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Clinical and Financial Implications of 2 Treatment Strategies for Donor-derived Hepatitis C Infections

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Background. Transplanting hepatitis C viremic donor organs into hepatitis C virus (HCV)-negative recipients is becoming increasingly common; however, practices for posttransplant direct-acting antiviral (DAA) treatment vary widely. Protracted insurance authorization processes for DAA therapy often lead to treatment delays. **Methods.** At our institution, 2 strategies for providing DAA therapy to HCV$^-$ recipients of HCV$^+$ transplants have been used. For thoracic organ recipients, an institution-subsidized course of initial therapy was provided to ensure an early treatment initiation date. For abdominal organ recipients, insurance approval for DAA coverage was sought once viremia developed, and treatment was initiated only once the insurance-authorized supply of drug was received. To evaluate the clinical impact of these 2 strategies, we retrospectively collected data pertaining to the timing of DAA initiation, duration of recipient viremia, and monetary costs incurred by patients and the institution for patients managed under these 2 DAA coverage strategies. **Results.** One hundred fifty-two transplants were performed using HCV viremic donor organs. Eighty-nine patients received DAA treatment without subsidy, and 62 received DAA treatment with subsidy. One patient who never developed viremia posttransplant received no treatment. Subsidizing the initial course enabled earlier treatment initiation (median, 4 d [interquartile range (IQR), 2–7] vs 10 [IQR, 8–13]; $P<0.001$) and shorter duration of viremia (median, 16 d [IQR, 12–29] vs 36 [IQR, 30–47]; $P<0.001$). Institutional costs averaged $9173 per subsidized patient and $168 per nonsubsidized patient. Three needlestick exposures occurred in caregivers of viremic patients. **Conclusions.** Recipients and their caregivers stand to benefit from earlier DAA treatment initiation; however, institutional costs to subsidize DAA therapy before insurance authorization are substantial. Insurance authorization processes for DAAs should be revised to accommodate this unique patient group.

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INTRODUCTION

Despite a record 33 309 deceased donor solid organ transplants performed in the United States in 2020, over 108 000 candidates were awaiting transplant at the start of 2021.[1] This massive organ shortage has been the impetus for novel strategies to increase the potential donor pool, including the use of hepatitis C virus (HCV)-positive (HCV$^+$) donor organs for transplantation into HCV-negative (HCV$^-$) recipients. The opioid epidemic and the resultant spike in overdose deaths has produced a surge of HCV$^+$ organ donors,[2-4] a donor pool that is only projected to increase.[2,5] The advent of oral direct-acting antiviral (DAA) agents inspired the first pilot studies of transplantation of HCV viremic kidneys into HCV$^-$ recipients. These studies yielded encouraging results[2,4] and have been followed by single-center reports of this practice in all solid organ types.[6-14]

The overarching messaging from these reports is that transplanting HCV$^+$ donor organs into HCV$^-$ recipients is safe and that posttransplant cure of donor-derived HCV infection

is nearly universal. The merits of this practice are notable: decreasing discards of otherwise excellent donor organs[15] and transplanting patients more quickly with grafts that appear to perform well.[2,16] Consequently, HCV+ to HCV− transplants are being offered by a growing number of transplant centers, and the practice has transitioned from one that was initially limited to formal clinical trials to one that is considered a standard clinical care practice at many centers.[17]

The current American Association for the Study of Liver Diseases recommendation for HCV− solid organ recipients of HCV+ donors is for either (1) prophylactic/preemptive pangenotypic DAA treatment or (2) DAA initiation within the first week of transplant even in the absence of detectable recipient viremia.[18] In published series, DAA treatment strategies vary widely from center to center with regard to the timing of initiation of DAA therapy. Often, timing is determined by the insurance authorization process for DAA coverage.[19] In other cases, DAA initiation is intentionally delayed for several months, perhaps based on the assumption that outcomes are independent of the duration of viremia.[20] Nonetheless, serious adverse events such as fibrosing cholestatic hepatitis in recipients of HCV viremic donor organs have occurred, specifically in patients in whom DAA initiation was delayed.[20,21]

In January 2018, our program began offering HCV− thoracic and abdominal transplant candidates the option to list for HCV+ donor organs. Our institutional protocols were designed to facilitate early initiation of DAA therapy for HCV− recipients of HCV viremic organs. Two strategies were used: one in which insurance authorization was needed to initiate treatment and the second in which treatment was automatically initiated within days of transplantation with institution-subsidized DAA therapy as a bridge until insurance authorization was obtained. Herein we report our large solid organ transplant series, including the viremia clearance kinetics, incidence of HCV-related adverse events, and financial implications of these 2 strategies.

MATERIALS AND METHODS

Patient Selection and Regulatory Oversight

The study population consisted of all HCV− recipients of solid organ transplants from HCV+ donors who were transplanted between January 2018 and December 2020 at the New York University (NYU) Langone Transplant Institute. Three liver transplant recipients had history of prior HCV infections that were treated and cleared before being listed for transplantation. All other recipients were HCV naive. This series included combined organ transplant recipients. Recipients were grouped according to their primary organ as follows: for multiorgan transplants involving a kidney, the nonrenal organ was considered the primary organ, and for heart-lung transplants, the heart was considered the primary organ. All data reported here were acquired by retrospective review of electronic medical records. Approval for this study was obtained from the NYU Grossman School of Medicine Institutional Review Board. This retrospective institutional review board protocol encompassed the collection of data from some patients who had previously enrolled in clinical trials. For these patients, all data reported here were collected de novo, and no clinical trial study databases were used to generate the data set used in these analyses. All data analyses were performed using Stata/SE V.16.1 (StataCorp, College Station, TX).

