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Review

New Frontiers in Solid Organ Transplantation from Donors with Human Immunodeficiency Virus, Hepatitis C Virus Infection, and Multidrug Resistant Organisms

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Abstract

Despite the advances that have been made in the field of solid organ transplant (SOT), organ shortage remains a persistent problem. In addition, the donor pool has been changing with the ongoing opioid epidemic and increase in deaths related to drug overdose each year. More donors are meeting the 2013 United States (U.S.) Public Health Service criteria for increased risk donors (IRDs), or donors who are at higher risk for transmission of Human Immunodeficiency Virus (HIV), Hepatitis C virus (HCV), and other multidrug resistant organisms (MDROs). While previously not considered due to concerns about recipient and allograft outcomes, organs from IRDs or donors with HIV, HCV and MDROs are now being utilized for transplant as therapies for HIV and HCV have improved and more studies have become available that demonstrate favourable outcomes post-transplant. This paper reviews the current literature on the use and management of IRDs and donors with HIV, HCV and MDROs to potentially expand the donor pool for transplant.

Keywords
Solid organ transplant; human immunodeficiency virus; hepatitis C virus; multidrug resistant organisms; increased risk donors

1. Introduction

The number of patients who are awaiting SOT greatly outweighs the supply of available organs. The Organ and Procurement Transplant Network (OPTN)/Scientific Registry of Transplant Recipients (SRTR) 2016 Annual Data Report found that the number of new active listings for heart transplant increased by 57% between 2005 and 2016 [1]. While the total number of kidney, liver, and lung transplants performed increased from 2015 to 2016 [2-4], many patients still remained on the waitlist. As of October 2018, approximately 114,500 candidates were waitlisted for organ transplant. About 95,000 patients were listed for kidney transplant, 13,700 patients for liver transplant, and 3,900 patients for heart transplant [5].

As the organ shortage persists, expanding the donor pool by using IRDs and donors with known infections such as HIV, HCV, and MDROs has become more enticing. With the opioid epidemic and increase in deaths related to drug overdose, there have been more potential donors who are meeting the U.S. Public Health Service (PHS) criteria for IRDs [6]. New advancements in medical management have made the use of IRDs and donors with HIV, HCV, or MDRO possible. Detecting potential donor derived infections prior to accepting an IRD organ has improved with nucleic acid testing (NAT). Since 2014, the OPTN has required that all potential deceased donors are screened for HCV using NAT and all IRDs are screened for HIV using NAT. NAT has decreased the time for detecting infection in a donor after an acute exposure compared to using serology alone [7, 8]. Newer direct acting antiviral (DAA) therapies have high cure rates for HCV, therefore allowing the possible use of HCV positive organs for transplant. The life expectancy of HIV positive individuals has increased, and HIV is now a more chronic and manageable disease with the use of antiretroviral therapy (ART). The feasibility of using liver and kidneys from HIV positive donors for HIV positive recipients is currently being evaluated in the U.S.

This article will review the current literature regarding use of IRDs and how the drug overdose epidemic is changing the field of SOT. We will review the use of donors with HIV, HCV, and MDROs, and discuss the advantages and challenges to consider.

2. Increased Risk Donors

In 1994, the Centers for Disease Control (CDC) published guidelines that identified “high risk” transplant donors with risk factors for the acquisition of HIV. Guidelines were later modified by the U.S. PHS in 2013. Criteria in the updated guidelines identified IRDs based on 11 behaviors in the preceding 12 months that increased a donor’s risk for acute infection with HIV, hepatitis B virus (HBV), or HCV [7]. This includes donors who used non-medical injection drugs, men who have sex with men (MSM), sex in exchange for money, newly diagnosed with syphilis, gonorrhoea, Chlamydia, or genital ulcers, donors on hemodialysis, hemodiluted donor blood specimens, or when a deceased potential organ donor’s medical/behavioural history cannot be obtained.

