Introduction
The availability of direct-acting antiviral (DAA) agents that reliably offer cure rates exceeding 95% for patients with CKD and patients with ESKD infected with hepatitis C virus (HCV) (1) has had a significant effect on the retrieval and allocation of kidneys from HCV-infected donors. Presented with increasing numbers of kidney offers from viremic donors, the transplant community has studied the feasibility of using these kidneys in an effort to increase access to kidney transplantation. Many transplant centers are now routinely performing transplants from HCV-viremic donors into HCV-positive recipients and initiating DAA treatment early after transplantation with excellent outcomes (2,3). This approach has translated into shorter waitlist times, increased access to transplantation, and a potential decrease in long-term morbidity and mortality for this patient population (2–5). In the context of studies demonstrating the safety and efficacy of the DAs in kidney recipients (2,3,6,7), there has been increased interest in transplanting kidneys from HCV-positive donors into uninfected recipients. Agreeing to accept a kidney from a Public Health Service increased risk, HCV-infected donor requires informed consent at the time of listing, and in this context, many patients are being presented with this option and often seek advice and recommendations from their nephrologist. Understanding the pertinent literature on this topic will enable the nephrologist to actively participate in this decision and offer valuable guidance.

DAAs in the Treatment of HCV Infection Post-Transplantation
Following the discovery of HCV and the availability of an ELISA to identify anti-HCV antibody, many cases of transmission of HCV with kidney transplantation were reported (8,9). Adverse consequences of transmission at the time of transplantation with resulting de novo HCV infection in the setting of intense immunosuppression included an aggressive form of fibrosing cholestatic hepatitis (FCH) and an immune complex injury to the allograft resembling membranoproliferative GN (10,11). The use of kidneys from HCV-infected donors was discouraged, and to a great extent, these kidneys were either not retrieved or discarded (2).

HCV-Positive to HCV-Positive Transplantation
The first generation DAAs were approved by the Food and Drug Administration (FDA) in 2013 for the treatment of chronic HCV infection. Reese et al. (2) offered a perspective on how DAA therapy could change the perception of using HCV-positive organs in transplant candidates with or without preexisting HCV infection. The main advantage of this approach is a significant reduction in waiting time compared with an HCV-negative kidney (12). Initial interest was focused on transplanting HCV-positive kidneys into HCV-positive recipients, and early reports described excellent outcomes (13). Accepting an HCV-positive kidney was associated with a significantly decreased waiting time with excellent safety and efficacy of the DAAs (1,3,14–17). In one study, Bhamidimarri et al. (3) reported a median waiting time to transplant of 58 days after entering the patient into UNet® to accept an offer from an HCV-positive donor. Of importance, these studies brought attention to potential drug-drug interactions and the need to be vigilant with calcineurin inhibitor dosing to maintain therapeutic levels. The sustained viral response (SVR) in these studies was consistently above 96%.

HCV-Positive to HCV-Negative Transplantation
Two pilot clinical trials have explored the feasibility of transplanting kidneys from HCV-infected donors into HCV-negative recipients with early initiation of DAA therapy (Table 1). In the Transplanting Hepatitis C Kidneys into Negative Kidney Recipients (THINKER) trial, 20 patients without HCV infection were transplanted with a kidney from an HCV-infected donor; the median waiting time for kidney transplantation after informed consent was 57 days. DAAs were initiated when viremia was first detected (mean of 3 days post-transplant), and all recipients obtained an SVR post-transplant (18). In the Exploring Renal Transplants Using Hepatitis-C Infected Donors for HCV-Negative Recipients (EXPANDER-1) trial, ten HCV-negative patients were transplanted with a kidney from a viremic donor. In contrast to the THINKER trial, DAA therapy was started preoperatively, and all patients also obtained an SVR (19). Although encompassing only a small number of patients, these pilot trials were proof of concept that transplanting HCV-positive kidneys

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Clinical Trials Versus the Real World

HCV-Infected Donor

Deciding If a Patient Should Accept a Kidney from an HCV-Infected Donor

Clinical Trials Versus the Real World

Although both the THINKER trial and the EXPANDER-1 trial offered encouraging results, they left many questions to be answered before this strategy could be considered standard of care. Both of these studies were performed in a strict research setting, which included reliable and early availability of DAAs coupled with the close monitoring that accompanies a clinical trial. Both trials were industry funded with provision of DAA medications, and no third-party payers were involved. In a real-world setting, rapid access to DAAs may not be easily achievable because these drugs are only FDA approved for the treatment of chronic and not acute HCV infection. There is a possibility that approval from third-party payers could be delayed if the case must be appealed and reviewed.