Counseling and Consenting

All patients were counseled regarding the option to list for HCV+ donor organs during the evaluation process or while on the waitlist. The HCV+ organ counseling occurred before patients being listed for HCV+ organs. This sequence prevented patients from being unduly influenced by the pressure of an active offer during their decision-making process. Patients willing to consider receiving HCV+ donor organ offers indicated this by signing a "Willingness to Participate" document. The transplant pharmacy team then ran a test claim for DAA therapy on the patient's insurance to ensure that each patient had a coverage benefit for at least 1 pangenotypic DAA. Confirmation of DAA coverage benefit was required to update the patient's United Network for Organ Sharing listing status as willing to accept HCV+ donor organs. This confirmation of a coverage benefit did not constitute preapproval nor did it assure that the authorization requests would be approved upon submission. Further, it did not provide copayment estimates, and patients were informed that substantial copayments might be incurred.

For all HCV+ organ offers, patients were notified of the HCV+ status of the donor. Patients choosing to proceed with HCV+ transplantation signed written consent indicating their acceptance of the HCV+ donor organ(s). Standard surgical procedure consents were obtained separately. The transplant operations and the management of immunosuppression were conducted as per standard practices.

Donor and Recipient HCV Testing

For all HCV+ transplants, including antibody-positive nonviremic donors, 1 tube of blood accompanying the donor organ was used for HCV genotyping. The tube was labeled only with the donor United Network for Organ Sharing identification number and was processed by the NYU Langone laboratory with that identifier. This testing was paid for by the institution.

HCV viremia surveillance with quantitative polymerase chain reaction (PCR) assays was initiated for all recipients within the first week after transplant. Weekly HCV PCR testing was done for a minimum of 12 wk. When no positive PCR tests were observed after 12 wk, it was concluded that no transmission of viremia occurred. HCV PCR testing was repeated at 1 y posttransplant. In the instance that HCV viremia was detected posttransplant, PCR testing was continued for 16 total weeks from the start of DAA therapy. An additional PCR test was performed at 3 mo after completion of treatment to ensure sustained virologic response at 12 wk and again at 1 y posttransplant (Figure 1).

DAA Use and Treatment Initiation Protocols Followed

The DAAs used in these patients included glecaprevir/pibrentasvir (116 patients; 300 mg/120 mg; Mavyret, AbbVie, Inc., North Chicago, IL), sofosbuvir/velpatasvir (34 patients; 400 mg/100 mg; Epclusa, Gilead Sciences, Inc., Foster City, CA), or sofosbuvir/velpatasvir/voxilaprevir (1 patient; 400 mg/100 mg/100 mg, Vosevi, Gilead Sciences, Inc., Foster City, CA). For patients who were intubated at the time DAA initiation, glecaprevir/pibrentasvir was used and administered by nasogastric tube as described previously.[22] Patients