Several challenges with screening IRDs for HIV, HBV, and HCV exist. Challenges may include maintaining organ perfusion while awaiting the processing of screening laboratory tests. False-negative results may occur if plasma is diluted in donors who were transfused large volumes of blood or administered large volumes of fluid [9]. Tests screening for infections may not be as accurate if laboratory specimens are collected after blood flow ceases [9]. While routine serological tests can diagnose donors who are infected with HIV, HBV, or HCV months prior to transplantation [7], donors who are acutely infected may not be identified by serological testing alone. This limitation is highlighted by Ison et al in a report of four transplant recipients with co-transmission of HIV and HCV from a "high risk donor" with negative screening serological tests [10]. To investigate these four cases of transmission further, NAT was performed on donor sera and was positive for both HIV and HCV. Possible explanations for the negative donor serologies were that samples may have been hemodiluted after the donor received a massive blood transfusion and that serologies were likely obtained during the window period. Understanding the window period and the risk for missing a transmissible virus is important when considering using IRDs.

The eclipse and window periods occur after a donor is initially exposed to a virus. During the eclipse period, viremia is undetectable by testing, but the virus can still be replicating in the bloodstream and has the potential to be transmitted with organ transplantation [9]. The window period is defined as the time from acquisition to the time when a disease is serologically detectable. However, during the window period, viremia may potentially be detected with NAT. While HIV antibodies may take approximately 22 days up to 6 months to develop after an exposure to HIV, NAT decreases time until detection to 5.6-10.2 days [7, 11]. NAT also reduces the time to detect HCV from 38-94 days to 6.1-8.7 days and for HBV from 38.3-49.7 days to 20.4-25.7 days [11]. Since 2014, OPTN policy was updated and mandated that NAT for HCV is performed in all potential deceased donors regardless of risk factors and HIV NAT or HIV antigen/antibody combination is performed in all IRDs [12].

More IRDs are being identified since the 2013 U.S. PHS guidelines were implemented [13], and the number of IRDs continues to increase with the opioid epidemic and large number of deaths related to drug overdose. From 2003-2014, the largest relative increase in cause of death among organ donors in every OPTN region was due to drug overdose (350% relative increase) [14]. A total of 7313 overdose death donors (ODDs) were identified through the Scientific Registry of Transplant Recipients (SRTR) from January 2000 to September 2017. The number of ODDs increased by 17% per year (66 ODDs in the year 2000 compared to 1263 ODDs in 2016) [6]. A large proportion of ODDs had HCV infection (18.6%) and were labelled as IRDs (56.4%) [6]. ODDs were more likely to be Caucasian, from the Northeast and Midwest, and of younger age [6, 14]. Donor characteristics were found to be favourable for transplant, and ODDs were less likely to have hypertension, diabetes, or a previous myocardial infarction compared to donors who died from medical problems. Recipients of organs from ODDs had equivalent or slightly higher unadjusted rates of 5-year patient survival and graft survival when compared to recipients who had organs from a donor who died from trauma or medical co-morbidities [6].

While the donor pool has the potential to increase with using organs from IRDs and ODDs, the risk for donor derived HIV, HBV, or HCV remains a concern. The risk for transmission of infection with transplant is always a possibility. However, the estimated risk for viral transmission from a donor with increased-risk behaviors and negative results of NAT testing is low with <1 case per

1000 donors for HCV and 1 per 10,000 for HIV [15]. To address the concerns for disease transmission, Massachusetts General Hospital developed a protocol to manage transplant recipients receiving organs from IRDs. Of the 257 SOT recipients who received organs from IRDs, there were no cases of transmission of HIV, HBV, or HCV that occurred [16]. Another study in Canada by L'Huillier et al did not find any cases of transmission of HIV, HBV, or HCV from IRDs whose pre-transplant testing was negative [17].

Despite data demonstrating a low risk for transmission of HIV, HBV, or HCV, there is still reluctance to accept organs from IRDs. Goldberg et al found that although donors who died from a drug overdose had the highest rates of donation, there was a lower average number of organs transplanted per donor compared to donors who died from other causes ($p< 0.001$) [14]. In a review by Durand et al, data showed that compared to organs from donors who died from trauma, there were higher rates of discard of ODD organs including kidneys (14.1% vs 8.8%), livers (8.8% vs 6.8%), hearts (1% vs 0.6%) and lungs (8.1% vs 5.9%) [6]. In a 2017 retrospective study, 104,988 adult kidney transplant candidates were offered a kidney from IRDs, but only 6521 candidates accepted the offer [18]. While candidates declining an offer for an IRD organ may potentially avoid the low possibility of donor derived infection, there may be risks with waiting for a non-IRD organ.

