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Editorial Board Member of *World Journal of Transplantation*, Albino Eccher, MD, PhD, Professor, Section of Pathology, Department of Medical and Surgical Sciences for Children and Adults, University of Modena and Reggio Emilia, University Hospital of Modena, Modena 41124, Italy. albino.eccher@aovr.veneto.it

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REVIEW

Expanding the liver donor pool worldwide with hepatitis C infected livers, is it the time?

Mai Hashem, Mohammed A Medhat, Doaa Abdeltawab, Nahed A Makhlouf

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Mai Hashem, Fellow of Tropical Medicine and Gastroenterology, Assiut University Hospital, Assiut 71515, Egypt

Mohammed A Medhat, Nahed A Makhlouf, Department of Tropical Medicine and Gastroenterology, Faculty of Medicine, Assiut University, Assiut 71515, Egypt

Doaa Abdeltawab, Department of Tropical Medicine and Gastroenterology, Al-Rajhi Liver Hospital, Assiut University, Assiut 71515, Egypt

Corresponding author: Mai Hashem, MBChB, MD, MHSc, Lecturer, Department of Tropical Medicine and Gastroenterology, Assiut University Hospital, Assiut University Campus, Assiut 71515, Egypt. maihashem@med.aun.edu.eg

Abstract

Liver transplantation (LT) provides a life-saving option for cirrhotic patients with complications and hepatocellular carcinoma. Despite the increasing number of liver transplants performed each year, the number of LT candidates on the waitlist remains unchanged due to an imbalance between donor organ supply and the demand which increases the waitlist time and mortality. Living donor liver transplant had a great role in increasing the donor pool and shortened waitlist time for LT candidates. Nevertheless, further strategies can be implemented to increase the pool of potential donors in deceased donor LT, such as reducing the rate of organ discards. Utilizing hepatitis C virus (HCV) seropositive liver grafts is one of the expanded donor organ criteria. A yearly increase of hundreds of transplants is anticipated as a result of maximizing the utilization of HCV-positive organs for HCV-negative recipients. Direct-acting antiviral therapy's efficacy has revolutionized the treatment of HCV infection and the use of HCV-seropositive donors in transplantation. The American Society of Transplantation advises against performing transplants from HCV-infected liver donors (D+) into HCV-negative recipient (R-) unless under Institutional Review Board-approved study rules and with full informed consent of the knowledge gaps associated with such transplants. Proper selection of patients to be transplanted with HCV-infected grafts and confirming their access to direct-acting antivirals if needed is important. National and international consensuses are needed to regulate this process to ensure the maximum benefit and the least adverse events.

Key Words: Donor pool; Hepatitis C-viremic organs; Non-viremic organs; Direct acting antivirals; Hepatitis C virus treated; Liver transplantation.

Core Tip: There is an imbalance between donor organ supply in liver transplantation and the demand. Unfulfilled demands in organ transplant communities prompt new approaches to increasing donor pools. Direct acting antiviral (DAA) regimens have proved higher efficacy in treating hepatitis C virus (HCV). Available data shows that HCV non-viremic donor organs can be used in HCV-negative or positive liver transplant candidates safely. Furthermore, using liver grafts from HCV-viremic donors in liver transplant candidates, even if they were HCV negative, is showing favorable outcomes. Preoperative informed consent and easy access to DAAs with the engagement of clinical pharmacists are indispensable to ensuring these good outcomes.

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INTRODUCTION

Liver transplantation (LT) provides a life-saving option for cirrhotic patients with complications and hepatocellular carcinoma[1]. There were 10.6 million cases of decompensated cirrhosis globally in 2017, with a mortality rate of 2.4% of total mortality[2]. The increasing cirrhosis and its sequelae globally mean increasing demand for LT. The volume of LT is increasing, with 34694 liver transplants performed globally in 2021 and 23% from living donors[3]. There will be changing trends in liver transplant indications in the future. Non-alcoholic steatohepatitis-related cirrhosis will be the leading indication for LT in Europe, the United States, and the Middle East[4]. The declining trend of hepatitis C virus (HCV) prevalence, with the resurgence of alcoholism, has resulted in alcoholic liver disease becoming the first indication for LT in the United States, passing HCV[5]. Nowadays, non-alcoholic fatty liver disease is the second most common indication for LT in the United States and is expected to be the first in the future. These changes in LT indications will project new and unique challenges to the liver transplant community[6].

The demand for LT exceeds the supply of available organs, leading to a death rate of approximately 20% among patients on the waiting list[7]. Thus, reducing mortality and improving overall outcomes could be achieved by any means of increasing the organ pool to provide patients with faster access to transplants. One potential strategy for increasing the number of patients served by organ banks is using organs from HCV-infected donors in HCV-uninfected recipients[8]. This review will discuss the advantages, disadvantages, and reported outcomes of using HCV-infected organs in LT.

FACTS ON DONOR SHORTAGE AND UNMET NEEDS FOR DIFFERENT STRATEGIES TO EXPAND DONOR POOLS

Despite the increasing number of liver transplants performed each year, the number of LT candidates on the waitlist remains unchanged. This is due to an imbalance between donor organ supply and demand, which increases the waitlist time and mortality[9]. In 2020, 470 liver transplant candidates died while waiting for a suitable donor[10]. Unfulfilled demands in organ transplant communities prompt new approaches to increasing donor pools[11]. Of these, using high-risk organs, such as organs donated after cardiac death, from advanced donor age, and grafts with minimal hepatic steatosis[12,13].

