Expanding the donor pool: Hepatitis C, hepatitis B and human immunodeficiency virus-positive donors in liver transplantation

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Abstract

Liver transplantation (LT) remains the best option for patients with end-stage liver disease but the demand for organs from deceased donors continues to outweigh the available supply. The advent of highly effective anti-viral treatments has reduced the number of patients undergoing LT for hepatitis C (HCV) and hepatitis B (HBV) related liver disease and yet the number of patients waiting for LT continues to increase, driven by an increase in the patients listed with a diagnosis of cirrhosis due to non-alcoholic steatohepatitis and alcohol-related liver disease. In addition, human immunodeficiency virus (HIV) infection, which was previously a contra-indication for LT, is no longer a fatal disease due to the effectiveness of HIV therapy and patients with HIV and liver disease are now developing indications for LT. The rising demand for LT is projected to increase further in the future, thus driving the need to investigate potential means of expanding the pool of potential donors. One mechanism for doing so is utilizing organs from donors that previously would have been discarded or used only in exceptional circumstances such as HCV-positive, HBV-positive, and HIV-positive donors. The advent of highly effective anti-viral therapy has meant that these organs can now be used with excellent outcomes in HCV, HBV or HIV infected recipients and in some cases uninfected recipients.

Key words: Hepatitis C; Hepatitis B; Human immunodeficiency virus; Liver transplantation

Core tip: The optimal utilization of organs from hepatitis C (HCV), hepatitis B (HBV) and human immunodeficiency virus (HIV)-positive donors may help attenuate the current organ shortage. Transplantation of organs from patients with HCV viremia to uninfected recipients can be accomplished safely when coupled with the timely initiation of post-transplant direct-acting antiviral therapy. Suppression of HBV with antiviral
therapy allows for the safe transplantation from HBV core antibody-positive donors to unexposed recipients, while transplantation of organs from patients who are HBV surface antigen-positive remains investigational. The early experience with HIV-to-HIV positive transplantation via the HOPE act is promising, and allows patients living with HIV improved access to transplantation.

**INTRODUCTION**

Approximately 14400 patients are currently awaiting liver transplantation (LT) throughout the United States[1]. Despite an increase in the number of adult liver transplants performed over the past several years, the demand for deceased-donor LT continues to outweigh the available supply of donor organs. While the number of deceased donors has increased slightly, the number of new patients listed for LT continues to increase[2,3]. Furthermore, waitlist mortality remains a concern; of patients who were waitlisted for LT in 2013, only 55% underwent LT 3 years later, while 13% (1362 patients) died and 19% (1991 patients) were removed from the LT list, most commonly for being too ill to undergo transplantation[4]. The increase in waitlist registration appears to be driven by an increase in the number of new listings for patients aged > 65 years, as well as an increase in the proportion of patients listed with a diagnosis of cirrhosis due to non-alcoholic steatohepatitis and alcohol-related liver disease[4,5]. The demand for LT among these patient groups is projected to increase in the future, thus driving the need to investigate potential means of expanding the pool of potential donors. One mechanism for doing so is utilizing organs from donors that previously would have been discarded or used only in exceptional circumstances such as hepatitis C (HCV)-positive, hepatitis B (HBV)-positive, and human immunodeficiency virus (HIV)-positive donors. The advent of highly effective anti-viral therapy has meant that these organs can be used with excellent outcomes in HCV, HBV or HIV infected recipients and in some cases uninfected recipients.

**HCV-POSITIVE DONORS**

HCV-positive donors encompass donors at any stage of HCV infection (Table 1). This includes patients who are seropositive for anti-HCV antibody (Ab) only (i.e., resolved infection), or those who are HCV-viremic, either in the acute (anti-HCV Ab-negative) or chronic (anti-HCV Ab-positive) phase of infection[6]. The distinction between a viremic donor and one who is seropositive-only is critical when discussing transplantation of an organ from an HCV-positive donor to an uninfected recipient, as the risks of disease transmission differ greatly. While the risk of HCV infection in the recipient approaches 100% when receiving an organ from an HCV-viremic donor, if the donor is only HCV-seropositive and aviremic, the risk of transmission is much lower, ranging from 0-16%[7]. This residual risk of transmission-despite aviremia-is postulated to be due to one of several mechanisms, including interval re-infection among persons who inject drugs (PWID), the presence of low-level viremia, or occult HCV infection in transplanted hepatocytes[7].

