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Twelve-Month Outcomes After Transplant of Hepatitis C–Infected Kidneys Into Uninfected Recipients

A Single-Group Trial

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Background: Organs from hepatitis C virus (HCV)–infected deceased donors are often discarded. Preliminary data from 2 small trials, including THINKER-1 (Transplanting Hepatitis C kidneys Into Negative KidnEy Recipients), suggested that HCV-infected kidneys could be safely transplanted into HCV-negative patients. However, intermediate-term data on quality of life and renal function are needed to counsel patients about risk.

Objective: To describe 12-month HCV treatment outcomes, estimated glomerular filtration rate (eGFR), and quality of life for the 10 kidney recipients in THINKER-1 and 6-month data on 10 additional recipients.

Design: Open-label, nonrandomized trial. (ClinicalTrials.gov: NCT02743897)

Setting: Single center.

Participants: 20 HCV-negative transplant candidates.

Intervention: Participants underwent transplant with kidneys infected with genotype 1 HCV and received elbasvir–grazoprevir on posttransplant day 3.

Measurements: The primary outcome was HCV cure. Exploratory outcomes included 1) RAND-36 Physical Component Summary (PCS) and Mental Component Summary (MCS) quality-of-life scores at enrollment and after transplant, and 2) posttransplant renal function, which was compared in a 1:5 matched sample with recipients of HCV-negative kidneys.

Results: The mean age of THINKER participants was 56.3 years (SD, 6.7), 70% were male, and 40% were black. All 20 participants achieved HCV cure. Hepatic and renal complications were transient or were successfully managed. Mean PCS and MCS quality-of-life scores decreased at 4 weeks; PCS scores then increased above pretransplant values, whereas MCS scores returned to baseline values. Estimated GFRs were similar between THINKER participants and matched recipients of HCV-negative kidneys at 6 months (median, 67.5 vs. 66.2 mL/min/1.73 m^2; 95% CI for between-group difference, −4.2 to 7.5 mL/min/1.73 m^2) and 12 months (median, 72.8 vs. 67.2 mL/min/1.73 m^2; CI for between-group difference, −7.2 to 9.8 mL/min/1.73 m^2).

Limitation: Small trial.

Conclusion: Twenty HCV-negative recipients of HCV-infected kidneys experienced HCV cure, good quality of life, and excellent renal function. Kidneys from HCV-infected donors may be a valuable transplant resource.

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Kidney transplantation extends life, improves quality of life, and reduces health care costs (1, 2). Waiting times for deceased-donor kidney transplants exceed 5 years in many areas, and 5% to 8% of eligible patients die each year while on the waitlist (3). Yet, approximately 800 kidneys from donors with hepatitis C virus (HCV) infection were discarded in the United States in 2016. Hundreds more kidneys from HCV-infected donors were never procured because of concern that no center would accept them; these organs go uncounted in registry data. Maximizing use of good-quality HCV-infected organs could be a substantial opportunity to expand access to kidney transplantation (4, 5).

Although organs from HCV-infected donors have historically been transplanted only into recipients with preexisting HCV infection, direct-acting anti-HCV drugs achieve cure rates greater than 95% with well-tolerated side effects, thus enlarging the pool of organs for waitlisted patients who might consider accepting HCV-infected organs (6, 7). Over the past decade, the opioid epidemic has driven an increase in the number of HCV-infected deceased donors, who are often young (8). Our group conducted the THINKER (Transplanting Hepatitis C Kidneys Into Negative KidnEy Recipients) trial, in which HCV-infected kidneys were transplanted into HCV-negative recipients. The design involved open-label treatment of all participants with elbasvir–grazoprevir when HCV was detected, with the rationale that this approach should minimize HCV-related risks. In 2017, we reported 6-month outcomes for the first 10 recipients, all of whom were cured and experienced good allograft function (9). EXPANDER (Exploring Renal Transplants Using Hepatitis C Infected Donors for HCV Negative Recipients) reported HCV cure among