Living donor liver transplant (LDLT) greatly increased the donor pool and shortened waitlist time for LT candidates [14]. Therefore, expanding LDLT is a goal in North America and Europe, where deceased donor LT (DDLT) represents a major LT practice. Nevertheless, further strategies can be implemented to increase the pool of potential donors in DDLT, such as reducing the rate of organ discards[1].

RATIONALE FOR USING HCV-POSITIVE ORGANS IN LIVER TRANSPLANT

Using less-than-ideal organs, provided the risk/benefit ratio is still beneficial compared to the patient's chances of staying on the transplant list without an organ, is one strategy to improve the supply of organs. Expanded criteria donors have been used for many years, pushing the bounds of what is considered appropriate to enhance organ access for recipients and reduce organ discarding. Donors with chronic diseases, such as hepatitis viruses, or acute illnesses, such as bacterial infections, can be deemed appropriate donors if a successful treatment to prevent or treat the recipient's infection is available[15].

Utilizing HCV seropositive liver grafts is one of the expanded donor organ criteria[16]. A yearly increase of 300-500 transplants is anticipated as a result of maximizing the utilization of HCV-positive organs for HCV-negative recipients (R-)[17]. Figure 1 illustrates the impact of adopting HCV-infected liver grafts in transplantation.

There were some concerns regarding the utilization of HCV-infected liver donors (D+) into (R-). These concerns were related to the risk of HCV transmission, the outcomes, and complications to the graft and patients, including accelerated graft hepatitis, acute rejection, premature graft failure, or the risk of fibrosis progression post-transplantation up to death. Also, the previous standard of care for HCV management, including pegylated interferon and ribavirin, restricted the acceptance of using D+ into R-, fearing undesirable side effects post-transplant triggering treatment discontinuation[18,19].

A revolutionary event was raised in the management of chronic HCV with the emergence of direct acting antivirals (DAA) in 2011, with a cure rate of nearly > 95% and high efficacy and tolerability for patients[20]. The efficacy of direct-acting antiviral therapy has dramatically altered the treatment of HCV infection and the use of HCV-seropositive donors in transplantation. Patients who developed viremia following transplantation from an HCV-seropositive donor have been successfully treated for HCV post-transplantation at multiple institutions[21,22].

Data obtained for a national survey from 57 of the largest LT centers of the United States, mainly from hepatologists (82.5%), to learn more about their practices for donors, recipients, and HCV positive (HCV+) candidates before and after DAAs, revealed that 21 centers (38.9%) were willing to consider using HCV+ donors for HCV negative (HCV-) candidates after DAAs, in contrast to 3 centers (5.6%) that reported it before DAAs. Six centers had at least 1 HCV+ to HCV- LT, for a total of 12 LTs, during the pre-survey phase. This number increased to 26 centers through the post-survey period, for a total of 129 HCV+ to HCV- LTs[23].

There are currently no restrictions under the Organ Procurement and Transplantation Network (OPTN) that limit the transplantation of infected donors to recipients who are either HCV+ or HCV-. In the next ten years, this is expected to be the primary source of accessible HCV-infected livers due to the rise in drug overdose mortality[8].

Liver allografts from donors who are HCV-RNA positive - as determined by the extremely sensitive HCV NAT testing - have been transplanted into HCV-negative recipients at a significantly higher rate than before. Since the introduction of DAA medication, the frequency of transplanting HCV viremic donor organs into recipients who do not have HCV infection has grown by more than 30 times[24].

Donors with detectable levels of HCV antibodies are considered to be HCV+. The window period, or the interval between infection and diagnosis using a particular testing approach, may enhance the possibility of HCV transmission in a donor with high-risk behavioral features[25]. For these high-risk donors, it is recommended to use a nucleic acid testing (NAT) assay that finds HCV viral RNA in the donor's blood. The duration between HCV infection and detection was shortened from 70 days to 3–5 days by using NAT tests[8].

The American Society of Transplantation (AST) has redefined the term "HCV-positive donor" in light of the introduction of NAT[8]. A donor with HCV who tests negative for NAT (non-viremic) suggests that the infection has either resolved on its own or has been effectively treated. Active infection and a high risk of disease transmission are indicated by an HCV-seropositive and NAT-positive donor (viremic) (D NAT+)[26]. Traditionally, all donors were serologically tested for HCV infection in accordance with the OPTN guideline recommendations. It was modified in 2014 to incorporate NAT testing for HCV infection in addition to serological testing[27,28].

THE RISK OF HCV TRANSMISSION AFTER LIVER TRANSPLANTATION

The risk of HCV transmission to recipients is highest for D NAT+, whereas the risk of transmission is likely negligible for allografts that test negative for HCV NAT[16]. HCV non-viremic donor (D NAT-) is considered safe for transplantation into R- in the absence of other risk factors such as increased risk donors (IRDs). Despite the safety of using HCV non-viremic graft into R-, the risk of HCV transmission still exists, with IRDs reaching up to 16%[29]. IRDs are defined according to the United States Public Health Service guidelines as donors who are recently exposed to HCV infection, and HCV RNA may not yet be detectable[8,30].

According to the data mentioned earlier, the utilization of IRD grafts is considered the highest risk for unexpected HCV transmission during the eclipse period. Therefore, in the absence of additional risk factors, donors who are HCV antibody positive (HCV Ab+) but NAT- are not thought to be at an elevated risk of HCV transmission. This is supported by studies reporting no HCV transmission by organ transplantation from (HCV Ab+/D NAT-)[31-33]. Consequently, post-transplant recipient testing is mandated by OPTN policies exclusively in cases where the transplant center expresses concern over the possibility of disease transmission[8]. Liver transplant recipients who receive HCV NAT+ donor livers are invariably infected with HCV[15,33-36].