In the United States population, HCV-positive donors derive primarily from either the baby boomer birth cohort (born between 1946-1964) or PWID. While baby boomers remain the age group in which HCV prevalence is greatest (2.23% vs 1.19% in the general United States population), important demographic shifts are occurring in the epidemiology of HCV[8,9]. A large part of this change is owed to the opioid epidemic, where a high prevalence of injection drug use-especially in Appalachia and the Western United States-has contributed to a tripling of the incidence of HCV infection[9]. In Kentucky, one study suggested a 54.6% prevalence of HCV-seropositivity among a network of PWID. The risk of disease transmission among PWID in these states may be exacerbated by a lack of harm reduction services,
Table 1 Terminology for hepatitis C virus-positive donors

| Donor testing      | Anti-HCV antibody | HCV RNA |
|--------------------|-------------------|---------|
| Donor terminology if positive | “Seropositive”    | “NAT positive” or “Viremic” |
| Acute infection    | (-)               |        |
| Chronic infection  | +                 |        |
| Resolved           | +                 | (-)    |

HCV: Hepatitis C virus; NAT: Nucleic acid test.

including safe injection sites, needle exchanges, and pharmacologic treatment\[^{10}\]. While HCV incidence and prevalence are increasing among PWID, the number of baby boomers with HCV are in decline due to birth cohort screening and treatment of HCV, but also due to liver related and overall mortality\[^{11,12}\].

In addition to a high prevalence of HCV infection among PWID, deaths in this population due to opioid overdose have increased. In 2017, there were over 70000 deaths in the United States related to drug overdose, a 9.6% increase from the prior year. The greatest increase in deaths occurred related to synthetic opioids like fentanyl, and occurred in young patients, including those aged between 25-54 years\[^{15}\]. Given their young age and that many develop hypoxic brain injury before ultimately having brain death declared, many of these individuals may ultimately be evaluated as potential organ donors. Among donors evaluated in 2017, 18% were classified as Public Health Service increase risk donors (IRD), 13.4% had drug intoxication listed as a cause of death, with 8% of these individuals having a history of injection drug use. Among all donors in 2017, HCV-seropositivity was 7.3%, while HCV RNA-positivity was 4.9%; among those who were classified as IRD, HCV-seropositivity and RNA-positivity were 22% and 16%. Taking together both the increased prevalence of HCV in young rural PWID, as well as the young age at which many of these individuals die of overdose-related deaths, the median age of HCV-positive donors has decreased from 48 years in 2010 to 35 years in 2016\[^{16}\]. One study assessing the utilization of HCV-positive livers in HCV-positive recipients showed that in the era of direct-acting antivirals (DAAs), HCV-positive donors were more likely to be between the ages of 0-30 years, Caucasian, and without a history of diabetes, compared to HCV-positive donors in the pre-DAA era\[^{14}\].

**HISTORICAL USE OF HCV-POSITIVE DONORS**

Before the advent of DAAs, transplantation of organs from HCV-positive donors into uninfected recipients could not be considered due to the low efficacy and high risks associated with interferon (IFN)-based therapy in the post-transplant setting. Thus, organs from such patients were reserved for patients with active HCV infection. Because reinfection of the graft is nearly universal regardless of the donor’s HCV status, it would seem reasonable to utilize HCV-positive organs for such patients, as they will remain viremic whether they receive an HCV-positive or -negative graft\[^{15}\]. It should be noted that before 2014, nucleic acid testing (NAT) was not routinely performed on potential donors, so it was generally not possible to know whether the donor was actively viremic and to assess the risk of disease transmission\[^{16}\]. In older studies, therefore, HCV-positive donors refer only to HCV-seropositive donors.

Early data suggested that this strategy was not associated with impaired outcomes. Of 202 patients with end-stage liver disease (ESLD) related to HCV cirrhosis who underwent LT at a single center from 1992 to 1995, 23 patients received grafts from HCV-positive donors. There was no significant difference in either 1-year or 5-year graft or patient survival, thus supporting the use of organs from HCV-seropositive donors in HCV-infected recipients\[^{16}\]. A larger study using the United Network for Organ Sharing Scientific Registry of Transplant Recipients confirmed these findings. In this study the outcomes of 96 HCV-infected recipients of HCV-positive organs were compared to those of 2827 patients who received organs from HCV-negative donors. Patient and graft survival were similar and in fact slightly better in the group that received organs from HCV-positive donors (90% vs 77% 2-year survival, \(P = 0.01\)). This is likely because patients who accepted HCV-positive were less sick at the time of transplantation\[^{14}\].

