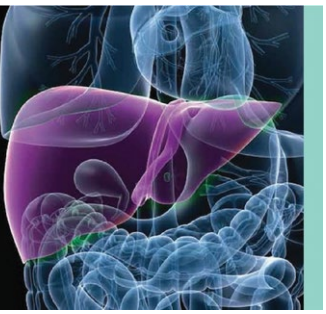

Pro: Use of Hepatitis C Virus–Positive Donors Should Be Considered Standard of Care

William A. Werbel, M.D., and Christine M. Durand, M.D.

KEY POINTS

- Hundreds of high-quality deceased-donor organs are discarded each year because of detection of hepatitis C infection, delaying lifesaving transplants.
- Multiple studies have shown that direct-acting antiviral (DAA) therapy is both safe and highly effective in preventing or treating donor-derived hepatitis C infection in patients with solid organ transplant.
- Pan-genotypic DAA therapy is cost-effective, and insurance coverage has not proven to be a major issue for patients post transplant.

There are more than 125,000 individuals in need of solid organ transplant in the United States.[1] Depending on the organ type, national data indicate that approximately half of these patients will undergo transplantation within 1 year, whereas nearly 20% will be removed from the wait list because of clinical deterioration or death.[1] Expanding the donor pool to include hepatitis C virus–infected (HCV^+) donor organs is an important means to bridge this gap.

HCV^+ ORGANS ARE INCREASINGLY AVAILABLE YET FREQUENTLY DISCARDED

Due to the catastrophic opiate epidemic, the proportion of deceased HCV^+ donors has risen significantly, with an overall prevalence rate of 8.5% among potential donors and more than 30% prevalence rate among those dying of drug overdose.[2] Nearly 4% of donors may be viremic by screening nucleic acid test (NAT) at donation. These potential donors are younger and have little comorbidity.[2,3] Despite these qualities, HCV^+ organs are discarded at high rates. A 2018 study showed 3.7-fold higher discard of HCV^+ kidneys compared with matched HCV-uninfected (HCV^-) donor kidneys, including discard of 388 HCV^+ kidneys in 2017 alone.[3]

Abbreviations: anti-HBc^+, hepatitis B core antibody–positive; AWP, average wholesale price (US $); CMV, cytomegalovirus; DAA, direct-acting antiviral; DNH, *de novo* hepatitis; FW, follow-up week; HCV^+, hepatitis C virus–infected; HCV^-, hepatitis C virus-uninfected; Ig, immunoglobulin; IU, international unit; NAT, nucleic acid test; POD, postoperative day; SVR, sustained virological response; TW, treatment week.

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TABLE 1. RELATIVE COSTS OF COMMON THERAPIES USED FOR TRANSPLANT RECIPIENTS

Indication	Therapy	Treatment Cost (AWP*)
HCV infection	Glecaprevir/pibrentasvir (Mavyret)	$47,520/12 weeks
	Elbasvir/grazoprevir (Zepatier)	$65,520/12 weeks
	Sofosbuvir/velpatasvir (Epclusa)	$89,712/12 weeks
	Ledipasvir/sofosbuvir (Harvoni)	$113,400/12 weeks
	Daclatasvir (Daklinza) + sofosbuvir (Sovaldi)	$176,400/12 weeks
Hepatitis B virus infection	Entecavir (Baraclude)	$15,996.60/12 months
	Lamivudine (Epivir)	$5,799.96/12 months
Cytomegalovirus infection	Valganciclovir (Valcyte)	$47,684.52/6 months
End organ support	Hemodialysis (Maintenance)	$250,000/12 months
	Left ventricular assist device (Placement)	$732,000/once
	Left ventricular assist device (Maintenance)	$30,000-$580,000/12 months

Estimates based on Lexicomp drug data (https://online.lexi.com) and UnitedHealth Group Analysis (2009-2015). (US $).