USE OF HCV NON-VIREMIC LIVER DONORS INTO HCV-NEGATIVE RECIPIENTS

There have been controversies regarding the risk of HCV transmission from (HCV Ab+/D NAT-) into R-. Some reported no evidence of infection, while others reported a risk of transmission up to 16%.

Aqel *et al*[32] reported that up until a median of 6 months (range 3-18 months) post-LT follow-up, 14 recipients of HCV non-viremic grafts had undetectable HCV RNA. In another study by Crismale *et al*[33], none of the patients who received livers from (HCV Ab+/D NAT−) developed HCV viremia post-transplant.

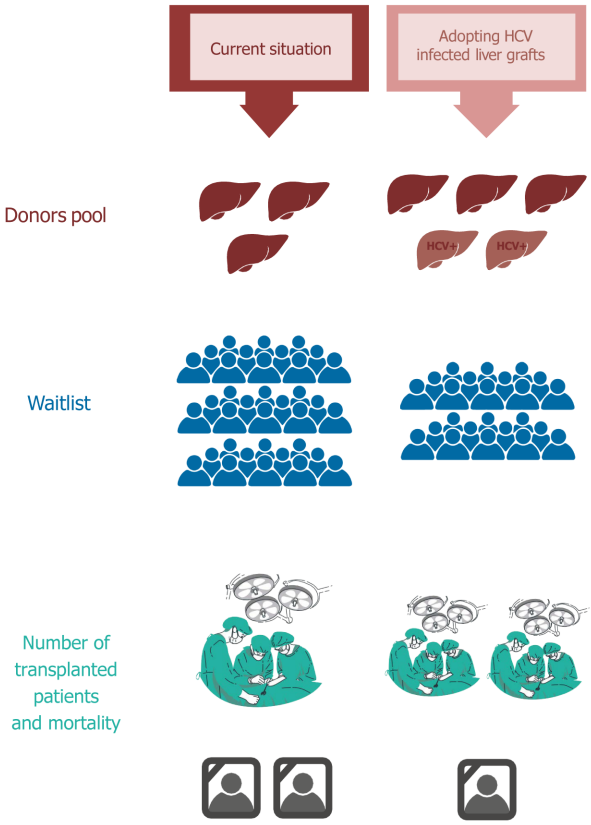

Figure 1 Impact of adopting hepatitis C virus-infected liver grafts in transplantation. HCV+: Hepatitis C virus infected liver.

A 16% risk of HCV transmission was documented by Bari *et al*[29] following LT from (HCV Ab+/D NAT−) to R-. Donors who transmitted HCV were all IRDs who died from drug overdose.

HCV viremia was experienced by 10% of the 21 R- who received LT from (HCV Ab+/D NAT-) in a study by Sobotka *et al*[37], with a high rate of reaching SVR in patients who develop HCV post-transplant. Prior research has documented a comparable incidence of HCV viremia, approximating 10%[29,34,38].

The existing literature supports various possible mechanisms of HCV transmission in these circumstances. One reasonable cause for HCV transmission in HCV Ab+ donors could be false negative NAT tests[38]. Sensitivity estimates for HCV NAT testing range from 96% to 99%, and their negative predictive value exceeds 99%[39-41].

Some donors may have been within the eclipse period for NAT detection. The report of Suryaprasad *et al*[42] on organ transplantation from seronegative, NAT-negative, high-risk donors resulting in HCV transmission to non-HCV recipients provides supporting literature for eclipse period infection. Sources of the HCV genome were isolated from stored donor splenocyte or lymphatic tissue samples despite the fact that none of the six recipients who developed HCV had received a liver transplant.

Transient low-level viremia, which occurs during the early phase of acute HCV infection when the innate and cellular immune systems are attempting to eliminate the virus and is below the limit of detection for current assays, is an additional potential mechanism by which HCV is transmitted[43,44].

Occult hepatitis C infection (OCI) in the donated tissue could cause HCV to be transmitted. The clinical significance of OCI remains uncertain, as spontaneous relapse of viremia appears to be exceptionally rare, even in immunocompromised patients post-solid organ transplant (estimated 1% to 2% after successful treatment with interferon-based regimens)[45]. Estimates of OCI prevalence vary widely, ranging from 0% to 95%, depending on the study population and methodology [46,47].

USE OF HCV-VIREMIC LIVER DONORS INTO HCV-NEGATIVE RECIPIENTS

Introducing HCV D NAT+ into HCV-transplant programs represents an innovative approach that holds promise for expanding the donor pool, enhancing transplanted organ quality, and reducing transplant list waiting times. The results of the clinical trials undertaken thus far have been encouraging[48].

Ten non-viremic recipients who underwent liver transplantation with HCV-infected livers were described by Kwong *et al*[49]. They all acquired hepatitis C infection and achieved sustained virologic response at 12 wk post-treatment (SVR-12) when treated with DAA-based regimens.

In a retrospective study by Ting *et al*[50], the 20 R- of HCV D NAT+ all acquired active HCV infection post-LT. Twelve of them reached SVR12, while the remaining were in different stages of treatment when the study was published.

In a study that included 14 R-, 9 of them underwent LT from HCV D NAT+, and viremia developed in all 9 recipients post-transplantation. The recipients received a 12-wk course of oral DAAs within 5 d after transplantation, all achieving SVR. In this study, it was reported that immediate use of DAAs post-transplantation in NAT-positive recipients is safe and effective; in addition, they did not record any cases with HCV-related complications[51].

