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Patient's Perspectives of Experimental HCV-positive to HCV-negative Renal Transplantation

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Abstract

Background: With growing transplant wait times, clinical trials are evaluating the safety and efficacy of transplanting HCV-infected donor (HCV+) organs into HCV-noninfected recipients (HCV D+/R-). Such transplants raise ethical questions about safety, consent, and access to organs.

Methods: We interviewed eight of the ten total HCV D+/R- transplant recipients enrolled in a pilot clinical trial examining the safety and feasibility of these novel transplants regarding their experiences in the trial, including their decision-making and perceptions of the informed consent process.

Results: All interviewees reported positive experiences and expressed confidence regarding their decision to participate. Participants accepted an HCV+ organ based on their assessments of the risks and potential benefits of HCV D+/R- transplants. For many, the risks of HCV were minimal compared to the risks of not receiving a transplant. All participants recalled providing informed consent, reporting that the process was thorough and that all their questions were addressed. Participants did not regret receiving an HCV D+/R- transplant and did not report experiencing stigma. However, given their understanding of HCV cure rates in the general population and the

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SE Van Pilsum Rasmussen participated in study design, data collection, data analysis, data interpretation, and drafting of the manuscript. S Seaman participated in data analysis, data interpretation, and drafting of the manuscript. D Brown, N Desai, M Sulkowski, and DL Segev participated in data interpretation, and drafting of the manuscript. CM Durand and J Sugarman participated in study conception, study design, data interpretation, and drafting of the manuscript.

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DISCLOSURE

Niraj Desai and Christine Durand have received grant support and served as scientific advisors to Merck. Jeremy Sugarman serves on Merck KGaA's Bioethics Advisory Panel and Stem Cell Research Oversight Committee as well as IQVIA's Ethics Advisory Panel, unrelated to the data described in this manuscript.

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survival benefit associated with kidney transplantation, participants may have conflated research regarding HCV D+/R- transplantation with clinical care, suggesting potential therapeutic misconception.

Conclusions: Recipients of experimental HCV D+/R- transplants generally seemed to recognize the risks and benefits of these novel transplants and did not regret participating. Such salutary reported experiences are important in assessing the appropriateness of further research into the feasibility of HCV D+/R- transplants.

Keywords

transplantation; research ethics; hepatitis C; qualitative research; interview

INTRODUCTION

For patients with end stage renal disease, kidney transplantation has a significant survival benefit of several years over dialysis (Reese et al. 2015; Schold et al. 2014; Rana et al. 2015) and improves quality of life (Jofre et al. 1998; Gross et al. 2000; Dew et al. 1997). However, over 90,000 people are currently waiting for a deceased donor kidney transplant (KT) in the United States (U.S. Department of Health & Human Services Organ Procurement and Transplantation Network Data 2018). Hepatitis C Virus (HCV) -infected (HCV+) organs have been successfully transplanted into HCV+ recipients; and HCV can now be safely and effectively treated with direct-acting antiviral medications (Levitsky et al. 2017). HCV cure rates are high in the general population, and HCV cure rates are high among HCV-infected transplant recipients, which is similar to the general population (Chen et al. 2017; Colombo et al. 2017; Lin et al. 2016; Saxena et al. 2017). Despite these observations and the severe organ shortage, large numbers of HCV+ organs are discarded and not used for transplantation (Bowring et al. 2017a; Kucirka et al. 2010).

A recent consensus statement calls for research on HCV+ organ donor transplants for HCV- recipients (HCV D+/R-) (Levitsky et al. 2017). The statement emphasizes that the informed consent process should include information about the risks and benefits of HCV D+/R- transplants. These risks include complications due to HCV infection, graft failure, HCV treatment failure, and HCV transmission to sexual partners (Levitsky et al. 2017). However, there also may be risks of not accepting an HCV+ organ, such as the increased risk of morbidity and mortality due to longer organ wait times (Levitsky et al. 2017). Two separate small clinical trials conducted at different institutions subsequently found short-term safety and success in a combined total of thirty HCV D+/R- transplants (Goldberg et al. 2017; Durand et al. 2018; Reese et al. 2018).

The novelty of HCV D+/R- transplants also raises other ethical questions, such as the potential for the recipient to experience HCV-related stigma. Accordingly, and consistent with the consensus statement's call for the study of patient perceptions of their experience and the informed consent process (Levitsky et al. 2017), we conducted a qualitative interview study to assess the experiences and perspectives of HCV D+/R- transplant recipients in one of the two pilot clinical trials, "Exploring Renal Transplants Using Hepatitis C Infected Donors for HCV-negative Recipients (EXPANDER)" ().