Studies have shown that candidates who accept IRD organs have shorter waitlist times and may have better survival outcomes than candidates who decline IRD organs. In a study by Bowring et al, only 31% of renal transplant candidates who declined offers for IRD kidneys were transplanted non-IRD kidneys within 5 years [18]. Recipients of IRD kidneys had a 48% reduced risk of death that continued 6 months beyond their decision to accept an IRD kidney compared to candidates who declined an IRD kidney [19]. In an intention-to-treat analysis evaluating liver transplant outcomes, candidates who accepted an IRD liver had a significantly higher survival ($p <0.001$) compared to recipients who declined an IRD liver [20].

To better utilize available organs from IRDs, providers and teams will need to help educate candidates about the organ shortage and address concerns regarding accepting organs from IRDs and ODDs. Candidates should know the potential for having a longer waitlist time if declining an IRD organ and choosing to wait for a non-IRD organ. Based on current data, the risk for transmission of infection from IRDs may be lower compared to the risk from dying on the waitlist [14, 19]. Further studies will need to continue to look at long-term outcomes of using IRDs and challenges of using IRDs in order to help transplant recipients make the decision on whether to accept an IRD organ.

3. HIV

An amendment to the National Organ Transplant Act (NOTA) in 1988 banned the use of organs from donors with known or suspected HIV in the United States [21, 22]. Transplant was not available to HIV positive individuals due to concerns about allocating scarce organs to recipients who would be at risk for poor outcomes. Concerns included disease transmission, progression from HIV to AIDS while on immunosuppression post-transplant, and risk for opportunistic infection and malignancy [22-24]. However, with the development of effective ART, HIV is now a manageable chronic disease and is no longer considered a contraindication for transplant. More HIV-positive individuals are living longer and are dealing with comorbidities that also afflict HIV negative individuals. Approximately one third (33.3%) of HIV-positive individuals have kidney

disease, and liver disease is a leading cause of death in patients with HIV [24]. Transplant is now a viable treatment option for HIV positive patients with end organ dysfunction.

HIV positive patients have barriers to being listed for transplant that HIV negative candidates do not have to face. Providers need to establish that candidates on ART have well controlled HIV based on CD4 counts (minimum CD4 count >200cells/mm^3 for kidneys and >100cells/mm^3 for livers) and viral loads [25]. In a 2009 single-center, retrospective review of 309 HIV positive patients who were eligible for kidney transplant evaluation, only 20% were listed for transplant compared to 73% of HIV-negative patients ($p<0.00001$) [26]. Transplant evaluations took about 16 months to complete before a candidate was listed. The most common reason why candidates failed to be listed was that they did not have documentation of their viral load and CD4 count, thus highlighting the importance of communication of information between HIV providers for transplant evaluation of HIV positive candidates.

HIV positive patients who are listed and undergo transplant have had favourable outcomes. Studies have examined the impact of transplantation in HIV positive patients compared to HIV negative patients. A prospective cohort of 150 HIV positive kidney transplant recipients reported survival rates of 94.6% at 1-year post-transplant which was similar to HIV negative kidney transplant recipients [22]. HIV positive patients have a survival benefit from transplant compared to remaining on the waitlist [21, 24, 27]. Multi-center trials have shown that graft rates were acceptable with transplant in HIV positive patients. However, HIV positive patients on the waitlist also face the challenges of a limited supply of available organs for transplant, and compared to HIV negative individuals, they may have a higher morbidity and mortality while on the waitlist [24].