Another study conducted at a single center examined the application of HCV-viremic allografts in non-viremic recipients; of these, 6 underwent LT (4 patients received a liver transplant, and 2 patients received a liver-kidney transplant). HCV infection was universally transmitted to the recipients. Three patients reached SVR12, 1 patient finished DAA therapy, and 2 were still receiving treatment when the study was published[52].

In another retrospective study, 61 R- that received LT from HCV D NAT+ (study group) were compared to 231 R- that received a liver from NAT- donors (control group). It was reported that 83.3% of the study group developed viremia by detecting HCV RNA within the first week and 98.3% by the end of the second week post-LT. The study concluded that using HCV D NAT+ in R- followed by DAA treatment provides good outcomes comparable to the control group[53].

In a prospective multicenter study that Aqel *et al*[32] had conducted, the study enrolled 34 donors (20 HCV-viremic, 14 non-viremic) used for graft donation to R-. The 20 recipients from HCV D NAT+ were confirmed to be infected with HCV by detection of HCV RNA within 3 d post-transplant, and they all achieved SVR12 following DAA therapy.

In a prospective multicenter study where 24 patients received organs from HCV-viremic donors (13 liver transplants and 11 kidney transplants), all 13 liver recipients had detectable HCV RNA in their serum on day 3 following transplant, and all achieved SVR12[15].

Table 1 shows the estimated risk of HCV transmission and SVR rate in HCV negative LT recipients of HCV viremic and non-viremic donors, as reported in the literature.

OBSTACLES FACED IN CASE OF USING HCV-POSITIVE DONOR ORGANS

The ethical dilemma surrounding HCV D+/R- LT pertains to the balance between the potential risks of intentionally infecting the patient with HCV and subjecting them to the consequences of HCV infection, such as fibrosing cholestatic hepatitis (FCH), heightened rates of graft rejection, DAA side effects or ineffective treatment leading to chronic HCV infection and the advantages, which could include mitigating patient mortality and waitlist abandonment rates caused by extended waiting periods, especially in a time when donor grafts are scarce[54-58].

Conversely, some experts contend that the utilization of infected donors is not a novel concept in transplantation, as evidenced by the routine use of organs from donors exposed to other infections (*e.g.*, cytomegalovirus) with adequate measures in place to control infections; therefore, HCV should not be regarded differently[59].

One of the most significant impediments to using organs from HCV D NAT+ is the expensive cost of DAAs, as well as the possibility that the recipient will not be able to get HCV treatment after transplantation. The Food and Drug Administration has not yet approved the use of DAAs for the prevention or treatment of donor-derived HCV, and it is unknown if insurance companies will pay for these drugs[35].

Certain insurance companies have the right to refuse payment for various reasons. For example, they can insist on documentation of a chronic infection for a minimum of six months, excluding treatment in an acute situation[60].

Furthermore, there is a considerable variation in perspective recipients' willingness to accept an HCV+ donor. The potential use of HCV+ organs in recipients who are HCV- also presents some ethical issues and is still debatable, especially when considered as a purposeful spread of an infectious disease to accomplish a desired result[61,62].

ETHICAL CONSIDERATIONS AND INFORMED CONSENT

The AST advises against performing HCV D+/R- transplants unless under Institutional Review Board (IRB)-approved study rules and with full informed consent of the knowledge gaps associated with such transplants[8]. A number of recent single-center studies demonstrate how quickly transplant doctors in the United States have adopted this practice [49,52,63]. However, significant questions remain about the most effective way to use antiviral medication in this situation[15].

The following factors should be taken into account while planning and carrying out HCV D+/R- transplants[64]: (1) Transplant centers should design and maintain a plan for educating and obtaining informed consent from HCV-negative transplant candidates who are considering receiving an organ from an HCV-viremic donor[64]. Standardization and use of specialized informed consent will be required to provide patients with unbiased, comprehensive information so they may make independent decisions about their care[65]; (2) Centers performing transplants from HCV-viremic donors should have a diagnostic and treatment regimen in place for HCV-negative transplant candidates[64]; And (3) Transplant centers should make sure that obstacles pertaining to payment and reimbursement will not cause a delay in the HCV diagnosis or treatment of recipients who receive organs from HCV-viremic donors[64].

An expert multidisciplinary team is required to transmit the labs and begin the approval process of getting DAA while the patient is hospitalized following transplantation to speed the start of treatment, including a committed pharmacy team to expeditiously provide data for cost assistance, prior authorizations, and appeals[35].

Table 1 The estimated risk of hepatitis C virus transmission and sustained virologic response rate in hepatitis C virus negative liver transplantation recipients of hepatitis C virus viremic and non-viremic donors