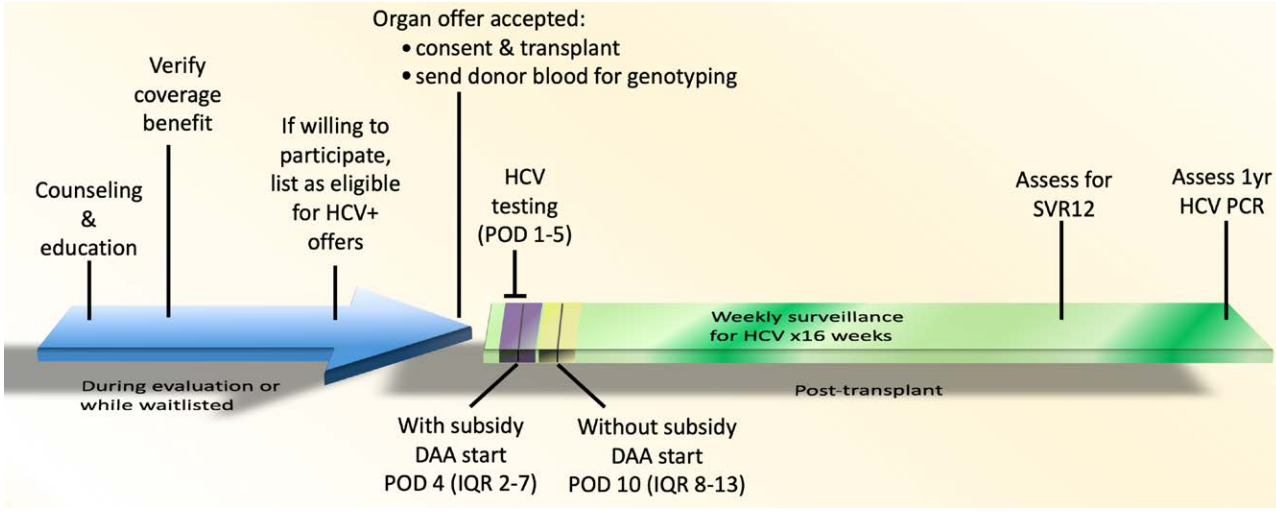

FIGURE 1. NYU Langone protocol for HCV⁺ organ transplantation. Potential recipients received education and indicated willingness to list for HCV⁺ organ offers. Transplant pharmacy confirmed DAA insurance coverage. Patient waitlist status converted to acceptance of HCV⁺ organ offers. Once an organ offer was received and accepted, patients consented to HCV⁺ transplant and donor blood was sent for genotyping. HCV surveillance began POD 1–5 and continued for 16 wk or until documentation of SVR12, with final HCV PCR 1 y posttransplant. DAA initiation occurred earlier in the subsidized group (purple band) than in the nonsubsidized group of patients (yellow band). DAA, direct-acting antiviral; HCV, hepatitis C virus; HCV⁺, hepatitis C virus positive; IQR, interquartile range; NYU, New York University; PCR, polymerase chain reaction; POD, postoperative day; SVR12, sustained virologic response at 12 wk.

enrolled in clinical trials received glecaprivir/pibrentasvir. Nontrial participants received a pangenotypic DAA dictated by their insurance.

Two strategies for initiation of DAA therapy were used. For abdominal transplant recipients, DAAs were obtained and initiated after insurance authorization to fill the prescription was obtained. These patients constituted the group treated "without subsidy" of their DAA course. The process for this was as follows: once recipient viremia was documented posttransplant and once the donor genotype had resulted, this information was provided to the patients' insurer and request for authorization of DAA was made. Results of donor genotyping tests were submitted and accepted as the presumptive recipient genotype. Once insurance authorization was obtained, the prescription for the DAA approved by the insurer was sent to the pharmacy to be filled. In some cases, initial approval was denied by insurers and required appeals, including in some cases peer-to-peer conversations with insurers. Copayments were only known once insurance authorization was obtained. In the instance of copays deemed unaffordable by the patients, financial assistance with copayment cards or company-sponsored patient assistance programs were sought. If no financial assistance resources were secured, unaffordable copayments were covered by the institution, ensuring that all patients did ultimately receive DAA therapy.

Recipients of thoracic organ transplants at our institution were managed "with subsidy" of at least part of their DAA courses. Some of these patients had been transplanted under formal clinical trials (NCT03382847[11] and NCT03523871), which stipulated that DAA would be started on postoperative day (POD) 1 for lung recipients and started immediately upon detection of recipient viremia for heart recipients. Following the completion of the research protocols, the thoracic teams opted to continue the same timing of DAA initiation for patients receiving these transplants under standard clinical care. The institution agreed to pay for the initial course of bridge therapy while insurance authorization was awaited. Thus, the process for DAA acquisition for the thoracic patients was as follows. The first 25 heart and 20 lung patients had their entire courses of therapy covered as part of participation in the respective clinical trials. For all other heart or lung recipients, DAA was initiated from an institution-provided supply while results of recipient HCV PCR and donor HCV genotyping were awaited. The institution acquired a stock supply of DAA from its wholesaler, which was purchased at cost ($12 738 for each 28-dose supply). This stock was maintained in the pharmacy for distribution to patients until insurance authorization was obtained. The process for insurance authorization proceeded as described above for abdominal recipients once the results of the recipient HCV PCR and donor HCV genotyping were available. Once the insurance-provided source of drug was received, the patients transitioned from the institution-subsidized supply to the insurance-provided supply.

RESULTS

Transplant, Donor, and Recipient Characteristics

In a 3-y period, 152 HCV⁻ patients received 172 organs from HCV⁺ donors (Table 1). A total of 20 dual organ transplants were performed. The distribution of primary organs was 66 kidney, 36 heart, 26 lung, 13 liver, and 11 pancreas transplants.

The median donor age for all organs was 35 y (interquartile range [IQR], 30–41; Table 2). Pancreas donors were the youngest (28 [IQR, 23–33]), and kidney donors were the oldest (38 [IQR, 32–46]). Two-thirds of the donors (67.1%) were male, and the median kidney donor profile index was 67 (IQR, 54–77). Blood type distribution was 52% group O, 36.8% group A, 10.5% group B, and 0.7% group AB. 3.9% of organs were local allocation, and 88% of organs allocated via national share. Donors after circulatory death comprised 30.3% of the kidney donors. The mean cold ischemia time was 15.3 ± 12.5 h overall and was the longest for kidneys (28.2 ± 7.4 h) and shortest for hearts (3.6 ± 0.9 h).

