Preemptive antiviral therapy in lung transplantation from hepatitis C donors results in a rapid and sustained virologic response

Mauricio A. Villavicencio, MD,[a] Selena S. Li, MD,[b] Ann Marie Leifer, NP,[b] Jenna L. Gustafson, RN,[c] Asishana Osho, MD,[b] Stanley Wolfe, MD,[b] Yuval Raz, MD,[d] Jason Griffith, MD, PhD,[d] Isabel Neuringer, MD,[d] Emily Bethea, MD,[c] Thais Gift, RPh,[e] Georgina Waldman, RPh,[e] Todd Astor, MD,[d] Nathaniel B. Langer, MD,[b] and Raymond T. Chung, MD[c]

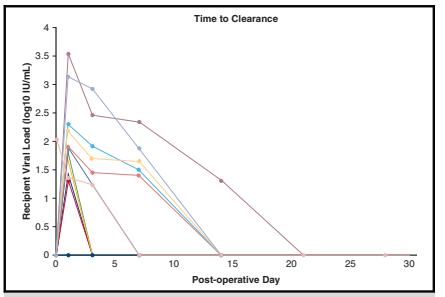
ABSTRACT

Objective: The study objective was to assess the safety and efficacy of a preemptive direct-acting antiviral therapy in lung transplants from hepatitis C virus donors to uninfected recipients.

Methods: This study is a prospective, open-label, nonrandomized, pilot trial. Recipients of hepatitis C virus nucleic acid test positive donor lungs underwent preemptive direct-acting antiviral therapy with glecaprevir 300 mg/pibrentasvir 120 mg for 8 weeks from January 1, 2019, to December 31, 2020. Recipients of nucleic acid test positive lungs were compared with recipients of lungs from nucleic acid test negative donors. Primary end points were Kaplan–Meier survival and sustained virologic response. Secondary outcomes included primary graft dysfunction, rejection, and infection.

Results: Fifty-nine lung transplantations were included: 16 nucleic acid test positive and 43 nucleic acid test negative. Twelve nucleic acid test positive recipients (75%) developed hepatitis C virus viremia. Median time to clearance was 7 days. All nucleic acid test positive patients had undetectable hepatitis C virus RNA by week 3, and all alive patients (n = 15) remained negative during follow-up with 100% sustained virologic response at 12 months. One nucleic acid test positive patient died of primary graft dysfunction and multiorgan failure. Three of 43 nucleic acid test negative patients (7%) had hepatitis C virus antibody positive donors. None of them developed hepatitis C virus viremia. One-year survival was 94% for nucleic acid test positive recipients and 91% for nucleic acid test negative recipients. There was no difference in primary graft dysfunction, rejection, or infection. One-year survival for nucleic acid test positive recipients was similar to a historical cohort of the Scientific Registry of Transplant Recipients (89%).

Conclusions: Recipients of hepatitis C virus nucleic acid test positive lungs have similar survival as recipients of nucleic acid test negative lungs. Preemptive direct-acting antiviral therapy results in rapid viral clearance and sustained virologic response at 12 months. Preemptive direct-acting antiviral may partially prevent hepatitis C virus transmission. (JTCVS Open 2023;14:602-14)



Preemptive antivirals in HCV donor lung transplants result in a rapid response.

CENTRAL MESSAGE

Preemptive DAA therapy in LTx recipients from HCV donors results in a rapid viral clearance and SVR at 12 months.

PERSPECTIVE

Lung transplant recipients are frequently maintained nil per os in the postoperative period. DAA therapy requires administration as a crushed drug via a nasi-enteric tube, which is contrary to advice from manufacturers. Nonetheless, preemptive therapy results in rapid and sustained viral clearance. Future studies of a shortened course might reduce cost and improve access.

From the [a]Department of Cardiovascular Surgery, Mayo Clinic, Rochester, Minn; [b]Division of Cardiac Surgery, Department of Surgery, [c]Gastrointestinal Division, Department of Medicine, [d]Division of Pulmonary and Critical Care Medicine, Department of Medicine, and [e]Division of Pharmacology, Massachusetts General Hospital, Boston, Mass.

Clinicaltrials.gov record number NCT03625687.

Massachusetts General Hospital, Institutional Review Board, Protocol Number 2018P001697, approved January 3, 2019.

Informed written consent was obtained from each patient to include their study data in research publications.

There was no specific funding for this study. Dr Wolfe is funded as the Martignetti Outcomes Cardiac Surgery Fellow. Dr Chung was supported by the MGH Research Scholars Program.

Drs Villavicencio and Li contributed equally to this study.

Drs Langer and Chung are equal senior authors.

Received for publication Oct 30, 2022; revisions received Feb 4, 2023; accepted for publication Feb 16, 2023; available ahead of print April 7, 2023.

Address for reprints: Mauricio A. Villavicencio, MD, Department of Cardiovascular Surgery, 200 First St SW, Rochester, MN, 55905 (E-mail: villavicencio.mauricio@mayo.edu).

2666-2736

https://doi.org/10.1016/j.xjon.2023.02.014

Abbreviations and Acronyms

Ab = antibody
ALT = alanine aminotransferase
DAA = direct-acting antiviral
EVLP = ex vivo lung perfusion
GP = glecaprevir-pibrentasvir
HCV = hepatitis C virus
LTx = lung transplantation
NAT = nucleic acid test
PGD = primary graft dysfunction
SRTR = Scientific Registry of Transplant Recipients
SVR = sustained virologic response

▶ Video clip is available online.

Lung transplantation (LTx) continues to be limited by donor availability. Waitlist mortality rates remain high at 15% in the United States,[1] with ranges of 13% to 37% worldwide.[2] Historically, hepatitis C virus (HCV) infection was considered a contraindication to organ donation due to an approximately 100% transmission rate and decreased recipient survival.[3,4] However, with the advent of direct-acting antiviral (DAA) therapy, HCV has become a curable disease. With high compliance rates and sustained virologic response (SVR) rates greater than 95%,[5] DAA therapy has reopened the possibility of transplantation from HCV donors into HCV-naive recipients.

The pioneering work of Woolley and colleagues[5,6] in the DONATE HCV trial demonstrated excellent early survival (100% at 1 year) in heart transplantation and LTx from HCV nucleic acid test (NAT)+ donors. DAA therapy after transplantation resulted in undetectable HCV after months of follow-up. Since then, several institutions have followed this path in the United States, with a recent review demonstrating comparable survival in a national patient population.[7]

As this practice becomes more widely adopted, new questions arise regarding the optimal timing and course of DAA therapy. In the United States, there are insurance reimbursement challenges when expensive DAAs are prescribed before patients become viremic, and commercial entities have deemed patients to be disease-free until viremia is demonstrated, which can delay treatment and force a reactive, rather than preemptive, strategy.[8]

We have previously reported our group's experience with preemptive HCV DAA treatment in heart transplantation.[9] Preemptive DAA administration may decrease transmission, reduce viral loads, and facilitate viral clearance. We hypothesize that preemptive administration of DAA therapy after LTx will be well tolerated, will halt the development of HCV infection, and will produce noninferior survival results.

