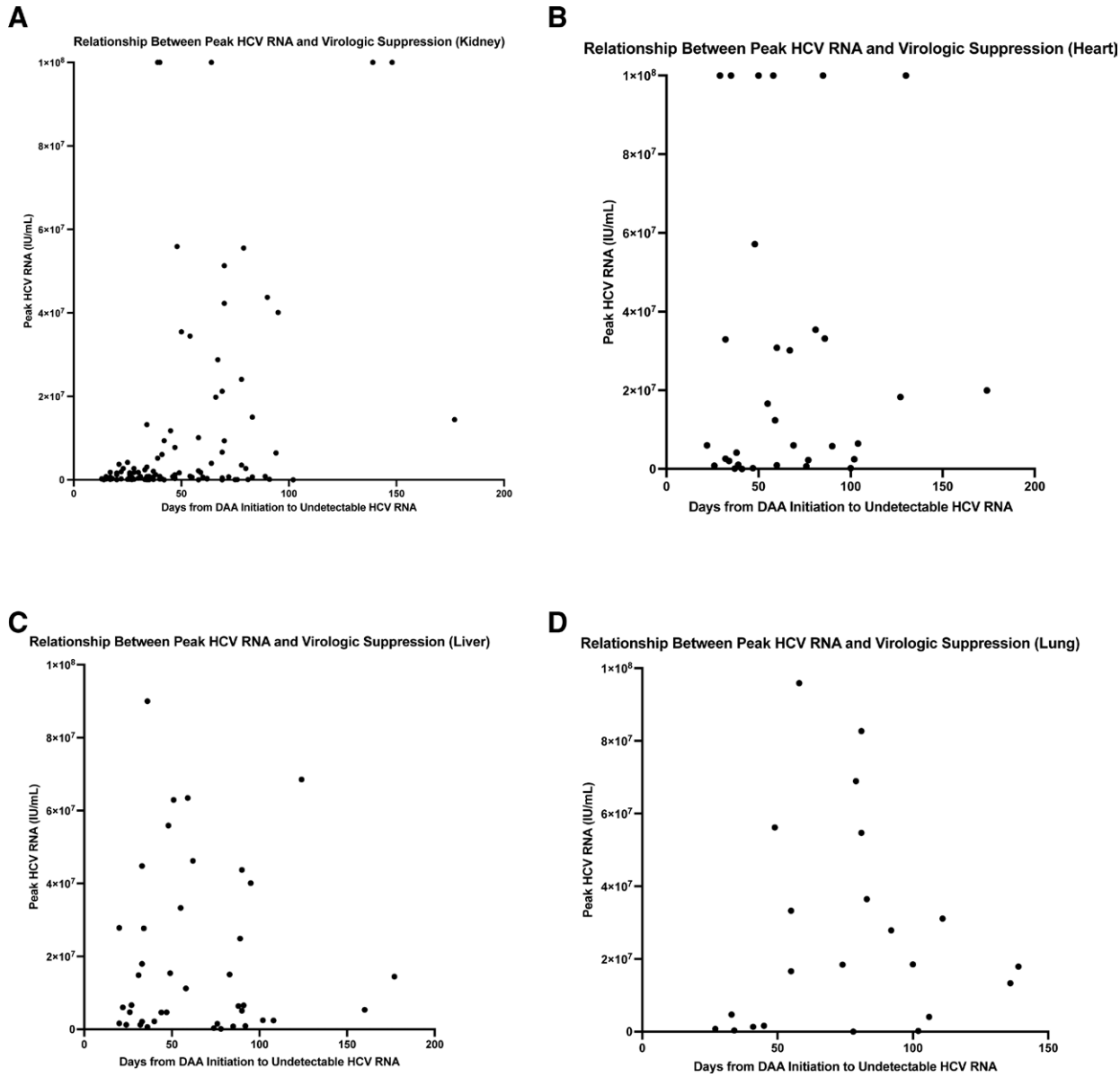

FIGURE 3. Scatterplots depicting the relationship between HCV peak RNA and time to undetectable HCV RNA after antiviral initiation in (A) kidney, (B) heart, (C) liver, and (D) heart transplant recipients. Days from antiviral initiation to undetectable HCV RNA are plotted on the x-axis, peak HCV RNA (in IU/mL) on the y-axis. DAA, direct-acting antiviral; HCV, hepatitis C virus; RNA, ribonucleic acid.