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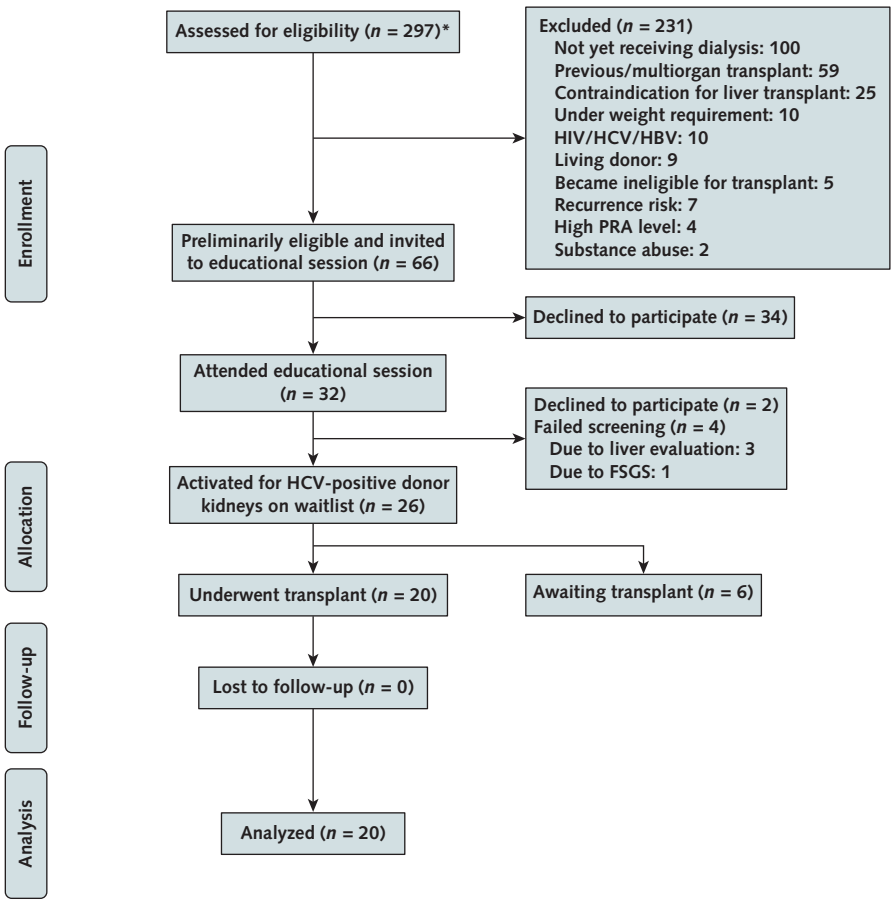
Figure 1. Flow chart of recruitment, enrollment, and follow-up of study participants.



Data are as of 28 June 2017, the date of the 20th kidney transplant. Between the completion of THINKER-1 and the end of THINKER-2, 12 additional patients were prescreened and 41 who had been excluded because they were not receiving dialysis subsequently started dialysis, but among these 53 patients, 25 were newly recognized to have other reasons for exclusion. FSGS = focal segmental glomerulosclerosis; HBV = hepatitis B virus; HCV = hepatitis C virus; PRA = panel reactive antibody; THINKER = Transplanting Hepatitis C kidneys Into Negative KidnEy Recipients.
* Participants met criteria for blood type, age, and priority based on waiting time or time on dialysis on the kidney transplant waitlist at our institution.

all 10 recipients of HCV-infected kidneys who received HCV treatment at the time of transplant. EXPANDER did not restrict transplantation to donors infected with HCV genotype 1 and therefore used elbasvir–grazoprevir supplemented with sofosbuvir for 12 weeks for recipients of kidneys infected with genotype 2 or 3 HCV (10).

Despite these favorable short-term results, key intermediate-term end points, such as durable HCV cure and 1-year graft function, remain unknown. In addition, no information is available about posttransplant quality of life for recipients, who may have a different experience due to concerns about stigma or the risks of HCV infection or treatment. Such data are needed for this practice to become the standard of care.

Thus, we continued the THINKER trial and performed an additional 10 transplants using kidneys from HCV-infected donors. The aims of the study were to determine HCV treatment outcomes and adverse events in the expanded cohort of 20 patients, assess whether allograft function showed any evidence of durable injury from HCV, and describe trajectories in quality of life of recipients after transplant of HCV-infected kidneys.

METHODS

THINKER was a single-group clinical trial conducted at the Hospital of the University of Pennsylvania and approved by the University of Pennsylvania Institutional Review Board (ClinicalTrials.gov: NCT02743897). Adverse events and outcomes were also reviewed by a data and safety monitoring board. The main purpose of THINKER was to demonstrate feasibility and generate preliminary data; no power calculation was performed.