MATERIALS AND METHODS

Study Design

This study is a prospective, open-label, nonrandomized, pilot trial including adult HCV– patients who underwent LTx with donor lungs from HCV NAT+ or antibody (Ab)+ donors between January 2019 and December 2020. The study protocol was reviewed and approved by the Institutional Review Board of the Massachusetts General Hospital, Protocol Number 2018P001697, approved January 3, 2019 (Video Abstract). Informed written consent was obtained from each patient to include their study data in research publications. LTx recipients' crude survival from NAT+ donors was compared per protocol with a historical group of the Scientific Registry of Transplant Recipients (SRTR). However, a statistically appropriate retrospective comparison with an institutional simultaneous NAT– cohort of patients was added for further granularity. HCV status was determined by NAT. Patients who had a seropositive (Ab+) donor but without detectable viremia were included in the NAT– cohort. One patient was excluded because of unknown donor HCV status.

Patient Selection

At initial evaluation, the risks and benefits of transplantation from HCV+ donors were discussed, and all patients provided written consent for receipt of HCV Ab+ and NAT+ lungs. Patients were approached for consent independent of their age and diagnosis. Thirteen of 19 patients consented before listing, and the remaining 6 recipients gave consent while on the waitlist. Patients with preexisting liver disease, including cirrhosis, severe steatosis, or chronic hepatitis B, were not consented for HCV+ or Ab+ lungs. There was concern of the effects of the added immunosuppression in highly sensitized patients (panel-reactive antibody $\geq$ 75%) at the time of protocol writing; therefore, they were excluded from the NAT+ donors and not consented. Those with the potential for malabsorption of DAA were also excluded. Use of HCV donors was not randomized but rather was based on organ availability. No power calculation was used to estimate the sample size because this was a pilot study and no previous studies were available at that time. The protocol aimed to enroll up to 100 patients, with 25 receiving the study drug. However, 2 of the 3 principal investigators left the institution in 2021 for unrelated reasons, and therefore, recruitment was terminated early.

Hepatitis C Virus Treatment Protocol

Recipients of HCV NAT+ lungs underwent preemptive DAA therapy with a pan-genotypic regimen of glecaprevir 300 mg/pibrentasvir 120 mg (glecaprevir-pibrentasvir [GP]) (Mavyret, AbbVie Inc) for 8 weeks. No ex vivo lung perfusion (EVLP) irradiation, ezetimibe, or other hepatitis C inhibitor was used. The first dose was administered orally before transport to the operating room. All patients received the medication crushed through a nasogastric tube in the immediate postoperative period and were then transitioned to oral therapy once cleared for oral intake. Patients who received lungs from HCV NAT–/Ab+ donors without detectable viral loads were managed with a reactive approach, and therapy was planned to be initiated upon detection of HCV viremia.

HCV viral load was monitored by polymerase chain reaction on postoperative days 1, 3, 7, and 14, and then every 2 weeks for 24 weeks and at 1-year follow-up. Serologies were tested at 1 week and 1 year, with variable additional tests. Alanine aminotransferase (ALT) was measured at 1, 3, and 6 months.

Outcomes

The primary end point was the safety of transplanting HCV NAT+ donor lungs into HCV– recipients as measured by incidence of HCV donor-to-recipient transmission, 12-month survival, and freedom from HCV RNA. SVR was defined as persistently undetectable HCV RNA. In the original protocol, the SVR end point was 12 weeks. However,

we wanted to provide additional data consistent with most surgical studies; therefore, the follow-up was extended to 12 months.

Secondary end points were median time to undetectable HCV RNA, highest median viral load, and incidence of liver dysfunction defined as an ALT level 3 times baseline or more during follow-up.[10] Clinical LTx end points were incidence of grade 3 primary graft dysfunction (PGD) at 72 hours (as determined using the International Society for Heart and Lung Transplantation consensus classification[11]), rejection needing treatment, and infection requiring hospitalization.

Data Analysis

Statistical analyses were conducted with R software (Lucent Technologies). Missing data were excluded from calculations, and percent missingness is included in Tables 1 and 2. The majority of variables had no missing data, and the few with missing data had less than 10% of values missing. Normality was tested with the Shapiro–Wilk test, with null hypothesis (normal distribution) rejected if P less than .05 (Table E1). Categorical variables were compared with the Fisher exact test, normal continuous variables with the 2-way t test, and non-normal continuous variables with the Mann–Whitney U test.

We report descriptive trends in variables, with the caveat that type II statistical errors may occur due to the small cohort size. Propensity-matched analysis was performed 1:1 with the nearest-neighbor method, matching for recipient age, recipient gender, and lung allocation score at the time of transplant. Adequate matching was evaluated with standard mean deviation less than 0.100. Table E2 shows propensity-matched scores. Kaplan–Meier survival curves were generated for overall survival in both the total and propensity-matched cohorts. The log-rank test was used for survival comparisons. Donor and recipient viral load, and time to clearance were evaluated using Pearson's correlation.

RESULTS

Donor, Recipient, and Operative Characteristics

During the study period, a total of 59 LTx recipients met inclusion criteria, 43 were NAT– and 16 were NAT+.

TABLE 1. Baseline recipient characteristics

	NAT–	NAT+	*P*	% missing data
n	43	16		
Age, median [IQR]	59.0 [54.0-65.0]	59.0 [55.8-66.2]	.898	0.0
Male (%)	23 (53.5)	8 (50.0)	>.99	0.0
Ethnicity (%)			<.001	0.0
White	37 (86.0)	15 (93.8)		
Black	2 (4.7)	1 (6.2)		
Hispanic	4 (9.3)	0 (0.0)		
Asian	0 (0.0)	0 (0.0)		
Other	0 (0.0)	0 (0.0)		
HCV seropositive (%)	1 (2.3)	0 (0.0)	>.99	0.0
Diabetes (%)	10 (23.3)	0 (0.0)	.084	0.0
History of smoking (%)	17 (39.5)	7 (43.8)	>.99	0.0
Previous transplant (%)	4 (9.3)	0 (0.0)	.496	0.0
LAS at listing, (median [IQR])	40.0 [35.4-53.1]	38.2 [33.8-42.0]	.125	0.0
LAS at transplant, median [IQR]	48.8 [38.3-73.2]	40.8 [35.0-46.4]	.021	0.0
Diagnosis (%)			.045	0.0
CF/bronchiectasis	4 (9.3)	0 (0.0)		
Obstructive	8 (18.6)	7 (43.8)		
Other	11 (25.6)	0 (0.0)		
Pulmonary hypertension	2 (4.7)	0 (0.0)		
Restrictive	18 (41.9)	9 (56.2)		
FEV1, median [IQR]	42.5 [24.0-57.5]	32.0 [25.0-57.5]	.779	3.4
FVC, mean (SD)	49.3 (16.7)	56.1 (16.7)	.182	3.4
mPAP at transplant, median [IQR]	24.5 [21.2-31.8]	26.5 [22.0-28.0]	.740	1.7
Creatinine at transplant, median [IQR]	0.8 [0.7-1.0]	0.7 [0.6-0.8]	.091	0.0
Total bilirubin at transplant, median [IQR]	0.4 [0.3-0.6]	0.5 [0.4-0.7]	.370	0.0
MELD-XI, median [IQR]	2.4 [–0.8 to 6.4]	2.3 [–0.6 to 4.6]	.639	0.0
Mechanical ventilation at transplant (%)	3 (7.0)	0 (0.0)	.676	0.0
ECMO before transplant (%)	3 (7.0)	0 (0.0)	.676	0.0
O2 requirement (L/min) at transplant, median [IQR]	6.0 [4.0-8.8]	4.0 [3.0-8.0]	.248	8.5

NAT, Nucleic acid test; *HCV*, hepatitis C virus; *LAS*, Lung Allocation Score; *IQR*, interquartile range; *CF*, cystic fibrosis; *FEV*, forced expiratory volume; *FVC*, forced vital capacity; *SD*, standard deviation; *mPAP*, mean pulmonary artery pressure; *MELD-XI*, Model for End-stage Liver Disease without INR; *ECMO*, extracorporeal membrane oxygenation.