Somewhat conflicting data arose from a study published by a group from Europe. In this more recent (but still pre-DAA, IFN-only era) multicenter study, among 694
patients who underwent transplantation for liver disease due to chronic HCV, 11% received organs from HCV-positive donors. When comparing the 63 patients who received HCV-positive organs to 63 controls who received HCV-negative organs, there were no significant differences in patient or graft survival. Secondary outcomes were less favorable, however, with more rapid clinical recurrence of HCV in the HCV-positive donor group, as well as a greater incidence of biliary complications and rejection. Time to recurrence did seem to be shorter in patients who received organs from viremic donors, who comprised 43% of the population of HCV-seropositive donors. Time to post-LT HCV recurrence was also shorter in patients who received grafts that had F1 vs F0 fibrosis. The authors concluded therefore, that caution should be exercised in graft selection but that overall there was no detriment to patient or graft survival when transplanting patients with HCV-positive grafts. Given these data, it has been standard of care to offer HCV-positive grafts to HCV-positive recipients for the last 15-20 years.

**THE IMPACT OF DAA THERAPY**

Despite the promising data showing the essentially neutral effects of utilizing HCV-positive donors for HCV-positive recipients, until the IFN-free DAA era, HCV-positive liver grafts were underutilized and discarded at a high rate. Indeed, 28% of such livers were discarded between 2005 and 2010. In the DAA era, the discard rate has declined to around 11%, owing in large part to a change in physician attitudes regarding the treatment of HCV in the post-transplant setting; as DAAs made treatment easier, there has been an increased acceptance of utilization of HCV-positive livers. Mirroring this, the proportion of HCV-positive recipients who were transplanted with HCV-positive grafts increased, from 6.2% in the IFN era to 16.9% in the DAA era. Such donor-recipient pairings were more common in patients who were on dialysis prior to transplant, those who had a low MELD at listing, and those in a region with relatively lower organ availability. At the center-level, most centers (69%) experienced an increase in utilization of HCV-positive livers.

This increase in utilization and decrease in discard of HCV-positive livers has been driven by the development of DAAs, which have been proven to be safe and effective in the post-LT setting. A number of considerations affecting the use of DAAs, including drug-drug interactions (DDIs) and use in patients with renal dysfunction must, however, be taken into account. Protease inhibitor-based regimens interact in various degrees with calcineurin inhibitors (CNIs), especially cyclosporine. For example, elbasvir/ grazoprevir or simprevir should not be co-administered with cyclosporine due to potentially toxic increases in blood concentrations (increases of 5- to 15-fold) of the protease inhibitors. Co-administration of paritaprevir/ritonavir/ombitasvir + dasabuvir with tacrolimus may lead to a 57-fold increase in the concentration of tacrolimus, which has been shown to lead to significant toxicity in the absence of dramatic dose adjustments. Sofosbuvir-based regimens, including ledipasvir/ sofosbuvir (LDV/SOF) and SOF/velpatasvir do not appear to interact significantly with CNI therapy, though there may be some interaction with everolimus leading to increased everolimus trough levels. The primary concern with SOF-based therapy is that SOF is not currently recommended for use in patients with renal dysfunction due to an accumulation of a SOF metabolite of unclear significance. Data from the HCV-TARGET cohort suggest that SOF can be used with high efficacy among patients with renal failure (including those on hemodialysis) but with an increase in anemia, worsening renal function, and other serious adverse events. This suggests that SOF-based regimens may be used in patients with renal dysfunction, albeit with caution.

Clinical trial data exist for a number or regimens in the post-transplant setting, including LDV/SOF, daclatasvir and sofosbuvir (DAC+SOF), simprevir and sofosbuvir (SMV+SOF), and glecaprevir/pibrentasvir (GLE/PIB). These studies included a majority of genotype (GT) 1 patients, most of whom were treatment experienced, though with varying degrees of fibrosis. Rates of sustained viral response (SVR) were universally high in these studies, except among patients with decompensated cirrhosis post-LT. Most recently, a high rate of SVR (97%) was achieved among LT recipients treated with 12 wk of GLE/PIB, a pangenotypic regimen. Importantly, immunosuppression levels did not fluctuate significantly during treatment with GLE/PIB. Further, real-world data from the HCV-TARGET cohort as well as other smaller studies confirm the high rates of SVR and low rates of HCV relapse and adverse events among patients with chronic HCV infection. Predictors of SVR included the absence of cirrhosis and hepatic decompensation, suggesting that treatment earlier in the post-transplant course may be of benefit.
Table 2 Drug-drug interactions among direct-acting antivirals and calcineurin inhibitors