All recipients achieved undetectable HCV RNAs before death except one lung recipient who was never started on antivirals. No episodes of graft loss were directly attributable to HCV infection. One-year survival with a functioning graft was 95% in kidney transplants, 95% in livers, 85% in hearts, and 88% in lungs. This is in comparison with our institution's overall Scientific Registry of Transplant Recipients data, wherein the probability of 1-y survival with a functioning graft is reported as 94.5% in kidneys, 94.6% in livers, 95.6% in hearts, and 84.0% in lungs.[17-20] Small numbers preclude us from definitively understanding why this difference exists only in heart recipients, although it may potentially be due to organs initially being allocated to candidates with a more acute risk of waitlist mortality.

Twenty-six organ recipients (12%) developed biopsy-proven allograft rejection of sufficient severity to warrant treatment during the study period. Proportions of treated rejection were highest in the lung transplant recipients (44%), followed by heart, liver, and kidney recipients. One liver-kidney recipient developed rejection of both organs and 2 heart-kidney recipients had evidence of cardiac but no kidney allograft rejection. Rejection was most commonly treated with high-dose steroids. In comparison, institutional rejection rates within 12 mo of transplant in recipients of both HCV-positive and HCV-negative donors are 14% (kidney), 8% (liver), 29% (heart), and 50% to 60% (lung).

Twenty-one percent of transplant recipients had evidence of CMV DNA >200 IU/mL. CMV DNAemia proportions were similar between organ groups. CMV infection occurred most frequently in recipient-seropositive cases for all organ groups except the kidney, where CMV occurred most frequently in donor-seropositive/recipient-seronegative cases.

DISCUSSION

The use of organs from HCV-NAAT–positive donors for HCV-uninfected recipients has increased the available organ

TABLE 3.
Transplant outcomes

Demographics	Total (N = 211)	Kidney (N = 111)	Liver (N = 41)	Heart (N = 34)	Lung (N = 25)
Biopsy-proven and treated rejection, n (%)	26 (12)	5 (2)	4 (10)	6 (18)	11 (44)
CMV DNAemia, n (%)	83 (39)	39 (35)	18 (44)	18 (53)	8 (32)
Peak DNAemia >200 IU/mL	44 (53)	20 (51)	10 (55)	9 (50)	5 (63)
CMV serostatus, n (%)					
D^-/R^-	20 (9)	11 (10)	4 (10)	4 (12)	1 (4)
D^+/R^-	64 (30)	36 (32)	12 (29)	6 (18)	10 (40)
D^-/R^+	33 (16)	21 (19)	7 (17)	1 (32)	4 (16)
D^+/R^+	81 (38)	41 (37)	17 (41)	13 (38)	10 (40)
–/Equivocal, historical positive	3 (1)	2 (2)	1 (2)	0 (0)	0 (0)
CMV DNAemia >200 by Serostatus, n (%)					
D^-/R^-	2 (5)	2 (10)	0 (0)	0 (0)	0 (0)
D^+/R^-	14 (32)	9 (45)	2 (20)	2 (22)	1 (20)
D^-/R^+	11 (25)	1 (5)	6 (60)	3 (33)	1 (30)
D^+/R^+	17 (39)	8 (40)	2 (20)	4 (44)	3 (60)
CMV DNAemia >200 while on valganciclovir antiviral prophylaxis, n (%)	8 (18)	6 (30)	1 (10)	0 (0)[a]	1 (20)
Time from transplant to peak CMV DNAemia >200, d, median (IQR)	147 (49–244)	86 (41–172)	239 (180–278)	194 (148–289)	453 (435–458)
Graft losses, n (%)	16 (8)	6 (5)	2 (5)	5 (15)	3 (12)
Mortality first year posttransplant[b], n (%)	6 (3)	1 (1)	1 (2)	3 (9)	1 (4)

[a]One heart transplant recipient was on valacyclovir prophylaxis with preemptive CMV monitoring.
[b]No deaths were directly attributable to HCV infection or treatment.
CMV, cytomegalovirus; HCV, hepatitis C virus; IQR, interquartile range.

pool for transplant candidates. Ongoing research is helping to define the optimal timing and duration for the recipients of such organs. Currently, practices differ significantly between institutions. We describe our single-center experience with >200 HCV-NAAT–positive organs to NAAT–negative recipients across organ types in a real-world setting with coordinated outpatient DAA treatment.