TABLE 2. Donor and operative characteristics

	NAT–	NAT+	*P*	% missing data
n	43	16		
Age, median [IQR]	35.0 [28.0-44.5]	31.0 [27.8-33.5]	.275	0.0
Male (%)	23 (53.5)	7 (43.8)	.710	0.0
Ethnicity (%)			<.001	0.0
White	30 (69.8)	14 (87.5)		
Black	5 (11.6)	2 (12.5)		
Hispanic	7 (16.3)	0 (0.0)		
Asian	1 (2.3)	0 (0.0)		
Other	0 (0.0)	0 (0.0)		
History of cocaine use (%)	17 (40.5)	8 (53.3)	.577	3.4
History of other drug use (%)	27 (65.9)	13 (81.2)	.412	3.4
History of heavy alcohol (%)	12 (28.6)	3 (21.4)	.862	5.1
History of smoking (%)	3 (7.1)	3 (21.4)	.318	5.1
PaO2/FiO2 ≥300 (%)	36 (83.7)	15 (93.8)	.567	0.0
Infiltrates on CXR (%)	20 (60.5)	13 (81.2)	.234	0.0
Purulence on bronchoscopy (%)	8 (18.6)	5 (31.2)	.491	0.0
CDC high-risk donor (%)	19 (44.2)	14 (87.5)	.007	0.0
Transplant type (%)	0 (0.0)	1 (6.2)	.604	0.0
Gender mismatch female > male (%)	3 (7.0)	1 (6.2)	>.990	0.0
ABO identical (%)	41 (95.3)	13 (81.2)	.229	0.0
CMV donor/recipient (%)			.455	0.0
−/−	13 (30.2)	6 (37.5)		
−/+	7 (16.3)	2 (12.5)		
+/−	13 (30.2)	2 (12.5)		
+/+	10 (23.3)	6 (37.5)		
EBV donor/recipient (%)			.283	0.0
−/+	2 (4.7)	0 (0.0)		
+/−	6 (14.0)	0 (0.0)		
+/+	34 (79.1)	15 (93.8)		
Unknown	1 (2.3)	1 (6.2)		
Total waitlist, d, median [IQR]	39.0 [21.5, 91.0]	52.5 [32.0, 82.5]	.959	0.0
Distance (miles), median [IQR]	164.0 [97.5, 243.0]	499.5 [237.5, 630.5]	.002	0.0
Total ischemic time (h), mean (SD)	6.8 (2.2)	6.6 (1.3)	.789	1.7
Donor type (%)	5 (11.6)	0 (0.0)	.368	0.0
EVLP (%)	1 (2.3)	1 (6.2)	.468	0.0
CPB (%)	17 (41.5)	3 (18.8)	.192	3.4
ECMO in operating room (%)	23 (56.1)	2 (12.5)	.007	3.4

NAT, Nucleic acid test; *IQR*, interquartile range; *CXR*, chest x-ray; *CDC*, Centers for Disease Control and Prevention; *CMV*, cytomegalovirus; *EBV*, Ebstein–Barr virus; *SD*, standard deviation; *EVLP*, ex vivo lung perfusion; *CPB*, cardiopulmonary bypass; *ECMO*, extracorporeal membrane oxygenation.

Three NAT– donors were Ab+. Three recipients were excluded from NAT+ or Ab+ donors because of concomitant liver disease, 2 because of high sensitization, and 1 because of potential for medication malabsorption. One patient refused to consent (Figure E1). In the NAT+ cohort, White ethnicity and obstructive lung disease were more common. The Lung Allocation Score was higher in the NAT– cohort (Table 1).

Viremic donors were more likely to be White and less likely to be Hispanic (Table 2). The average distance traveled for NAT+ transplants was 2-fold higher than for NAT–. This did not lead to a significant difference in ischemic time. Intraoperative extracorporeal membrane oxygenation was more common in the NAT– group. Normothermic EVLP with no irradiation was used infrequently and only for expanded criteria donors (Table 2).

Hepatitis C Virus Treatment and Outcomes

The 16 recipients of NAT+ lungs received preemptive GP. Fifteen patients completed the full course of treatment (94%). The 1 patient who did not complete the therapy died after 7 weeks of severe PGD and secondary multiorgan failure thought to be unrelated to HCV infection (viral clearance at day 2). The 3 recipients of HCV NAT–/Ab+ lungs were closely monitored and did not develop viremia or require reactive treatment (Table 3). The median time to oral intake of DAA therapy was 6 days (interquartile range, 2.5-28.25). Three patients received the entire 8-week course as a crushed medication with nasoenteric feeding due to poor swallowing function. There was no relationship between time to oral intake of DAA therapy and time to HCV clearance.

Twelve recipients of HCV NAT+ lungs (75%) developed viremia, all within the first postoperative day (Table 3). The average time to viral clearance was 7 days, and 5 patients (41.7%) had undetectable viral loads by postoperative day 2 (Figure 1). The initial viral loads ranged from 20 to 3450 IU/mL and correlated with donor viral loads at the time of transplant (Table 3 and Figure 2, $P = .002$, $r = 0.51$). Time to clearance depended on initial recipient viral loads ($r = 0.92$, $P < .001$) as well as donor viral loads ($r = 0.50$, $P = .047$) (Figure 2). All 16 patients had undetectable HCV RNA by week 3 of DAA therapy and remained negative for the remainder of their follow-up. There was 100% SVR at 12 months on all alive patients (n = 15). No recipients of HCV NAT–/Ab+ lungs underwent seroconversion, whereas 13 patients (81.2%) who received NAT+ lungs developed seropositivity at a median of 7 days ($P = .004$). The time to seroconversion varied widely from postoperative day 1 to 109.

Immunosuppression, Rejection, and Infections

There were no differences in acute rejection between the groups. After discharge, no recipients of HCV viremic lungs required treatment for acute rejection at 6 months or 1 year, compared with 4 (9.8%) patients at 6 months and 5 (12.2%) patients at 1 year in the HCV NAT– cohort ($P = .35$ and $P = .28$, respectively, Table 4). Six recipients of NAT+ lungs required hospitalization for infection within 1 year (37.5%) compared with 15 recipients of NAT (36.6%).

Graft and Survival Outcomes

There were no differences in major postoperative complications. PGD grade 3 was approximately 10% in the NAT– cohort and 12.5% in the NAT+ cohort without significant difference ($P = .112$, Table 4). There were no deaths within the early postoperative period (30 days). During the first

TABLE 3. Characteristics of hepatitis C virus–positive donor organs and recipient's treatment response

	HCV NAT	HCV Ab	Time from HCV+ consent to transplant (d)	Donor HCV genotype	Donor viral load (IU/mL)	Peak recipient viral load (IU/mL)	Time to viral clearance (d)	SVR 12 mo
1	+	+	62	1a	1210	Undetectable	N/A	Yes
2	+	+	0	1a	2,030,000	Undetectable	N/A	Yes
3	+	+	61	1a	3,180,000	26	2	Yes
4	+	+	61	1	2,700,000	53	2	N/A
5	+	+	5	3	36,400,000	3450	20	Yes
6	+	+	52	2	1,590,000	204	13	Yes
7	+	+	65	1a	30,400,000	68	2	Yes
8	+	+	13	3	941	Undetectable	N/A	Yes
9	+	+	22	3	33,400	20	2	Yes
10	+	+	37	3	560,000	40	2	Yes
11	+	+	33	3	8,420,000	76	6	Yes
12	+	+	29	1a	511,000	80	13	Yes
13	+	+	63	1a	473,000	Undetectable	N/A	Yes
14	+	+	51	1a	2,110,000	155	13	Yes
15	+	+	191	1a	28,400,000	1370	13	Yes
16	+	+	50	3	714,000	23	7	Yes
17	-	+	107	N/A	Undetectable	Undetectable	N/A	N/A
18	-	+	123	N/A	Undetectable	Undetectable	N/A	N/A
19	-	+	61	N/A	Undetectable	Undetectable	N/A	N/A

HCV, Hepatitis C virus; *NAT*, nucleic acid test; *Ab*, antibody; *SVR*, sustain virologic response; *N/A*, not applicable.