METHODS

Clinical trial

The clinical trial aimed to assess the safety and efficacy of a strategy for preventing HCV transmission in HCV-noninfected recipients of HCV-infected donor organs (Durand et al. 2018). HCV-noninfected patients on the waitlist for a deceased donor KT and age ≥ 50 years were eligible for the trial (clinicaltrials.gov). The study surgeon phoned 15 potentially eligible patients and provided general information about the trial. Interested patients met with the surgeon face-to-face for approximately one hour to review detailed information about the trial including that delineated in the consent form. Risks discussed included, but were not limited to, the side-effects of HCV treatment and the possibility of acquiring HCV, which could result in fulminant hepatitis and death (described in the informed consent form as a “very rare possibility”). The informed consent form did not mention the potential benefits of receiving an HCV+ donor organ, such as the likelihood of receiving a younger donor organ or a decreased wait time to transplant. However, the surgeon who obtained consent discussed with all potential participants that this pilot trial was the first to study the use of direct acting antiviral medications to prevent transmission, and that receiving a younger donor organ or a decreased wait time to transplant were likely benefits. Patients had the opportunity to ask questions and then provided written informed consent, which was obtained by the study surgeon. The first 10 patients to provide consent to participate in the clinical trial received a transplant from a HCV + donor (positive HCV antibody and nucleic acid test results). An additional oral confirmation of consent to receive an HCV+ organ was obtained at the time of the transplant surgery. The HCV D+/R– transplants were performed from August 2016-February 2017; median time to transplant after enrollment in the clinical trial was 1 month. All HCV D+/R– transplant recipients received pre-exposure prophylactic treatment with grazoprevir (100 mg) and elbasvir (50 mg) immediately before the transplant operation (Durand et al. 2018). The donor HCV genotype was sent at the time of transplant and results were available within 7 days. For donor genotype 1, grazoprevir (100 mg) and elbasvir (50 mg) were continued for 12 weeks (Durand et al. 2018). In three cases, donors were identified to have non-genotype 1 virus which necessitated the addition of a third direct-acting antiviral agent sofosbuvir (Durand et al. 2018). Sofosbuvir has been shown to be highly active for genotype 2 and 3 infection and clinical trials have demonstrated the efficacy of grazoprevir-elbasvir in combination with sofosbuvir for genotype 3 infection (Lawitz et al. 2017, Foster et al. 2017).

Experiences of clinical trial participants

We attempted to contact all transplant recipients in the trial either in person or by phone to request their participation in this interview study. All participants provided written or oral informed consent. The interviewer was trained in qualitative research methods and was uninvolved in the clinical trial (SVPR). Each participant was interviewed twice. The first interview occurred within two months post-transplant and focused on experiences during recovery (“at-transplant”); the second interview occurred four months post-transplant and focused on experiences one month after completing HCV treatment (“post-transplant”). Interviews were conducted in-person or by phone and lasted an average of 27 minutes.

Participants were assured that their participation would not affect their care at Johns Hopkins.

A semi-structured interview guide was developed by the research team, which included a transplant-infectious disease physician and an ethicist (Appendix 1). The interview guide was adapted from one that is currently being used for recipients of HIV+ to HIV+ organ transplants (Henderson 2017). The interview guide consisted of twenty open-ended questions about participants' decision making process, including their motivations for participation, concerns about accepting an HCV+ organ, experience with informed consent, and who or what factors influenced their decision. Participants were also asked about any benefits, regrets, or instances of stigma experienced after their transplant. Probing questions were used to prompt thorough responses.

The interviews were audio recorded, transcribed verbatim, and checked for accuracy. Using a qualitative descriptive approach, which allows for an understanding of a phenomena from the perspective of those experiencing it (Neergaard et al. 2009; Chafe 2017), qualitative codes were derived based upon domains of the interview guide and inductively derived from the interviews. The codes were iteratively refined by two independent coders (SVPR and SS). Codes were applied using NVivo (QSR International) and differences in coding were reconciled until reaching consensus. The time point ("at" or "post" transplant) of each quotation is listed after each quote. Themes from both time points were reviewed and compared to assess any changes in responses in the at-transplant and post-transplant interviews.

The interview study was approved by the Johns Hopkins Medicine Institutional Review Board (IRB00103150).

RESULTS

Study Population

Two of the total 10 clinical trial participants declined to be interviewed, resulting in a sample of 8 interview study participants. One recipient declined participation in the interview study after reading the informed consent script, the other was unable to be reached for an interview after several attempts. Both recipients who declined to be interviewed were men and similar in age to those who were interviewed.

Most interview participants were male, white/Caucasian, and college educated; their median age was 71 years. Interviewees had been on the KT waitlist for a median of 8.1 months and median time from enrollment to KT was 4.1 weeks. Six were on dialysis prior to KT; among those, median time on dialysis was 26.4 months. Dialysis was expected imminently in the recipients not already on dialysis; all had a glomerular filtration rate of less than 15 mL/min/1.73 m² at the time of transplant.

Overall Experiences of Recipients of HCV D+/R- Transplants

All interviewees reported overall positive experiences in the clinical trial (Table 1). One said they were "thrilled," "blessed," and "thankful" to have been in the study (post-transplant,

#5). Another said they would recommend it to anybody, and that it was the “best thing since canned beer” (post-transplant, #3).