Ref.	Study design	Study group	Post LT viremia *n*/*N* (%)	SVR12	Time from transplant to start of DAA (d)
Luckett *et al* [38], 2019	Prospective	55 HCV non-viremic candidates received HCV Ab+/NAT- LT, including 6 SLKT	5/53 (9)	4/5 SVR12	NA
Kwong *et al* [49], 2019	Single-center, retrospective	10 HCV non-viremic candidates received HCV NAT+ LT	10/10 (100)	10/10 SVR12	Median 43 (IQR 20–59)
Ting *et al*[50], 2019	Single-center, retrospective	6 seronegative candidates received HCV NAT+ LT, including 2 SLKT	6/6 (100)	3/6 SVR12	Median 37 (range 9-74)
				1/6 completed DAA	
				2/6 ongoing DDA	
Bethea *et al*[51], 2020	Single-center, prospective	14 HCV negative recipients, including 4 SLKT:			
		9 received HCV NAT+ LT	9/9 (100)	9 SVR12	Range 0-29
		5 received HCV Ab+/NAT- LT	1/5 (20)	NA	
Kapila *et al*[52], 2020	Single-center, retrospective	26 HCV negative recipients:			
		20 received HCV NAT+ LT	20/20 (100)	11/20 SVR12	Median 51 (range 19-121)
				3/20 completed DAA	
				5/20 ongoing DAA	
				1/20 pending insurance approval	
		6 received HCV Ab+/NAT- LT	2/5 (40)	1/5 SVR12	
				1/5 ongoing DAA	
Anwar *et al* [34], 2020	Single-center, prospective, matched cohort trial	32 NAT- recipients received HCV NAT+ LT, including 7 SLKT	31/31 (100)	19/30 SVR12	Median 47 (IQR 18-140)
				6/30 ETR	
				5/30 ongoing DAA	
				1/30 is yet to start treatment	
Crismale *et al* [33], 2020	Single-center prospective observational	19 HCV negative recipients, including 4 SLKT:			
		13 received HCV NAT+ LT	13/13 (100)	12/13 SVR12	Median 42 (IQR 35-118)
		6 received HCV Ab+/NAT- LT	0/6 (0)		
Aqel *et al*[32], 2021	Multicenter, prospective study	34 HCV negative recipients, including 6 SLKT:			Median 27.5
		20 received HCV NAT+ LT	20/20 (100)	20/20 SVR12	
		14 received HCV Ab+/NAT- LT	0/14 (0)		
Sobotka *et al* [37], 2021	Single-center, retrospective	42 HCV-seronegative recipients:			
		21 received HCV NAT+ LT	20/21 (95)	15/15 (patients with data) SVR12	Mean 38
		21 received HCV Ab+/NAT- LT, including 1 SLKT	2/21 (9.5)	2/2 SVR12	
Bohorquez *et al* [53], 2021	Single-center, retrospective, case-control study	61 HCV negative recipients, including 3 SLKT, received HCV NAT+ LT	60/61 (98.3)	51/56 SVR12	Median 66.9 (IQR, 36-68.5)
				5/56 ongoing DDA when study published	
Hudson *et al* [36], 2021	Single-center, retrospective	18 HCV negative recipients, including received HCV NAT+ LT	18/18 (100)	18/18 SVR12	mean ± SD, 48 ± 23

Terrault *et al* [15], 2021	Multicenter (6 US centers), prospective study	13 HCV non-viremic candidates received HCV NAT+ LT	13/13 (100)	13/13 SVR12	Median 7 (IQR 6-12)
Nair *et al*[104], 2021	Retrospective cohort	23 HCV negative recipients received an HCV Ab+/NAT+ LT	23/23 (100)	23/23 SVR12	Median 118 (IQR 46-129)
Bova *et al*[35], 2022	Single-center, retrospective	29 HCV-negative recipients received HCV-viremic or HCV-seropositive LT, including 4 SLKT	29/29 (100)	NA	Median 29 (range 0-84)

Ab+: Antibody positive; DDA: Direct acting antiviral; HCV: Hepatitis C virus; IQR: Interquartile range; LT: Liver transplantation; NA: Not applicable; NAT-: Non-viremic; NAT+: Viremic; SLKT: Simultaneous liver kidney transplant; SVR12: Sustained virologic response at 12 wk post-treatment.

According to an expert consensus report from the 2019 Controversies in Transplantation workshop, the best treatment should be proactive, and all HCV-naive patients should have insurance coverage for DAAs following transplantation. Most experts agree that treatment should be preemptive. However, in real life, this is not feasible because most insurance plans require HCV testing in the recipient to approve medicine[66].

Next, it must be determined whether the recipient has viremia for treatment to be warranted. Another element is the HCV genotype, which may have a significant role in determining the particular antiviral treatment used in each case. Hence, early genotype assessment and therapy matching may be necessary for treatment considerations; however, the advent of pangenotypic antiviral regimens may eliminate this requirement. Pharmacological interactions and renal function are two other issues to be taken into account, along with the planning of DAA therapy[60].

Given that HCV D+/R- LT is already taking place, guaranteeing its fairness and justice for patients in need of LT is critical. It is imperative for LT providers to guarantee that the provision of HCV D+/R- LT does not pose a disadvantage to patients or communities that might have outdated or misguided information regarding HCV pathology and therapy following LT. According to a recent study on patient surveys, African Americans had a lower acceptance rate of HCV+ kidney transplants than White people. While it is uncertain if this perspective also applies to liver grafts, more research is required to ascertain whether attitudes toward HCV D+/R- LT differ[65].

Additionally, transplant centers that do not practice HCV D+/R- LT should notify their patients that other transplant centers might be performing HCV D+/R- LT in order to promote equality in liver graft allocation[65].

ASSESSMENT OF DONOR GRAFTS PRIOR TO TRANSPLANTATION

An optimal evaluation of the HCV-viremic liver allograft would consist of three tissue samples: Two 16-gauge needle cores, each measuring 2 cm, taken from the right and left lobes, and a wedge biopsy measuring 1 cm subcapsular from the right lobe[67]. Experts advise transporting biopsies from donor hospitals back to the recipient hospital with the donor's liver for examination by a skilled liver pathologist.

The recommendations from a consensus meeting report in 2019 regarding the obtainment of liver biopsy from HCV+ donors were: (1) Younger HCV viremic donors (less than 35 years old) probably have less fibrosis and do not need a liver biopsy prior to donation; (2) To rule out donors with advanced (F3 or F4) fibrosis, older donors (≥ 35 years old) with a chronic infection may have a liver biopsy; and (3) Donor liver biopsy results of F2 or lower are suitable for transplant[66].