The median recipient age was 59 y (IQR, 48–65) overall, although the pancreas recipients were notably younger than

TABLE 1.
Case distribution

Transplant type	No. of cases
Kidney	66
Heart	28
Lung	26
Liver	11
Pancreas-kidney	10
Heart-kidney	6
Liver-kidney	2
Heart-lung	2
Pancreas alone	1
Total	152

the other recipients (41 [IQR, 31–48]). A majority of recipients were male (79.6%) and had public insurance (59.9%). Recipient race distribution was 48% White, 30.3% Black, and 21.7% were other self-reported races. The recipient blood type distribution generally paralleled the donor blood type distribution. For each patient, the days on the waiting list from the time of HCV+ listing to transplant was calculated ("Days waited," Table 2). The median time waited from HCV+ eligibility to transplant was 28 d overall (IQR, 6–69). Heart transplants occurred most rapidly at a median of 6 d (IQR, 3–31)) from HCV+ eligibility listing. Kidney and liver transplants occurred most slowly at a median of 41 d (IQR, 15–102) and 46 d (IQR, 10–63) from HCV+ eligibility listing, respectively.

Rates of HCV Transmission and Donor Genotype Distributions

Overall, 96.1% (146/152) recipients of HCV+ donors developed HCV viremia posttransplant (Table 3). One hundred percent of liver, pancreas, and heart recipients of HCV viremic donors became viremic. One recipient of a viremic donor kidney never developed viremia. With early DAA initiation on the study protocol, 5 (19.2%) recipients of HCV viremic lungs never developed detectable viremia.

TABLE 2.
Donor and recipient characteristics

	Primary organ type					
	Kidney	Liver	Pancreas	Heart	Lung	All
N	66	13	11	36	26	152
Donor characteristics						
Age (y), median (IQR)	38 (32–46)	33 (29–40)	28 (23–33)	35 (30–41)	30 (28–39)	35 (30–41)
Male sex, n (%)	41 (62.1%)	8 (61.5%)	6 (54.6%)	30 (83.3%)	17 (65.4%)	102 (67.1%)
KDPI, median (IQR)	67 (54–77)	–	–	–	–	68 (56–78)
ABO, n (%)						
O	29 (43.9%)	7 (53.8%)	7 (63.6%)	21 (53.8%)	15 (57.7%)	79 (52%)
A	14 (21.2%)	2 (15.4%)	2 (18.2%)	3 (8.3%)	4 (15.4%)	25 (16.4%)
A1	8 (12.1%)	0	0	6 (16.7%)	4 (15.4%)	18 (11.8%)
A2	8 (12.1%)	1 (7.7%)	0	3 (8.3%)	1 (3.8%)	13 (8.6%)
B	6 (9.1%)	3 (23.1%)	2 (18.2%)	3 (8.3%)	2 (7.7%)	16 (10.5%)
AB	1 (0.7%)	0	0	0	0	1 (0.7%)
Share type, n (%)						
Local	1 (1.5%)	1 (7.7%)	1 (9.1%)	3 (8.3%)	0 (0%)	6 (3.9%)
Regional	7 (10.6%)	1 (7.7%)	2 (18.2%)	1 (2.8%)	0 (0%)	11 (7.2%)
National	58 (87.9%)	11 (84.6%)	8 (72.7%)	32 (88.9%)	26 (100%)	135 (88.8%)
DCD, n (%)	20 (30.3%)	0	0	0	0	20 (13.2%)
CIT (h), mean ± SD	28.2 ± 7.4	6.4 ± 2.0	8.8 ± 2.9	3.6 ± 0.9	5.7 ± 2.5	15.3 ± 12.5
Recipient characteristics						
Age (y), median (IQR)	58 (48–65)	57 (53–63)	41 (31–48)	60 (53–64)	64 (55–69)	59 (48–65)
Male sex, n (%)	55 (83.3%)	10 (76.9%)	6 (54.5%)	29 (80.6%)	21 (80.5%)	121 (79.6%)
Race, n (%)						
White	32 (48.5%)	5 (38.5%)	3 (27.3%)	17 (47.3%)	16 (61.5%)	73 (48%)
Black	28 (42.4%)	0	3 (27.3%)	12 (33.3%)	3 (11.5%)	46 (30.3%)
Other	6 (9.1%)	8 (61.5%)	5 (45.4%)	7 (19.4%)	7 (27%)	33 (21.7%)
ABO, n (%)						
O	29 (43.9%)	6 (46.2%)	5 (45.4%)	18 (50%)	12 (46.2%)	70 (46.1%)
A	20 (30.3%)	3 (23.1%)	3 (27.3%)	12 (33.4%)	11 (42.3%)	49 (32.2%)
B	12 (18.2%)	4 (30.7%)	3 (27.3%)	3 (8.3%)	3 (11.5%)	25 (16.4%)
AB	5 (7.6%)	0	0	3 (8.3%)	0	8 (5.3%)
Insurance type						
Private, n (%)	22 (33.3%)	6 (46.1%)	5 (45.4%)	19 (52.8%)	9 (34.6%)	61 (40.1%)
Public, n (%)	44 (66.7%)	7 (53.9%)	6 (54.6%)	17 (47.2%)	17 (65.4%)	91 (59.9%)
D waited,[a] median (IQR)	41 (15–102)	46 (10–63)	21 (6–35)	6 (3–31)	20 (6–35)	28 (6–69)

[a]Since listing as eligible for HCV+ donor organs.
CIT, cold ischemia time; DCD, donation after circulatory death; HCV+, hepatitis C virus positive; IQR, interquartile range; KDPI, kidney donor profile index.