Transplanting kidneys from HIV positive donors to HIV positive recipients was first considered to address the clinical needs of the HIV positive population in South Africa. South Africa has a high incidence of HIV, and HIV-associated nephropathy is a leading cause of end stage renal disease [22, 28]. A large challenge in South Africa is providing renal replacement therapy to HIV-infected individuals when there are limited resources and where HIV is considered a contraindication for dialysis. In 2015, Muller et al published a prospective non-randomized study that evaluated the outcomes of 27 HIV positive individuals in South Africa who underwent kidney transplant from HIV positive donors [28]. Recipients were only included if they had CD4 counts >200 and an undetectable viral load while on ART. Rates of survival were 84% at 1 year, 84% at 3 years, and 74% at 5 years, and rates of graft survival were 93%, 84% and 84%; respectively [28]. Mueller's study demonstrated that transplanting kidneys from HIV positive deceased donors into HIV positive recipients who were carefully selected could be considered a feasible option for treating HIV positive individuals who require renal replacement therapy.

Based on the experience of South Africa with HIV positive to HIV positive transplant, policy changes were proposed to explore whether the outcomes seen in South Africa could be generalized to the U.S. On 11/21/2013, U.S. Congress passed the HIV Organ Policy Equity (HOPE) Act which had several components, including requiring the Department of Health and Human Services (DHHS) to revise the United States' federal ban on HIV positive donors [24]. The HOPE ACT mandated clinical research involving HIV positive organs with input from the CDC and health sources, and the OPTN was required to include policies for HIV positive organs. To further determine the potential benefit of utilizing HIV positive donors in the U.S., HOPE act allowed for a prospective clinical trial to explore the safety of deceased donor kidney and liver transplant from HIV positive donors to HIV positive recipients [24]. In 2015, the OPTN implemented the HOPE ACT.

Transplanting HIV positive organs will expand the donor pool and benefit both HIV positive recipients and HIV negative candidates who are on the same waitlist [24]. African Americans may also particularly have a large benefit with the utilization of HIV positive organs, as they are disproportionately impacted by HIV and have disparities in access to renal transplantation [22]. Boyarsky et al estimated that every year in the United States of America (USA), there are >500 potential HIV deceased donors [29]. A limitation to this estimate was donor demographics and information that could affect organ quality and donor eligibility were not examined. A study by Richterman et al 2015 examined HIV patients in 6 HIV clinics in Philadelphia who died from 2009-2014 to assess the impact of adding HIV deceased donors to the donor pool [27]. Patient specific data was included in the study. In Philadelphia, annually there were about 4-5 potential deceased donors with HIV. Data was extrapolated nationally to predict that there may be approximately 356 HIV positive deceased donors annually. Estimates of the number of potential HIV positive deceased donors are encouraging, but the number of available HIV positive organs for transplant will also depend on whether HIV positive individuals are willing to be organ donors. In a study examining the attitudes of HIV positive patients and transplant, HIV positive patients seemed willing to consider donating an organ to another HIV positive patient. About 113 out of 206 participants (55%) who were surveyed would consider receiving a transplanted organ from a HIV positive donor [30].

There are potential risks with using a HIV positive organ that need to be considered. Although there were reasonable outcomes in South Africa, the HIV positive population in the U.S. is different from South Africa. The U.S. has a lower incidence of HIV but a greater prevalence of resistant strains [23]. The genotype of a HIV positive deceased donor may not be known at the time of transplant, and teams may only have a short window period to decide whether to accept an organ. There is a potential risk for HIV superinfection if a donor has a genotype mutation causing viral resistance [23]. X4 tropic virus has been associated with rapid progression of HIV. Cases of superinfection have not been reported yet to date.

Opportunistic infections may occur in HIV positive recipients, especially in the setting of immunosuppressive therapy post-transplant. A major challenge will be determining if a HIV positive donor may have an opportunistic infection at the time of transplant which can be transmitted. In South Africa, Mueller et al found a low incidence of opportunistic infections within the first year after transplant [28].