Participant criteria targeted patients who were anticipated to have prolonged waiting times for HCV-negative kidney transplants and sought to exclude patients with conditions that would substantially elevate risks for liver disease, death, or allograft failure after transplant (9). Inclusion criteria included receipt of long-term dialysis; having no more than 548 days of priority status on the kidney transplant waitlist at our

institution; having blood type A, B, or O; being aged 40 to 65 years; and having a panel reactive antibody level less than 97%. Participants were seronegative for HIV, HCV RNA, and hepatitis B surface antigen and had no acceptable living kidney donor. No substantial evidence of liver disease was detected via FibroScan (Echosens) imaging or hepatic serologic testing. Evaluation by a hepatologist and/or a transplant surgeon had to show no overt contraindication for liver transplant in the unlikely event of acute liver failure after HCV transmission during kidney transplant. **Table 1** of **Supplement 1** (available at Annals.org) lists all inclusion and exclusion criteria and the rationale for each, and the protocol is provided in **Supplement 2** (available at Annals.org). All participants underwent the same informed-consent process: 1) a telephone call from 1 of the principal investigators describing the study; 2) a physician-led, in-person educational session that addressed general risks of HCV infection as well as the potential risks and benefits of participation in the THINKER study; and 3) a discussion with the patient, including review of the THINKER consent, conducted by 1 of the principal investigators at least 24 hours after the educational session.

Criteria for kidney allograft suitability included donor age 60 years or younger, absence of diabetes, and kidney donor profile index (KDPI) score less than 85%. The KDPI is a continuous metric (ranging from 1% to 100%, with lower scores being better) that estimates risk for allograft failure based on characteristics of deceased donors (11). Because of historical data showing that HCV-seropositive kidneys have worse posttransplant outcomes, donor HCV seropositivity substantially increases (worsens) the KDPI score. However, the association of donor HCV infection with allograft failure may be confounded by the fact that the data were chiefly derived from recipients with pretransplant HCV infection and poor treatment options (12). In the U.S. organ allocation process, the KDPI score is reported for all deceased-donor kidney offers.

Donors had positive results for HCV on qualitative nucleic acid testing. All donors had genotype 1 HCV infection, which is highly responsive to elbasvir–grazoprevir, a drug approved by the U.S. Food and Drug Administration only for genotypes 1 and 4 (6). We developed a process for genotyping donors during allocation (13).

Posttransplant Antiviral and Immunosuppression Therapies

The quantity of HCV RNA in plasma or serum was determined in the molecular pathology laboratory at our hospital using the COBAS AmpliPrep/COBAS TaqMan HCV Test, version 2.0 (Roche Diagnostics). Participants were assessed for HCV transmission on posttransplant day 3 (±1 day, per protocol). Participants started daily use of elbasvir–grazoprevir when results were positive. Participants with viral genotype 1a were assessed for baseline nonstructural protein 5A (NS5A) resistance-associated substitutions to determine treatment duration and need for ribavirin. The protocol specified 12 weeks of elbasvir–grazoprevir for participants infected with HCV who did not have NS5A resistance-associated substitutions and 16 weeks of elbasvir–grazoprevir with oral ribavirin for those infected with HCV who did have NS5A resistance-associated substitutions (14).

All participants received our standard induction regimen of intravenous corticosteroids and rabbit antithymocyte globulin, followed by oral tacrolimus, mycophenolate mofetil, and prednisone. Participants underwent routine screening for anti-HLA donor-specific antibody at 1, 3, 6, and 12 months after transplant and in the event of allograft dysfunction requiring biopsy (see the Center Induction and Immunosuppression Protocol section in **Supplement 1**).

Outcomes

The primary outcomes were HCV cure (sustained virologic response at 12 weeks, defined as undetectable HCV RNA 12 weeks after completion of HCV therapy) and adverse events attributable to HCV infection or its therapy during 1 year of follow-up. Secondary outcomes included spontaneous HCV clearance without treatment and allograft failure. Prospectively collected, exploratory outcomes included quality of life, renal allograft function at 6 and 12 months, and proteinuria (15–18).

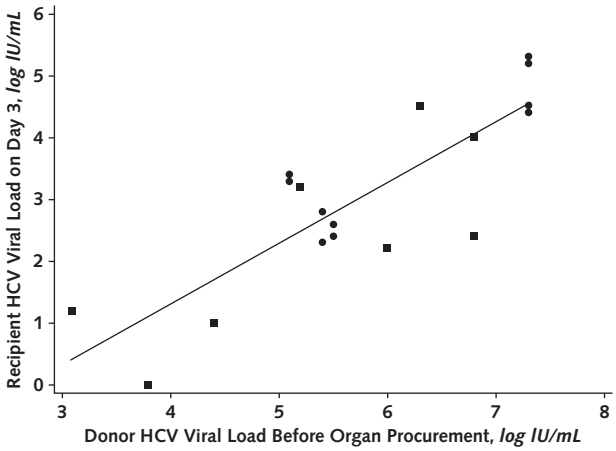
Quality of life was assessed via in-person administration of the RAND-36 questionnaire at enrollment and posttransplant weeks 4, 16, 24, and 52 (19, 20). The Physical Component Summary (PCS) and Mental Component Summary (MCS) scores were calculated from the 8 RAND-36 domains and normalized to population standards, with higher scores indicating better quality of life (19).