Two real-world, single-center studies have recently reported their findings using a similar strategy as the THINKER trial and the EXPANDER-1 trial (Table 1). Molnar et al. (20) described outcomes in 53 HCV-negative patients who received a kidney from an HCV-positive donor. All patients became viremic and received DAA therapy; however, the median time for DAA initiation was 76 days. Of interest, they reported a 19% rate of transient transaminitis, a higher incidence of cytomegalovirus and polyoma virus viremia compared with historical controls, and an increase in the development of de novo donor-specific antibodies in the 2.5 months that elapsed between transplantation and the initiation of antiviral therapy. One patient developed FCH that responded favorably to DAA treatment. In the other study, 64 HCV-negative patients received a kidney from an HCV-positive donor (21). The median waitlist time was 128 days but only 23.5 days after consent was obtained for an HCV-positive donor. Patients who received DAA therapy initiated treatment at a median of 72 days after transplantation. One patient was a nonresponder to DAA therapy due to NS5A resistance, two patients developed FCH responsive to DAA treatment, and one patient died 77 days after transplant (unrelated to HCV infection) (22).

Does the Evidence Support Accepting a Kidney from an HCV-Infected Donor?

Transplanting a kidney from an HCV-infected donor into an HCV-positive or HCV-negative recipient is an exciting opportunity to increase access to transplantation. This has been made possible by the unique coincidence of timing and events, whereby highly effective antiviral therapies became available at the same time that we have been witness to a dramatic increase in the number of kidneys available from HCV-infected donors as a consequence of the opioid epidemic. For the patient already infected with HCV, the available evidence suggests that the answer to this question is yes in most circumstances. In contrast, the trials in which kidneys from viremic donors were transplanted into uninfected recipients are limited by their small size and short follow-up time. Nevertheless, they have caught the attention of both transplant professionals and patients with ESKD facing long waiting times for a deceased donor kidney (23).

Discussions with the patient about the pros and cons of accepting a kidney from an HCV-positive donor should include their dialysis vintage, regional waitlist times, urgency of transplantation, and how highly sensitized the patient is (and therefore, more difficult to transplant). In geographic regions where waiting times exceed 5 years and patients are preemptive or with short dialysis vintage, the option of accepting an HCV-positive organ may be more compelling. In addition to a significant reduction in wait times, kidneys from HCV-positive donors are often of excellent quality because the donors tend to be younger than the general donor population. Given the outstanding results delivered by the new DAA regimens in treating post-transplant HCV infection, one could argue that the current kidney donor profile index (KDPI) calculation should be modified because it includes “HCV-positive status” as a negative predictor of allograft outcome. In their study of transplanting HCV-positive kidneys into HCV-negative recipients, Graham et al. (24) recalculated the KDPI for the HCV-positive donors by removing “HCV-positive status” from the KDPI formula. This resulted in an adjusted KDPI of 40.9% from 64%. As long as the current KDPI system remains unchanged, patients should be aware that a “high” KDPI associated with the HCV-positive kidney donor might not accurately reflect the quality of the organ.

The implied advantages of accepting an HCV-infected kidney (i.e., shorter wait time and higher-quality kidney)
must be weighed against the risk of FCH, altered immune responsiveness leading to the emergence of other viral infections (i.e., cytomegalovirus and polyoma), and potential logistical challenges to obtain the DAA medications. In addition, any patient that is considered for an HCV-positive organ should be evaluated by a hepatologist to ensure that he or she will be a candidate for DAA treatment and for a liver transplant should antiviral treatment fail and progressive liver injury occur after acquiring de novo HCV post-transplant.

From this discussion, it is apparent that the patient’s nephrologist should be well informed about all of the variables that might factor into an appropriate informed consent before the patient accepts a kidney from an HCV-infected donor. The patient will be faced with a complex decision, with many nuances that may not be prepared to make. In all likelihood, the patient will turn to the nephrologist for recommendations and guidance.

Disclosures
M. Ladino, J. Pagan, and D. Roth have nothing to disclose.

References
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