Drug interactions post-transplant are a recognized challenge. Antiretrovirals such as protease inhibitors (PIs) interact with immunosuppressive medications, including calcineurin inhibitors. Both PIs and calcineurin inhibitors are metabolized through the hepatic cytochrome P450 3A4 pathway, leading to a decrease in calcineurin inhibitor metabolism when co-administered with a PI [31]. Providers may need to change a recipient's ART to avoid drug interactions and/or ensure close monitoring of calcineurin inhibitor levels. Candidates who are on PI based regimens may also need to consider switching to a non-PI based regimen in order to avoid the increased risk for mortality. Sawinski et al found that HIV positive kidney transplant recipients who were on PI-based regimens had a 1.8-fold increased risk for allograft loss and 1.9-fold increased risk of death when compared to recipients on non-PI based regimens [31].

HIV positive recipients receiving an HIV positive kidney may be at risk for developing recurrent kidney disease. Recurrent HIV-associated nephropathy (HIVAN) developed in 3 out of 27 HIV positive kidney recipients in the South African study by Mueller et al even though recipients had

undetectable viremia [27]. Canaud et al found that 68% of kidney transplant recipients with HIV-1 have detectable virus in the kidney allograft, and this is correlated with the presence of HIV-1 in the urine [32]. Genetic variants of apolipoprotein L1 in African Americans has been linked to HIVAN, suggesting that a donor's race could possibly affect outcomes of HIV positive recipients.

To further evaluate the feasibility of using HIV positive donors in the U.S. and determine the possible risks of transplant, a multi-center clinical trial looking at HIV positive to HIV positive kidney and liver transplant is being conducted by Johns Hopkins. Initial data from the HOPE in Action trial described the cases of 10 suspected false positive donors between March 2016-2018. These donors did not have any known history of HIV and did not have any risk factors for recent HIV infection and had discordant HIV testing HIV antibody and NAT results). Their organs were transplanted in 21 HIV positive patients. There were 8 donors who were HIV antibody positive and NAT negative, and there were 2 donors who were HIV antibody negative and NAT positive. Confirmatory tests for all 10 patients were negative indicating false positive HIV tests [33]. None of the HIV positive recipients had HIV breakthrough or opportunistic infections. Evaluating the true number of potential donors with false positive HIV screening assays could help to identify organs that would have previously been discarded but now would potentially be used for transplantation.

While studies have been published using HIV positive deceased donors, data using HIV positive living donors is limited. Living donors with HIV have not been previously been described except in a case report from South Africa by Botha et al that described HIV positive living donor liver transplant [34]. A HIV negative 7-month-old child with biliary atresia was listed for liver transplant. The child clinically deteriorated while on the waitlist, and after weighing the risks and benefits, the mother who was HIV positive was approved to be a living donor. The mother was on tenofovir, efavirenz, and lamivudine throughout her pregnancy and had a CD4 count of 164 cells/μL. The recipient was started on ART to prevent transmission. Seroconversion was documented within 43 days post-transplant, but by 379 days, HIV antibody titers approached undetectable levels. HIV-1 RNA and DNA were undetectable, and the recipient and donor were doing well at one-year post-transplant. Transplants using HIV positive living donors will be further studied and will potentially help to expand therapeutic options and alleviate the organ shortage.

4. Hepatitis C Virus

Approximately 4.1% of deceased donors from 1995-2016 were HCV seropositive (hepatitis C antibody positive) [35]. It is predicted that most HCV positive donors will come from individuals with undiagnosed chronic HCV who were born in 1945-1965 and injection drug users. Utilizing HCV positive donors may help to decrease the waitlist times. Accepting a HCV positive organ is very different for HCV positive recipients compared to HCV negative recipients as the latter will have high likelihood of acquiring a new infection. New HCV DAAs have made using HCV organs a considerable option. Unlike other viruses such as HIV that can be controlled but not fully eradicated with therapy, HCV has high cure rates with the DAA therapy. The OPTN policy was updated in December of 2014 so that all donors were screened with HCV NAT along with serology [35]. With the use of the NAT, the window period decreased from 60-70 day to 5-7 days within viral exposure. In 2017, the American Society of Transplant (AST) published consensus guidelines for the use of HCV positive donors and clarified several definitions regarding HCV "positive donors":

- A positive HCV NAT was considered to be diagnostic of an active HCV infection regardless of HCV antibody status.
- HCV ab positive/NAT positive donor indicates active infection and high risk for disease transmission
- HCV ab negative NAT positive donor indicates acute infection in the past 2 months and therefore is considered higher risk for transmission.
- HCV ab positive/NAT negative donor indicates spontaneously cleared or treated infection or a false positive antibody result.