Table 1. Characteristics of Kidney Transplant Recipients in the THINKER Study (*n* = 20)

Variable	Value
Mean age at consent (SD), *y*	56.3 (6.7)
Female, *n (%)*	6 (30)
Black, *n (%)*	8 (40)
Cause of end-stage renal disease, *n (%)*	
Diabetes	9 (45)
Hypertension	3 (15)
Polycystic kidney disease	3 (15)
IgA nephropathy	2 (10)
Congenital obstructive nephropathy	1 (5)
Chronic interstitial nephritis	1 (5)
Secondary focal and segmental glomerulosclerosis	1 (5)
Blood type, *n (%)*	
A	6 (30)
B	1 (5)
O	13 (65)
Median calculated panel reactive antibody level (range)	0 (0–48)
History of diabetes, *n (%)*	10 (50)
Prior transplant, *n (%)*	0 (0)
Median time receiving dialysis at enrollment (IQR), *d*	352.5 (232–403)
Median weight (IQR), *kg*	86.2 (77.6–98.9)
Highest education level, *n (%)*	
High school diploma	6 (30)
Some college/trade school	4 (20)
College degree	6 (30)
Master's degree or higher	4 (20)

IQR = interquartile range; THINKER = Transplanting Hepatitis C kidneys Into Negative KidnEy Recipients.

Figure 2. HCV viral load detected by polymerase chain reaction among kidney transplant recipients (n = 18) and their deceased donors (n = 13).



Five donors each had 2 kidneys recovered for THINKER participants (*circles*). The other 8 donors each had 1 kidney recovered for a THINKER participant (*squares*). The last 2 donors had detectable HCV on qualitative nucleic acid testing but insufficient samples to obtain a quantitative HCV viral load (not shown). Donor and recipient HCV RNA levels were strongly correlated. In a linear regression model, the β-coefficient was 0.95 (95% CI, 0.60 to 1.31; $P < 0.001$), meaning that the slope of the line is close to 1. HCV = hepatitis C virus; THINKER = Transplanting Hepatitis C kidneys Into Negative KidnEy Recipients.

Renal function was assessed using estimated glomerular filtration rate (eGFR), which was calculated with the 4-variable MDRD (Modification of Diet in Renal Disease) equation (21, 22). We compared eGFR between THINKER participants and 2 sets of matched recipients of HCV-negative kidneys identified using Organ Procurement and Transplantation Network (OPTN) registry data. The Organ Procurement and Transplantation data system includes data on all donors, waitlisted candidates, and transplant recipients in the United States, submitted by the members of OPTN. The Health Resources and Services Administration, U.S. Department of Health and Human Services, provides oversight to the activities of the Organ Procurement and Transplantation contractor. Transplant centers submit serum creatinine data to the contractor at 6 and 12 months after transplant (23).

Statistical Analysis

We summarized transplant recipient characteristics, HCV RNA values, and adverse events during posttransplant follow-up. To assess the correlation between donor HCV RNA levels and initial posttransplant levels among recipients, we fit a mixed-effects linear regression model for recipient HCV RNA level, with clustering on donor. We needed to account for clustering on donor because 5 donors each provided 2 kidneys to THINKER participants (10 total transplants) and 10 others donated 1 kidney to participants (10 total transplants). We used paired t tests to compare within-patient changes in PCS and MCS scores from before the transplant to 12 months after (see the Methods section in **Supplement 1**).

For the exploratory analysis of eGFR and serum creatinine level, we generated 2 sets of matched comparators. We restricted comparators to recipients of deceased-donor kidney transplants from 1 January 2014 through 1 September 2016. Because THINKER was conducted at a high-volume transplant center, we restricted comparators to kidney recipients at centers in the top 20% by volume of deceased-donor transplants. We also restricted comparators to recipients who met nominal THINKER inclusion and exclusion criteria (see the Methods section in **Supplement 1**). Comparators in the first group ("allocation KDPI") were matched on KDPI scores used by OPTN to allocate the THINKER allografts. For the second group ("optimal KDPI"), we recalculated THINKER KDPI scores as if donors were HCV-negative, which has the effect of assigning the kidney a better quality than the allocation KDPI.