TABLE 3.

Rates of viral transmission and genotyping results

	Primary organ type					
	Kidney	Liver	Pancreas	Heart	Lung	All
Viral transmission						
Donors, N	66	13	11	36	26	152
Recipients viremic, n (%)	65 (98.5%)	13 (100%)	11 (100%)	36 (100%)	21 (80.8%)	146 (96.1%)
Genotypes, n (%)						
1a	40 (61.6%)	11 (84.6%)	9 (81.8%)	22 (66.7%)	15 (60%)	97 (66 %)
1b	1 (1.5%)	0	0	2 (6.1%)	3 (12%)	6 (4.1%)
2b	3 (4.6 %)	1 (7.7%)	0	2 (6.1%)	0	6 (4.1%)
3	20 (30.8%)	1 (7.7%)	2 (18.2%)	7 (21.2%)	7 (28%)	37 (25.1 %)
4	1 (1.5%)	0	0	0	0	1 (0.7%)

The HCV genotype distribution observed was consistent between the primary organs (Table 3). Overall, genotype 1a was the most frequently observed (66%). Genotyping was performed using donor blood samples for 142 of the 152 viremic donors (93.4%). In the remaining 10 cases, donor viral load was either too low to yield a genotyping result or there was an insufficient quantity of donor blood for the assay. These latter recipients were genotyped after they developed adequate viral load for testing.

Detection of Viremia, Timing of DAA Initiation, and Viremia Clearance Kinetics

The median time from transplant to detection of viremia across the entire cohort was 3 d (IQR, 2–5; Table 4). Surveillance for HCV transmission was not performed daily; therefore, these data do not necessarily reflect the first day that viremia could have been detected. The median peak measured viral load across the overall cohort was 4.3 log copies (IQR, 2.5–6.1). Peak viral loads were greatest in liver recipients (median, 6.6 log copies; IQR, 6.4–7.3) and lowest in lung recipients (median 2.0 log copies; IQR, 1.4–2.7). Viral loads were measured weekly thus these figures may not necessarily indicate the actual peak experienced by the patient. There was a linear correlation between time to DAA initiation and maximum viral load ($r = 0.547$, $P < 0.0001$; Figure 2A) and between time to DAA initiation and time to clearance of viremia ($r = 0.614$, $P < 0.0001$; Figure 2B).

The median time from transplantation to the initiation of DAA therapy was 8 d (IQR, 5–11) for the overall cohort (Table 4). Thoracic recipients had institutionally subsidized DAA therapy per the clinical trial protocols, thus they started DAAs sooner than abdominal organ recipients. Comparing those with and without DAA subsidy, those with subsidy started treatment at a median of 4 d (IQR, 2–7) posttransplant and those without subsidy started treatment at a median of 10 d (IQR, 8–13) posttransplant ($P < 0.001$; Figure 3A).

Total time spent viremic, defined as the time from transplant to clearance of HCV viremia, was also shorter in patients with subsidy (median 16 d [IQR, 12–29]) compared with those without subsidy (median 36 d [IQR, 30–37]; Figure 3B; $P < 0.001$). Duration of viremia was also evaluated by primary organ type (Figure 3C) and revealed that the heart and lung recipients (with subsidy) cleared viremia sooner than kidney, liver, or pancreas patients (without subsidy).

No DAA treatment failures occurred, and sustained virologic response at 12 wk was achieved in 100% of patients who became viremic posttransplant, regardless of subsidy. No cases of fibrosing cholestatic hepatitis occurred.

Caregiver Exposures

Importantly, there were 3 incidents of caregiver HCV exposure. In these instances, a family member assisting with diabetes management sustained a needlestick injury when the recipient was viremic. HCV surveillance was implemented for each exposed individual, and no transmission of HCV occurred.

Financial Responsibilities of Patients and the Institution

For the 90 patients treated without subsidy, all prescribed DAA courses were billed to insurance. In 14 cases, initial requests for insurance authorization of DAA were denied, but all were subsequently approved on appeal (Table 5). Twenty-three patients qualified for financial assistance to defray the cost of copayments. Three patients with incomes exceeding the qualifications for copayment assistance incurred high copayments ($2310.88, $3312.75, and $5702.79). One patient could not afford a DAA copayment of $2525.46, and the institution covered this cost. For all other patients, total out-of-pocket expense for the full DAA course was $150 or less, and the median copayment was $11.40. The overall costs to the institution averaged per patient in the group without subsidy was $168.38. The majority of this was the cost of the donor genotyping, which was $140 per test.

TABLE 4.

Hepatitis C viral infection kinetics

	Primary organ type					Subsidized bridge DAA		
	Kidney	Liver	Pancreas	Heart	Lung	With	Without	All
D, transplant to viremia detection	3 (2–3)	2 (1–2)	4 (2–4)	6 (2–7)	2 (1–5)	5 (1–7)	3 (2–3)	3 (2–5)
Maximum[a] log viral load	5.3 (3.5–6.2)	6.6 (6.4–7.3)	5.9 (4.3–6.4)	3.8 (2.0–5.2)	2.0 (1.4–2.7)	2.7 (1.7–4.2)	5.5 (3.7–6.4)	4.3 (2.5–6.1)
D, transplant to DAA initiation	10 (8–13)	9 (5–10)	12 (10–17)	7 (4–8)	1.5 (1–3)	4 (2–7)	10 (8–13)	8 (5–11)
D, transplant to viremia clearance	37 (30–47)	36 (25–41)	36 (32–51)	16 (12–29)	16 (11–25)	16 (12–29)	36 (30–47)	31 (19–43)

All d reported as median (IQR).

