Current Hepatology Reports (2019) 18:233–241
https://doi.org/10.1007/s11901-019-00466-0

HEPATITIS C (H VARGAS AND S FLAMM, SECTION EDITORS)

The Use of Grafts from HCV+ Patients in Transplantation: Are we There Yet?

Kathy M. Nilles[1] · Steven L. Flamm[1]

Published online: 2 May 2019

Abstract

Use of organs from donors previously or currently infected with hepatitis C virus is gaining interest in the transplantation realm.

Purpose of Review Here we will outline the historical perspectives for discarding such organs, review the reasons for revitalized interest in their use, and highlight available data on the use of hepatitis C virus (HCV)-viremic grafts in transplantation. We will summarize arguments supporting and against such practices and offer our recommendations.

Recent Findings HCV can now be safely and effectively treated post transplantation with direct-acting antivirals (DAAs). Several reports are highlighted in which HCV-viremic organ donation was performed, followed by DAA treatment. However, opinions abound on the appropriateness of this practice.

Summary Use of viremic organs requires further study and additional larger-scale data with longer-term follow-up, but overall appears safe. It is a viable method to expand the donor pool in both liver and non-liver organ transplantation, but must be carefully weighed with the risks.

Keywords Organ transplantation · Liver transplantation · Hepatitis C positive · Hepatitis c viremic donor

Abbreviations

HCV	Hepatitis C virus
AASLD	American Association for the Study of Liver Disease
IDSA	Infectious Diseases Society of America
PCR	Polymerase chain reaction
NAT	Nucleic acid testing
SVR12	Sustained virological response at 12 weeks
DAA	Direct-acting antiviral
CMV	Cytomegalovirus
EBV	Epstein-Barr virus
IRD	Increased-risk donor
AST	American Society of Transplantation
HCC	Hepatocellular carcinoma

This article is part of the Topical Collection on *Hepatitis C*

✉ Steven L. Flamm
s-flamm@northwestern.edu

[1] Division of Gastroenterology and Hepatology and Comprehensive Transplant Center, Northwestern University Feinberg School of Medicine, Chicago, IL 60601, USA

Introduction

The number of patients on the liver transplantation waitlist continues to grow, and the demand for liver grafts persistently exceeds the supply [1]. As a result of the relatively low supply, approximately 20% of patients awaiting liver transplantation die or are removed from the waitlist due to worsening clinical condition [2].

One method to expand the donor supply is to utilize organs from patients infected with hepatitis C virus (HCV). This practice previously had been discouraged but in the last few years has gained renewed interest. The following article will review the historical context and current literature regarding HCV infection in the transplantation realm. Finally, we will provide discussion of the current controversies surrounding this topic and opinions on future directions.

Historical Perspectives on HCV and Organ Transplantation

Hepatitis C is one of several infectious diseases that can be transmitted from organ donor to recipient. The term "donor-derived infection" is used to describe any infection transmitted

to an organ recipient from the organ donor [3]. If organs from such a donor are allocated to multiple recipients, any or all recipients may contract the infection.

All organ donors are screened at the time of donation for HCV as well as many other infectious diseases. When such infections are passed from donor to recipient, they can be further characterized into expected and unexpected transmissions. *Unexpected* transmissions occur when the donor infection was not identified at the time of organ donation. This can occur due to donation during the serological window period, when antibodies to a pathogen have not yet developed, or due to false negative testing. The use of nucleic acid testing (NAT) or polymerase chain reaction (PCR) testing has reduced this risk. Unexpected transmission can still occur if donation occurs during the eclipse period, the time between acquisition of infection and the detection of pathogen by NAT or PCR. This time period is shorter than the serological window period [3].

In contrast to unexpected transmission, *expected* transmissions occur when the donor is known to carry the infection at the time of donation. In liver transplantation, common expected transmissions include cytomegalovirus (CMV) and Epstein-Barr virus (EBV). Donors who are hepatitis B core antibody positive are another example of a potential source of expected transmission. HCV is also considered an expected viral transmission, except in uncommon cases when donation occurs during the eclipse period, approximately 10 days after exposure [3]. The risk of transmission of HCV during the eclipse period is estimated to be 0.3 to 3%, depending on the behavior at risk and the time interval between the behavior and organ donation [4, 5•, 6].

The high risk of HCV transmission in solid organ transplantation from donors infected with HCV was recognized as early as 1991 [7], with transmission risk 96% in early studies [8]. As a result, organs from donors testing positive for HCV were historically not recommended for use.

In addition to transmitting virus from organ donors, HCV has an extremely high recurrence rate in patients who undergo liver transplant for this indication. Recurrence of HCV is universal if the recipient had viremia during the transplant itself [9, 10], whereas there is virtually no risk of recurrence if the patient has been successfully treated (SVR12) prior to liver transplantation [11, 12]. In patients with virologic clearance at least 30 days prior to transplantation, the chance of remaining free of HCV is 95% [13]. Recurrent HCV after liver transplantation was difficult to manage in the interferon age due to poor tolerance and low efficacy [14]. Furthermore, HCV viral loads are higher with immunosuppression in the post-transplantation setting and accelerated fibrosis progression was common [15, 16]; in fact, cirrhosis develops as early as 5 years after transplantation in 20–30% of patients [17–19], with the associated risk of hepatocellular carcinoma (HCC) and graft failure. Graft survival for patients with HCV had previously been lower than for patients transplanted for other reasons, due to accelerated HCV progression [20–23]. For those able to tolerate treatment, data suggests treating HCV recurrence after liver transplantation has improved outcomes if cure is achieved [21, 24–27]. Historically, recipients of other organs who also had HCV infection had worse outcomes when they received an organ from a donor that was "HCV positive" [28].

Given the high risk of HCV infection to the recipient with attendant morbidity and mortality including graft failure and the lack of effective therapies, organs from donors with active HCV previously were not used for patients not already infected with HCV, although this idea has been debated since 1995 [29]. If no suitable potential organ recipients were available that were not infected with HCV, "HCV-positive" donors were discarded [30, 31, 32•]. Rarely, they were used in emergency settings such as fulminant hepatic failure [33].