The AST consensus guidelines state there is no increased risk for transmission of HCV from donors who are HCV antibody positive/NAT negative as long as the donor does not have any other risk factors for HCV [35]. In this scenario, HCV negative recipients are only required to undergo testing post-transplant if the transplant center is concerned about risk for transmission of HCV. If the donor meets the criteria for a PHS IRD, then post-transplant screening should comply with the OPTN policy. A study by de Vera et al 2018 reviewed 32 HCV negative recipients who received a kidney from donors who were HCV antibody positive/NAT negative. Although 14 patients seroconverted to having positive hepatitis c antibodies, none of the patients had evidence of viremia [36].

Concerns have been raised regarding utilization of HCV positive donors. Drug interactions with protease inhibitors and calcineurin inhibitors are a possibility but are manageable with close monitoring and dose adjustments [35]. A donor's genotype may not always be known prior to transplant, so HCV positive recipients may be at risk for dual infection if they receive an organ from a donor with a different HCV genotype. Hepatitis in HCV negative candidates post-transplant is a concerning complication. However, trials evaluating outcomes of patients with HCV who are treated with DAAs have shown high rates of SVR. The ALLY-1 study evaluated the efficacy and safety of combination daclatasvir, sofosbuvir, and ribavirin in HCV positive patients with different genotypes [1-6] and either compensated/decompensated cirrhosis or recurrence of HCV post-transplant [37]. High rates of SVR were achieved in patients with genotype 1 (95%) and genotype 3 (91%) who were treated post-transplant. Although DAAs are effective, obtaining approval for DAAs could limit the use of HCV positive organs. DAAs are usually restricted to patients with chronic HCV and advanced hepatic fibrosis, so obtaining coverage for transplant recipients who have an acute donor derived infection without any liver injury may be a possible challenge [35]. If there are any difficulties in having DAAs approved by insurance for post-transplant therapy, teams and physicians will need to rely on protocols to monitor for HCV infection. Side effects with DAAs may occur, but most DAAS are well tolerated. Chascsa et al reported in a review of HCV positive kidney transplant recipients treated with DAA therapy that headache and fatigue were the most commonly reported side effects [38].

Several studies have looked at the impact of using HCV positive donors for different organs including kidney, liver, lung, and heart and concerns related to using a HCV positive donor. These studies will be discussed further by organ type.

4.1 Kidney

About 5-10% of ESRD patients in the USA have HCV [35]. Although some HCV positive patients undergo transplant, many are still on the waitlist and have a higher morbidity and mortality.

Shelton *et al* 2017 found that for HCV positive recipients, time to transplantation was shorter when using HCV positive donors compared to those who used HIV negative donor kidneys (0.6 vs 1.3 years) [39]. These kidney recipients who received HCV positive organs were also more likely to be African American (P<0.001) and have HIV co-infection. Another study found that about 35% of HIV positive kidney recipients receive organs from HCV positive donors [40]. 30% of donors who are hepatitis C antibody positive are not viremic (NAT negative) [40].