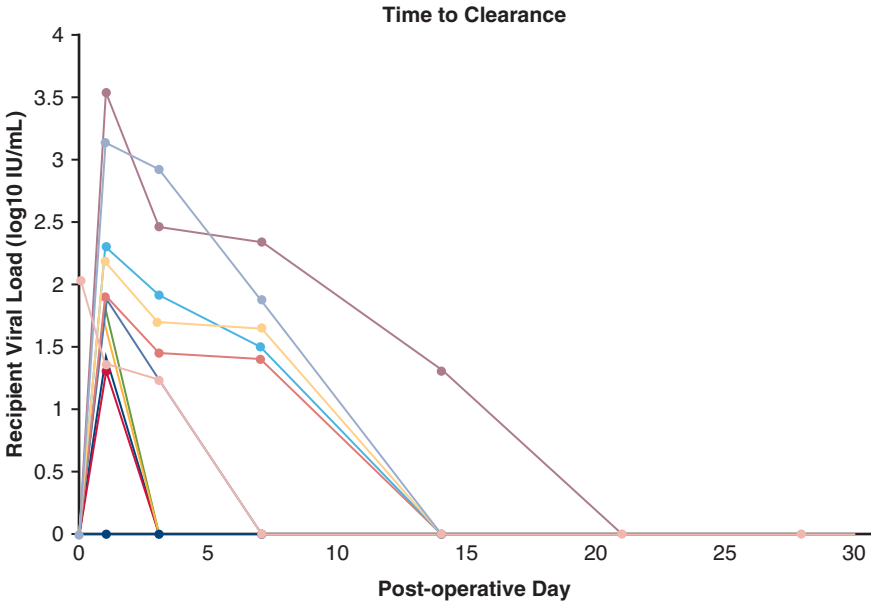


FIGURE 1. Hepatitis C viral load after transplantation.

year there was a trend, although not significant, to more rejection in the NAT– recipients (Table 4).

Kaplan–Meier survival curves were generated with a median follow-up of 438 days, and there was no difference in overall survival between the 2 cohorts (Figure 3, unadjusted $P = .34$, propensity matched $P = .67$). One-year survival was 94% for NAT+ and 91% for NAT– recipients. In 2019, LTx survival to 1 year in the SRTR national cohort was 89.4%.[12] There were no instances of retransplantation during follow-up.

Safety

There was no ALT elevation difference between the 2 groups, and the absolute ALT values never tripled during follow-up (Figure 4).

DISCUSSION

HCV is now a curable disease due to DAA therapy, reopening the possibility of LTx from HCV+ donors into naive recipients. In this study, we report that HCV NAT+ LTx is associated with similar survival to HCV NAT– transplants in a single institution cohort. Moreover, survival was similar to a historical SRTR cohort. Preemptive pangenotypic antiviral therapy results in a mean viral clearance of 7 days and 100% SVR at 6 months of follow-up without the need for EVLP and irradiation. We did not find serious adverse events due to DAA therapy.

Drug of Choice

We believe pangenotypic agents should be the standard in LTx because there is not adequate time to classify the HCV

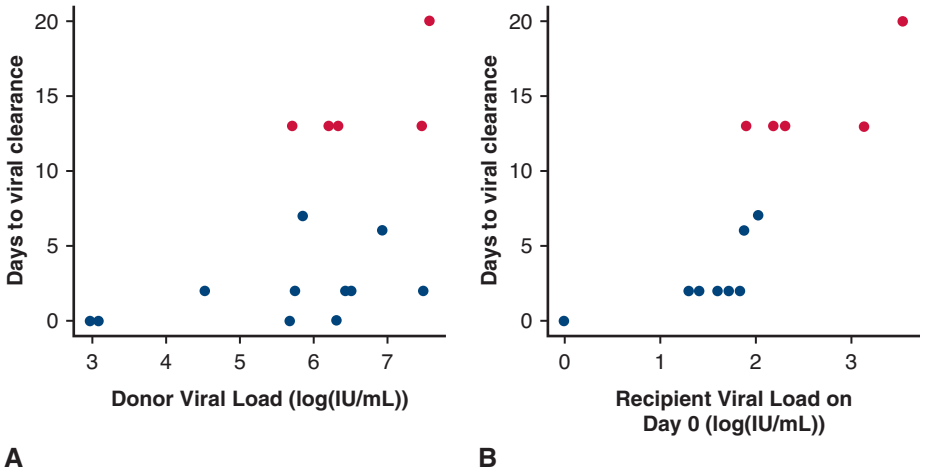


FIGURE 2. Correlation of hepatitis C viral load in donors and recipients. (A) Donor viral load. (B) Recipient viral load.

TABLE 4. Postoperative outcomes

	NAT–	NAT+	*P*	% missing data
n	43	16		
Reintubated (%)	12 (27.9)	5 (31.2)	>.99	0.0
Tracheostomy (%)	11 (27.5)	4 (25.0)	>.99	5.1
Dialysis (%)	2 (4.7)	1 (6.2)	>.99	0.0
Hospital length of stay (d), median [IQR]	30.0 [19.5-41.0]	32.0 [20.8-42.2]	.885	0.0
Primary graft dysfunction at 72 h (%)			.112	3.4
0	18 (43.9)	12 (75.0)		
1	15 (36.6)	2 (12.5)		
2	4 (9.8)	0 (0.0)		
3	4 (9.8)	2 (12.5)		
Hospitalized for infection (6 mo) (%)	10 (24.4)	6 (37.5)	.508	3.4
Hospitalized for infection (1 y) (%)	15 (36.6)	6 (37.5)	>.99	3.4
Treated for rejection (6 mo) (%)			.353	3.4
0	36 (87.8)	15 (93.8)		
1	4 (9.8)	0 (0.0)		
N/A	1 (2.4)	1 (6.2)		
Treated for rejection (1 y) (%)			.284	3.4
0	35 (85.4)	15 (93.8)		
1	5 (12.2)	0 (0.0)		
N/A	1 (2.4)	1 (6.2)		
Graft failure (30 d) (%)	0 (100.0)	0 (100.0)	>.99	0.0
Graft failure (6 mo) (%)	2 (4.7)	1 (6.2)	>.99	0.0
Graft failure (1 y) (%)	4 (9.3)	1 (6.2)	>.99	0.0
Death (30 d) (%)	0 (100.0)	0 (100.0)	>.99	0.0
Death (6 mo) (%)	2 (4.7)	1 (6.2)	>.99	0.0
Death (1 y) (%)	4 (9.3)	1 (6.2)	>.99	0.0