Interviewees expressed confidence in their decision to participate in the trial, and optimism regarding the study’s benefits and risks. As one participant said, “It was kind of a no brainer, I really thought this was the best thing for me” (post-transplant, #4). Another said, “[People] were amazed when I told them what the presumed success rate was before I did it... my assumptions really from the get go was that it was going to work” (post-transplant, #3). Likewise, participants expressed optimism regarding the success of their own transplants, as well as HCV D+/R– transplants more broadly. One explained, “I’m just thinking positively, and you know, the drugs have been effective in curing hep C independent of the transplant, I haven’t been affected [by the HCV] for some time now. So that’s giving me a lot of confidence” (post-transplant, #7). Another said,

I just feel that this drug is going to cure the hep c, I know there’s a slight, there’s some percentage that something could go wrong but I think there’s gonna be more successes than failures... I think the study is going to help, it’s going to make a difference. Cause they’re throwing away kidneys... I think this is big, this is really big, I feel glad to be part of it. (at-transplant #5)

One participant described their perception of the risks of the trial, saying:

I’ve been following the medical information of the hepatitis C treatment and so I was aware that it wasn’t just the treatment it was the virtual 99% cure now. So I just thought the concept was good because it’d be extremely low risk for me. I’d get rid of the Hepatitis C and I’d get a kidney. So I was very positive. (at-transplant #4)

Reasons to Accept an HCV+ Organ

Participants reported many reasons for accepting an HCV+ organ, but the overriding motivation was to avoid or discontinue dialysis because of the treatment’s health and lifestyle implications (Table 2). Participants who hadn’t started dialysis wanted to avoid long wait times for an organ, particularly because they “really didn’t want to go on dialysis” (at-transplant, #4). Others were eager to discontinue dialysis. One participant explained that dialysis was “a real ball and chain” (post-transplant, #3). The improved life expectancy of transplant recipients compared to dialysis patients was another motivating factor for some.

Additionally, participants were motivated to enroll by the possibility of receiving a younger, higher quality donor organ (Table 2). One explained that they “could benefit greatly from a younger kidney sooner” (at-transplant, #6). Some participants believed that as older recipients they were likely to receive a kidney from an older donor, which, as one participant said, “might only be good for 5 or 8 years, and I’d be back on dialysis at age 80” (at-transplant, #3).

Age also factored into deciding to accept an HCV+ organ (Table 2). Some believed that because of the wait times for a transplant, they would be older and less fit for a transplant if they received an organ in the normal match, and that the trial was an opportunity to receive

an organ while younger and healthier. Participants also explained that because of their older age, they were less concerned about the long-term implications of HCV.

Concerns about Accepting an HCV+ Organ

Participants had many concerns that were not specific to HCV D+/R-, including graft function, operative mortality, and immunosuppressive regimens (Table 3). Most participants expressed some concern about the risk of HCV infection, specifically being exposed to HCV while on immunosuppressants and the risk of infecting others with HCV (Table 3). However, some said they had no particular concerns about accepting an HCV+ organ.

All participants with initial concerns about accepting an HCV+ organ found them addressed during recruitment and the informed consent process. When asked about their initial concerns, one participant responded “just the fact that it’s hep C, but I didn’t have any fears ‘cause I talked to the doctor” (at-transplant, #2). Another responded: “Actually, that’s been my least concern the last few months since I had the operation... My focus has just been on the hassles of recovery... the hepatitis has been virtually no concern” (at-transplant, #4).

The Decision-Making Process

While participants had concerns about accepting an HCV+ organ, they were motivated by several factors that they consciously balanced against those concerns. To many, the risks of HCV were minimal compared to the risks of not receiving the transplant: “[I was] concerned but you have to weigh that against not getting the transplant... I think I made the right decision” (at-transplant, #7). Participants especially considered the risks and burdens of dialysis:

I spent 3.5 years on dialysis. I did not want to die on that machine. I would rather take my chances with the hep C and medication and cure it than to stay on that machine for the rest of my life. (post-transplant, #2)

All participants sought information about HCV D+/R- transplants and HCV from other sources besides the clinical study team prior to enrolling, including online research or discussions with physicians or friends with medical backgrounds (Table 1). Many discussed the trial with clinicians outside of the study and reported that they were supportive; one participant’s nephrologist was initially concerned about the safety of the HCV treatment regimen in kidney failure patients, but was reassured after discussion with the study team. However, some participants did not do research online because, as one explained, there is “a lot of misinformation online” (post-transplant, #5).

Participants found that friends and family were supportive of their decision to accept an HCV+ organ. Participants usually framed these discussions by balancing the risks and benefits as they understood them. One said: “Well once you gave them the statistics my daughter and son were both like right on from the get go... I kept telling them all the results are positive and they relaxed about it” (post-transplant, #4). Others presented family and friends with their decision rather than engage them in the decision: “We presented it to my daughter like this is what I am doing and it is a no brainer so she wouldn’t worry” (post-transplant, #3).