DAA Therapy Safely and Effectively Cures HCV Infection in Transplant Recipients

Discard of HCV+ donor organs should be reconsidered because DAA therapy has revolutionized HCV treatment via well-tolerated, highly effective regimens (Table 1) exhibiting sustained virological response rates (SVR12) greater than 95%.[4] Several large series demonstrate that DAA therapy is equally effective among HCV+ transplant recipients, with cure rates near 100% predominately using 12-week, interferon- and ribavirin-free regimens.[5] As a result of these data, national guidelines clearly support the use of DAAs to cure HCV post transplant.[4]

The organ shortage, increase in availability of HCV+ donors, and success with DAAs have prompted a series of single-center trials of HCV NAT+ donor organs into HCV− recipients (HCV D+/R−), with excellent outcomes. First, in the Transplanting Hepatitis C Kidneys into Negative Kidney Recipients (THINKER) trial,[6] 10 HCV D+/R− transplants using genotype 1 NAT+ kidneys were performed with preemptive elbasvir/grazoprevir for 12 weeks after detection of viremia (seen in all patients by day 3). Our center conducted the Exploring Renal Transplants Using Hepatitis C Infected Donors for HCV Negative Recipients (EXPANDER) trial,[7] performing 10 HCV D+/R− transplants using prophylactic

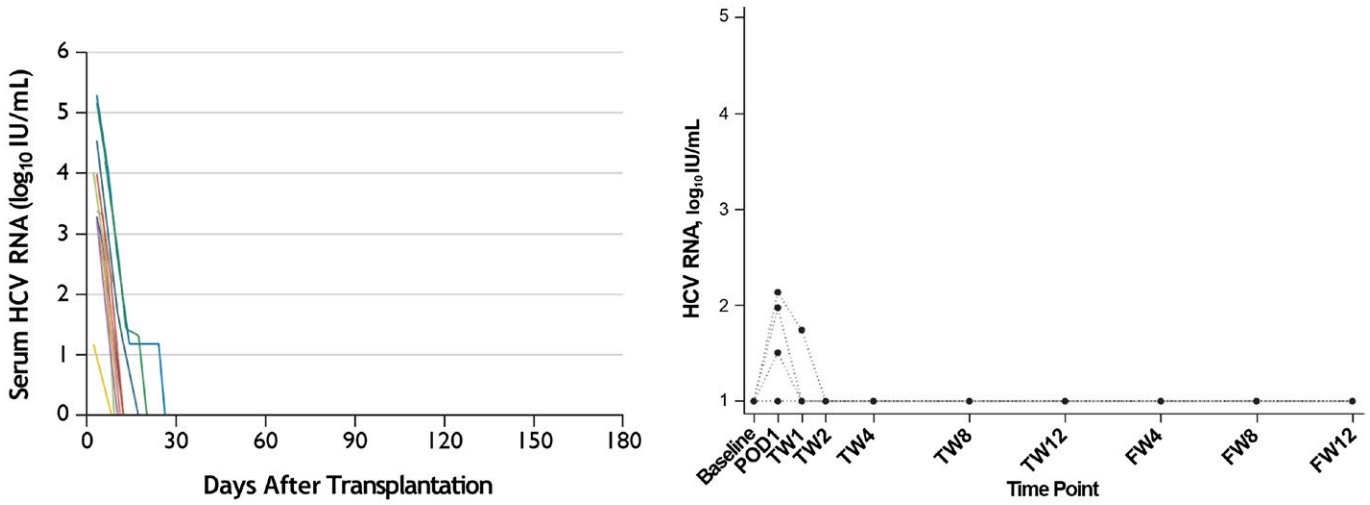

FIG 1 HCV RNA serum levels in HCV-uninfected recipients of kidneys from HCV-infected donors. (Left) Data from the THINKER trial[6] in which 10 participants received preemptive posttransplant DAA therapy: 12 weeks of elbasvir/grazoprevir once HCV RNA was detected. (Right) Data from the EXPANDER trial[7] in which 10 participants received prophylactic pretransplant and posttransplant DAA therapy: elbasvir/grazoprevir +/– sofosbuvir for 12 to 16 weeks. Abbreviations: FW, follow-up week; IU, international unit; POD, postoperative day; TW, treatment week. Adapted with permission from *The New England Journal of Medicine*[6] and *Annals of Internal Medicine*[7].