In recent years, the advent of direct-acting antivirals (DAAs) revolutionized the treatment of HCV in the non-transplantation population, providing highly efficacious interferon-free regimens with minimal side effects. The ability to cure HCV was dramatically increased, including for patients with renal dysfunction, cirrhosis, viral resistance, and those intolerant to interferon. The post-liver transplantation population was eagerly studied; numerous trials have been conducted with DAAs for recurrent HCV demonstrating similar safety and efficacy as in non-transplantation patients, including those with cirrhosis. Patients with HCV and HIV co-infection can also be safely treated [34–45]. Joint guidelines from the American Association for the Study of Liver Disease (AASLD) and the Infectious Diseases Society of America (IDSA) can assist in treatment choices [46]. Since 2011 and the approval of the first DAAs, post-transplantation outcomes for HCV patients have improved; 5-year survival of HCV patients currently matches outcomes for those transplanted for other reasons [47].

One strategy that has been employed is treatment in the peri-transplantation setting to prevent recurrence [13, 48, 49]. During the transplantation hepatectomy, serum viral levels drop rapidly [50]; this nadir may represent the ideal time to initiate treatment. Treating patients at the time of transplantation has been shown to prevent reinfection, and patients who are started on DAA treatment on the day of transplantation can be treated successfully with an abbreviated 4-week regimen [51••].

In addition to treating recurrence of HCV, DAAs have been used to cure HCV in cases of unexpected donor-derived HCV infection [52, 53], such as increased-risk donors (IRD) who were tested during the eclipse period. The efficacy and ease of treatment post-transplantation including early treatment to prevent recurrence, and safe and effective treatment in cases of unexpected viral transmission, has led to the increased interest in using organs from donors with HCV in the uninfected recipient population as well.

The ability to distinguish organ donors with positive HCV antibody testing as actively or previously infected with HCV is critical. Since 2014, all donors with a positive HCV antibody must be tested with NAT/PCR to determine if viremia is present [54]. Patients with a positive HCV antibody without active viremia may have been previously treated and cured, spontaneously cleared, or potentially have a false positive antibody. A consensus conference from the American Society of Transplantation (AST) proposed the term "HCV-viremic donor" to distinguish those with active infection, rather than "HCV positive" [28]. Separating viremic from non-viremic donors is important for studying risks and outcomes. UNOS data have shown that from 2015 to 2016, only 4.4% of all donors are HCV viremic [55]. An additional analysis from 1993 to 2008 determined that only 53% of "HCV-positive" donors were actually viremic [56]. However, viremic donors are projected to increase with the current opioid epidemic.

Interest in using donors with active HCV raised attention to current organ allocation and resource utilization, given that these organs are declined frequently. The increase in drug overdose deaths has expanded the overall supply of organs: an OPTN data analysis from 2003 to 2014 demonstrated a 350% increase in drug overdose as a cause of donor death [57]. Many viremic donors come from people who have recently injected drugs [58]. Baby boomers with HCV are also a source of viremic donors, but as this population ages, these organs are more likely to be declined for transplantation. Donors who have died from opiate overdoses are generally younger (the median viremic donor age is now much lower than before) and have high-quality organs as they are often otherwise healthy [28]. Currently, such organs are unfortunately discarded frequently. Analysis of data from 2015 to 2017 demonstrated that 31% of HCV seropositive livers were discarded, whereas 14% of seronegative livers were discarded; this trend was starting to decrease over the time period studied. A total of only 30 livers from HCV-viremic donors were used, with no overall decrease in discard rates over the study time period [59].

The number of HCV-infected recipients on the waitlist has decreased as DAA treatment has become more widely advertised. As demand continues to exceed supply of liver grafts, modeling studies have shown an increase in waitlist mortality with a hazard ratio of 2.36 when increased-risk donors are turned down [60••]. For "HCV-positive donors" (either viremic or not), accepting such an organ at a MELD of 20 or higher was associated with increased life expectancy, with the highest benefit when the recipient's MELD score is 28 [61••].

For many reasons including increasing risk of waitlist mortality, ability to easily treat recurrent HCV in the post-transplantation setting as well as prevent recurrence with early treatment, ease of treating cases of unexpected viral transmission, ability to accurately determine active infection in donors by testing for HCV viremia, an increase in opioid-related deaths in young healthy potential donors, analysis showing high discard rates of such organs, and modeling studies showing survival benefit of accepting "HCV-positive organs," there is now a rising interest in using organs from donors with HCV in non-traditional settings, including for recipients in need of an organ who do not have HCV.

Current Data on Liver Transplantation with HCV-Positive Donors

One of the first considerations in the use of "HCV-positive" grafts for liver transplantation is graft fibrosis related to the HCV, particularly if the donor is older or has had longstanding infection. Biopsy of donors with active or prior HCV infection is recommended [62]. Numerous studies have found that no difference in patient or graft survival occurs as long as there is no more than stage 2 fibrosis on biopsy [31, 63–71].

HCV-Infected Recipients

Transplantation of organs from donors with either prior exposure or current infection with HCV into HCV recipients is a standard consideration at most centers. Between 2010 and 2015, the number of HCV seropositive recipients who received an "HCV-positive" liver increased from 7 to 17% [32•]. The AST supports the use of HCV-viremic donors for viremic recipients [28]. Prior concerns about potential genotype switching have been allayed with the availability of pan-genotypic treatment regimens [46].

Non-viremic but Exposed Donors ("HCV +") to Non-infected Recipients

This practice has generally been avoided due to limited data, but the infectious risk has been thought to be low [28]. It has been performed in liver as well as other organs [72–75]. Unexpected infections have occurred, particularly from donors during the serological window or NAT eclipse period [52, 76], particularly in donors who recently engaged in high-risk behaviors. However, as mentioned above, such unexpected infections have been successfully treated with DAAs [52, 53]. The concept of "occult HCV" in hepatocytes has been discussed [77–80], but the clinical significance of this is unclear. It was raised by one group in a description of unexpected transmission, but this was more likely eclipse period transmission [3]. In a larger study of 55 recipients who received livers from donors who were HCV antibody positive but non-viremic, five viral transmissions occurred. Notably, 76% of these donors had a history of injection drug use, but the study reported that no cases of viremia occurred from such IRD donors. While eclipse period/false negative NAT testing

could have occurred, this study does raise concern about potentially higher risk of infection than previously recognized. However, four of the five patients were treated with DAAs (the fifth died of unrelated issues). SVR was achieved in all four, and there was no difference in survival or outcomes [81••].