NAT, Nucleic acid test; *IQR*, interquartile range; *SD*, standard deviation.

genotype during the transplant process. In addition, atrial arrhythmias are common after LTx, affecting up to 25% of patients in the postoperative period,[13] and for many, amiodarone is the first line of treatment.[14] Woolley and colleagues[5] and Cypel and colleagues[15] originally chose sofosbuvir–velpatasvir, which has a significant interaction with amiodarone, potentially causing life-threatening bradycardia. There is no mention in their articles on amiodarone, so it was probably avoided. GP was the drug of choice for us, as it was for the Toronto group in their second article, because it has no interaction with amiodarone and has pangenotypic coverage.[16]

Route of Administration

Our study is the first to report the outcomes of preemptive HCV treatment specifically in LTx. Additionally, unlike many other solid organs, LTx recipients are frequently maintained nil per os in the postoperative period to prevent aspiration, and DAA therapy requires administration as a crushed drug via a nasoenteric tube, which is contrary to advice from manufacturers.[17] In this study, we show that DAA therapy is well tolerated and effective as a crushed medication, even in patients who receive their entire course of DAA therapy via this route. The median time to clearance was 7 days, and the initial transmission rate was 75%. SVR at 12 months was 100%, and no cases required re-treatment. We treated all recipients of NAT+ lungs empirically for 8 weeks; however, all but 1 patient had viral clearance within 2 weeks, which is similar to the 2-week clearance time reported in the DONATE HCV trial.[6]

Preemptive Therapy in Other Organ Transplants

To decrease transmission rates and reduce the length of the viremic period, preoperative initiation of DAA therapy has been proposed.[18] It was first demonstrated in kidney transplants.[19,20] In the DAPPeR REFORM HEPC trial, the first DAA dose was given to all recipients of viremic organs, but only those who developed viremia underwent the full course of treatment. Of these 6 patients, 3 (50%) required re-treatment with a second-line agent, and SVR at 12 weeks was only 83%. This may have been caused by a delay in treatment between the initial prophylactic

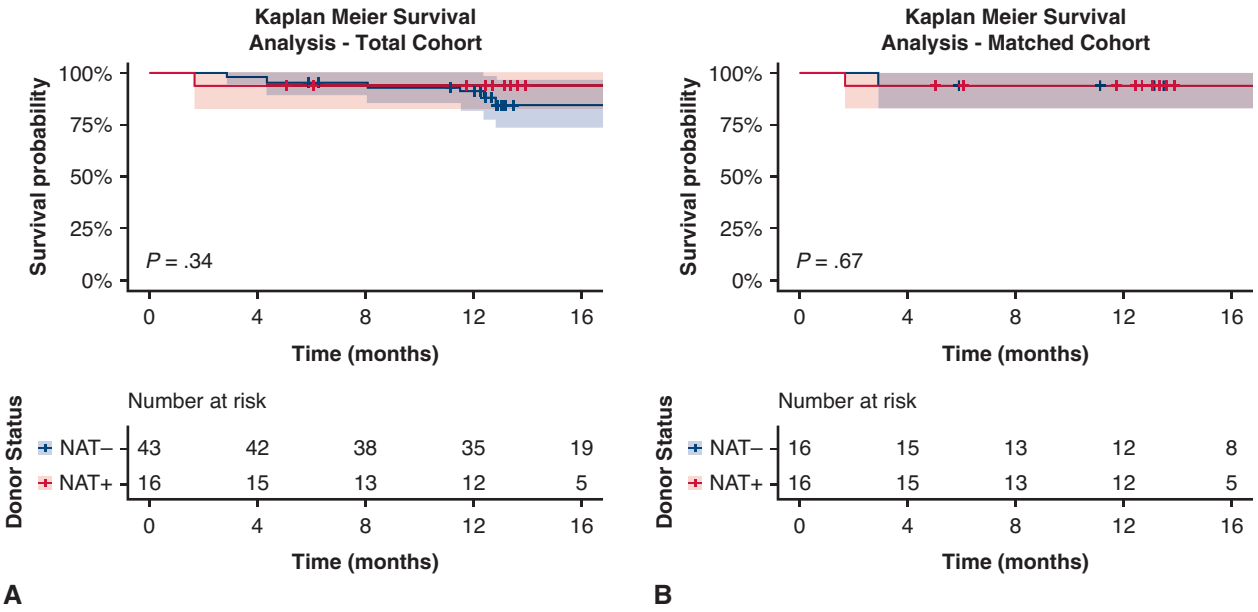


FIGURE 3. LTx recipient survival from hepatitis C NAT+ and NAT– donors. There is no difference in survival in both (A) the total cohort and (B) a propensity-matched analysis accounting for age, gender, and LAS. *NAT*, Nucleic acid test.

dose and the full course of treatment that was initiated after detection of viremia. In contrast, recipients of preoperative DAA therapy who continued treatment without delay demonstrated 100% SVR with no evidence of recurrence or need for re-treatment.[21] In heart transplants, the efficacy of preemptive treatment has been demonstrated in 2 studies in which the transmission rates were 60% to 67% and SVR was 100% at 12 weeks.[9,16]

	NAT– (n = 43)	NAT+ (n = 16)	*P*
Pretransplant	15.00 [11.50, 27.50]	15.00 [14.00, 18.25]	.925
1 month	32.00 [21.00, 57.50]	24.50 [15.25, 39.50]	.226
3 months	17.00 [13.00, 33.00]	17.00 [13.00, 24.50]	.977
6 months	19.00 [15.50, 24.00]	17.00 [14.00, 24.00]	.456

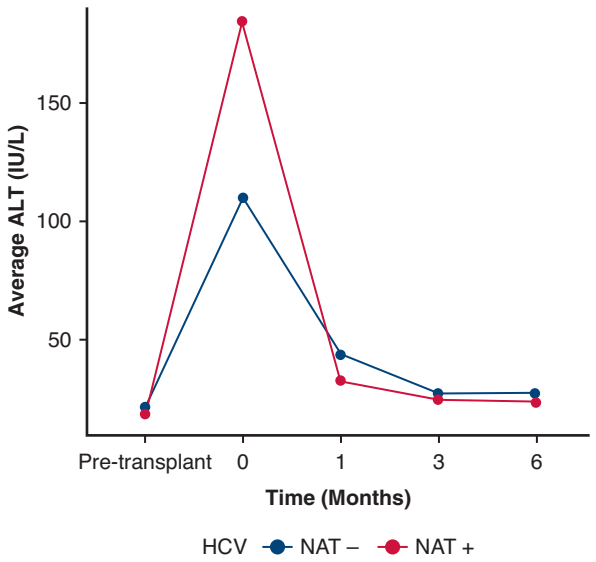


FIGURE 4. ALT profile after transplantation from HCV+ and HCV–donors. *NAT*, Nucleic acid test; *ALT*, alanine aminotransferase; *HCV*, hepatitis C virus.