[a]Maximum measured viral load reported as median (IQR).

DAA, direct-acting antiviral; IQR, interquartile range.

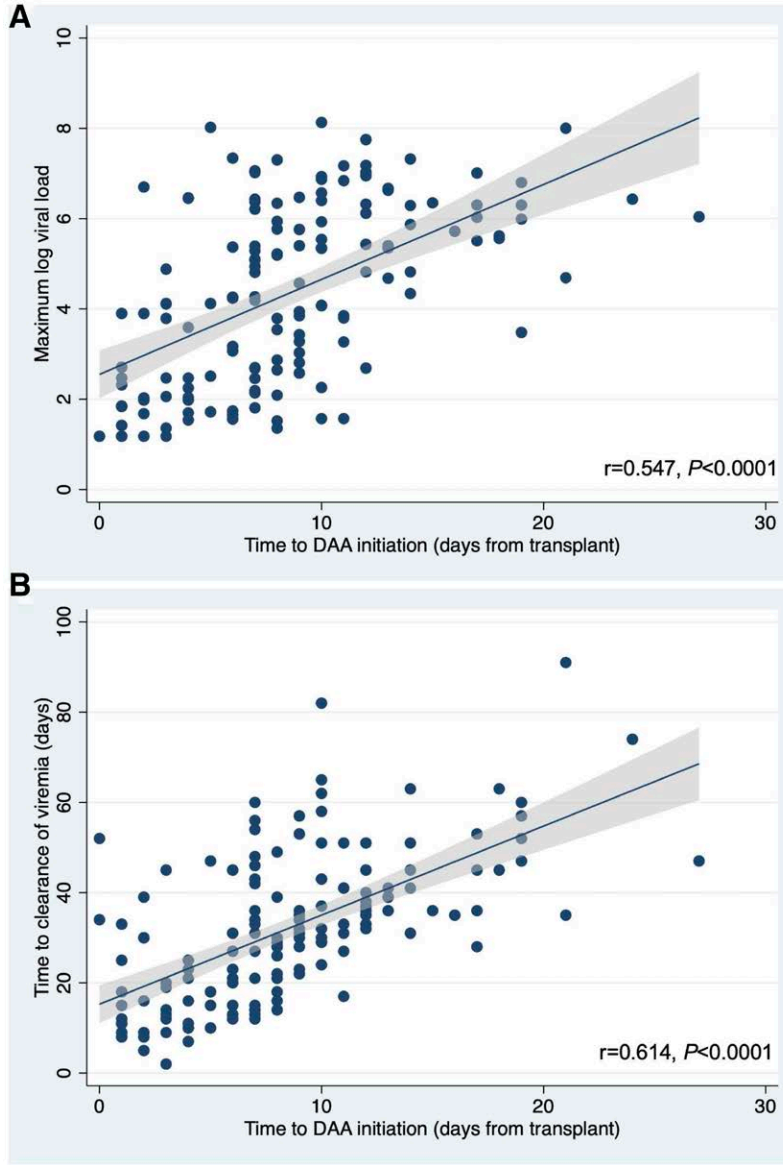

FIGURE 2. Correlation of viral kinetics with timing of DAA initiation. A, For patients who developed HCV viremia posttransplant, scatterplots of posttransplant days until clearance of viremia vs posttransplant days to DAA initiation were performed. Each marker indicates a single patient. B, Scatterplots maximum measured log viral load vs postoperative days to DAA initiation were similarly performed. Best-fit lines with shaded confidence intervals illustrating linear correlation are overlaid. DAA, direct-acting antiviral; HCV, hepatitis C virus.

Sixty-two patients received subsidized doses of DAA so that their course could be initiated before formal insurance authorization. Among these, 20 initial requests for insurance coverage were denied but all were approved upon appeal (Table 5). Twelve patients had unaffordable copayments and received financial assistance. One patient incurred and paid a high copayment ($652.80). Three patients had unaffordable copayments and did not qualify for financial assistance ($959.73, $2265.16, and $2581.00). These were covered by the institution. For all other patients, total out-of-pocket expense was $150 or less, and the median copayment was $3.00 for the portions of their DAA courses that were paid by insurance. Costs to the institution for the subsidized patients were substantially higher than for the nonsubsidized patients. Providing bridge DAA therapy averaged out to $8939.36 spent per patient treated. Contributing to this average sum was the cost of the full course of DAA therapy paid for the 5 lung recipients described above who never developed detectable viremia ($38 214 per 12-wk course of therapy). The average total institutional cost per subsidized patient was $9173.00.