Many participants emphasized that they made their decisions independently: “I pretty much decided on my own and the opinions I got were supporting” (post-transplant, #4). Some decided to enroll in the trial almost immediately: “the final decision was mine which really was a no-brainer. It took me 30 seconds to say yes to it” (post-transplant, #8). Others took longer to decide: “I was dragging my feet a little bit... then a peace came over me and I decided to go with it” (at-transplant, #5).

Experience with Informed Consent Process

All participants remembered giving informed consent to enroll in the clinical trial and receive an HCV+ kidney. All also reported that the consent process was thorough and that they felt adequately aware of the trial’s risks and benefits: “[The study surgeon] explained everything to me and that was no problem. I was willing to sign everything... I knew, high risk I knew. Everything was discussed with me. I don’t feel like anything was kept from me.” (post-transplant, #5). Another described the consent process, saying:

[The study surgeon] would explain ...a gajillion parts, and he would explain what each of the parts meant and what it applied to and then gave us the opportunity to sign and we did and he would move on to the next part and explain it totally, what we would be signing up for... and if we had specific questions about any of the forms we discussed it right then and there... I was impressed at his level of effort and time and explanation. (at-transplant, #6)

Participants reported that the information they received during the informed consent process was “thoroughly explained” (at-transplant, #2), and “pretty understandable... not complex... or overly legalistic” (post-transplant, #3), and that the consent process was “lengthy” (at-transplant, #6). One participant said they felt they were given “plenty of chances to change my mind. I appreciated that” (post-transplant, #4).

Participants reported feeling adequately informed prior to giving consent to participate in the study. One said “I was told everything I needed to know.” (post-transplant, #5). No participants reported wishing they had been told anything else before agreeing to participate.

Participants also reported feeling that the information they received during informed consent was “practical” (at-transplant, #4). One said:

[The study surgeon], he’s not the kind of person that is like ‘oh you know this is the greatest thing since apple pie.’ I mean he tells you the truth, he tells you how it is... he’s not putting any frills on it or anything like that. (post-transplant, #1)

Interviewees reported asking a variety of questions before agreeing to participate in the clinical trial, mostly regarding the effectiveness of the HCV treatment (Table 1, Table 4). All of those who asked questions indicated that they were adequately answered. One said “[The study surgeon] answered every question so thoroughly and I could understand it... I didn’t feel stupid” (at-transplant, #5). Another said “The doctor was great about it... he didn’t hold nothing back and I made a decision” (post-transplant, #2).

After the Transplant: Impact of Receiving a Transplant

Interviewees believed that the main benefit of participating in the clinical trial was receiving a transplant, especially considering the standard wait times for an HCV-noninfected donor organ. One said, “when you are faced with the ‘I don’t know if I would ever get one’ and then you get one, it’s like wow” (post-transplant, #1). When asked why they felt they might never get a transplant, the participant explained: “[because of] how many people are on the list. And my age” (post-transplant, #1). Some participants reported contributing to science as a benefit of participating in the clinical trial: “As far as I know, this overall small group, it’s being real successful and it’s on the way to making this an accepted procedure to make a lot more kidneys available to people so I feel like I have really helped” (post-transplant, #4).

Many of the benefits described by participants are benefits of transplants in general (Table 1). However, participants credited their acceptance of an HCV+ organ with the relatively rapid realization of these benefits, including a new chance at life, improved quality of life (such as simpler dietary restrictions and the ability to travel), improved overall health, the ability to return to work, and improved relationships with partners, families and friends. These benefits were attributed to discontinuing dialysis: “The concept and the results are incredible... If you have never been on dialysis you don’t fully appreciate the freedom... that has been renewed in your life” (post-transplant, #3).

Participants also recounted some negative impacts of receiving a transplant; however, none of these was specific to HCV D+/R– transplants (Table 1). These included surgical recovery, the effects of and lifestyle modifications due to immunosuppression, and traveling for follow-up visits. No participant reported being stigmatized or being treated differently after telling someone they received an HCV D+/R– transplant.

Differences in responses over time

Most themes were discussed at both the at-transplant and post-transplant interviews; however, seven themes were only raised at one time-point (Table 1). Regarding HCV-specific issues, concerns about the risk of infecting others with HCV and questions regarding the outcomes of other trial participants who had already received a transplant were raised only during at-transplant interviews. Questions and concerns regarding the effect of maintenance immunosuppression on HCV were raised only during post-transplant interviews.