We implemented 1:5 matching without replacement by using the R package designmatch (24). The algorithm exactly matched THINKER participants and OPTN comparators on sex, race, and cause of end-stage renal disease. Subject to these constraints, we used optimal matching to minimize the total Mahalanobis distance based on age at transplant, panel reactive antibody level, donor KDPI score, and a propensity score for the THINKER status (25). We completed matching before examining outcomes (26) and assessed balance using the cobalt package in R (27).

We compared eGFRs and serum creatinine levels between THINKER participants and matched comparators and calculated between-group differences and 95% CIs using m-statistics (28–31). Statistical analyses were performed with R (R Foundation for Statistical Computing) and Stata, version 14.0 (StataCorp).

Role of the Funding Source

Merck funded the study and provided elbasvir–grazoprevir through an investigator-initiated grant. The principal investigators (D.S.G. and P.P.R.) designed the trial; wrote the protocol; and had complete control over data collection, analysis, interpretation, manuscript writing, and the decision to submit the manuscript for publication. Merck staff reviewed the manuscript before submission. Dr. Reese took final responsibility for submitting the manuscript.

RESULTS

Figure 1 shows study recruitment and enrollment. The first 10 transplants occurred between June and November 2016 (THINKER-1). After the data and safety monitoring board reviewed the initial results, the next 10 transplants were done between February and June 2017 (THINKER-2). Sixty-six patients were contacted by telephone, 32 (48%) attended an educational session, 30 (45%) consented to screening, 28 (42%) were eligible, and 26 (39%) were enrolled. Twenty HCV-negative patients underwent transplant with HCV-infected kidneys from 15 donors. The mean participant age was 56.3 years (SD, 6.7), 70% were male, and 40% were black (**Table 1**). The median number of days between

activation in the allocation system for HCV-infected allografts and transplant was 57 (interquartile range [IQR], 12 to 91 days).

The median donor KDPI score was 46% (IQR, 33% to 54%). All donors were categorized as meeting U.S. Public Health Service criteria for increased risk for bloodborne viral infection because of injection drug use or other behaviors. Seventeen allografts were from donors with genotype 1a HCV infection. No kidneys underwent perfusion pumping (**Table 2** of **Supplement 1**).

Donor HCV RNA levels ranged from 1332 to 20 513 681 IU/mL (median, 290 760 IU/mL) among 13 donors; 2 donors had insufficient serum available to assess quantitative HCV RNA (**Figure 2**). Nineteen of 20 kidney recipients had detectable HCV RNA at the first assessment (postoperative days 2 to 4). One patient had an undetectable HCV RNA level on day 2 that increased to 288 IU/mL on day 5. Donor and recipient HCV RNA levels were strongly correlated (β-coefficient for linear regression model, 0.95 [95% CI, 0.60 to 1.31]; $P < 0.001$). Higher HCV RNA level on day 3 was correlated with longer time to the first day of undetectable viral load (**Figure 1** of **Supplement 1**; **Table 3** of **Supplement 1** shows HCV detectability over time).

In all 20 participants, HCV RNA was undetectable within 4 weeks of initiation of HCV therapy. Seventeen participants were treated for 12 weeks. Three patients with NS5A mutations received 16 weeks of therapy with elbasvir–grazoprevir and were prescribed ribavirin per protocol. One patient with anemia received only 63 days of ribavirin, and another received only 54 days. All participants achieved sustained virologic response at 12 weeks with their initial course of treatment. The 10 THINKER-1 participants remained HCV-negative 12 months after transplant.