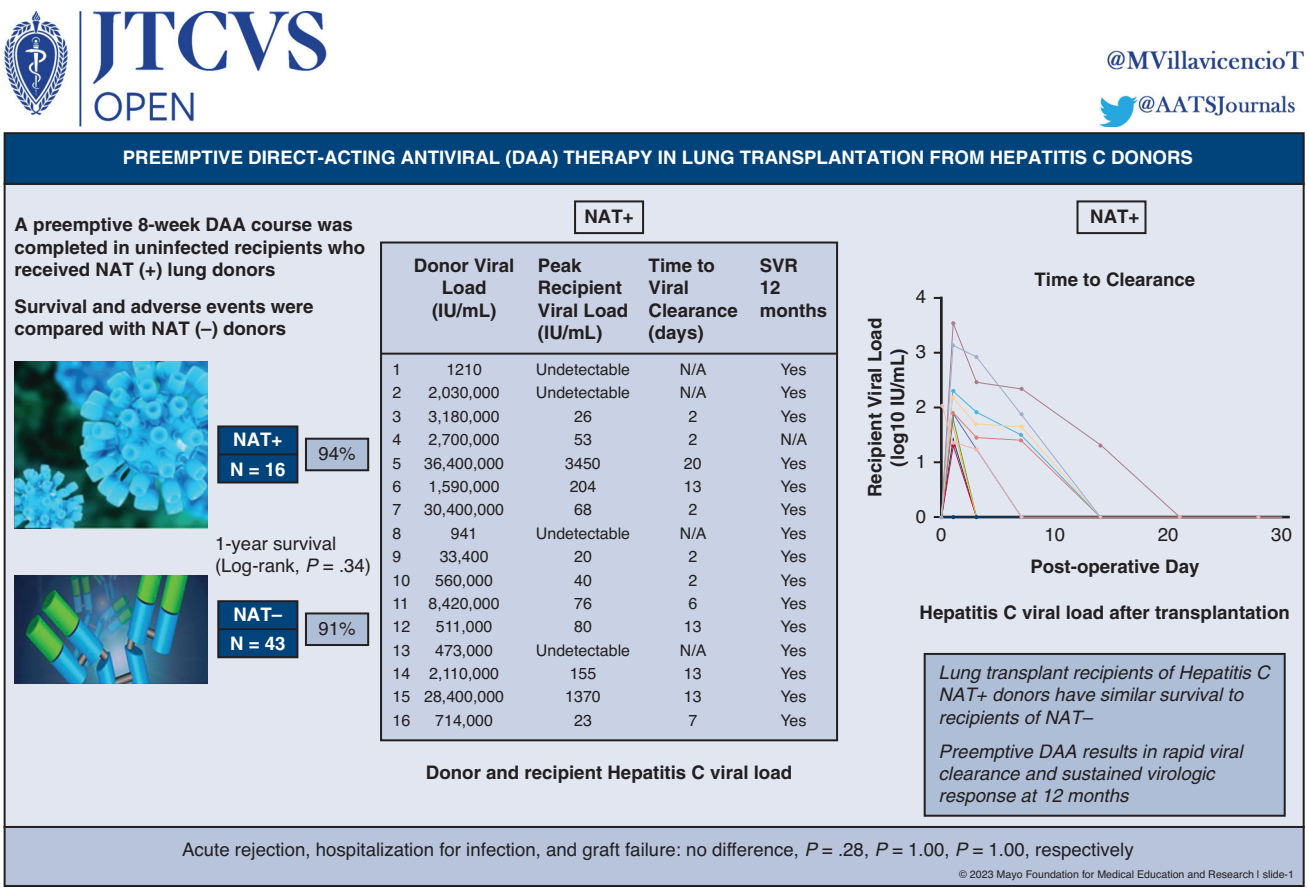


FIGURE 5. Graphical abstract. *NAT*, Nucleic acid test; *SVR*, sustain virologic response; *N/A*, not applicable.

Unfortunately, DAA reimbursement uncertainty has been cited as justification for a reactive approach to treating HCV infection after transplantation.[8,22] However, recent reports noted increased rates of chronic allograft vasculopathy in heart transplant recipients who underwent reactive DAA treatment with regimens initiated within 3 months of transplant.[23,24]

Preemptive Versus Reactive Treatment in Lung Transplantation

Cypel and colleagues[15] initially adopted a reactive approach to DAA therapy in patients who underwent LTx with NAT+ donors. They started DAA once the recipient became viremic, which occurred between 2 and 6 weeks after transplantation. This approach yielded a suboptimal SVR of 86% after 6 months of follow-up. Although they elegantly demonstrated a potential benefit of 4 to 6 hours of EVLP and irradiation of the perfusate in lowering viral loads, the need for this intervention remains unclear.

A completely different approach was used by Feld and colleagues[16] in the same center. Preemptive GP and ezetimibe treatment was initiated 6 to 12 hours before transplant and maintained for 7 days after transplantation, resulting in SVR at 12 weeks post-transplant. However, this study also used EVLP and irradiation in 7 of 13 lung transplants, a process that can be expensive, logistically difficult, and time-consuming.

Woolley and colleagues[5] also provide important data on the timing of treatment and the need for EVLP. In their report, EVLP was not used, and DAA was started a few hours after LTx. In 30 patients, 95% had a detectable HCV viral load immediately after transplantation, but the SVR was 100% at 6 months of follow-up.

In our study, 16 patients were treated preemptively, and there was detectable virus in 75% of the patients and an SVR of 100% at 12 months of follow-up. Taken together, our data support the efficacy and benefit of preemptive therapy.

Duration of Therapy

There is mounting pressure in the health system to decrease the costs of DAA. Treatment for HCV-infected patients outside of the transplant community has ranged between 8 and 12 weeks, with an SVR between 90%

and 100%. Nonetheless, high cost and poor compliance have pushed the duration down to as low as 3 weeks.[25] In kidney transplants, a 2- to 4-day DAA course failed to prevent HCV transmission in 13% of patients, whereas a 7-day "prophylaxis protocol" reduced the rate of transmission of HCV to 4%.[19] Feld and colleagues[16] demonstrated that a 7-day course, in association with ezetimibe, resulted in undetectable virus at 12 weeks post-transplant in 13 LTx recipients. Of these, 7 were subjected to EVLP irradiation to decrease the viral load. Serious complications such as fibrosing cholestatic hepatitis can arise from recurrence,[15] so caution is recommended until longer-term follow-up is reported that better defines the consequences of failed treatment.

Because time to clearance correlated with peak recipient viral load and donor viral load at the time of procurement, shorter, individually adjusted courses based on either donor viral load, peak or initial recipient viral load may be possible. Early results from 2 clinical trials in chronic HCV suggest that a response-based, more personalized regimen can be effective while maintaining a 97% to 100% SVR.[25,26]

Ex Vivo Lung Perfusion

In previous reports, the Toronto group used EVLP in LTx from HCV donors.[15,16] They demonstrated that irradiation during EVLP decreased the viral load within the first 7 days after transplantation, providing proof of concept for this novel approach. However, it is not clear that EVLP is completely necessary. Our results, in addition to those of Woolley and colleagues,[5] suggest that EVLP is not required to achieve SVR.

Lung Transplantation Outcomes

Previously reported early outcomes are promising with no significant difference in 1- to 2-year survival or graft outcomes.[6,15] Our study adds to a growing body of evidence that demonstrates the safe transplantation of organs from HCV viremic donors to naive recipients. We found no difference in overall survival or graft function at a median follow-up of 438 days, and the rates of acute rejection and infections requiring hospitalization were comparable. The initial trend toward increased rejection in the original DONATE HCV trial[5] (although statistically insignificant) was not seen in our study, and longer follow-up of the DONATE HCV cohort also dispels this concern.[6]

Impact on the Donor Pool

Unfortunately, the age-adjusted rate of overdose deaths increased by more than 4% from 2018 (20.7 per 100,000) to 2019 (21.6 per 100,000) in the United States.[27] Donors from drug overdoses have an 18% rate of HCV infection. However, between 2016 and 2019, only 189 hepatitis C lung transplants were performed nationwide, prompting the need for improvements in use.[7]

Safety

All the previously mentioned studies on DAA have shown good patient tolerance and no major hepatotoxicity. Major hepatotoxicity was not found in our study, and the ALT measurements did not differ. We did not find augmented rejection, infection, or PGD.