DISCUSSION

In this study of participants in a pilot clinical trial of HCV D+/R– transplants, all interviewees conveyed positive experiences. They decided to accept an HCV+ donor organ based on their perceptions of the benefits and risks of HCV D+/R– transplants; the primary potential benefit of accepting an HCV+ organ was discontinuing or avoiding dialysis and the risks associated with that treatment, likely sooner than if they waited for an HCV-noninfected organ. Some factors discussed by participants, such as the improved life expectancy and quality of life of transplant recipients compared to dialysis patients, were not specific to accepting an HCV+ organ, but are reasons to pursue a renal transplant in general

(Tonelli et al. 2011; Jofre et al. 1998). However, these factors still motivated participants to accept an HCV+ kidney, as they were able to enjoy the benefits of transplantation more quickly as a consequence of their decision. Additionally, participants were motivated to possibly receive a kidney from a donor younger than they might otherwise be expected to receive in the normal organ match process, as HCV+ organ donors are significantly younger than HCV-non-infected organ donors (Bowring et al. 2017b; Chute and Sise 2018).

Benefits of participating in clinical trials have been classified into three categories: direct, collateral, and aspirational benefits (King 2000), all of which were reportedly experienced by participants in this study. Receiving a timely transplant, particularly from a younger donor with few comorbidities, was perceived as a direct benefit, stemming directly from the study's intervention. The close attention afforded to clinical trial participants could be considered a collateral benefit, or a benefit of being a participant in the study regardless of receiving the intervention. Participants also believed they had contributed to efforts to reduce the organ shortage and had contributed to science through their participation, an aspirational benefit of accepting an HCV+ organ.

Many interviewees had initial concerns about the efficacy of the HCV treatment regimen in the transplant setting and the risks of HCV if treatment failed. However, participants reported that these concerns were addressed adequately and that all their questions were answered prior to enrolling in the trial. All described positive and thorough experiences with the informed consent process. They felt confident in their decision to accept an HCV+ organ and recalled great optimism about the successful treatment of HCV in this setting, about the success of their own HCV D+/R- transplant, and about the success of the trial in general. Participants were perhaps understandably optimistic about their chances of successful HCV cure given that the surgeon who obtained consent for the trial discussed the high rates of cure with direct acting antiviral treatment outside of this unique transplant setting, which were the only potentially relevant data concerning this treatment available at the time of enrollment in the trial.

Nevertheless, while current HCV treatments have a very high cure rate in the general population (Burstow et al. 2017), at the time of the trial the efficacy of direct acting antiviral medications to prevent HCV infection in an HCV-non-infected transplant population had never been studied. While results of small single center pilot trials have subsequently demonstrated early success of HCV D+/R- transplants (Durand et al. 2018; Goldberg et al. 2017), these results were unknown at the time of enrollment in the clinical trial, and at the time participants gave consent to enroll it would have been a mistake to assume that this treatment would certainly be effective. The ability to prevent durable transmission of HCV due to transplantation was novel at the time of this trial, and there was no existing data directly suggesting that trial participants would in fact have a successful course of HCV treatment concurrent with a successful transplant. Despite this, given their understanding of the cure rates of HCV in the general population and the survival benefit associated with kidney transplantation, participants may have confounded these independent outcomes with the likelihood of a successful HCV D+/R- transplant.

This may indicate potential therapeutic misconception, which is characterized by the conflation of research with clinical care, and a belief that a research study is designed to benefit the patient directly (Horng and Grady 2003). Furthermore, therapeutic misconception is more likely in studies where the study design and clinical care are similar, among subjects who have otherwise limited treatment options, and among subjects directly invited to participate by their clinical team (Horng and Grady 2003). All of these risk factors for therapeutic misconception are present in the clinical trial examined in this interview study. In particular, the only other treatment option for trial participants was remaining on or initiating dialysis and likely enduring a longer wait for a donor organ, and some participants reported having no HCV-related concerns prior to their experimental HCV+/HCV– transplant. Of note, therapeutic misconception has been a concern in other experimental transplants, such as uterine and stem cell transplantation (Petrini et al. 2017; Cooper et al. 2017; Cote et al. 2017), as well as in the context of the prevention of transmission and cure of infectious diseases, specifically HIV (Katz et al. 2019; Annas 2017; Peay and Henderson 2015). While the populations in these studies related to HIV infection differ from the transplant population in our study, all raise concerns about therapeutic misconception with regard to the transmission and cure of infectious diseases.

While findings of a potential therapeutic misconception may signal ethical concerns related to inappropriate enrollment, in this context they do not seem especially worrisome for a variety of reasons. First, participants were satisfied with the consent process and reported that their questions were answered. Second, the participants seemed to have a solid general understanding of the trial itself and the inherent related risks. Third, enrollment and participation did not seem in aggregate to pose a threat to their welfare, despite the uncertainty related to the ability to cure HCV in this setting at the time of enrollment. Furthermore, Horng and Grady state that a therapeutic misconception may be tolerable when there is a high likelihood that participants will personally benefit, especially when there is also a low risk. This clinical trial of HCV D+/R– transplants arguably meets the former criterion since the benefits of receiving a transplant were significant and the risks of durable HCV transmission were expected to be low.