The influence of donor steatosis on the outcomes of liver transplants differs across studies due to the fact that the majority of transplant surgeons decline these organs, and there is presently no data regarding the use of HCV-positive fatty grafts[68].

RECIPIENT SELECTION AND PRIORITIZATION

Who is the appropriate R- for LT from D+? Who should be prioritized? These significant questions require further research because the solutions are not entirely obvious. Based on the HCV-infected donor pool, the total supply and demand for organs, the Model for End-Stage Liver Disease (MELD) score, and the blood type, this could differ in each location[69].

In general, this strategy may be applicable to certain recipient situations[69]: (1) Individuals suffering from acute liver failure, for whom the timing of LT is crucial; (2) Patients with hepatocellular cancer in whom there is the possibility of waitlist dropout; And (3) Patients who have substantial complications from portal hypertension despite having a low MELD score, where their MELD score does not accurately reflect the severity of their condition. How long a patient stays on the waitlist depends on the number of offered grafts and their MELD score, or exception MELD score, while on the list [66].

The MELD score has demonstrated efficacy in predicting mortality among cirrhotic patients[70]. However, it has long been known that, even within a single MELD score, clinical manifestations of liver disease can vary greatly, and patients with the same MELD scores can have widely different mortality risks. Access to the larger pool of donors, made possible by HCV viremic liver allografts, may help many currently underprivileged populations, such as women, people of short stature, people with low frailty index scores, and people with sarcopenia[71-73].

While some patients and providers are willing to offer or accept HCV-positive organs, others are not. A study examined 50 individuals awaiting organ transplants. Just 30 of them were aware that HCV could be cured, and only 23 were open to receiving an infected organ. Furthermore, there were also expressions of concern regarding the curability of HCV, insurance coverage, and failed allografts[74].

HCV-infected organs should not be offered to individuals who are expected to experience a complicated posttransplant course. The following would be recipients of concern: Individuals who undergo complex transplant procedures such as liver re-transplantations, encounter early allograft dysfunction, are recipients of donations from donors who have passed away of circulatory death, are afflicted with posttransplant seizure disorders that necessitate multiple anti-epileptic medications (which are contraindicated with all DAAs) or have cardiopulmonary diseases that demand prolonged posttransplant intubation or arrhythmias that require amiodarone (contraindicated with sofosbuvir) and require high-dose proton-pump inhibitors (most DAAs)[66].

DIRECT ACTING ANTIVIRAL DRUGS

Strategies to start DAA

Strategies for liver recipients may differ from those for non-liver recipients. Preventing HCV infection in recipients can be achieved through prophylactic, preemptive, or delayed treatment. Prophylactic treatment aims to prevent the occurrence of post-transplant viremia, while preemptive treatment involves initiating therapy shortly after transplantation, even before any clinical symptoms manifest. On the other hand, delayed treatment is typically administered several weeks to months after transplantation, when clinical disease may already be evident[15].

The advantages and disadvantages of prophylactic and preemptive versus delayed methods are subjects of intense discussion in the transplant field[15].

Multiple studies suggested that administering preemptive treatment to individuals receiving HCV viremic grafts, starting at the time of transplantation and continuing for a specified period after liver transplantation, may provide the most favorable outcome in terms of achieving viral clearance and preventing early hepatic and extrahepatic complications associated with HCV[32,66,75].

A comparative analysis was conducted on the time of initiation of DAA treatment. DAA therapy was given prior to transplantation, at the time of transplantation, and during disease recurrence. Based on the premise of a 96% likelihood of attaining sustained SVR, DAA medication retained its status as the most economically efficient option when administered prior to transplantation in individuals with decompensated cirrhosis and possessing a MELD score below 20. Nevertheless, in the case of a MELD score over 20 or for patients diagnosed with HCV, administering medication upon recurrence has demonstrated superior efficacy in comparison to treatment administered pre-transplantation or at the time of transplantation[76].

When to begin DAA therapy varies among guidelines. Early therapy with pangenotypic DAA regimens should start during the first month following LT, with initiation preferred within the first week if patients are clinically stable, according to the American Association for the Study of Liver Diseases (AASLD)[16]. According to AST guidelines, until larger multicenter trials are available, peri-operative DAA introduction should be part of an IRB-approved study protocol [8].

Considerations with DAA regimens

The post-LT recipient's newly acquired genotype will determine the type and length of DAA therapy. Additional variables that have been found to impact the choice of DAA include the patient's capacity to swallow, renal function, and medication interactions[77].

Pharmacodynamics and pharmacokinetics regarding administering DAA medications *via* nasogastric tube while crushed are poorly documented. Crushing (GLE/PIB) tablets decreased glecaprevir exposures by 27%-61% and increased pibrentasvir exposures by 21%-83% in a phase 1, single-dose study involving 25 healthy adults[78]. These findings may or may not have clinical significance. Additionally, a case report describes a patient who exhibited a sustained virologic response subsequent to using a percutaneous gastrostomy tube for administration of ledipasvir/sofosbuvir[79].

Data demonstrating the safety of sofosbuvir/velpatasvir in individuals with any degree of renal impairment led three studies to acknowledge that kidney function would no longer be a determining factor in DAA selection[15,51,53].

Avoiding protease inhibitors is recommended in the presence of liver dysfunction, such as increased bilirubin levels. Certain medications shouldn't be taken with specific DAA agents or are contraindicated, such as but not restricted to high-dose antacid treatment (such as taking a proton pump inhibitor twice a day), amiodarone (contraindicated with regimens including sofosbuvir), and certain statins, such as atorvastatin[77].