| Drug-drug interactions | Cyclosporine (CSA) | Tacrolimus (TAC) | Sirolimus (SRL) | Everolimus (EVR) |
|------------------------|--------------------|------------------|----------------|-----------------|
| Sofosbuvir (SOF)       | 4.5-fold ↑ in CSA AUC | 13% ↑ in CSA AUC | Not studied, no interaction | Not studied, no interaction |
| Ledipasvir             | Not studied, no interaction | Not studied, no interaction | Not studied, no interaction | Not studied, may increase EVR concentrations due to mild inhibition of P-gp by ledipasvir |
| Paritaprevir / ritonavir / ombitasvir + dasabuvir (PrOD) | 5.8-fold ↑ in CSA AUC | 57-fold ↑ in TAC AUC | 38-fold ↑ in SRL AUC Do NOT co-administer | 27.1-fold ↑ in EVR AUC Do NOT co-administer |
| Elbasvir / grazoprevir (EBR/GZR) | 15-fold ↑ in CSA AUC | 43% ↑ in TAC AUC | Not studied, may increase SRL concentrations due to mild inhibition of P-gp by elbasvir | Not studied, may increase EVR concentrations due to mild inhibition of P-gp by elbasvir |
| Velpatasvir | No interaction observed; no a priori dose adjustment necessary | No data; no a priori dose adjustment necessary | No data; no a priori dose adjustment necessary | Not studied, may increase EVR concentrations due to mild inhibition of P-gp by velpatasvir |
| Glecaprevir / pibrentasvir (GLE/PIB) | 5-fold ↑ in GLE AUC with higher doses (400 mg) of CSA Not recommended in patients requiring stable CSA doses > 100 mg/day | 1.45-fold ↑ in TAC AUC | Not studied, may increase SRL concentrations due to mild inhibition of P-gp by pibrentasvir | Not studied, may increase EVR concentrations due to mild inhibition of P-gp by pibrentasvir |
| Sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) | 9.4-fold ↑ in VOX AUC | No data; no a priori dose adjustment necessary | Not studied, may increase SRL concentrations due to mild inhibition of P-gp by velpatasvir and voxilaprevir | Not studied, may increase EVR concentrations due to mild inhibition of P-gp by velpatasvir and voxilaprevir |

Adapted from [www.hcvguidelines.org](www.hcvguidelines.org) and [www.hep-druginteractions.org](www.hep-druginteractions.org). CsA: Cyclosporine; TAC: Tacrolimus; SRL: Sirolimus; EVR: Everolimus; SOF: Sofosbuvir; AUC: Area under the curve; PrOD: Paritaprevir/ritonavir, ombitasvir, and dasabuvir; ELB/GZR: Elbasvir/grazoprevir; P-gp: P-glycoprotein; VOX: Voxilaprevir; VEL: Velpatasvir.

before these complications develop[39]. Based on the available data, guidance in the United States recommend treatment with 12 wk of various regimens depending on HCV genotype and the presence of (decompensated) cirrhosis[36].

RATIONALE AND EARLY DATA FOR TRANSPLANTATION OF LIVERS FROM HCV-POSITIVE DONORS TO HCV-NEGATIVE RECIPIENTS

DAA therapy has allowed for safe and highly effective treatment of HCV infection in LT recipients. Because of the high efficacy of these treatments in the pre-LT setting as well, the number of patients placed on the LT waiting list for liver disease related to HCV infection has been in decline since 2016[31], while the number of HCV-positive donors is on the rise. These donors are mostly young people dying of causes unrelated to their HCV infection, and therefore may be good candidates for organ donation. If organ quality is good, and the risks related to post-LT HCV infection can be eliminated by prompt and effective antiviral therapy, then it would be ethically questionable to withhold the transplantation of such organs to sick patients awaiting LT.

Early case reports suggested the overall safety of this approach. Three patients received organs (2 kidney recipients and 1 liver recipient) from a high-risk donor who was HCV NAT test negative, but recently had sexual contact with an HCV-infected male partner. The donor was likely in the eclipse phase of HCV infection, prior to detectable viremia, and transmitted HCV infection to all three recipients. All recipients were treated with DAA therapy, and all achieved SVR without adverse effects on their graft[30]. Another case report described the utility of using an HCV-viremic organ in an uninfected recipient who had multiple complications of portal hypertension but low priority on the LT waiting list and had no potential living donors. The recipient rapidly became viremic at 3-d post-LT and was ultimately treated starting on post-operative day 25 with a 24-wk course of LDV/SOF, and...
successfully achieved SVR with no adverse effect on the graft[36].