That said, it is important to keep in mind that these findings are viewed through a retrospective lens following a highly successful trial as well as a similar successful trial elsewhere. Moreover, interviewees in our study had all recently survived a transplant so their recollections and perspectives may understandably have a survivor bias. Regardless, therapeutic mis-estimation and misconception need to be taken seriously. Unfortunately, based on the methods we used and the nature of our data we are neither able to comprehensively assess the implications of these findings nor identify their origins. For example, whether these findings were related to the consent process or other factors is impossible to determine from our data. In a retrospective interview study, we are unable to clearly determine the content of the actual communications with the surgeon or any members of the clinical or research teams.

Nonetheless, this study contributes to discussions of the ethical issues related to HCV D+/R– transplantation. In a 2017 consensus conference statement, Levitsky et al. argue that it is ethically acceptable to transplant HCV non-infected recipients with HCV-infected donor

organs under IRB approved research protocols with special attention paid to the adequacy of informed consent (Levitsky et al. 2017). More recently, deliberations have focused on whether or not HCV D+/R- transplantation should become standard of care or should continue to be conducted only under IRB approved protocols (Werbel and Durand 2018; Lee et al. 2018).

The findings of this study should be interpreted in light of several limitations. First, our findings may be limited by its small sample size and the relatively homogenous study population. However, we interviewed eight of the ten total participants who received transplants in this single-center pilot study, and the two HCV D+/R- transplant recipients who did not participate in the interview study were similar demographically to those who did participate. Nevertheless, patients who declined participation in the clinical trial may have different perspectives on the relative risks and benefits of HCV D+/R-transplants and/or participation in research. Furthermore, younger patients may face greater lifetime risk of complications from HCV infection and may differently weigh the benefits and risks of HCV D+/R- transplantation. These factors limit the generalizability of our findings to a general transplant waitlist population. Second, participants were interviewed after receiving information from and consultation with the surgeon and clinical team; any concerns or fears may have been alleviated before the interviews were conducted. We attempted to account for this by prompting participants to discuss their concerns and questions when first approached about the clinical trial. Third, since all ten recipients of HCV D+/R- transplants in this trial had successful transplants and HCV treatment courses, and since the median time to transplant from enrollment was only one month, respondents' perceptions of the study may be biased by the positive outcomes. Had a recipient's recovery or HCV treatment been more complicated it would have likely changed their views on the balance of risks and benefits of HCV D+/R- transplantation. Lastly, while all participants recalled and expressed positive experiences with the informed consent process, we did not assess whether or not participants retained information presented to them at the time of consent. Nor did we formally assess comprehension at the time of consent. Such assessments would have allowed for a more robust assessment of the informed consent process, including potential therapeutic misconception or mis-estimation and the adequacy of informed consent. Future work might be directed at both capturing the actual conversations about enrollment and consent as has been done in other settings such as early phase oncology research (Kass et al. 2009), as well as assessing informed consent comprehension more proximate to the consent process (Sugarman et al. 2005). Such data would help improve the informed consent process for further trials of HCV D+/R- transplantation. Despite these limitations, responses were largely consistent across both the at-transplant and post-transplant interviews, suggesting that perceptions were relatively stable over time.

In summary, all interviewees reported positive experiences and expressed confidence regarding their decision to participate in the clinical trial and to receive an HCV D+ transplant. They seemed to generally recognize the risks and benefits of experimental HCV D+/R- transplants and did not regret participating. For many, the risks of HCV were minimal compared to the risks of not receiving a transplant. All participants recalled providing informed consent, reporting that the process was thorough and that all their questions were addressed. However, at enrollment, participants described optimism

regarding the study's benefits and risks, even though the clinical trial of HCV D+/R- transplants was the first of its kind. In addition, participants may have conflated research regarding HCV D+/R- transplant with clinical care, suggesting a potential therapeutic misconception. Accordingly, participants' beliefs and perceptions should be carefully monitored as HCV D+/R- transplantation is further studied.

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APPENDIX I

Recipients of HCV+ organs interview guide

Thank you for talking with me today about your transplant. As you know, I will be recording our conversation. During the interview, if you don't want to discuss a particular question or topic, that is fine, just let me know. Are you ready to begin?

1. How has the transplant experience been for you?

Decision making and consent process

2. Tell me about how you decided to accept an HCV+ organ. From the time you first heard about HCV+ transplants until you received the transplant, what was the decision process like?

(If they don't answer these in their response to #2):

- a. When did you decide to accept an HCV+ organ?
- b. How long did it take you to decide to accept an HCV+ organ?
- c. What things did you think about when making your decision?
- d. Did you talk about your decision with anyone? If so, with whom?
- e. Who or what was helpful in making your decision?
 - i. Were any family/friends helpful?
 - ii. Were any healthcare workers helpful?
 - iii. How so?
- f. Who or what was unhelpful in making your decision?
 - i. Were any family/friends unhelpful?
 - ii. Were any healthcare workers unhelpful?
 - iii. How so?
- g. Did you have any questions about accepting an HCV+ organ?