After receiving a liver transplant from an HCV-positive donor, the best time to start taking DAAs is yet unknown. In a recent systematic review including 16 studies and 2 case reports, the mean or median duration to DAA commencement after transplant varied from 1.7 d to 118 d among the included studies. Although studies differed in the time required to initiate DAA, this factor did not seem to have an impact on the rate at which SVR was achieved[11].

HCV-negative recipients of HCV-viremic liver allografts seem to respond very well to treatment with a pangenotypic DAA for 12 wk, in compliance with treatment recommendations[11]. However, the duration of DAA therapy may be prolonged at the discretion of the transplant team and sometimes due to insurance preference[49].

DAA and immunosuppressive regimen

A significant worry about the potential interaction between DAA and immunosuppressive regimens, particularly for

protease inhibitors containing regimens, remains present. Nevertheless, recent small clinical trials have provided evidence for their safety in kidney and LT without necessitating any adjustments to baseline immunosuppressive regimens' dosage[80-82].

Drug interactions between DAA agents and calcineurin inhibitors are complicated and hard to predict without standardized drug interaction studies. The metabolism of grazoprevir and elbasvir shows that when cyclosporine is added, the area under the curve for grazoprevir will rise 15 times, and the area under the curve for elbasvir will rise two times. Hence, it is advisable to refrain from utilizing this particular combo. When tacrolimus is co-administered with grazoprevir, its level is expected to rise by 40% to 50%. Although no dosage modifications are expected, tacrolimus levels should be monitored. As for regimens containing sofosbuvir, there have been no reports of clinically significant drug-drug interactions[77].

Protocols for DAA treatment following LT and the optimal management of immunosuppression to prevent drug interactions with DAA therapy are additional issues that should be investigated. Risk-benefit analysis will have to be performed on an individual basis for each patient until more data are presented[65].

POST-TRANSPLANT FOLLOW UP

Post-transplant documentation of the chosen HCV treatment regimen and duration, any barriers to initiating HCV therapy, exposure to immunosuppressive agents, HCV RNA viral kinetics, liver chemistry profile, and renal function, modifications to immunosuppression, and any potential complications, such as rejection, HCV-related hepatitis, acute kidney injury, graft failure, and mortality is recommended during the post-transplant follow-up[49].

Considering the similar characteristics exhibited by all presently accessible pangenotypic DAA agents and their notable efficacy in managing donor-derived HCV infection subsequent to liver transplantation, payor choice appears to be the main factor in DAA selection[11].

These examples show that insurance formulary rather than the most recent recommendations from the AASLD and the Infectious Diseases Society of America govern the choice of DAA regimen for HCV therapy[77]. In a study, two patients were given ledipasvir/sofosbuvir + ribavirin because it was covered by their insurance[32]. In another one, a patient received sofosbuvir/daclatasvir plus ribavirin for HCV treatment after his insurance denied glecaprevir/pibrentasvir[49].

Monitoring for HCV viremia and the efficacy of DAA treatment varied among various studies of a recent systematic review. A significant proportion of research investigations evaluated donor-derived viremia through the assessment of the recipient's HCV viral load by post-operative day 7. Following transplantation, the majority of the authors reported continuous surveillance in non-viremic recipients, with weekly monitoring for the first month and then monthly monitoring for the next two months. The HCV genotype was ascertained, and DAA therapy was instituted following confirmation of HCV viremia[11].

While the results of R- utilizing D NAT+ organs are promising, there are several concerns and unknowns. It is still unclear how long HCV surveillance is required after LT. Although late conversion is uncommon, it is possible, as one patient in the Anwar *et al*[34] report became viremic on day 84 and another patient in a study by Bohorquez *et al*[53] remained HCV-free for 10 months after LT before becoming viremic. These results indicate that persistent aviremic patients require long-term HCV surveillance.

OUTCOMES OF LT FROM HCV-INFECTED DONORS

Even though the aim of expanding the use of organs from D+ is to overcome the organ shortage, the absence of favorable short-term and long-term outcomes will rule out this process. Short-term outcomes include the length of in-hospital stay, inpatient mortality, and inpatient acute rejection, while long-term outcomes include graft failure and mortality rates. In general, using D+ may allow earlier transplantation for patients with a lower MELD score and decrease the rate of worsening complications, hospitalization, and death (dropout from the waiting list). Furthermore, studies showed that D+ are usually young with lesser comorbidities and lower BMI, meaning that their grafts are healthier. These criteria of recipients and donors are associated with better outcomes[24,83]. Additionally, a 2019 cost-effectiveness analysis found that accepting either an HCV+ or HCV-free liver is cost-effective in patients with a MELD score of 22, and even at lower MELD scores if the patient's quality of life is worse than taking solely HCV-free livers[84]. Another study illustrated that receiving any liver, regardless of HCV status, in contrast to accepting only an HCV negative liver, demonstrated a survival benefit if the recipient's MELD was ≥ 20 and an even more significant benefit with MELD scores > 28[85].

A large retrospective study compared the outcomes of liver transplantation using organs from HCV+ and HCV- donors between 1995 and 2013. Patients who had liver transplants from HCV+ donors had better short-term outcomes in the initial analysis and similar outcomes when the year of the transplant was taken into account. The long-term outcomes were comparable in both groups. The mortality rates at 1 and 2 years after transplantation were slightly better in patients who received their transplants from HCV donors. However, this was once again entirely explained by the bias in the year of the transplant. Moreover, the 10-year mortality and graft failure rates were similar in both groups[86]. It is noteworthy that these good results were obtained before the DAAs.