Further proof of this concept was demonstrated in the context of renal transplantation in the THINKER trial where 10 patients who had long anticipated waiting times accepted kidneys from HCV-viremic donors. All donors were known to be GT 1 prior to transplantation, and all recipients received elbasvir/grazoprevir for a 12-wk course when viremia was detected in the recipient. All recipients developed HCV viremia on day 3 post-transplantation and were started on treatment immediately; all achieved SVR without significant changes in kidney or liver function[37]. Further follow-up demonstrated good 1-year outcomes in the initial patient population, as well as 6-month outcomes for an additional 10 patients with good long-term renal and quality-of-life outcomes[38]. More recently, in an open-label trial in heart transplant recipients, pangenotypic antiviral therapy with GLE/PIB was provided pre-emptively to 20 recipients of hearts from NAT-positive donors. All patients tolerated treatment well and achieved SVR[39].

In the context of LT, modeling data suggests that for any HCV-uninfected patient with decompensated cirrhosis awaiting LT, accepting any liver (HCV-positive or -negative) is associated with a survival benefit compared to accepting only HCV-negative organs once the recipient’s MELD score exceeds 20. This was noted to be the case irrespective of geographic location or prevalence of HCV-positivity among the donor population[37] and was cost effective compared to restricting acceptance to HCV-negative livers only at a recipient MELD score of 22[38]. This is an important finding as one potential complication of transplanting HCV-viremic organs into uninfected recipients could be a lack of insurer coverage for DAA treatment, leaving the patient with the potential for complications of a newly acquired HCV infection in an immunocompromised state.

More recent data suggests a growing acceptance of this practice. Kwong et al[39] reported the transplantation of 10 HCV-uninfected recipients with liver grafts from HCV-viremic donors. These grafts were offered to patients with a high estimated risk of waitlist dropout, including those with hepatocellular carcinoma. All recipients developed HCV viremia on day 4 post-LT. Contrary to the THINKER trial, which was an industry-sponsored study, in this study providers were required to obtain insurance approval for each patient prior to initiation of therapy, just as if the patient were being treated in any other clinical context. Therefore, treatment was not initiated until a median time of 43 d. Treatment regimen was at the discretion of the provider, and consisted of SOF-based therapies and all patients achieved SVR[39]. Adverse events included 1 patient who developed leukopenia and anemia and 3 patients who developed biopsy-proven rejection. Recipient HCV was not seen in any of the allografts. Two of the patients developed rejection within 1 month of LT, prior to initiation of HCV treatment (one with both acute cellular rejection and antibody-mediated rejection, the other with only acute cellular rejection), and one developed antibody-mediated rejection 5 mo after transplant, after completing HCV treatment. Immunosuppression levels did not vary appreciably to explain the development of rejection in these patients, though it is possible that either HCV infection itself or treatment with DAAs may have led to some immunologic changes that increased the risk of rejection in this population. The authors concluded that it is difficult to draw conclusions given the small sample size, and that this connection should be further investigated among HCV-uninfected patients who receive HCV-viremic grafts[39].

Another recent study by Cotter and colleagues examined the practice of transplantation from HCV-seropositive and/or -viremic donors to HCV-uninfected recipients from January 2008 to January 2018 in the United States (Table 3). During this time, there were 2635 transplants performed with using HCV-seropositive livers, of which 2378 were given to 2378 HCV-seropositive recipients. The number of HCV-seropositive to -negative transplants increased from 7 in 2008 to 107 in 2017, or from 55 in the pre-DAA era to 202 in the post-DAA era. HCV-uninfected patients who received -seropositive livers had higher MELD scores and waitlist times, and received livers from younger and lower body-mass index donors[39]. Three-year graft survival in the DAA era was essentially equivalent at 85.1% compared with 84.5% among patients who received HCV-seropositive versus -negative grafts. Similar results were seen in HCV-viremic donor to HCV-uninfected recipient transplants with no difference in 2-year graft survival among recipients of grafts from HCV-viremic donors compared to HCV-aviremic donors[39].

RISKS ASSOCIATED WITH POST-LIVER TRANSPLANT HCV INFECTION

There is still a concern that acute HCV in the post-transplant setting can be severe,
Table 3  Graft survival is similar in HCV-negative recipients of livers from HCV NAT-positive or -negative donors (Data from Cotter et al.[40])

|       | 1-yr | 2-yr |
|-------|------|------|
| DNAT-/R- | 93%  | 88%  |
| DNAT-/R+ | 93%  | 88%  |
| DNAT+/R- | 93%  | 86%  |
| DNAT+/R+ | 94%  | 90%  |

DNAT: Donor HCV NAT status; R: Recipient HCV NAT status.

especially if there is a delay in initiating treatment with DAAs. Effective and timely treatment for HCV-infected individuals post-LT is essential as the course of HCV is accelerated in the post-transplant setting, with up to 30% of patients developing cirrhosis within 5 years of LT. In addition, up to 9% of patients may develop a severe form of HCV, fibrosing cholestatic hepatitis (FCH), with a very high viral load, progressive cholestasis and early graft loss. With DAAs, progression of FCH can be aborted, with data from a number of studies suggesting rates of SVR ranging from 73%-100%[24,25,41,42]. In the IFN era, these complications made it such that LT for HCV-related cirrhosis was associated with the worst outcomes post-LT compared with other etiologies of liver disease[21]. In the current era, however, post-LT survival has improved significantly for patients who undergo LT for HCV, equivalent to that of recipients transplanted for etiologies other than HCV[43].