Although the infectious risk of a liver graft from an exposed but non-viremic donor is low, use of vessels from such donors is currently prohibited due to transmission of virus in this setting [82, 83].

HCV-Viremic Donors to Non-infected Recipients

This is unarguably the most controversial form of transplant, but is not prohibited by OPTN. While this practice has previously been highly discouraged, it has become more acceptable with the advent of effective DAAs [28]. An analysis from the OPTN/UNOS database from 2015 to 2017 found that a total of 30 livers from HCV-viremic donors were transplanted into non-infected recipients, with no difference in survival at 1 year. The study did not discuss whether the patients were treated afterwards [59]. Case reports of non-infected recipients of livers from HCV-viremic donors have demonstrated cure with DAA therapy, with excellent short-term outcomes and no graft loss or death [84, 85].

Use of HCV-Viremic Donors in Other Organs

Interest for use of HCV organs in the non-liver transplantation community is also high. While previous data suggest outcomes were worse in patients who received "HCV-positive" organs in infected recipients, the data were collected before the use of NAT/PCR testing [28]. Data also show higher rejection and DSA formation during HCV infection in kidney transplantation recipients [86, 87]. However, these studies evaluated patients before DAA treatment was routine, and thus may not be pertinent.

The use of HCV-viremic organs transplanted into non-viremic recipients has been studied in other organs [88••, 89]. HCV treatment with DAAs post-transplantation in kidney recipients, despite the expense, is still more cost effective than patients not receiving kidney transplantation and remaining on dialysis [90•]. Transmission of HCV in non-hepatic transplantation recipients has also been successfully treated with DAAs [91–96] with excellent outcomes. In addition, the larger THINKER [88••] and EXPANDER [97••] clinical trials both demonstrated excellent outcomes using HCV-viremic donor kidney organs to non-infected recipients. Such excellent transplantation outcomes in recipients of other organs further generates interest in use of HCV-viremic organs for all organ transplants.

Current Controversies and Points of Debate

The use of HCV-viremic donor organs into non-viremic recipients is widely debated (Table 1). There have been arguments against this process. Ethical concerns have been raised about introducing iatrogenic infection in non-infected patients, with concerns about social stigma and healthcare system mistrust raised. Many still perceive this as "experimental" [98]. Rigorous informed consent is recommended when this is considered, and some believe that IRB-approved clinical trials are most appropriate for this practice [28, 99].

Medical issues include concerns about potential increased rejection rates in the setting of HCV post-transplantation. Patients with HCV appear to have increased risks of rejection [100]; in one report of patients who received livers from HCV-viremic donors, two of ten had antibody-mediated rejection, although it is uncertain that HCV was the cause [84]. Immune-mediated graft dysfunction has been reported in up to 3.4% of patients receiving DAAs, including acute and chronic rejection and plasma cell hepatitis [101•].

In addition to rejection, concerns about allografts with bridging fibrosis have been raised, including risk by genotype. Genotype 1 patients have the highest risk of advanced fibrosis, and the lowest rates of SVR with DAA [102]. These risks must be discussed with the recipient. Expert consensus opinion recommends that grafts with fibrosis of more than F2 should not be used [28], although there is always a concern of biopsy sampling error underestimating true degree of fibrosis.

Although DAAs seem to be effective and safe for treatment of HCV post-liver and other organ transplantation, trials have been small, and further study with larger patient numbers is needed. In addition, there have been concerns that pan-genotypic DAA regimens have not been studied in the post transplantation setting. In addition, pertinent drug-drug interactions exist and have not yet been assessed in this population [103].

Logistical and cost issues such as insurance coverage (delays in obtaining treatment approval, or insurance denial for coverage of an iatrogenic known infection) are also of concern. Treatment delay raises fear of development of fibrosing cholestatic hepatitis. Although this only occurs at a rate of 5–10%, it has led to graft loss and death in liver transplantation [104] and kidney transplantation recipients [105]. If insurance approval for DAA therapy is not expeditious, a backup approach must be available for timely treatment [106].

DAAs are approved for chronic HCV therapy, and the treatment of acute donor-derived HCV infection is an off-label use that may require further study. Finally, in non-hepatic transplantation patients who receive an HCV-infected organ, concerns have been raised regarding the need for evaluating patients for underlying, undiagnosed liver disease. For instance, a potential kidney transplantation recipient with NASH risk factors may require evaluation since HCV infection may be poorly tolerated in a liver with underlying

Table 1 Arguments for and against use of viremic donors

Arguments supporting use of viremic donors	Arguments against use of viremic donors
-Young drug overdose donors have excellent organs	-Ethical (iatrogenic), social stigma, healthcare system mistrust
-Available data supports the efficacy and safety of treating HCV with DAAs	-Concerns of increased rejection rates
-Pan-genotypic regimens are available	-Concerns of graft fibrosis
-Expands the donor pool and reduces discarding of otherwise excellent grafts	-Data on DAAs in this setting are all from small trials
-Less expensive than care on the transplant waitlists	-Pan-genotypic regimens not studied in post-transplant setting
-Allows transplantation at lower MELD scores	-Risks of treatment delays and uncertainty on best timing of treatment
-Many centers are considering/in favor of, actively studying, or routinely doing	-Concerns of insurance denial/cost of treatment
-Interest persists across all organs	-Not FDA-approved for acute HCV treatment
	-Risk of HCV in undiagnosed liver disease in non-hepatic recipients
	-Drug interactions with PIs and CNIs

disease [98]. However, early treatment of HCV would likely obviate any liver-related issues from acute transmission of infection after transplantation. Finally, treatment of HCV with DAA regimens after transplantation may involve drug-drug interactions between protease inhibitors and calcineurin inhibitors [107–109]. This may make treatment more problematic, and immunosuppression levels must be closely monitored.