elbasvir/grazoprevir started preoperatively and continued for 12 to 16 weeks, plus sofosbuvir for genotype 2 or 3 donor infections (Fig. 1). No recipients in either trial experienced chronic hepatitis C infection, significant hepatopathy, rejection, graft loss, or death. In both trials, wait times were short (1-2 months), and organ quality was excellent (kidney donor profile index 42%-45%). There were no definite treatment-attributable adverse events, although one THINKER patient with pretransplant immunoglobulin A (IgA) nephropathy had proteinuria and focal segmental glomerulosclerosis after SVR12, of uncertain significance.

Since then, other centers have presented or published results of 124 HCV D^+/R^- transplants (97 HCV NAT^+) now totaling 55 heart, 40 liver, 20 kidney, 7 lung, and 2 heart/kidney grafts (Table 2).[8-13] Several DAA regimens were used against multiple HCV genotypes, resulting in universal prevention or SVR12 in all treated patients with sufficient follow-up. This included observational studies in which patients received DAAs several weeks after transplantation, obtained outside of the trial setting. Neither treatment-attributable adverse effects nor insurmountable insurance barriers were reported, and wait times were brief after consent to accept HCV^+ donors.

TRANSITIONING FROM STUDIES TO STANDARDS IN TRANSPLANT MEDICINE

Controversy surrounding the use of HCV D^+/R^- transplantation remains in determining whether the field can now transition from research studies to standard clinical care. Practice guidelines are ideally achieved through graded, high-quality studies such as multicenter, blinded, randomized controlled trials. Multiple factors limit this process in transplantation. Populations of interest are smaller and exhibit significant heterogeneity with respect to underlying disease processes and immune suppression protocols. In addition, fully blinded interventions are rarely feasible or ethical. As such, less robust data appropriately drive standard clinical practice and guideline development. For example, as acknowledged in the 2013 American Society of Transplantation Infectious Diseases Guidelines,[14] which inform current transplant infectious diseases practice, most recommendations are based on evidence level II (ie, "nonrandomized trials, cohort or case-control analyses, uncontrolled experiments") or III (ie, "consensus opinion"). The HCV D^+/R^- studies to date already meet or surpass data for these current standards.

"ACCEPTABLE" DONOR-DERIVED INFECTIONS: THE HAZARDS OF CYTOMEGALOVIRUS AND HEPATITIS B VIRUS

Additional reticence to proceed with HCV D^+/R^- transplantation centers on dangers of donor-derived infection, extrapolating from experience in the pre-DAA era when medications were poorly tolerated and often ineffective. Ironically, however, transmission of higher-risk, incurable, donor-derived viral infections are currently standards of care in transplantation. For example, transplantation of a hepatitis B core antibody–positive (anti-HBc^+) graft into the nonimmune, unexposed recipient occurs in ~3% of liver transplants each year.[15] This standard practice occurs despite historical data of high rates of *de novo* hepatitis (DNH) associated with increased graft fibrosis and a 2.5-fold higher risk for death by 5 years post transplant.[16] DNH may occur despite antiviral therapy and vaccination, thus requiring lifelong treatment to suppress this incurable donor-derived infection. A more widespread and perhaps more hazardous intervention is the use of cytomegalovirus (CMV) mismatched grafts (ie, donor IgG^+, recipient IgG^- [D^+/R^-]). More than 50% of the CMV antibody–negative recipients in 2016 to 2017 received a CMV D^+ organ, accounting for more than 5000 transplants.[15] CMV D^+/R^- transplantation is associated with high rates of viremia, even after antiviral prophylaxis, which itself incurs significant cost (Table 2) and serious negative side effects.[17] Posttransplant mortality is higher in CMV D^+/R^- transplantation, and late-onset CMV disease post prophylaxis is associated with increased rejection, graft loss, and opportunistic infection.[18] Notwithstanding, both anti-HBc^+ D^+/R^- and CMV D^+/R^- transplantation remain acceptable clinical practice given the survival benefit of transplantation.