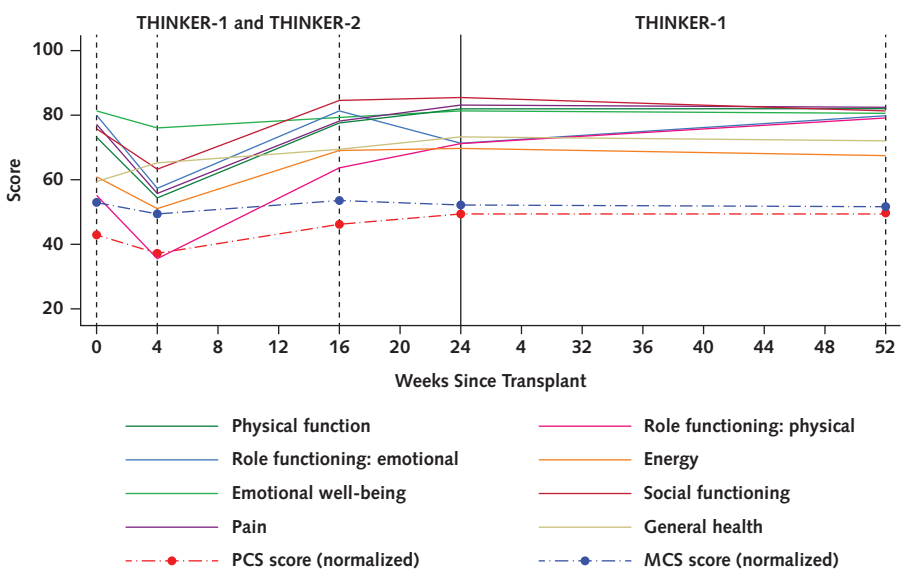
Adverse Events

Five patients had transient elevations in aminotransferase levels (**Table 4** of **Supplement 1**). As noted previously (9), before THINKER participation 1 patient had received a diagnosis of IgA nephropathy (demonstrated on biopsy of the native kidney) as part of the diagnostic work-up for chronic kidney disease. After undergoing transplant with an HCV-infected kidney, this patient completed 12 weeks of elbasvir–grazoprevir therapy, achieved HCV cure, and subsequently developed proteinuria. Spot urine protein–creatinine ratio showed that the estimated 24-hour urine protein excretion was 400 mg at 6 months after transplant and peaked at 2.6 g by 8 months. Allograft biopsy showed focal segmental glomerulosclerosis. Podocyte foot process effacement was limited, with no evidence of recurrent IgA nephropathy or transplant glomerulopathy. The patient was treated with an angiotensin-receptor blocker, and proteinuria decreased to an estimated 374 mg per 24 hours at 13 months after transplant (**Table 5** of **Supplement 1**). During the posttransplant period, the patient's creatinine level never exceeded 80 µmol/L (0.9 mg/dL).

No additional serious adverse events were adjudicated as being related to HCV or elbasvir–grazoprevir. Two patients were rehospitalized within 30 days of transplant (**Table 6** of **Supplement 1**).

No patients experienced allograft rejection. One patient developed de novo donor-specific antibodies, and another had weakly positive pretransplant donor-specific antibodies that intensified by 3 months after

Figure 3. Trajectories of PCS, MCS, and domain scores over time among 20 HCV-negative recipients of HCV-infected kidneys.



Vertical lines represent when surveys were conducted. Twenty patients were analyzed at the screening visit (week 0), 19 were analyzed at 24 wk, and 10 were analyzed at 52 wk. HCV = hepatitis C virus; MCS = Mental Component Summary; PCS = Physical Component Summary; THINKER = Transplanting Hepatitis C kidneys Into Negative KidnEy Recipients.

Table 2. Comparison of eGFRs and Creatinine Levels at 6 and 12 Months Between THINKER Participants and Matched Comparator Recipients of Kidneys From HCV-Negative Donors

Variable	Median Value (IQR)			Difference Between Matched Sets of THINKER Recipients and Allocation Comparators (95% CI)‡	*P* Value for Comparison With Allocation Comparators‡	Difference Between Matched Sets of THINKER Recipients and Optimal Comparators (95% CI)‡	*P* Value for Comparison With Optimal Comparators‡
	THINKER Recipients (n = 10 or 20)*	Matched Allocation KDPI Comparators (n = 50 or 100)*	Matched Optimal KDPI Comparators (n = 50 or 100)*†				
6-mo outcomes							
Creatinine level					<0.001		0.37
μmol/L	103 (90 to 118)	117 (95 to 150)	106 (88 to 124)	−20 (−29 to −11)		−4 (−11 to 4)	
mg/dL	1.2 (1.0 to 1.3)	1.3 (1.1 to 1.7)	1.2 (1.0 to 1.4)	−0.2 (−0.3 to −0.1)		−0.04 (−0.1 to 0.1)	
eGFR, *mL/min/1.73 m²*	67.5 (57.8 to 85.7)	56.6 (48.3 to 74.6)	66.2 (55.3 to 81.9)	10.5 (4.8 to 16.2)	<0.001	1.6 (−4.2 to 7.5)	0.56
12-mo outcomes							
Creatinine level					<0.001		0.33
μmol/L	98 (84 to 111)	106 (95 to 141)	97 (80 to 115)	−21 (−31 to −12)		−4 (−12 to 4)	
mg/dL	1.1 (1.0 to 1.3)	1.2 (1.1 to 1.6)	1.1 (0.9 to 1.3)	−0.2 (−0.4 to −0.1)		−0.04 (−0.1 to 0.1)	
eGFR, *mL/min/1.73 m²*	72.8 (58.6 to 74.4)	57.7 (46.0 to 68.6)	67.2 (55.8 to 78.3)	13.6 (7.9 to 19.2)	<0.001	1.4 (−7.2 to 9.8)	0.76
Delayed graft function, *n* (%)	5 (25)	45 (45)	32 (32)	NA	0.076	NA	0.59