Conversely, there are numerous points in favor of HCV-viremic transplantation [103, 110]. First, HCV-viremic donors have been increasingly available from opioid overdose patients, and such younger donors may be ideal in terms of graft quality despite infection with HCV. As discussed above, DAAs are effective and safe and use is supported in the post-transplantation setting by the current guidelines. Pan-genotypic and salvage regimens are currently available. Although the ideal timing of treatment is uncertain, the immediate or early post-operative period seems to be appropriate [51••]. Treatment with DAAs post-liver transplantation is less expensive than remaining on the waitlist [111•], for which the risk of waitlist death is as high as 20% [2]. MELD scores of recipients who receive HCV-viremic organs may be lower [112] than waiting for a non-viremic graft. This strategy may facilitate patients with lower MELD scores to receive an excellent graft earlier. Adverse long-term outcomes have not been demonstrated in liver transplantation associated with HCV donor "positivity" [113•].

The concept of transmitting a virus from an infected donor to a non-infected recipient is not new. It is standard with HBV (cAb), CMV, and EBV, for example. Whereas those viruses have significant morbidity and mortality, HCV is easily treatable and curable.

Author Recommendations and Conclusions

Given the availability of efficacious and safe DAA therapy for HCV and the issue of limited organ availability for solid organ transplantation, it is our opinion that the use of HCV-viremic donors be considered for any organ transplantation recipient including non-infected patients. This is being actively studied at many centers and will likely soon become standard. The concept continues to gain favor; a recent national survey conducted in 2018 revealed that 39% of transplantation centers were willing to consider "HCV-positive" grafts into uninfected recipients, a trend that changed with the availability of DAAs [114].

We suggest that all patients listed for organ transplantation be educated about the option (risks and benefits) of accepting an HCV-viremic organ and that informed consent be obtained if the patient is willing. Currently, patients must opt in by the UNOS guidelines for consideration of HCV+ organs. Insurance clearance for post-transplantation HCV DAA therapy (including iatrogenic, expected transmission) should also be sought to avoid potential delays in treatment after transplantation.

Results of ongoing studies assessing long-term outcomes in patients are eagerly awaited. Time to transplantation, organ quality, organ and patient survival, graft function, degree of fibrosis in the donor graft, SVR, and potential post-transplantation immunological issues (acute or chronic rejection, plasma cell hepatitis) must be defined [28].

Conclusion

The current time is an exciting time in organ transplantation. We now have the ability to transplant grafts from HCV-viremic donors in liver transplantation, as well as in other organs, and effectively treat the infection afterward. This practice serves to both expand the donor pool and, for patients who opt in for these grafts, may allow access to transplant with a shorter wait and decreased risk of waitlist mortality. It is time to capitalize on this opportunity.