One potential consequence of effective HCV treatment is the development of immune-mediated graft dysfunction (IGD). IGD was seen in approximately 7.2% of LT recipients treated with IFN-based therapies and was characterized predominantly by the development of plasma cell hepatitis and was associated with lower long-term survival (61.5% vs 91.3%) compared to patients without IGD[44]. IGD appears to be less common following DAA therapies, occurring with a rate of 3.4%. While the mechanism for IFN-associated IGD is likely related to an augmentation of the immune response, the mechanism driving IGD in patients treated with DAAs is less clear[45]. Patients should be monitored closely for the development of rejection during treatment with DAAs, especially among HCV-uninfected recipients receiving grafts from viremic patients.

Extrahepatic complications that must be monitored for in the post-LT setting in untreated patients include new-onset diabetes mellitus, glomerulonephritis, and lymphoproliferative disorders. While most patients are at risk for the development of DM in the post-transplant setting owing to the metabolic effects of calcineurin inhibitors, the presence of concomitant chronic HCV infection increases that risk, with a prevalence ranging from 13 to 28%[46]. Along with its metabolic effects, HCV contributes to post-LT renal dysfunction through a variety of mechanisms, in some cases via induction of cryoglobulinemia or HCV-associated glomerulonephritis. Finally, HCV is an independent risk factor for the development of lymphoproliferative disorders, including non-Hodgkin lymphomas[46]. With timely antiviral therapy, the occurrence of these complications may be limited; however, it is critical to consent patients who may be interested in receiving HCV-seropositive or -viremic donor livers for these risks in the even that antiviral therapy is delayed.

**HBV**

Prior to effective anti-viral therapy, recurrence of HBV after LT for HBV related liver disease was a feared complication with high rates of allograft failure and mortality[47,48]. The use of hepatitis B immune globulin (HBIG) as passive immunization after LT dramatically reduced the risk of recurrent HBV and improved survival[46], and the addition of anti-virals such as lamivudine further reduced the risk of HBV recurrence such that long term survival after LT is better than most other indications[49]. The current strategy to prevent HBV recurrence after LT consists of indefinite oral anti-viral therapy with or without HBIG, with most centers in the United States using only a very short course (less than 3 mo) of HBIG.

Unlike the situation with HCV-infection where DAA therapy is a cure, current therapy for chronic HBV-infection [defined as patients with persistently positive HBV surface antigen (HBsAg)] aims to suppress viral replication. Chronic HBV infected patients can be further defined by the presence or absence of HBV envelope antigen (HBeAg) as either HBeAg positive or negative. In the non-immunosuppressed patient therapy can be finite if HBeAg positive patients develop durable HBeAg negativity and the development of positive anti-HBe with a negative HBV DNA. However, in
HBV core antibody positive donors

The virology of HBV is complex and complete clearance of virus after infection is difficult to achieve with current therapies. The reactivation of HBV after chemotherapy is well recognized and in the United States guidelines from the American Society of Clinical Oncology recommend starting antiviral therapy for HBsAg-positive/anti-HBc-positive patients before or with chemotherapy and monitoring HBsAg-negative/anti-HBc-positive patients for reactivation with HBV DNA and ALT levels, starting antivirals if reactivation occurs but in those undergoing chemotherapy associated with a high risk of HBV reactivation antivirals can be started pre-emptively[51]. Much of the concern over chemotherapeutic regimens and reactivation of HBV has occurred recently with the advent of biologic therapies with direct effects on immunity. The original reports of HBV reactivation from immunosuppression came from the transplant arena more than 20 years ago.

The National Institute of Diabetes and Digestive and Kidney Diseases Liver Transplantation Database examined 674 LT recipients and their donors for evidence of transmission of HBV between 1989 and 1994[52]. Of the 23 HBV-negative recipients of livers from anti-HBc positive donors, 18 (78%) developed HBV infection with appearance of HBsAg even though donors had been HBsAg negative, with reduced survival. This time period coincided with the use of HBIG and in small series it appeared to be effective in preventing HBV infection in recipients of anti-HBc positive live donor allografts[53].