- i. If so, what were your questions?
 - ii. If so, who did you ask?
 - iii. How did you feel about their responses?
- h. Was the organ you received the first organ you were offered? Had you turned down an organ before accepting the organ you received?
- 3. Do you remember giving consent to receive an HCV+ organ?
 - a. Can you describe the process of giving consent?
 - b. Was there anything good or bad about giving consent?
- 4. Is there anything you wish you had been told when making your decision?

Overall Experience

- 5. Before being offered a HCV+ transplant had you heard of this type of transplant before? If so, please tell me about that.
- 6. What were some reasons you accepted an HCV+ organ?
 - a. Have any of those reasons/expectations come true?
 - b. Have any of those reasons/expectations not come true?
- 7. What were some of your concerns or fears about accepting an HCV+ organ?
 - a. Have any of those concerns/fears come true?
 - b. Have any of those concerns/fears not come true?
- 8. Has anything about the experience been different than you expected? If so, how?
- 9. Has anything surprised you? If so, how?
- 10. What were some positive things about the experience?
- 11. What were some negative things about the experience?
- 12. Is there anything you regret about having a transplant?
 - a. Is there anything you regret about accepting an HCV+ positive transplant?
- 13. Does anything about your transplant make you afraid?
 - a. Does anything about accepting an HCV+ transplant make you afraid?
- 14. As a reminder, HCV+ to HCV– transplants are new and experimental. We don't yet know if they are safe and effective. How does that make you feel?

Effect of transplant on relationships and daily life

- 15. How has the transplant affected your life?

- a. (If in a relationship) How has the transplant affected your relationship with your partner?
 - b. How has the transplant affected your relationships with family?
 - c. How has the transplant affected your relationships with friends?
 - d. (If employed) How has the transplant affected your work life?
 - e. How has the transplant affected your day to day life?
 - f. How has the transplant affected your overall health?
16. How do you think your life would be different if you hadn't accepted and HCV+ organ?

Communication of transplant

17. Who knows that you received an HCV+ organ?
- a. How did [each person listed in #17] learn you received an HCV+ organ?
 - b. How did [each person listed in #17] react when they learned you received an HCV+ organ?
 - c. [If they have told people they received and HCV+ organ] How did you tell them? Are there good ways to tell people? Are there bad ways to tell people?

Stigma

18. Has anyone treated you differently after learning you received an HCV+ organ?
19. Is there anything else we could do better with these types of transplants?
- a. Any ways we could improve the experience for other recipients of HCV+ organs?
20. Is there anything else you'd like me to know about receiving an HCV+ organ?

General Probing Questions

- If concerns: Does that worry you? How does that make you feel?
- If states information, data, etc: Where did you learn that?

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U.S. Department of Health & Human Services Organ Procurement and Transplantation Network Data. 2018 “Current U.S. Waiting List Candidates by Organ.”

Table 1:**Major Themes and Subthemes Derived from Interview Transcripts**

MAJOR THEME	SUBTHEMES	
Overall Experiences	Good experience	
	Confidence, Optimism	
Decision making process	Balanced risks and benefits	
	Conducted own research	
	Did not conduct own research ^b	
	Discussed with other healthcare providers	
	Discussed with friends with medical backgrounds	
	Discussed with family and friends	
	Made their own decision	
	Took some time to decide	
	Decided almost immediately	
Concerns about undergoing a transplant	General Transplant Concerns	Delayed graft function
		Risk of mortality during operation
		Adjusting to immunosuppressive regimen
	HCV-specific Concerns	Risk of HCV infection
		Risk of infecting others with HCV ^a
		Elevated risk of HCV due to immunosuppression ^b
		Had no concerns about HCV+ organ
Reasons to accept an HCV+ Organ	Avoid dialysis	
	Discontinue dialysis	
	Avoid long wait for organ	
	Receive younger, higher quality donor organ	
	Recipient's age: receive transplant while younger	
	Recipient's age: not concerned about long-term risks of HCV	
	Improve life expectancy	
	Improve quality of life	
	Effectiveness and safety of HCV treatment	
	Contribute to science	
	Cost of HCV drug covered	
Experience with Informed Consent Process	Asked questions	Effectiveness and safety of HCV drugs
		Effect of maintenance immunosuppression on HCV ^b
		Would doctors recommend the study to their own families
		Status of EXPANDER participants who had already received a transplant ^a
	All questions were answered	

MAJOR THEME	SUBTHEMES	
Positive Impacts of Receiving an HCV+ organ	Consent process was thorough	
	Good experience with consent process	
	Got a transplant	
	Stayed or went off dialysis	
	Contributed to science	
	Improved quality of life	Improved energy, independence, activity
		Able to travel
		Simpler dietary restrictions ^b
	New chance at life	
	Improved overall health	
	Able to return to work	
Negative Impacts of Receiving a Transplant	Recovery from surgery	
	Effects of and modifications due to immunosuppression	
	Frequent follow-up visits ^b	