Another study evaluated these outcomes in liver transplant HCV positive and negative recipients who received organs from HCV+ and HCV- donors before and after the era of DAAs. The 3-year survival of patients who received HCV Ab+ livers was significantly lower than that of patients who received HCV Ab- livers prior to the DAA era. However, this difference vanished after the DAA era, with identical 3-year survival rates in both groups. Additionally, donor's viremia

did not impact the survival rates in the study groups[24]. Another study reported that patients and graft survival rates were excellent in liver transplant recipients from HCV viremic and non-viremic donors[32].

Acute rejection of the graft is a post-transplant complication classified into acute cellular rejection (ACR) and antibody-mediated rejection. A liver biopsy from the graft is mandatory to differentiate between the two types and assess the rejection's severity[87]. About 10%-30% of liver transplant recipients experience ACR in general[88-91]. However, this percentage increases to 24%-80% among recipients of HCV seropositive grafts[92,93], which may be due to the interaction between DAAs and immunosuppression leading to decreased levels of immunosuppressive drugs[94]. In a small case series that included 10 liver HCV non-viremic transplant recipients from HCV D NAT+, 3 recipients developed acute rejection[49]. Notably, those recipients had an increased risk of acute rejection, and liver biopsies of the allograft did not reveal any signs of HCV infection[49,93]. ACR was also seen in 15% of liver transplant recipients from D+ in another larger study that included 34 patients who received livers from HCV D NAT+ and HCV D NAT-[32]. Greater evidence on whether rejection risk is actually elevated for recipients of HCV D NAT+ in the contemporary era - either from HCV therapy or HCV itself - may be more evident from larger prospective trials and randomized controlled trials with longer follow-up periods[49,65].

A multicenter prospective study showed that 13 HCV-negative liver transplant and 11 kidney transplant recipients who received allografts from HCV-viremic donors developed serious complications. These adverse events included AMR, biliary sclerosis, cardiomyopathy, and graft-versus-host disease[15]. Biliary complications were also noted to be more frequent in recipients of anti-HCV-positive grafts compared with the control group in a European multicenter study. However, this difference was not statistically significant[95]. Acute HCV-related glomerulonephritis and focal proliferative glomerulonephritis were rarely reported as complications of using HCV-infected liver grafts[32,96]. Patient and graft survival in R- of HCV-positive donors was evaluated in a comprehensive systematic review that included 15 studies. There was no difference in graft or patient survival in 6 of these studies, which were drawn from national LT registries from multicenter European databases and the United States. Sample sizes varied from 38 to 1930 patients. Overall, graft survival was independently predicted by the recipient's HCV serostatus rather than the donor graft[13,54].

Fibrosing cholestatic hepatitis is a rapidly progressive cholestatic hepatic inflammation associated with hepatocyte ballooning and advanced fibrosis, leading to significant hepatic impairment and potential mortality[97]. It has been documented in the past that FCH has a sub-fulminant course of hepatitis and fatal outcomes[98,99]. The fear of FCH evolution was one of the major obstacles hindering the expansion of using organs from D+ in HCV-infected recipients. Before the era of DAAs, some data showed that FCH in HCV-infected recipients after transplantation could respond well to interferon-α therapy. However, the duration of therapy for those patients was not precise, and they also required stoppage of azathioprine, which may affect graft survival in the long run[24]. The availability of DAA therapy for FCH following transplantation has been proven to be an effective and well-tolerated treatment option with high SVR rates[99, 100]. The early initiation of DAA regimens, even before grafts function, can treat FCH and prevent it[100].

CURRENT LT PRACTICE AND INSIGHT INTO THE FUTURE

To the best of our knowledge, HCV-infected donors were predominantly used in DDLT, with only 2 cases reported in LDLT. One of them was from an HCV-positive donor into an HCV-negative recipient, where LT was done after the end of DAA therapy. No DAAs were administered to the recipient perioperatively, and follow-ups revealed no HCV viremia [101]. The other was from an HCV-viremic donor who received DAA therapy before donating to an HCV-viremic recipient who received DAA therapy within 2 months post-transplantation with good 2-year graft survival of the recipient[102]. There were no remarkable incidents throughout the donors' recovery.

Thus, using HCV-infected organs would probably face many obstacles in countries that adopt LDLT programs, like Egypt. Egypt had the world's highest prevalence rate of HCV infection and succeeded in founding a successful program for HCV management through an amazing experience after treating more than 4 million patients and screening about 57 million[103]. In this context, the liver transplant community in Egypt will face some potential donors who are anti-HCV positive but are non-viremic (previously treated) and could be the primary source to expand the donor pool. Using organs other than the liver from HCV-infected living donors can be accepted with great precautions. However, using liver grafts from HCV infected living donors may be associated with significant risks as regards the donor's morbidity and mortality. Prospective trials and national and international consensuses are needed to determine whether using HCV-infected donors in LDLT is safe or not.

CONCLUSION

Based on all that was mentioned, it is clear that the benefits of using grafts from D+ in R-outweigh the risks. The outcomes of using organs from HCV seropositive donors were good even before the era of DAAs. The availability of DAAs allowed for more secure usage of organs from HCV-infected organs, even if they were viremic. Liver graft biopsies excluding hepatic fibrosis > grade 2 appear to be a good predictor of the graft's well-being before its adoption for transplantation. Ensuring the appropriate selection of patients undergoing HCV-infected graft transplantation and confirming their access to DAAs if needed may also increase this practice's benefits. National and international consensuses are needed to regulate this process to ensure the maximum benefit and the least adverse events.

FOOTNOTES

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Country of origin: Egypt

ORCID number: Mai Hashem 0000-0002-7877-0094; Mohammed A Medhat 0000-0002-3866-2283; Doaa Abdeltawab 0000-0002-1150-1113; Nahed A Makhlouf 0000-0003-2949-4369.

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