eGFR = estimated glomerular filtration rate; HCV = hepatitis C virus; IQR = interquartile range; KDPI = kidney donor profile index; NA = not applicable; THINKER = Transplanting Hepatitis C kidneys Into Negative KidnEy Recipients.
* As expected, 20 THINKER recipients had creatinine and eGFR values at 6-mo follow-up and 10 THINKER recipients had creatinine and eGFR values at 1-y follow-up. Each THINKER recipient was matched to 5 comparators.
† This group comprised recipients of kidneys with KDPI scores that were recalculated as if donors were HCV-seronegative.
‡ For between-group comparisons of creatinine level and eGFR, the comparator value was subtracted from the THINKER value. The differences, CIs, and *P* values were calculated using m-statistics (see the Methods section in **Supplement 1** [available at Annals.org]), which account for small numbers of THINKER recipients and the 1:5 matching. For between-group comparisons of delayed graft function, the *P* values were calculated using conditional logistic regression.

transplant. Both of these patients subsequently had undetectable donor-specific antibodies at the last follow-up. Two other patients developed weakly positive de novo donor-specific antibodies that remained detectable at the last follow-up (**Table 7** of **Supplement 1**). These abnormalities were detected during routine screening.

Quality of Life

Figure 3 shows trajectories in quality-of-life domains. Normalized mean PCS scores decreased at 4 weeks and then increased steadily to above pretransplant levels (the mean improvement in PCS score from consent to 12 months after transplant was 6.7 [P = 0.012]). Normalized mean MCS scores also decreased at 4 weeks and subsequently returned to baseline and remained stable by 12 months (P = 0.47).

Renal Function Outcomes

Five recipients had delayed graft function, defined as receipt of dialysis in the first week after transplant. The median creatinine level was 103 μmol/L (1.2 mg/dL) (IQR, 90 to 118 μmol/L [1.0 to 1.3 mg/dL]) at 6 months after transplant (n = 20) and 98 μmol/L (1.1 mg/dL) (IQR, 84 to 111 μmol/L [1.0 to 1.3 mg/dL]) at 12 months after transplant (n = 10) (**Table 2**). Trends in serum creatinine level are shown in **Figure 2** of **Supplement 1**.

The 20 THINKER participants and comparators were well matched, with standardized differences less than 0.1 for all covariate means (**Table 8** of **Supplement 1**; **Figure 3** of **Supplement 1** shows generation of the comparator cohort). The eGFRs were significantly better for THINKER participants than for allocation comparators (who underwent transplant using kidneys from donors with similar KDPI scores) at 6 months (median, 67.5 vs. 56.6 mL/min/1.73 m^2; CI for between-group difference, 4.8 to 16.2 mL/min/1.73 m^2) and 12 months (median, 72.8 vs. 57.7 mL/min/1.73 m^2; CI for between-group difference, 7.9 to 19.2 mL/min/1.73 m^2). THINKER participants had eGFRs that were similar to those among optimal comparators (based on donor KDPI scores that were recalculated as if the donors did not have HCV infection) at 6 months (CI for between-group difference, −4.2 to 7.5 mL/min/1.73 m^2) and 12 months (CI for between-group difference, −7.2 to 9.8 mL/min/1.73 m^2) (**Table 2** and **Figure 4** of **Supplement 1**).

DISCUSSION

In this report of outcomes in the first year after transplant for HCV-negative recipients of kidneys from HCV-infected donors, we show cure rates of 100% for acute HCV infection with a single round of antiviral treatment despite concomitant use of intense immunosuppression. Only 1 serious adverse event occurred (proteinuria adjudicated as being possibly related to HCV and with substantial improvement after treatment). Self-reported physical quality of life improved from pretransplant levels, and mental quality of life was similar to pretransplant levels. All 20 recipients had excellent renal allograft function that was better than among well-matched comparators with similar kidney

quality scores, suggesting that HCV did not cause clinically important injury to these kidneys. These encouraging findings should stimulate the transplant community to invest effort in expanding utilization of HCV-infected kidneys, generating best practices around education and consent, and developing pathways to pay for posttransplant HCV treatment (5).