Treatment of HCV post-transplant, duration of HCV therapy, and type of DAAs used depends on the donor's HCV genotype. Timing of initiating treatment should be individualized. Kiberd et al 2018 used a Markov medical decision analysis model and found that delaying treatment compared to immediate DAA therapy for HCV positive patients who were waitlisted depends on the transplant region and individual candidates [41]. Immediate therapy provided more life years compared to delayed therapy. However, in regions where there was greater access to HCV positive organs and more candidates with lower mortality associated with HCV, delaying therapy was preferred. To determine the impact of treating hepatitis C prior to transplant versus post-transplant, Mayo Clinic conducted a retrospective review of 36 hepatitis C positive candidates who were waitlisted for kidney transplant at 2 transplant centers within the same health care system. Candidates who were treated with DAAs post-transplant had a shorter waitlist time (P= 0.02) and had increased access to transplant (P=0.0013) [38]. The THINKER trial was a single-group clinical trial conducted at the University of Pennsylvania that included 20 HCV negative recipients who received kidneys from HCV positive donors [41]. All recipients received a course of elbasvir-grazoprevir +/- ribavirin (if NS5A resistant) once HCV transmission was detected. Within a month of starting a DAA, all recipients achieved undetectable HCV viral loads, and all patients were cured of acute HCV infection in the first year of their transplants. A previous concern regarding HCV treatment was that there were no DAAs available for patients with renal insufficiency. Glecaprevir-pibrentasvir is a pangenotypic DAA that was developed and is now available for the treatment of HCV in patients with stage 4 or 5 chronic kidney disease (CKD). In a multicenter trial, 104 HCV positive patients with stage 4 or 5 CKD were treated with 12 weeks of glecaprevir-pibrentasvir, and there was a 98% rate of SVR and low rate of adverse events [42].

A possible barrier to treatment for HCV positive recipients is the cost of DAAs. However, a 2018 study by Kadatz et al used a Markov model for a cost-effectiveness analysis and found that transplanting HCV NAT positive kidneys into HCV negative recipients and then treating with DAAs was cost saving [43]. It helped to shorten the waitlist time by two or more years. Gupta *et al* 2018 also found that using DAAs post-transplant for patients who were D+/R- for HCV was less costly compared to candidates remaining on the waitlist and receiving an organ from a HCV negative donor [44].

4.2 Liver

It is estimated that 16.9% of HCV positive liver transplant recipients had an HCV positive donor from 1995-2016, and that only half of the donors were viremic at the time of transplant [35]. A major concern with using a HCV positive donor is risk for allograft infection and clinical decompensation if the recipient is not able to complete DAA therapy or achieve sustained virologic response (SVR). Studies have shown that outcomes in HCV positive recipients with HCV positive donors are comparable to those with HCV negative donors [45]. In a study by Chhatwal et

al, a mathematical model simulated HCV positive recipients who were on the waitlist and compared those recipients who were willing to accept HCV positive/negative livers with recipients who were only willing to accept a HCV negative liver [46]. It also examined patients who received HCV positive livers and were treated after liver transplant pre-emptively with 12 weeks of a DAA. Patients who had MELD scores of 20 or higher had a greater benefit from transplant from HCV positive or negative donors. The highest benefit occurred in patients with a MELD score of 28 who received a HCV positive liver. The amount of clinical benefit from using HCV positive liver donors was proportional to HCV positive organ donor rates per region.

4.3 Lung

There is a high risk of disease transmission from HCV positive donors to HCV negative lung transplant recipients, and historical data have shown a poorer prognosis possibly be due to side effects from older HCV drugs and possible pulmonary side effects of HCV [47]. Of 16,604 HCV negative patients who underwent transplant from 2005-2014, only 28 patients had received a lung transplant from a HCV positive donor. With the newer DAAs that have a higher tolerability and less side effects, there is an opportunity to re-evaluate the use of HCV positive donors for lung transplantation. Khan et al 2017 described a case of a 44-year-old male with pulmonary fibrosis and chronic lung allograft dysfunction after a left single lung transplant [47]. A deceased donor who was HCV NAT positive was available, and a single lung transplant was performed due to the recipient's risk for death without transplant. The recipient had evidence of HCV viremia 2 weeks after transplant and was started on DAA therapy 6 weeks post-transplant. He achieved SVR after completing a 12-week course of ledipasvir/sofosbuvir. A case of donor-derived hepatitis C virus was reported in a 59-year-old woman with chronic obstructive pulmonary disease who underwent a left lung transplant [48]. At 66 days post-transplant, she was found to have a hepatitis C viral load of 536,164 IU/ml, but Hepatitis C antibody remained negative. She was treated successfully with simepravir and sofosbuvir for HCV genotype 1A. However, she later developed bronchiolitis obliterans syndrome and worsening graft rejection and died on post-operative day 615.