Five lung transplant patients who started DAA therapy on POD1 never developed detectable HCV viremia, despite having received their organs from HCV viremic donors. Insurance authorization for DAA treatment for these patients could not be obtained because of inability to document recipient HCV viremia. The full course of therapy was subsidized by the institution in these cases.

DISCUSSION

Numerous studies have demonstrated the safety and efficacy of organ transplantation from HCV$^+$ donors to HCV$^-$ recipients.[6-14] Critical challenges remain to establish standard

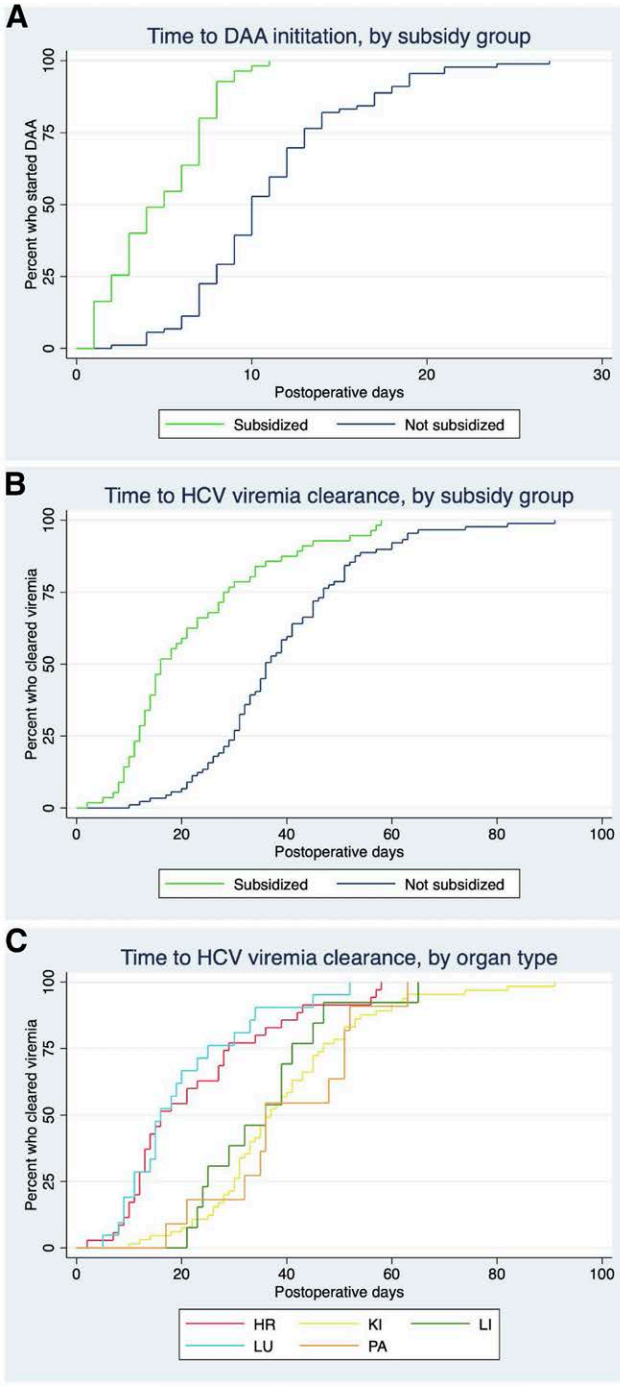

FIGURE 3. Time from transplant to clearance of HCV viremia. A, Time from transplantation to DAA initiation is illustrated to compare the impact of subsidizing the initial treatment course (with subsidy) vs working entirely within the constraints of the insurance approval process (without subsidy). B, Time from transplantation to clearance of HCV viremia is to compare the impact of DAA subsidy on the overall time patients spend viremic following transplantation. C, Time from transplantation to clearance of viremia is illustrated by the primary organ subgroups. Earlier initiation of DAA, by way of bridge coverage subsidy, in the heart and lung recipients likely explains the earlier time to viremia clearance in those patients. DAA, direct-acting antiviral; HCV, hepatitis C virus; HR, heart; KI, kidney; LI, liver; LU, lung; PA, pancreas.

best practices that maximize benefit and minimize risk with the increased utilization of HCV+ organs. Concerns for the feasibility of safely performing these transplants in "real-world" practice have been raised, leading some to suggest

TABLE 5.

Insurance coverage, patient copayments, and institutional expenditures

	Subsidized bridge DAA	
	With	**Without**
N	62	89
Prescription auth initially denied, n (%)	20 (32.3%)	13 (14.6%)
Approved after appeal, (%)	100%	100%
Received financial assist, n (%)	12 (19.4%)	23 (25.8%)
Patient incurred costs		
Median copay (range)	$3.00 ($0–$652)	$11.40 ($0–$5702)
Number with copay >$150	1	3
Institution incurred costs		
Donor genotyping (per unit test)	$140	$140
Unaffordable copays covered (per patient[a])	$93.64	$28.38
Cost of bridge DAA (per patient[a])	$8939.36	$0
Total per patient[a] cost	$9173.00	$168.38

[a]Sum institutional expenses averaged over the patients who were treated with DAA.
DAA, direct-acting antiviral.