Study Limitations

The treatment arm is a prospective, single-center, nonrandomized protocol. However, the control group is a retrospective analysis. Because of uneven cohorts and a small sample size, the study may be particularly prone to type II statistical errors and true differences that are not captured within the current samples. This is a pilot study and therefore not powered to detect differences. Although we report functional outcomes by viral load clearance for our current regimen and administration route, we do not have the data on drug levels required to study the true pharmacodynamics of the crushed drug.

CONCLUSIONS

LTx from HCV viremic donors may expand the donor pool and help reduce waitlist mortality. In concordance with previous studies, we demonstrate excellent early survival and graft outcomes in HCV viremic transplants, with no difference in rejection or infection rates. Because of the high rates of early transmission, we propose preemptive DAA treatment and demonstrate that this approach achieves both a rapid response and SVR without the need for EVLP. Further investigation into potentially shortened treatment courses and long-term outcomes may be warranted (Figure 5).

Conflict of Interest Statement

R.T.C. reports grants or contracts from AbbVie, BMS, Janssen, Gilead, Merck, and Boehringer in the last 36 months, and is part of the Governing Board of the American Association for the Study of Liver Diseases. T.A. reports participation on Merck's Data Safety Monitoring Board or Advisory Board. G.W. was on the 2020 to 2021 ISHLT Program Planning Committee, unpaid. T.G. reports consulting fees not related to this manuscript from eGenesis Bio. All other authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

References

1. Valapour M, Lehr CJ, Skeans MA, Smith JM, Uccellini K, Lehman R, et al. OPTN/SRTR 2017 annual data report: lung. *Am J Transplant*. 2019;19:404-84.

2. Kulkarni HS, Korenblat KM, Kreisel D. Expanding the donor pool for lung transplantation using HCV-positive donors. *J Thorac Dis*. 2019;11:S1942-6.
3. Englum BR, Ganapathi AM, Speicher PJ, Gulack BC, Snyder LD, Davis RD, et al. Impact of donor and recipient hepatitis C status in lung transplantation. *J Heart Lung Transplant*. 2016;35:228-35.
4. Gasink LB, Blumberg EA, Localio AR, Desai SS, Israni AK, Lautenbach E. Hepatitis C virus seropositivity in organ donors and survival in heart transplant recipients. *JAMA*. 2006;296:1843-50.
5. Woolley AE, Singh SK, Goldberg HJ, Mallidi HR, Givertz MM, Mehra MR, et al. Heart and lung transplants from HCV-infected donors to uninfected recipients. *N Engl J Med*. 2019;380:1606-7.
6. Woolley AE, Piechura LM, Goldberg HJ, Singh SK, Coppolino A, Baden LR, et al. The impact of hepatitis C viremic donor lung allograft characteristics on post-transplantation outcomes. *Ann Cardiothorac Surg*. 2020;9:42-8.
7. Li SS, Osho A, Moonsamy P, Wolfe S, Villavicencio MA, Langer N, et al. Outcomes of lung transplantation from HCV viremic donors. *Ann Thorac Surg*. 2021;113:1598-607.
8. Gowda C, Lott S, Grigorian M, Carbonari DM, Saine ME, Trooskin S, et al. Absolute insurer denial of direct-acting antiviral therapy for hepatitis C: a national specialty pharmacy cohort study. *Open Forum Infect Dis*. 2018;5:ofy076.
9. Bethea ED, Gaj K, Gustafson JL, Axtell A, Lebeis T, Schoenike M, et al. Preemptive pangenotypic direct acting antiviral therapy in donor HCV-positive to recipient HCV-negative heart transplantation: an open-label study. *Lancet Gastroenterol Hepatol*. 2019;4:771-80.
10. American College of Gastroenterology. Medications and the liver. Accessed March 30, 2023. https://gi.org/topics/medications-and-the-liver/
11. Snell GI, Yusen RD, Weill D, Strueber M, Garrity E, Reed A, et al. Report of the ISHLT working group on primary lung graft dysfunction, part I: definition and grading—a 2016 consensus group statement of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant*. 2017;36:1097-103.
12. Valapour M, Lehr CJ, Skeans MA, Smith JM, Uccellini K, Lehman R, et al. OPTN/SRTR 2020 annual data report: lung. *Am J Transplant*. 2022;22:438-518.
13. Orrego CM, Cordero-Reyes AM, Estep JD, Seethamraju H, Scheinin S, Loebe M, et al. Atrial arrhythmias after lung transplant: underlying mechanisms, risk factors, and prognosis. *J Heart Lung Transplant*. 2014;33:734-40.
14. Barnes H, Gurry G, McGiffin D, Westall G, Levin K, Paraskeva M, et al. Atrial flutter and fibrillation following lung transplantation: incidence, associations and a suggested therapeutic algorithm. *Heart Lung Circ*. 2020;29:1484-92.
15. Cypel M, Feld JJ, Galasso M, Pinto R, Marks RV, Kuczynski NM, et al. Prevention of viral transmission during lung transplantation with hepatitis C-viraemic donors: an open-label, single-centre, pilot trial. *Lancet Respir Med*. 2020;8:192-201.
16. Feld JJ, Cypel M, Kumar D, Dahari H, Pinto Ribeiro R, Marks N, et al. Short-course, direct-acting antivirals and ezetimibe to prevent HCV infection in recipients of organs from HCV-infected donors: a phase 3, single-centre, open-label study. *Lancet Gastroenterol Hepatol*. 2020;5:649-57.
17. Smolders EJ, Jansen AME, Ter Horst PGJ, Rockstroh J, Back DJ, Burger DM. Viral hepatitis C therapy: pharmacokinetic and pharmacodynamic considerations: a 2019 update. *Clin Pharmacokinet*. 2019;58:1237-63.
18. Pearlman BL, Hinds AE. Review article: Novel antivirals for hepatitis C-sofosbuvir/velpatasvir/voxilaprevir, glecaprevir/pibrentasvir. *Aliment Pharmacol Ther*. 2018;48:914-23.
19. Gupta G, Yakubu I, Bhati CS, Zhang Y, Kang L, Patterson JA, et al. Ultra-short duration direct acting antiviral prophylaxis to prevent virus transmission from hepatitis C viremic donors to hepatitis C negative kidney transplant recipients. *Am J Transplant*. 2020;20:739-51.
20. Durand CM, Bowring MG, Brown DM, Chattergoon MA, Massaccesi G, Bair N, et al. Direct-acting antiviral prophylaxis in kidney transplantation from hepatitis C virus-infected donors to noninfected recipients: an open-label nonrandomized trial. *Ann Intern Med*. 2018;168:533-40.
21. Durand CM, Barnaba B, Yu S, Brown DM, Chattergoon MA, Bair N, et al. Four-week direct-acting antiviral prophylaxis for kidney transplantation from hepatitis C-viremic donors to hepatitis C-negative recipients: an open-label nonrandomized study. *Ann Intern Med*. 2021;174:137-8.
22. Marshall AD, Pawlotsky JM, Lazarus JV, Aghemo A, Dore GJ, Grebely J. The removal of DAA restrictions in Europe–one step closer to eliminating HCV as a major public health threat. *J Hepatol*. 2018;69:1188-96.
23. Morris KL, Adlam JP, Padanilam M, Patel A, Garcia-Cortes R, Chaudhry SP, et al. Hepatitis C donor viremic cardiac transplantation: a practical approach. *Clin Transplant*. 2020;34:e13764.
24. Morris KL, James A, Beaudrie N, Patel A, Garcia-Cortes R, Walsh M, et al. Increased rates of rejection in discordant hepatitis C heart transplantation. *J Heart Lung Transplant*. 2021;40:S75.
25. Lau G, Benhamou Y, Chen G, Li J, Shao Q, Ji D, et al. Efficacy and safety of 3-week response-guided triple direct-acting antiviral therapy for chronic hepatitis C infection: a phase 2, open-label, proof-of-concept study. *Lancet Gastroenterol Hepatol*. 2016;1:97-104.
26. Etzion O, Dahari H, Yardeni D, Issachar A, Nevo-Shor A, Cohen-Naftaly M, et al. Response guided therapy for reducing duration of direct acting antivirals in chronic hepatitis C infected patients: a pilot study. *Sci Rep*. 2020;10:17820.
27. Durand CM, Bowring MG, Thomas AG, Kucirka LM, Massie AB, Cameron A, et al. The drug overdose epidemic and deceased-donor transplantation in the United States: a National Registry Study. *Ann Intern Med*. 2018;168:702-11.