Compliance with Ethical Standards

Conflict of Interest Kathy M. Nilles and Steven L. Flamm declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Kim WR, Lake JR, Smith JM, Schladt DP, Skeans MA, Harper AM, et al. OPTN/SRTR 2016 annual data report: liver. Am J Transplant. 2018;18(Suppl 1):172–253.
2. Network., N.D.O.P.a.T. 2018 July 7, 2018]; available from: https://optn.transplant.hrsa.gov/data/view-data-reports/national-data. Accessed 7 July 2018.
3. Nam H, et al. Donor-derived viral infections in liver transplantation. Transplantation. 2018;102(11):1824–36.
4. Kucirka LM, Sarathy H, Govindan P, Wolf JH, Ellison TA, Hart LJ, et al. Risk of window period hepatitis-C infection in high infectious risk donors: systematic review and meta-analysis. Am J Transplant. 2011;11(6):1188–200.
5. • Annambhotla PD, Gurbaxani BM, Kuehnert MJ, Basavaraju SV. A model to estimate the probability of human immunodeficiency virus and hepatitis C infection despite negative nucleic acid testing among increased-risk organ donors. Transpl Infect Dis. 2017;19(2) **The risk of transmission of HCV during the eclipse period is 0.3 to 3% depending on donor behavior**.
6. OPTN. Understanding the risk of transmission of HIV, hepattis B, and hepatitis C from U.S. PHS increased risk donors. Organ Procurement and Transplantation Network (OPTN). 2017; available from: https://optn.transplant.hrsa.gov/resources/guidance/understanding-hiv-hbv-hcv-risks-from-increased-risk-donors. Accessed 22 March 2018.
7. Pereira BJ, et al. Transmission of hepatitis C virus by organ transplantation. N Engl J Med. 1991;325(7):454–60.
8. Pereira BJ, et al. A controlled study of hepatitis C transmission by organ transplantation. The New England Organ Bank Hepatitis C Study Group. Lancet. 1995;345(8948):484–7.
9. Berenguer M, et al. Natural history of clinically compensated hepatitis C virus-related graft cirrhosis after liver transplantation. Hepatology. 2000;32(4 Pt 1):852–8.
10. Wright TL, Donegan E, Hsu HH, Ferrell L, Lake JR, Kim M, et al. Recurrent and acquired hepatitis C viral infection in liver transplant recipients. Gastroenterology. 1992;103(1):317–22.
11. Everson GT, Trotter J, Forman L, Kugelmas M, Halprin A, Fey B, et al. Treatment of advanced hepatitis C with a low accelerating dosage regimen of antiviral therapy. Hepatology. 2005;42(2):255–62.
12. Tekin F, et al. Safety, tolerability, and efficacy of pegylated-interferon alfa-2a plus ribavirin in HCV-related decompensated cirrhotics. Aliment Pharmacol Ther. 2008;27(11):1081–5.
13. Curry MP, Forns X, Chung RT, Terrault NA, Brown R Jr, Fenkel JM, et al. Sofosbuvir and ribavirin prevent recurrence of HCV infection after liver transplantation: an open-label study. Gastroenterology. 2015;148(1):100–107 e1.
14. Aytaman A, Kaufman M, Terrault NA. Management of posttransplant hepatitis C infection. Curr Opin Organ Transplant. 2010;15(3):301–9.
15. Samuel D, Feray C. Recurrence of hepatitis C virus infection after liver transplantation. J Hepatol. 1999;31(Suppl 1):217–21.
16. Gane EJ, Agarwal K. Directly acting antivirals (DAAs) for the treatment of chronic hepatitis C virus infection in liver transplant patients: "a flood of opportunity". Am J Transplant. 2014;14(5):994–1002.
17. Berenguer M, Ferrell L, Watson J, Prieto M, Kim M, Rayón M, et al. HCV-related fibrosis progression following liver transplantation: increase in recent years. J Hepatol. 2000;32(4):673–84.
18. Prieto M, Berenguer M, Rayón JM, Córdoba J, Argüello L, Carrasco D, et al. High incidence of allograft cirrhosis in hepatitis C virus genotype 1b infection following transplantation: relationship with rejection episodes. Hepatology. 1999;29(1):250–6.
19. Firpi RJ, Clark V, Soldevila-Pico C, Morelli G, Cabrera R, Levy C, et al. The natural history of hepatitis C cirrhosis after liver transplantation. Liver Transpl. 2009;15(9):1063–71.
20. Terrault NA, Berenguer M. Treating hepatitis C infection in liver transplant recipients. Liver Transpl. 2006;12(8):1192–204.
21. Crespo G, Mariño Z, Navasa M, Forns X. Viral hepatitis in liver transplantation. Gastroenterology. 2012;142(6):1373–1383 e1.
22. Thuluvath PJ, Krok KL, Segev DL, Yoo HY. Trends in post-liver transplant survival in patients with hepatitis C between 1991 and 2001 in the United States. Liver Transpl. 2007;13(5):719–24.
23. Forman LM, Lewis JD, Berlin JA, Feldman HI, Lucey MR. The association between hepatitis C infection and survival after orthotopic liver transplantation. Gastroenterology. 2002;122(4):889–96.
24. Carrion JA, et al. Efficacy of antiviral therapy on hepatitis C recurrence after liver transplantation: a randomized controlled study. Gastroenterology. 2007;132(5):1746–56.
25. Dhanasekaran R, Sanchez W, Mounajjed T, Wiesner RH, Watt KD, Charlton MR. Impact of fibrosis progression on clinical outcome in patients treated for post-transplant hepatitis C recurrence. Liver Int. 2015;35(11):2433–41.
26. Picciotto FP, Tritto G, Lanza AG, Addario L, de Luca M, di Costanzo GG, et al. Sustained virological response to antiviral therapy reduces mortality in HCV reinfection after liver transplantation. J Hepatol. 2007;46(3):459–65.
27. Berenguer M, Palau A, Aguilera V, Rayón JM, Juan FS, Prieto M. Clinical benefits of antiviral therapy in patients with recurrent hepatitis C following liver transplantation. Am J Transplant. 2008;8(3):679–87.
28. Levitsky J, Formica RN, Bloom RD, Charlton M, Curry M, Friedewald J, et al. The American Society of Transplantation consensus conference on the use of hepatitis C Viremic donors in solid organ transplantation. Am J Transplant. 2017;17(11):2790–802.
29. Sanchez-Tapias JM, Rodes J. Dilemmas of organ transplantation from anti-HCV-positive donors. Lancet. 1995;345(8948):469–70.
30. Saab S, Ghobrial RM, Ibrahim AB, Kunder G, Durazo F, Han S, et al. Hepatitis C positive grafts may be used in orthotopic liver transplantation: a matched analysis. Am J Transplant. 2003;3(9):1167–72.
31. Northup PG, Argo CK, Nguyen DT, McBride MA, Kumer SC, Schmitt TM, et al. Liver allografts from hepatitis C positive donors can offer good outcomes in hepatitis C positive recipients: a US National Transplant Registry analysis. Transpl Int. 2010;23(10):1038–44.
32. • Bowring MG, Kucirka LM, Massie AB, Luo X, Cameron A, Sulkowski M, et al. Changes in Utilization and Discard of Hepatitis C-Infected Donor Livers in the Recent Era. Am J Transplant. 2017;17(2):519–27 **HCV-positive liver grafts were previously discarded; they are being increasingly used but still are discarded at a rate nearly double that of non-HCV livers.**
33. Terrault NA, Berenguer M, Strasser SI, Gadano A, Lilly L, Samuel D, et al. International liver transplantation society consensus statement on hepatitis C management in liver transplant recipients. Transplantation. 2017;101(5):956–67.
34. Poordad F, Schiff ER, Vierling JM, Landis C, Fontana RJ, Yang R, et al. Daclatasvir with sofosbuvir and ribavirin for hepatitis C virus infection with advanced cirrhosis or post-liver transplantation recurrence. Hepatology. 2016;63(5):1493–505.