The introduction of lamivudine further improved the survival of recipients of anti-HBc positive donors. In a United States study of 15 patients (6 who were HBsAg positive and 9 who were HBsAg negative at time of LT) who received anti-HBc positive allografts were followed for a mean of 17 mo. All patients received lamivudine daily and HBIG was given to HBsAg positive patients. All 15 patients remained HBsAg negative and 9 underwent liver biopsy after LT with only 1 patient having detectable HBV DNA in liver tissue (although remained HBsAg negative and anti-HBs positive)[54]. Similar results were noted in a Taiwanese cohort of 16 recipients of anti-HBc positive live donor liver allografts with no evidence of de novo HBV infection after a mean follow up of 25 mo[55].

Despite the success of antiviral therapy there has been some controversy when examining long-term outcomes. A large prospective observational Italian study of 219 LT recipients who received anti-HBc positive deceased donor allografts between 2007-2009 suggested that recipients who were HBsAg positive who received these organs had an increased 3 year survival compared to recipients who were HBsAg negative[56]. Interestingly only 1 patient developed graft loss due to de novo HBV infection suggesting that other factors were responsible for the decreased survival in HBsAg negative recipients. However, good long-term survival was demonstrated in 64 HBsAg negative recipients of anti-HBc positive allografts with 69% 5-year survival using a regimen of HBIG at the time of LT and then daily lamivudine[57]. Nine patients developed de novo HBV infection despite this prophylaxis but were successfully treated with adefovir or tenofovir. Even better results have been seen in the pediatric population with 92% 10-year survival in 41 recipients of anti-HBc positive allografts using a combination of HBIG for 1 year post-LT and yearly HBV vaccine, without antivirals[58].

HBV surface antigen positive donors

With the continued organ shortage every effort should be made to use donor liver allografts that previously may have been discarded. This is particularly the case in areas of the world where HBV infection is endemic and the prevalence of anti-HBc positivity can be as high as 80%. The encouraging results using these types of liver donors who are HBsAg positive and therefore likely to have chronic HBV infection, appeared to be effective in preventing HBV infection in recipients of anti-HBc positive live donor allografts[59].

Several reports have emerged demonstrating that HBsAg positive deceased donors can be safely used in HBsAg positive or HBsAg negative recipients. A small Italian study of 10 patients followed for a median of 42 mo after LT using HBsAg positive donors with HBIG and antiviral therapy and showed no evidence of HBV hepatitis in any patient with half of HBsAg negative recipients remaining HBsAg negative after LT[60]. A larger study in Asia compared 42 adult recipients of HBsAg positive donors with 327 patients who received HBsAg negative donors and noted comparable graft and patient survival[61]. All the recipients of HBsAg positive allografts remained HBsAg positive without evidence of HBV hepatitis and were mainly receiving oral antiviral therapy without HBIG. Closer examination of viral activity suggests that
there is low level viremia early on after LT with HBsAg positive donors but this becomes undetectable within a few months\cite{61}.

In the United States the American Society of Transplantation published consensus guidelines regarding the use of HBV positive donors but only refers to anti-HBc positive allografts and suggests that these donors should be considered for all adult transplant candidates with lamivudine as the antiviral prophylaxis of choice without HBIG\cite{62}. Hence the use of HBsAg positive donors needs further investigation.

**HUMAN IMMUNODEFICIENCY VIRUS**

The advent of highly effective anti-retroviral therapy (HAART) for HIV infection in the mid 1990s meant that a previously fatal disease was now a chronic illness. Patients with HIV infection share some of the risk factors for acquiring viral hepatitis infection and it became clear that rather than dying of AIDS, liver disease was becoming the leading cause of death in HIV patients, mainly from HBV or HCV infection\cite{63-64}.

**Early reports**

The first reports of LT in HIV patients were in carefully selected patients with only short term follow up. Norris et al reported on 14 HIV-infected liver allograft recipients (7 with HCV infection, 7 non-HCV) transplanted over 8 years in a single institution\cite{65}. All the patients in the non-HCV infected cohort were alive at 1-year follow up but 4 of the HCV group died of complications from recurrent HCV infection and sepsis, despite HAART in the majority. Further reports confirmed that short-term outcomes were acceptable in patients with stable HIV after LT (91% at 1 year) but recurrent HCV infection was very common and affected patient and graft survival, decreasing to 64% at 3 years\cite{66}. The National Institutes of Health (NIH) Solid Organ Transplantation in HIV trial enrolled 232 patients with HIV infection who underwent primary LT over 12 years and compared them to non-HIV infected patients (with and without HCV infection) transplanted over the same time frame in the United States. Of these 232 patients, 72 had HIV mono-infection and 160 had HIV/HCV co-infection. The presence of HCV infection increased the risk of post-LT mortality with a hazard ratio of 1.46 in HCV mono-infected and 2.62 in HCV/HIV co-infected patients whereas HIV mono-infection did not affect post-LT mortality\cite{67}. Hence HIV patients could successfully undergo LT but recurrent HCV infection leading to allograft failure was the main determinant of long-term survival since interferon based therapy was largely ineffective and not well tolerated.