The largest number of transplants from HCV-NAAT–positive donors to uninfected recipients in this study was the kidney transplant population, followed by liver, heart, and lung transplant populations, consistent with our transplant center activity and volume. HCV-NAAT–positive donors were of a comparative age to non-HCV donors, predominantly of male sex, and were frequently identified as PWID. Induction and maintenance immunosuppression were not altered because of the presence of donor HCV infection. Most recipients of HCV-NAAT–positive organs rapidly developed detectable HCV RNA posttransplant and very quickly developed high RNA levels. Notably, 3 nonhepatic organ recipients did not develop detectable HCV RNA at any time after transplant; it remains unclear whether these cases represent false positive donor NAAT testing or lack of transmission from nonhepatic organs. All liver transplant recipients with an HCV-NAAT–positive donor developed detectable HCV RNA. HCV genotype 1a was most common at our center, followed by genotype 3, consistent with genotype trends reported in the literature, which note a prevalence of 75% genotype 1a followed by 20% to 25% genotypes 2 and 3.[21] Genotype 3 is associated with intravenous drug use, and because the majority of donors in this study were PWID and died of opioid overdose, the higher prevalence of this genotype is not surprising. However, this does have implications for treatment management even in the setting of highly potent DAAs, as genotype 3 is associated with accelerated hepatic fibrosis and decreased antiviral response.[21,22] In our kidney cases, in which initial DAAs failed, 3 of 4 recipients were genotype 3.[16] The liver and lung recipients with initial treatment failure were both genotype 2.

Our medical center had a protocolized delay of DAA initiation until after transplant hospitalization discharge, with most antivirals started in the outpatient setting in either Transplant Infectious Diseases or Transplant Hepatology clinic. The median time from transplant to antiviral initiation for all organ systems in this study was 52 d. Additional contributions to medication delays included time for prior authorization approval and logistical issues including outside mail order pharmacy delays, coordinating shipment with the Duke specialty pharmacy, coordinating medication pickup with a follow-up transplant appointment, and awaiting calcineurin inhibitor levels results to adjust transplant medications with DAA initiation. Furthermore, some patients required grant assistance because of a high copay—this necessitated additional time for patient coordination. Finally, the duration of the index hospitalization (and thus the time to initial outpatient follow-up in the clinic) differed between organ systems and was typically longer in particular for the thoracic organ transplants than the abdominal transplants, which contributed to further delays to antiviral therapy initiation. For other centers considering deferred outpatient DAA treatment, our experience suggests that a robust and engaged pharmacy team can help facilitate antiviral procurement and delivery but this remains a significant burden on the system.

Prior studies have demonstrated that starting DAAs prophylactically/preemptively may permit shorter antiviral duration.[23-25] All but 5 allograft recipients in our cohort were treated with a 12-wk DAA course per American Association for the Study of Liver Diseases/Infectious Diseases Society of America guidelines.[26] Five heart recipients were treated with 8 wk of glecaprevir–pibrentasvir, a median of 97 d from transplant, due to the inability to obtain insurance approval for a 12-wk course. Four achieved SVR12 with this abbreviated regimen; 1 recipient required an extension of antivirals to

14 wk because of persistently detectable HCV RNA at the end of the 8-wk course. A better understanding of viral load kinetics in transplanted patients will help avoid inadvertent undertreatment. Further study is needed to understand whether an 8-wk DAA course would suffice in the setting of delayed initiation as performed in our management protocol.

Variability in the frequency of HCV RNA monitoring after initial detection may have impacted quantitative peak HCV RNA and/or time to detection of peak HCV RNA between organ groups. This relationship did not solely correspond to the timing of antiviral initiation—median time from transplant to antiviral therapy was shortest for kidney transplant recipients, followed by lung, liver, and heart recipients; however, median peak HCV RNA was highest in lung recipients. The difference in antiviral timing between organ groups may reflect the impact of innately longer transplant hospitalizations for some organs, particularly thoracic organ recipients. Importantly, longer time to antiviral initiation did not necessitate slower time to undetectable RNA, which was shortest in the kidney transplant population and longest in the lung, although it must be acknowledged that this is additionally impacted by variability in HCV RNA testing.

Most importantly, delaying antiviral therapy to the outpatient setting did not appear to impact patient or allograft outcomes negatively and was generally well tolerated. None of our transplant recipients experienced a significant adverse effect as a direct result of their HCV infection. Ninety-seven percent of recipients (95% confidence interval [CI], 94-99) achieved SVR12 with standard first-line therapy. This is similar to published rates of SVR12 with glecaprevir–pibrentasvir: 98% (95% CI, 95-100) in kidney and liver transplant recipients and 98% (95% CI, 96-99) in the nontransplant setting.[27,28] However, this is slightly less than prior studies of sofosbuvir–velpatasvir in the general population, citing SVR12 rates of 99% (95% CI, 98-99).[29] In heart, kidney, and liver transplant groups, the most regularly chosen antiviral was glecaprevir–pibrentasvir, whereas lung transplant recipients were most frequently treated with sofosbuvir–velpatasvir. Similar rates of SVR were seen with both regimens. Antivirals were chosen for each organ system based on medication interaction, absorption, insurance approval, and financial expense.