35. Gutierrez JA, Carrion AF, Avalos D, O'Brien C, Martin P, Bhamidimarri KR, et al. Sofosbuvir and simeprevir for treatment of hepatitis C virus infection in liver transplant recipients. Liver Transpl. 2015;21(6):823–30.
36. Kwo PY, Mantry PS, Coakley E, te HS, Vargas HE, Brown R Jr, et al. An interferon-free antiviral regimen for HCV after liver transplantation. N Engl J Med. 2014;371(25):2375–82.
37. Guaraldi G, Rossotti R, Verucchi G, Tavio M, Pasulo L, Beghetto B, et al. Successful pre- and posttransplant Sofosbuvir-based anti-hepatitis C virus treatment in persons living with human immunodeficiency virus infection. Open Forum Infect Dis. 2017;4(2):ofx065.
38. Charlton M, Everson GT, Flamm SL, Kumar P, Landis C, Brown RS Jr, et al. Ledipasvir and Sofosbuvir plus ribavirin for treatment of HCV infection in patients with advanced liver disease. Gastroenterology. 2015;149(3):649–59.
39. Vinaixa C, Aguilera V, Blanes M, Maupoey J, Berenguer M, Prieto M. Peritransplant antiviral treatment of human immunodeficiency virus/hepatitis C virus-Coinfected patients. Liver Transpl. 2018;24(10):1476–80.
40. O'Leary JG, Fontana RJ, Brown K, Burton JR Jr, Firpi-Morell R, Muir A, et al. Efficacy and safety of simeprevir and sofosbuvir with and without ribavirin in subjects with recurrent genotype 1 hepatitis C postorthotopic liver transplant: the randomized GALAXY study. Transpl Int. 2017;30(2):196–208.
41. Antonini TM, Coilly A, Rossignol E, Fougerou-Leurent C, Dumortier J, Leroy V, et al. Sofosbuvir-based regimens in HIV/HCV coinfected patients after liver transplantation: results from the ANRS CO23 CUPILT study. Transplantation. 2018;102(1):119–26.
42. Campos-Varela I, Peters MG, Terrault NA. Advances in therapy for HIV/hepatitis C virus-coinfected patients in the liver transplant setting. Clin Infect Dis. 2015;60(1):108–16.
43. Londono MC, et al. IFN-free therapy for HIV/HCV-coinfected patients within the liver transplant setting. J Antimicrob Chemother. 2016;71(11):3195–201.
44. Grant JL, Hawkins C, Brooks H, Palella FJ Jr, Koppe SW, Abecassis MM, et al. Successful sofosbuvir-based therapy in HIV/hepatitis C virus coinfected liver transplant recipients with recurrent hepatitis C virus infection. AIDS. 2016;30(1):93–8.
45. Chen T, Terrault NA. Perspectives on treating hepatitis C infection in the liver transplantation setting. Curr Opin Organ Transplant. 2016;21(2):111–9.
46. Panel A-IHG. Hepatitis C guidance 2018 update: AASLD-IDSA recommendations for testing, managing, and treating hepatitis C virus infection. Clin Infect Dis. 2018;67(10):1477–92.
47. Mousa OY, L.N, Aqel B, et al. Impact of direct-acting antiviral (DAA) for HCV treatment on liver transplant outcomes: a multi-center 15 year experience., in The Liver Meeting: American Association for the Study of Liver Disease. Washington DC: Hepatology; 2017.
48. Tavio M, Vivarelli M, Menzo S, Gori A, Grossi PA, Marigliano A. Prophylaxis of HCV reinfection and direct-acting antiviral agents during liver transplantation. Liver Transpl. 2015;21(10):1327–9.
49. Donato MF, Monico S, Malinverno F, Aghemo A, Maggioni M, Reggiani P, et al. Bridging all oral DAA therapy from wait time to post-liver transplant to improve HCV eradication? Liver Int. 2015;35(1):1–4.
50. Garcia-Retortillo M, Forns X, Feliu A, Moitinho E, Costa J, Navasa M, et al. Hepatitis C virus kinetics during and immediately after liver transplantation. Hepatology. 2002;35(3):680–7.
51.•• Levitsky J, Verna EC, O'Leary JG, Bzowej NH, Moonka DK, Hyland RH, et al. Perioperative Ledipasvir-Sofosbuvir for HCV in liver-transplant recipients. N Engl J Med. 2016;375(21):2106–8 **DAAs given on the day of transplantation when viremia is at a nadir are effective enough that only 4 weeks of treatment is needed**.
52. Bari K, Luckett K, Kaiser T, Diwan T, Cuffy M, Schoech MR, et al. Hepatitis C transmission from seropositive, nonviremic donors to non-hepatitis C liver transplant recipients. Hepatology. 2018;67(5):1673–82.
53. Shah AP, Cameron A, Singh P, Frank AM, Fenkel JM. Successful treatment of donor-derived hepatitis C viral infection in three transplant recipients from a donor at increased risk for bloodborne pathogens. Transpl Infect Dis. 2017;19(2).
54. OPTN. Policy 2.0 Deceased Donor Organ Procurement (Policy 2.9) Organ Procurement and Transplant Network (OPTN). 2018; available from: https://optn.transplant.hrsa.gov/media/1200/optn_policies.pdf. Accessed 22 March 2018.
55. Kling CE, Perkins JD, Landis CS, Limaye AP, Sibulesky L. Utilization of organs from donors according to hepatitis C antibody and nucleic acid testing status: time for change. Am J Transplant. 2017;17(11):2863–8.
56. O'Leary JG, et al. Utilization of hepatitis C antibody-positive livers: genotype dominance is virally determined. Transpl Int. 2012;25(8):825–9.
57. Goldberg DS, Blumberg E, McCauley M, Abt P, Levine M. Improving organ utilization to help overcome the tragedies of the opioid epidemic. Am J Transplant. 2016;16(10):2836–41.
58. Suryaprasad AG, White JZ, Xu F, Eichler BA, Hamilton J, Patel A, et al. Emerging epidemic of hepatitis C virus infections among young nonurban persons who inject drugs in the United States, 2006-2012. Clin Infect Dis. 2014;59(10):1411–9.
59. Cholankeril G, Li AA, Dennis BB, Toll AE, Kim D, Bonham CA, et al. Increasing trends in transplantation of hepatitis C virus-positive livers into uninfected recipients. Clin Gastroenterol Hepatol. 2018.
60.•• Croome KP, Lee DD, Pungpapong S, Keaveny AP, Taner CB. What are the outcomes of declining a public health service increased risk liver donor for patients on the liver transplant waiting list? Liver Transpl. 2018;24(4):497–504**. the hazard ratio of turning down an increased-risk donor graft for a liver recipient is high at 2.36**.
61.•• Chhatwal J, Samur S, Bethea ED, Ayer T, Kanwal F, Hur C, et al. Transplanting hepatitis C virus-positive livers into hepatitis C virus-negative patients with preemptive antiviral treatment: a modeling study. Hepatology. 2018;67(6):2085–95 **The highest benefit of accepting an HCV-viremic organ is seen in patients with MELD scores of 28 or higher**.
62. Hoare M, Gelson WTH, Rushbrook SM, Curran MD, Woodall T, Coleman N, et al. Histological changes in HCV antibody-positive, HCV RNA-negative subjects suggest persistent virus infection. Hepatology. 2008;48(6):1737–45.
63. Vargas HE, Laskus T, Wang LF, Lee R, Radkowski M, Dodson F, et al. Outcome of liver transplantation in hepatitis C virus-infected patients who received hepatitis C virus-infected grafts. Gastroenterology. 1999;117(1):149–53.
64. Ballarin R, Cucchetti A, Spaggiari M, Montalti R, di Benedetto F, Nadalin S, et al. Long-term follow-up and outcome of liver transplantation from anti-hepatitis C virus-positive donors: a European multicentric case-control study. Transplantation. 2011;91(11):1265–72.
65. Testa G, Goldstein RM, Netto G, Abbasoglu O, Brooks BK, Levy MF, et al. Long-term outcome of patients transplanted with livers from hepatitis C-positive donors. Transplantation. 1998;65(7):925–9.
66. Marroquin CE, et al. Transplantation of hepatitis C-positive livers in hepatitis C-positive patients is equivalent to transplanting hepatitis C-negative livers. Liver Transpl. 2001;7(9):762–8.