that these transplants should be restricted to sites running formal research protocols.[15,23] Neither the necessary research infrastructure nor funding sponsorship to run such trials is ubiquitous; thus, such a restriction would limit access to these organs for many patients across the country. This would only serve to further exacerbate the already reported disparities in access to HCV+ organs[24] and could undermine recent progress that has been made in minimizing discard of these high-quality organs.[5,25,26] However, important barriers to broader implementation of this practice exist and include uncertainty in acquiring timely insurance approval of DAA treatment[17,19,27,28] and concern for the overall costs of these transplants.[29]

In this study, we retrospectively evaluated 2 different real-world practices for securing patient access to DAA treatment and compare their clinical and financial risks and benefits. These 2 strategies were (1) working entirely within the constraints of the insurance approval process to provide DAA treatment and (2) supplying an institution-subsidized source of DAA treatment as gap coverage while the insurance authorization process was ongoing. It is important to note that these 2 strategies are layered on top of our standard practice of using donor blood to obtain the HCV genotype at the earliest possible time to begin the process of obtaining insurance coverage without waiting for high-level recipient viremia. One limitation of our study is that the 2 treatment strategies were not independently compared within each given organ group. Rather, all thoracic recipients were managed with subsidy and all abdominal recipients were managed without. The results of the viral clearance kinetics should be interpreted in the context of this limitation.

For our patients, denials of insurance authorization for DAA treatment were encountered in many cases but were all ultimately approved upon appeal. Not surprisingly, there was a linear correlation between the timing of DAA initiation, the peak viral loads, and the overall duration of viremia in our patients. Subsidizing the initial DAA course effectively ensured patients of lower peak viral loads and shorter viremia duration. Without subsidy, the rate-limiting step to DAA initiation was indeed the insurance authorization process. Cases of coverage denials requiring lengthy appeals led to high peak

viral loads and, in a few unsubsidized patients, months of active viremia. Recent reports of fibrosing cholestatic hepatitis in recipients of HCV viremic kidneys[20,21] highlight the potential for serious risks of these transplants. It is notable that these reported cases all occurred when DAA initiation was delayed for months, and it is likely that earlier DAA initiation lowers the risk of this potentially life-threatening complication. In some organ groups, it has been suggested that prolonged viremia might be associated with increased risks for acute rejection.[30] Whether this is true among all solid organ transplant recipients remains to be investigated. Nonetheless, because duration of viremia can be minimized by early treatment initiation, it is appealing to be able to obviate even this potential risk by starting treatment as soon as possible.

It cannot be overlooked that the risks of prolonged viremia extend beyond those faced by the recipients themselves. In this series, 3 instances of caregiver exposure via needlestick injury occurred. In all cases, the exposed individual was a family member who was assisting the recipient with either glycemic monitoring or insulin administration. Diabetes is prevalent among recipients of transplants, and family member caregivers who generally are not trained medical professionals are often called upon to assist with tasks that require handling of lancets and hollow bore needles. The ability to minimize recipient peak viral load and to shorten the duration of active recipient viremia also decreases the risk for potential exposure to family members who provide this crucial posttransplant care. Fortunately, in our cases, no transmission to the caregivers occurred. However, the question must be raised of who is financially responsible for ensuring that exposed individuals receive proper surveillance for transmission and who would be responsible for providing DAA treatment in the event of viral transmission. Our institution provided hepatology consultation for the exposed individuals, covered the costs of surveillance, and was prepared to cover the costs of DAA therapy had it been necessary. Programs performing these transplants must consider that these unanticipated events and associated expenses might arise.

Here, patients who received DAA subsidy experienced lower viral loads and shorter durations of viremia. In addition to reducing the risks described above, these patients may have also derived a psychological benefit from the knowledge that their viral infection was cleared more rapidly. Stigmata associated with HCV infections are real and have the potential to impact recipient quality of life,[31] presumably in proportion to the duration of viremia. In our series, 5 patients in whom DAA treatment was initiated on POD1 never developed detectable viremia. In these cases, all 5 donors had quantifiable HCV viremia; therefore, we suspect that early initiation of therapy at a time when the viral inoculum was minimal led to either transient low-level viremia or no viremia at all. There is precedent for this in clinical trials in which pretransplant DAA administration has been implemented as a potentially preventative treatment strategy.[2,32] Although attractive from a patient perspective, the prevention of viremia actually imparted the highest cost burden in our series because the patients in whom we failed to document viremia never qualified for any insurance coverage of DAA treatment. The sum total institutional cost incurred for these patients was substantial and has mandated a reevaluation of this practice. This is unfortunate because this situation puts what is likely the best practice from a patient perspective in direct conflict with the financial viability of the practice itself.

Our series supports the findings of others that current insurance authorization processes delay initiation of DAA treatment in recipients of HCV^+ to HCV^- transplants. Through our strategy of using donor blood for genotyping, we were able to obtain insurance authorization substantially quicker than most reported series.[7,8,20,33,34] However, to be able to guarantee early posttransplant and potentially preventative treatment, our institution incurred a substantial cost. Although, presumably, insurance companies designed their authorization practices for patients with chronic HCV infections as opposed to the unusual situations where transmission of infection is effectively planned, our experience provides strong justification for the reevaluation of these authorization practices for the benefit of these patients.

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