Key Words: lung transplantation, hepatitis C, outcomes, antivirals

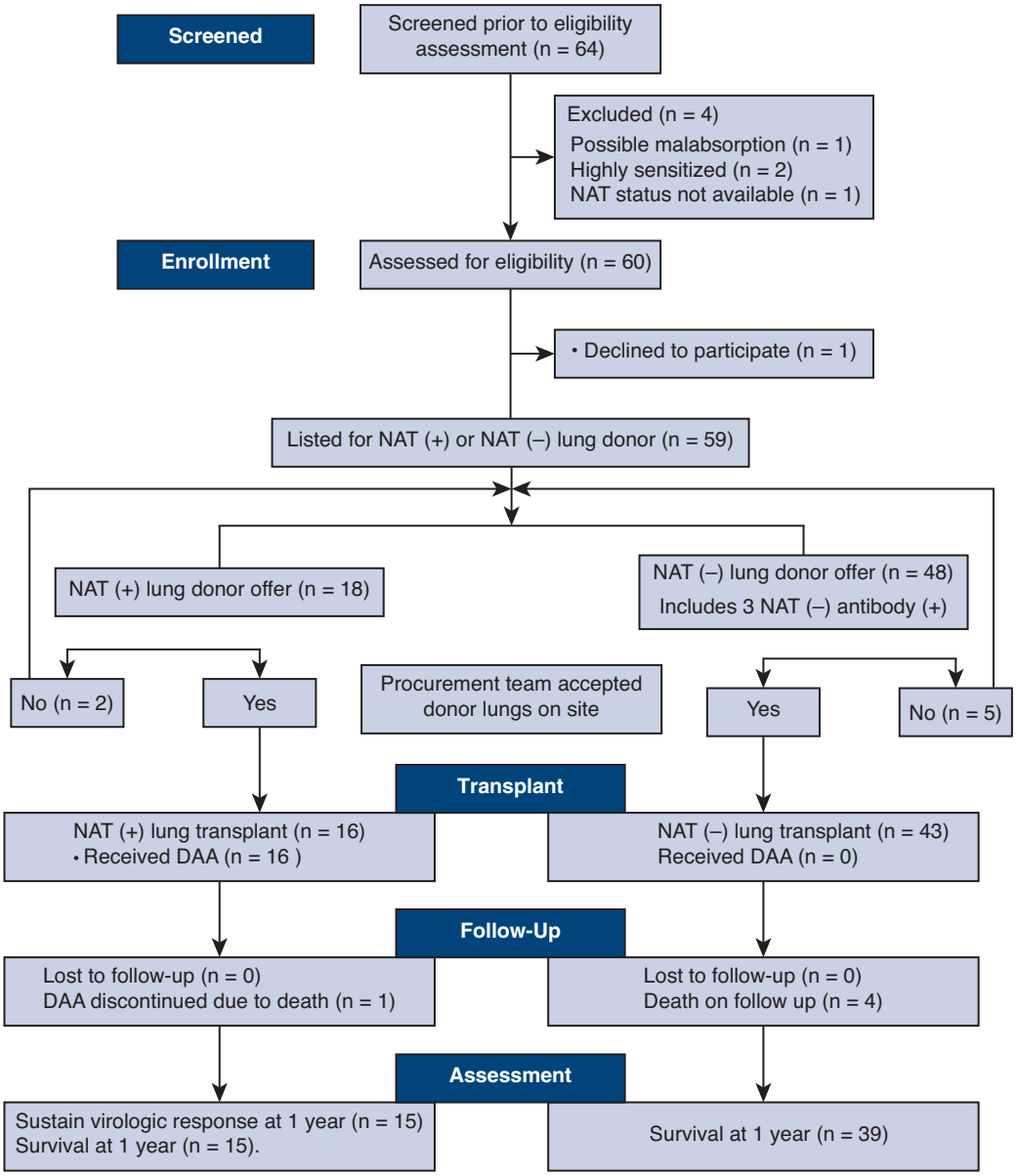


FIGURE E1. Consolidated Standards of Reporting Trial (CONSORT) diagram. *NAT*, Nucleic acid test; *DAA*, direct-acting antiviral.

TABLE E1. Shapiro-Wilk test for normality

	Statistic	*P* value	Normality
Age (recipient)	0.87	<.001	Nonnormal
Initial LAS	0.74	<.001	Nonnormal
LAS at transplant	0.85	<.001	Nonnormal
FEV1	0.94	.007	Nonnormal
FVC	0.97	.133	Normal
mPAP at transplant	0.88	<.001	Nonnormal
Creatinine at transplant	0.32	<.001	Nonnormal
Total bilirubin at transplant	0.32	<.001	Nonnormal
MELD-XI	0.89	<.001	Nonnormal
Oxygen (L/min) requirement at transplant	0.86	<.001	Nonnormal
Age (donor)	0.93	.003	Nonnormal
Total waitlist (d)	0.70	<.001	Nonnormal
Distance (miles)	0.81	<.001	Nonnormal
Ischemic time (h)	0.98	.639	Normal
Hospital length of stay (d)	0.63	<.001	Nonnormal

LAS, Lung Allocation Score; *FEV1*, forced expiratory volume in 1 second; *FVC*, forced vital capacity; *mPAP*, mean pulmonary artery pressure; *MELD*, model for end-stage liver disease.

TABLE E2. Propensity matching

	NAT–	NAT+	SMD	NAT–	NAT+	SMD
n	43	16		16	16	
Age (recipient), mean (SD)	56.49 (12.73)	58.94 (7.92)	0.231	58.50 (9.12)	58.94 (7.92)	0.051
Gender (recipient), mean (SD)	0.53 (0.50)	0.50 (0.52)	0.068	0.50 (0.52)	0.50 (0.52)	<0.001
LAS at transplant, mean (SD)	56.29 (20.51)	42.05 (8.05)	0.914	42.12 (8.20)	42.05 (8.05)	0.009

NAT, Nucleic acid test; *SMD*, standardized mean difference; *SD*, standard deviation; *LAS*, Lung Allocation Score.