67. Saab S, et al. Outcomes of hepatitis C- and hepatitis B core antibody-positive grafts in orthotopic liver transplantation. Liver Transpl. 2003;9(10):1053–61.
68. Lai JC, O'Leary JG, Trotter JF, Verna EC, Brown RS Jr, Stravitz RT, et al. Risk of advanced fibrosis with grafts from hepatitis C antibody-positive donors: a multicenter cohort study. Liver Transpl. 2012;18(5):532–8.
69. Velidedeoglu E, Desai NM, Campos L, Olthoff KM, Shaked A, Nunes F, et al. The outcome of liver grafts procured from hepatitis C-positive donors. Transplantation. 2002;73(4):582–7.
70. Alvaro E, et al. Liver transplantation from anti-hepatitis C virus-positive donors: our experience. Transplant Proc. 2012;44(6): 1475–8.
71. Burr AT, Li YF, Tseng JF, Saidi RF, Bozorgzadeh A, Shah SA. Survival after liver transplantation using hepatitis C virus-positive donor allografts: case-controlled analysis of the UNOS database. World J Surg. 2011;35(7):1590–5.
72. Takeichi T, et al. Liver transplant from an ABO-incompatible and hepatitis C antibody-positive but an HCV-RNA negative living donor in a familial amyloid polyneuropathy patient. Exp Clin Transplant. 2013;11(2):182–5.
73. Cruzado JM, Gil-Vernet S, Castellote J, Bestard O, Melilli E, Grinyó JM. Successful treatment of chronic HCV infection should not preclude kidney donation to an HCV negative recipient. Am J Transplant. 2013;13(10):2773–4.
74. Tokumoto T, Tanabe K, Simizu T, Shimmura H, Iizuka J, Ishikawa N, et al. Kidney transplantation from a donor who is HCV antibody positive and HCV-RNA negative. Transplant Proc. 2000;32(7):1597–9.
75. Hidaka M, Takatsuki M, Soyama A, Miyaaki H, Ichikawa T, Nakao K, et al. Living donor liver transplantation from a donor previously treated with interferon for hepatitis C virus: a case report. J Med Case Rep. 2011;5:276.
76. Suryaprasad A, Basavaraju SV, Hocevar SN, Theodoropoulos N, Zuckerman RA, Hayden T, et al. Transmission of hepatitis C virus from organ donors despite nucleic acid test screening. Am J Transplant. 2015;15(7):1827–35.
77. Elmasry S, Wadhwa S, Bang BR, Cook L, Chopra S, Kanel G, et al. Detection of occult hepatitis C virus infection in patients who achieved a sustained virologic response to direct-acting antiviral agents for recurrent infection after liver transplantation. Gastroenterology. 2017;152(3):550–553 e8.
78. Castillo I, Rodriguez-Inigo E, Lopez-Alcorocho JM, Pardo M, Bartolome J, Carreno V. Hepatitis C virus replicates in the liver of patients who have a sustained response to antiviral treatment. Clin Infect Dis. 2006;43(10):1277–83.
79. Koutsoudakis G, Perez-Del-Pulgar S, Forns X. Occult hepatitis C virus infection: are we digging too deep? Gastroenterology. 2017;152(3):472–4.
80. McHutchison JG, et al. Hepatic HCV RNA before and after treatment with interferon alone or combined with ribavirin. Hepatology. 2002;35(3):688–93.
81.•• Luckett K, Kaiser TE, Bari K, Safdar K, Schoech MR, Apewokin S, et al. Use of hepatitis C virus antibody-positive donor livers in hepatitis C nonviremic liver transplant recipients. J Am Coll Surg. 2019;228(4):560–7 **5 unexpected HCV transmissions occurred in HCV-Ab positive donors; most were successfully treated with DAAs**.
82. Centers for Disease, C. and Prevention. Potential transmission of viral hepatitis through use of stored blood vessels as conduits in organ transplantation-Pennsylvania, 2009. Am J Transplant. 2011;11(4):863–5.
83. OPTN. *Policy 16.6 Vessel recovery, transplant, and storage (policy 16.6B). Organ Procurement and Transplant Network (OPTN).* 2017; **Available from:** https://optn.transplant.hrsa.gov/media/1200/optn_policies.pdf. Accessed 22 March 2018.
84. Kwong AJ, Wall A, Melcher M, Wang U, Ahmed A, Subramanian A, et al. Liver transplantation for hepatitis C virus (HCV) non-viremic recipients with HCV viremic donors. Amer J Transpl 2019(19):1380–7.
85. Saberi B, Hamilton JP, Durand CM, Li Z, Philosophe B, Cameron AM, et al. Utilization of hepatitis C virus RNA-positive donor liver for transplant to hepatitis C virus RNA-negative recipient. Liver Transpl. 2018;24(1):140–3.
86. Cosio FG, Sedmak DD, Henry ML, Haddad CA, Falkenhain ME, Elkhammas EA, et al. The high prevalence of severe early posttransplant renal allograft pathology in hepatitis C positive recipients. Transplantation. 1996;62(8):1054–9.
87. Lefaucheur C, Loupy A, Vernerey D, Duong-van-Huyen JP, Suberbielle C, Anglicheau D, et al. Antibody-mediated vascular rejection of kidney allografts: a population-based study. Lancet. 2013;381(9863):313–9.
88.•• Goldberg DS, Abt PL, Blumberg EA, van Deerlin VM, Levine M, Reddy KR, et al. Trial of transplantation of HCV-infected kidneys into uninfected recipients. N Engl J Med. 2017;376(24):2394–5 **HCV viremic kidneys are being transplanted into non-viremic patients with DAA treatment with excellent graft function**.
89. Reese PP, Abt PL, Blumberg EA, Goldberg DS. Transplanting hepatitis C-positive kidneys. N Engl J Med. 2015;373(4):303–5.
90.• Trotter PB, Summers DM, Ushiro-Lumb I, Robb M, Bradley JA, Powell J, et al. Use of organs from hepatitis C virus-positive donors for uninfected recipients: a potential cost-effective approach to save lives? Transplantation. 2018;102(4):664–72 **Treating HCV in kidney recipients with DAAs is less expensive than an additional five years of remaining on dialysis**.
91. Theodoropoulos N, Whitson BA, Martin SI, Pouch S, Pope-Harman A. Successful treatment of donor-derived hepatitis C infection in a lung transplant recipient. Transpl Infect Dis. 2017;19(2).
92. Moayedi Y, Gulamhusein AF, Ross HJ, Teuteberg JJ, Khush KK. Accepting hepatitis C virus-infected donor hearts for transplantation: multistep consent, unrealized opportunity, and the Stanford experience. Clin Transpl. 2018;32(7):e13308.
93. Woolley AE, Baden LR. Increasing access to thoracic organs from donors infected with hepatitis C: a previous challenge-now an opportunity. J Heart Lung Transplant. 2018;37(5):681–3.
94. Schlendorf KH, Zalawadiya S, Shah AS, Wigger M, Chung CY, Smith S, et al. Early outcomes using hepatitis C-positive donors for cardiac transplantation in the era of effective direct-acting antiviral therapies. J Heart Lung Transplant. 2018;37(6):763–9.
95. Martins PN, Movahedi B, Bozorgzadeh A. Transplanting HCV-infected kidneys into uninfected recipients. N Engl J Med. 2017;377(11):1104–5.
96. Wettersten N, Tran H, Mekeel K, Pretorius V, Adler E, Aslam S. Successful heart-kidney transplantation from a hepatitis C viremic donor to negative recipient: one year of follow-up. Transpl Infect Dis. 2019;21(1):e13002.
97.•• 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(8):533–40 **Transplantation of kidneys from HCV viremic donors and treating HCV with DAAs is safe and effective with excellent outcomes**.
98. Lee GS, Anesi J, Besharatian BD, Bittermann T, Hamel S, Goldberg DS. Con: Use of Hepatitis C Virus-Positive Donors Should be Restricted to Research Protocols. Clin Liver Dis. 2018;12(4):105–8.
99. Goldberg DS, Levitsky J. Transplanting livers from HCV-infected donors into HCV-negative recipients: promise but mind the pitfalls. Amer J Transpl 2019;19(5):1264–5.