HCV D^+/R^- Transplantation Should Become Standard of Care

In summary, accumulated data and experience indicate that HCV D^+/R^- transplantation is an underused strategy and a mode to safely expand the donor pool to include lifesaving, high-quality organ transplants immediately for patients in need. With DAA therapy, HCV infection is readily curable in transplant recipients, with minimal side effects. Restricting HCV D^+/R^- transplantation to research protocols would result in the unnecessary deaths of hundreds of wait-list patients each year. Thus, we propose that

TABLE 2. SUMMARY OF RECENT STUDIES OF HCV+ DONOR ORGAN TRANSPLANTATION INTO HCV-UNINFECTED RECIPIENTS

Author	Center	Transplant Recipients (n)	HCV Donor NAT+ (n, %)	Genotype (n)	Prophylactic or Preemptive Design	DAA Therapy (n)	SVR12 or Virological Suppression* (n, %)
Goldberg et al. (2017)[6]	University of Pennsylvania	Kidney (10)	10/10 (100)	1a (9) Not typed (1)	Preemptive	Elbasvir/grazoprevir × 12 weeks (10)	10/10 (100)
Durand et al. (2018)[7]	Johns Hopkins University	Kidney (10)	10/10 (100)	1a/3 (1) 1a (3) 2 (1) 3 (1) Not detected (4)	Prophylactic	Elbasvir/grazoprevir × 12 weeks (7) Elbasvir/grazoprevir + Sofosbuvir × 12 weeks (3)	10/10 (100)
Bari et al. (2018)[11]	University of Cincinnati	Liver (26)	4/26 (15)†	1a (2) 3 (2)	Preemptive	Ledipasvir/sofosbuvir + Ribavirin × 12 weeks (1) Velpatasvir/sofosbuvir × 12 weeks (1) Sofosbuvir/daclatasvir × 12 weeks (1) Ledipasvir/sofosbuvir × 12 weeks (1)	3/3 (100)
Schlendorf et al. (2018)[8]	Vanderbilt University	Heart (13)	9/13 (69)	1a (6) 1b (1) 3 (2) Not detected (2)	Preemptive	Ledipasvir/sofosbuvir × 12 weeks (7) Sofosbuvir/velpatasvir × 12-24 weeks (2)	9/9 (100)
Alonso et al. (2018)[9]	Intermountain Healthcare	Liver (12)	12/12 (100)	1a/1b (5) 3a (5) 2b (1) Not typed (1)	Preemptive	Sofosbuvir/ledipasvir × 12 weeks (4) Sofosbuvir/velpatasvir × 12 weeks (1)	5/5 (100)
Aslam et al. (2018)[12]	University of California, San Diego	Heart (10) Heart/kidney (2)	10/12 (83)	1a (6) 2 (1) 2b (1) 3 (2)	Preemptive	Sofosbuvir/velpatasvir × 12 weeks (2) Glecaprevir/pibrentasvir × 12 weeks (6) Elbasvir/grazoprevir × 12 weeks (2)	10/10 (100)
Kwong et al. (2018)[10]	Stanford University	Heart (8) Liver (2)	9/10 (90)	1a (5) 1b (1) 3 (4)	Preemptive	Not reported in abstract	5/5 (100)
Woolley et al. (2018)[13]	Brigham and Women's Hospital	Heart (24) Lung (7)	31/31 (100)	Not reported in abstract	Prophylactic	Sofosbuvir/velpatasvir × 4-6 weeks (31)	20/20 (100)

*By the end of the study period. Patients who did not receive the intended DAA treatment were excluded. One recurrence was noted.
†All donors were HCV antibody–positive and NAT-negative, yet four recipients developed HCV viremia post transplant.

transplant teams consider HCV D+ organs for all prospective recipients as part of clinical care.

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