^aTheme was only brought up in at-transplant interviews

^bTheme was only brought up in post-transplant interviews

Table 2:**Reasons to accept an HCV+ Organ**

Theme	Representative Quote
Avoid dialysis	My options were to either start dialysis and be on the transplant list perhaps 4-6 years, and I thought the hep C organ was a better option for me. (<i>at-transplant, #7</i>)
Discontinue dialysis	Dialysis was tough and I thought having to do that for the rest of my life, I just, I just decided to go with hep C and I have no regrets. I'm so glad I did it. (<i>at-transplant, #5</i>)
Avoid long wait for organ	I really wanted to get a transplant and then, you know, I was put on a five year waiting list and I have to go on dialysis. (<i>at-transplant, #4</i>)
Receive younger, higher quality donor organ	You know at my age, I am 71, you were getting offered pretty, you know, secondary type situations in terms of donors you know which is understandable. But... with the hep C... he said we would offer you a kidney from somebody who was under 40 years old. (<i>post-transplant, #3</i>)
Recipient's age: receive transplant while younger	I took an attitude of this is my chance and that's it. And I don't know how much longer I would have had to wait for a kidney which would probably I feel have been anywhere from 4.5 to 5 years. And I would have been, by the time I did it that way I would have been 76 years old (<i>post-transplant, #1</i>)
Recipient's age: not concerned about long-term risks of HCV	I found that even if it failed as far as not being able to be rid of the hep C, that I wouldn't have too many issues for the remainder of my life. (<i>at-transplant, #3</i>)
Improve life expectancy	I think that [the study surgeon] also said that the life expectancy of a transplant was twice the life expectancy of someone on dialysis and I thought that that was a good option for me. (<i>at-transplant, #7</i>)
Improve quality of life	Thank god for dialysis, but it gets old... I also was aware that it's fairly stressful on your heart and blood pressure and the dietary restrictions.... Trying to go outside the country is impossible. You know my daughter lives [abroad], I can't visit her there. Things like that. (<i>at-transplant, #3</i>)
Effectiveness and safety of HCV treatment	[The study surgeon] clarified that the drug was actually, has been used on hepatitis positive recipients of kidneys and that the whole thing worked with them no side effects. (<i>post-transplant, #4</i>)
Contribute to science	I've helped people all my life and I thought if this was a way people could benefit from what they learned then I'd be willing to – I hate to use the word serve as a guinea pig – but I would be happy to participate in the trial so that they could get some valuable information to help other people. (<i>post-transplant, #8</i>)
Cost of HCV drug covered	We understood that insurance would be covering the vast majority of it, and that the drug would be paid for by Merck, so but those weren't major (<i>at-transplant, #6</i>)

Table 3:

Concerns about undergoing a transplant

Theme	Representative Quote
<i>General transplant concerns</i>	
Delayed graft function	There may be a sleepy kidney, it might take a week or a month but you might have to go back on dialysis. That was something I thought about but I didn't dwell on it. (<i>at-transplant #5</i>)
Risk of mortality during operation	Well just like anybody during surgery you could die (<i>post-transplant #1</i>)
Adjusting to immunosuppressive regimen	The new life living with immunosuppressant drugs. So that was unknown... we're still learning what restrictions there might be on travel, work, driving (<i>at-transplant #9</i>)
<i>HCV-specific concerns</i>	
Risk of HCV infection	Or they couldn't cure the hep c or couldn't do anything about it or if it would spread to the rest of my body (<i>post-transplant #2</i>)
Risk of infecting others with HCV	That was one question we had... would there be any possible danger to grandchildren, in terms of coming in contact, I could be a carrier if I'm not successfully treated (<i>at-transplant, #6</i>)
Elevated risk of HCV due to immunosuppression	I'm afraid of developing an infection because I'm immunosuppressed and I'm afraid that even though my viral load is negative and has been negative, I'm afraid that that might be irreversed [sic] and I might show positive culture at some point. (<i>at-transplant, #7</i>)
Had no concerns about HCV+ organ	The only time I think about it is when I know the blood tests are being done and they come back negative (<i>at-transplant, #1</i>)

Table 4:

Questions about HCV D+/R– transplants

Theme	Representative Quote
Effectiveness of the HCV drugs	Is it curable? What medicines I gotta take, how long I gotta take ‘em, how long I’d be in the program (<i>at-transplant, #2</i>)
If the doctors would recommend the study to their own families	I said if this was you or your family member what would you do and he goes, ‘I will [sic] do it’ (<i>post-transplant, #3</i>)
Effect of immunosuppression on HCV treatment	I wanted to know the risk factors and the medication I would need to take, the immunosuppression drugs, and the effect of that (<i>post-transplant, #7</i>)
Status of EXPANDER participants who had already received a transplant	“...the progress of the other people in the study, what the preliminary results have been...” (<i>at-transplant, #7</i>)