100. Levitsky J, Goldberg D, Smith AR, Mansfield SA, Gillespie BW, Merion RM, et al. Acute rejection increases risk of graft failure and death in recent liver transplant recipients. Clin Gastroenterol Hepatol. 2017;15(4):584–593 e2.
101.• Chan C, Schiano T, Agudelo E, Paul Haydek J, Hoteit M, Laurito MP, et al. Immune-mediated graft dysfunction in liver transplant recipients with hepatitis C virus treated with direct-acting antiviral therapy. Am J Transplant. 2018;18(10):2506–12 **Immune-mediated graft dysfunction including rejection and plasma cell hepatitis has been reported in patients being treated with DAAs**.
102. Campos-Varela I, Lai JC, Verna EC, O'Leary JG, Todd Stravitz R, Forman LM, et al. Hepatitis C genotype influences post-liver transplant outcomes. Transplantation. 2015;99(4):835–40.
103. Verna EC, Goldberg DS. Hepatitis C viremic donors for hepatitis C nonviremic liver transplant recipients: ready for prime time? Liver Transpl. 2018;24(1):12–4.
104. Verna EC, Abdelmessih R, Salomao MA, Lefkowitch J, Moreira RK, Brown RS Jr. Cholestatic hepatitis C following liver transplantation: an outcome-based histological definition, clinical predictors, and prognosis. Liver Transpl. 2013;19(1):78–88.
105. Siddiqui AR, Abbas Z, Luck NH, Hassan SM, Aziz T, Mubarak M, et al. Experience of fibrosing cholestatic hepatitis with hepatitis C virus in kidney transplant recipients. Transplant Proc. 2012;44(3):721–4.
106. Wadei HM, Pungpapong S, Cortese C, Alexander MP, Keaveny AP, Yang L, et al. Transplantation of HCV-infected organs into uninfected recipients: advance with caution. Am J Transplant. 2019;19(3):960–1.
107. Kirby BJ, Symonds WT, Kearney BP, Mathias AA. Pharmacokinetic, pharmacodynamic, and drug-interaction profile of the hepatitis C virus NS5B polymerase inhibitor Sofosbuvir. Clin Pharmacokinet. 2015;54(7):677–90.
108. Bifano M, Adamczyk R, Hwang C, Kandoussi H, Marion A, Bertz RJ. An open-label investigation into drug-drug interactions between multiple doses of daclatasvir and single-dose cyclosporine or tacrolimus in healthy subjects. Clin Drug Investig. 2015;35(5):281–9.
109. Burgess S, Partovi N, Yoshida EM, Erb SR, Azalgara VM, Hussaini T. Drug interactions with direct-acting antivirals for hepatitis C: implications for HIV and transplant patients. Ann Pharmacother. 2015;49(6):674–87.
110. Werbel WA, Durand C. Pro: Use of Hepatitis C Virus-Positive Donors Should Be Considered Standard of Care. Clin Liver Dis. 2018;12(4):100–4.
111.• Bethea ED, Samur S, Kanwal F, Ayer T, Hur C, Roberts MS, et al. Cost effectiveness of transplanting HCV-infected livers into uninfected recipients with preemptive antiviral therapy. Clin Gastroenterol Hepatol. 2019;17(4):739–47 **e8. Treatment of patients post liver-transplantation with DAAs who were transplanted with HCV organs is less expensive than remaining on the transplantation waitlist**.
112. Levitsky J, Formica RN. Response to: HCV viremic donors with hepatic bridging fibrosis: are we ready to use their livers in the era of direct-acting antivirals? Am J Transplant. 2017;17(11):2988.
113.• Stepanova M, Sayiner M, de Avila L, Younoszai Z, Racila A, Younossi ZM. Long-term outcomes of liver transplantation in patients with hepatitis C infection are not affected by HCV positivity of a donor. BMC Gastroenterol. 2016;16(1):137 **Longterm outcomes of patients who receive "HCV-positive" organs is no different than those who receive "negative" organs**.
114. Shaffer AA, Thomas AG, Bowring MG, van Pilsum Rasmussen SE, Cash A, Kucirka LM, et al. Changes in practice and perception of hepatitis C and liver transplantation: results of a national survey. Transpl Infect Dis. 2018;20(6):e12982.