The advent of direct acting anti-viral agents (DAA) has transformed the therapy of HCV infection and cure rates of almost 100% are common. Similar success has been reported after LT in both HCV mono-infected and HCV-HIV co-infected patients without significant side effects meaning recurrent HCV infection after LT can be treated or prevented in HIV patients that should lead to good long-term outcome\cite{68}.

**HOPE act**

Up until 2013 federal law prohibited the use of organs from deceased donors with HIV infection. Worldwide, there is a shortage of deceased donor organs and patients with HIV infection have higher wait-list mortality. Several countries with high HIV infection rates among the general population demonstrated that HIV infected donors could be an important source of deceased donor organs with excellent outcomes\cite{69}. In Europe reports emerged of long-term success of HIV-positive donors to HIV-positive recipients with undetectable HIV viremia on HAART\cite{70}. Eventually the HIV Organ Policy Equity (HOPE) Act was passed by the United States Congress in November 2013 allowing the use of HIV positive donors in HIV positive recipients.

Initial reports have been encouraging with several centers performing transplants under research protocol with excellent results since the first HIV positive donor to HIV positive recipient in March 2016 at Johns Hopkins\cite{71}. Guidelines have also been developed by the American Society of Transplantation regarding solid organ transplantation in HIV-infected recipients but await more data before making any firm recommendations for HIV-positive donors\cite{72}. A recent survey of transplant centers in the United States suggested that most were aware of the research restrictions of the HOPE Act that the use of HIV positive donors should be under protocol and supported this policy. In addition, the local HIV prevalence, HIV positive recipient volume, overall transplant volume and increased infectious risk donor utilization were important determinants of whether centers were planning HIV positive donor to HIV positive recipient transplants\cite{73}.

An unexpected benefit of the HOPE Act has been the utilization of organs from deceased donors that would previously have been discarded as they were thought to be from HIV-positive donors although this was the result of a false-positive HIV
screening test. This was examined in the HOPE in Action trial where donors who tested positive for anti-HIV antibody or HIV nucleic acid test but were not known to have HIV infection were classified as false-positive donors. From these 10 suspected false positive donors, 21 HIV-positive recipients were transplanted, including 5 liver and one liver-kidney recipient. All of the donors were subsequently shown to be HIV-negative. Extrapolating these results to all donors in the US, 50-100 false positive HIV donors can be expected[8].

Unlike the situation with HCV positive donors, at this time the use of HIV-positive donors to HIV-negative recipients cannot be advocated. The almost universal cure rate of current HCV therapy means that HCV-negative recipients of HCV positive liver allografts are almost guaranteed to clear the HCV infection after transplantation. A recent report described a live donor LT from an HIV-positive mother to her HIV-negative child in South Africa as a life-saving measure. Using pre-operative HIV-prophylaxis in the child, HIV infection in the child has not been observed after more than a year after transplantation[9].

CONCLUSION

The high efficacy and safety of antiviral therapy for the treatment of viral hepatitis has provided the transplant community with the opportunity to utilize organs from donors infected with HCV and HBV and these infections can be easily treated after LT. The HOPE Act in the United States has allowed the transplantation of organs from HCV-positive donors into HCV-negative recipients that previously would have been discarded. In the case of HCV, the almost 100% cure rates of DAA therapy means that HCV-positive organs can be considered for those patients on the LT waiting list not currently infected with HCV. Due at least in part to the tragic effects of the opioid epidemic in the United States, HCV-positive, HBV-positive and HIV-positive recipients are increasing in prevalence and come from younger people, a demographic associated with very favorable long-term outcome after LT. The success of DAA therapy even in HCV-infected cirrhotic patients means that HCV-related liver disease is declining as an indication for LT, and many of the sickest patients awaiting LT may be HCV-negative. The use of HBV-positive and HIV-positive organs in HBV-positive and HIV-positive recipients is an efficient method of utilizing organs that otherwise would be discarded. The use of these organs in HBV-negative or HIV-negative recipients is still not advised unless in highly exceptional circumstances as these infections can currently only be suppressed and not cured. Modeling and real-world data so far suggest that the practice of transplanting organs from HCV-positive donors into HCV-negative recipients is associated with good short-term outcomes and is becoming standard practice at many centers. Longer term data is needed to fully assess the effects of this practice.

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