Mortality was highest in the first year posttransplant in heart transplant recipients, followed equally by lung, liver, and kidney transplant recipients. However, no patient deaths were directly related to HCV infection, and in most of these recipients, HCV RNA was undetectable before patient death. Acute rejection rates with HCV-NAAT–positive donors were found to be similar or lower than historical rates of rejection at our institution, with the important caveat that not all covariates related to rejection are accounted for; thus, we are unable within the limits of this study to specifically analyze the impact of HCV on rejection rates. This contrasts with published literature reporting a higher incidence of acute cellular rejection in HCV-NAAT–positive transplantation compared with HCV-negative donors.[30,31]

CMV DNAemia rates were highest in the lung transplant population, followed by liver, kidney, and heart. At our center, low-risk CMV patients (D^-/R^-) receive universal herpes simplex virus prophylaxis with valacyclovir/acyclovir. In intermediate-risk populations (R^+), lung recipients receive universal ganciclovir/valganciclovir prophylaxis for a year posttransplant. Other organ systems typically use a preemptive strategy: valacyclovir/acyclovir for 90 d with weekly CMV PCR monitoring. High-risk CMV groups (D^+/R^-) receive universal CMV prophylaxis for at least 180 d in all organ groups aside from lung recipients with indefinite antivirals. This may explain why lung transplant recipients had a more prolonged time between transplant and peak CMV DNAemia compared with other organ systems. There have been conflicting data on the potential for increased rates of opportunistic viral infections in the setting of HCV transplantation, with the timing of DAA initiation thought to be a relevant variable and earlier DAA initiation felt to reduce the incidence of CMV infection.[8,10-12,32] Given the limitations of this study, we do not have a matched HCV-negative group to compare rates directly. However, our general CMV DNAemia rates are lower than other centers with a delayed antiviral initiation approach.[8] Additionally, in a recent large study of similarly delayed antiviral therapy at a separate institution in the setting of kidney transplantation, CMV DNAemia incidence was similar between HCV-positive and HCV-negative donor groups.[32]

Notably, initiating HCV antiviral therapy in the outpatient setting is a time-intensive approach that requires securing DAA financial coverage through a third-party payer. A dedicated pharmacy team at our institution assisted with prior authorizations, appeals, and financial grant applications. None of our recipients were screened for insurance coverage of DAAs pretransplant. This work of our pharmacy colleagues has been previously outlined.[33] Additionally, close follow-up is required to ensure antiviral adherence, monitor for medication interactions, and assess for adverse effects and treatment failures.

Although protocols still vary between institutions regarding the timing and duration of antivirals in the setting of donor-derived HCV, our experience at a high-volume transplant center demonstrates that a delayed treatment approach is a viable option across all organ groups with careful monitoring and standardized protocols to ensure optimal outcomes. There are benefits in waiting until the outpatient setting to start antivirals. First, it allows time for patient stabilization, particularly in thoracic organ transplantation. In the acute setting, patients may be on multiple medications that interact with DAAs, require enteral feeding, or have concerns regarding medication absorption. Additionally, although DAA prices have fallen over time, a significant financial burden remains in treating HCV. When hospitals and pharmaceutical companies cover the financial cost, antivirals can be started earlier in the posttransplant setting. Otherwise, this burden falls on the patient and third-party insurance payers; prior authorization processes can lead to further delays in therapy.

A strength of this study is its inclusion of multiorgan data, rather than focusing solely on outcomes within a single-organ group, allowing for a unique opportunity to inform the larger transplant community. There should be an ongoing collaboration between organ groups, sharing limited intellectual and financial resources in the real world of HCV transplantation, to reduce differences between organ systems and between transplant centers.

This study does have limitations. First, long-term follow-up of patients is needed to assess the longevity of the organs and make a more nuanced inference regarding organ quality. Additionally, there is a challenge in establishing a matched control group for these patients, as we sometimes used HCV-NAAT–positive donors preferentially in higher-risk recipients (particularly early in the adoption of

this protocol), who otherwise would not be able to achieve organ transplantation in a timely manner. Therefore, this may have skewed our selection of who received organs from HCV-infected donors.

In conclusion, HCV-NAAT–positive organ transplantation has increased the donor pool for transplant recipients. In a real-world setting, recipients from such donors from multiple organ systems develop rapidly detectable high levels of HCV RNA, yet achieve cure when treatment is delayed until after discharge from their transplant hospitalization, without apparent compromise of graft function or patient safety. Further studies including long-term follow-up are warranted.

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