Infection with HCV can injure kidneys via several biological mechanisms, but posttransplant allograft injury could be prevented or alleviated by prompt administration of direct-acting antiviral agents (32, 33). Renal function among THINKER participants at 6 and 12 months was better than among those in our first comparator group (allocation KDPI), who received kidneys with similar allocation KDPI scores. The eGFRs among THINKER participants closely resembled those in the second comparator group, who received kidneys that had better KDPI scores than the THINKER kidneys. These results suggest that the THINKER donor kidneys were not substantially harmed by HCV, which may be explained by a potential short duration of HCV infection in the donors from recent opioid abuse or the detailed organ-screening process that included serial assessments of creatinine level, proteinuria, and urine output. However, these results may also suggest that previous reports of worse posttransplant outcomes with kidneys from HCV-infected donors were at least partially due to recipient factors rather than donor factors. Specifically, during the era in which the KDPI was developed, nearly all kidneys from HCV-seropositive donors were transplanted into HCV-infected patients, so the increased risk for graft failure associated with HCV-seropositive kidneys may have been due to medical comorbidities among HCV-positive recipients. If validated, these findings from THINKER suggest that KDPI scores may need rescaling to diminish the predicted negative effect of HCV on allograft outcomes.

The physical quality-of-life trajectories are reassuring and are consistent with prior research in kidney transplant recipients (34–36). The MCS scores for THINKER participants generally returned to pretransplant levels, whereas some prior studies reported improvements in mental quality of life after kidney transplant (34, 36). However, few studies measured quality of life often enough to generate posttransplant trajectories (34). In THINKER, both physical and mental quality of life declined in the first 4 weeks after transplant, which likely reflects the cumulative effects of abdominal surgery, an immunosuppression regimen with diverse adverse effects, and early complications. These results suggest that concerns about adverse effects of HCV infection, stigma, spreading the virus to close contacts, or the burden of HCV treatment did not substantially impair quality of life and support our belief that patients who are willing to consider donor-derived HCV infection are highly motivated by the longevity and quality-of-life benefits associated with no longer needing long-term dialysis (37). Future studies should consider patient-reported outcome measures to better assess the decision-making or posttransplant experience of patients who receive HCV-infected kidneys.

This trial has limitations. The results may not be generalizable to other populations or centers with different protocols. For example, different induction or immunosuppression therapies might affect HCV cure rates. Larger trials must confirm the results and define complication rates with better precision. For example, 3 of the 20 THINKER participants developed de novo donor-specific antibodies, a rate higher than was reported in some other studies (38, 39). In larger studies, it is likely that some patients will not respond to initial antiviral therapy, such as in the setting of medication nonadherence or viral resistance. In general, as a result of trial participation, THINKER participants might have had better medication adherence or self-care behaviors than the general transplant population. We also restricted transplants to organs from donors with genotype 1 HCV infection. However, pangenotypic direct-acting antiviral agents may make this genotype restriction unnecessary in the future (40). Future studies should follow patients for a longer time to fully assess for possible risks of transient HCV infection, such as cardiovascular disease or diabetes.

These results should encourage transplant leaders, organ procurement organizations, and payers to consider infrastructure investments to augment the use of HCV-infected kidneys (2, 41). Direct-acting antiviral agents should be available promptly once hepatitis C viremia is detected, taking into consideration dose adjustment for renal impairment, especially for patients with delayed graft function who are dialysis-dependent. Moreover, because donor HCV genotyping is not routinely available, transplant programs should have access to a selection of HCV therapies sufficient to treat all genotypes. Given the higher cost and worse outcomes with dialysis versus kidney transplant, health systems and insurance programs should consider paying for direct-acting antiviral treatment if this practice proves safe and efficacious in larger studies. Trials are also needed to examine the use of nonrenal organs, such as hearts, from HCV-infected donors. Small trials in recipients of HCV-infected thoracic organs have reported sustained virologic response rates of 100% (42, 43).

In summary, this trial provides reassuring (albeit preliminary) evidence that kidneys from HCV-infected donors may be safely transplanted into HCV-negative recipients. The 20 recipients achieved a 100% cure rate, excellent renal function, and stable to improved quality of life. Kidneys from HCV-infected donors may represent an important opportunity to expand the donor pool and benefit patients without HCV who are well informed about risks.

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Reproducible Research Statement: *Study protocol:* See Supplement 2. *Statistical code:* Available from Dr. Reese (e-mail, peter.reese@uphs.upenn.edu). *Data set:* Deidentified elements of the study data set will be shared with investigators, with case-by-case review to ensure confidentiality of participants (e-mail, peter.reese@uphs.upenn.edu).

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