4.4 Heart

Data from the early 2000s looking at outcomes in heart transplant recipients with HCV-positive donors had variable results. A retrospective review of seven heart transplant recipients with Hepatitis C seropositive donors found similar 5- year survival rates compared to HCV–negative donors [49]. However, other studies demonstrated worse survival. In HCV negative heart transplant recipients at Cleveland Clinic, there was a 2.8-fold greater mortality and 3–fold-greater risk for vasculopathy in recipients with HCV seropositive donors compared to controls with HCV negative donors [50]. A 2006 multicentre cohort study found that 261 heart transplant recipients with hepatitis C positive donors had a significantly higher mortality compared to recipients with HCV negative donors at 1 year (16.9%), 5 years (41.8%), and 10 years (50.6%) [51]. The poor outcomes associated with using HCV positive donors were partly attributed to the poor tolerability and cure rates of older HCV regimens prior to the availability of DAA therapy. Interferon-based treatment of HCV was associated with risk of allograft rejection, side effects, drug interactions, variable response rates, and high treatment dropout rates [52].

With studies showing increased mortality using HCV positive donors, there was more reluctance to accept hearts from HCV positive donors. From 2004-2015, there were only 24 heart transplant recipients in the United States who either had HCV or had a HCV positive donor [35]. In 2016, only 7 out of 220 (3.7%) heart offers from donors who were HCV antibody positive, NAT negative were accepted [53]. Of the 213 hearts that were not accepted, 51 (24.46%) were declined due to hepatitis.

However, with the high success rates of DAAs for the treatment of HCV in immunocompetent individuals, heart transplant using HCV positive donors is of high interest and is being re-evaluated [54]. In one study, 14 heart transplant recipients with HCV antibody positive/NAT negative donors were followed up for a median of 256 days. Although 2 recipients became seropositive for HCV antibody and one recipient had a HCV antibody that was equivocal, there was no evidence of viral transmission in all 14 recipients [53]. Wetterston et al described a case of a HCV negative patient with a left ventricular assist device (LVAD) driveline infection and ESRD on hemodialysis who underwent heart-kidney transplant with organs from a HCV-viremic (NAT positive) donor [55]. The recipient developed HCV viremia (genotype 1a) the day after transplant and was started on a 12-week course of elbasvir-grazoprevir at the time of discharge and achieved SVR. At one year follow up, the recipient had no evidence of rejection or coronary artery vasculopathy. Two patients at Stanford University received hearts from HCV ab and NAT positive donors who were genotype 1a, and they achieved SVR after 12 weeks of treatment with DAAs [56]. Two weeks after heart transplant, one patient received sofosbuvi/ledipasvir, and the other received sofosbuvir/velpatasvir. In a case series by Schelndorf et al, 13 hearts were transplanted from HCV positive donors (11 had a positive HCV NAT), and HCV viremia only developed in 9 recipients who had HCV antibody positive/NAT positive donors [52]. There were 2 recipients who did not develop viremia despite having donors who were HCV NAT positive. Possible explanations include one donor may have had a viral load that was too low for transmission. All 9 recipients who acquired HCV were able to obtain insurance coverage for DAAs.

The success of transplant cases using HCV positive heart donors is encouraging. Patel *et al* predicted that accepting HCV NAT- hearts could possibly increase the number of heart transplants by 100 per year [53]. However, further studies will have to evaluate the safety and efficacy of DAA in transplant recipients on a larger scale. More data is needed to ensure that the onset HCV viremia does not occur in patients who are on immunosuppressive therapy. The optimal timing for initiating DAA therapy in recipients after transplant has to be determined. With further research, the use of HCV organs will hopefully help to decrease the shortage of organs.

5. Multi-Drug Resistant Organisms

Bacterial infections may be present in deceased donors, especially if they have risk factors that include co-morbid conditions, medical devices (central lines etc), and admission to the ICU. A study by Lumberas *et al* 2001 looked at 569 patients who underwent liver or heart transplant and found that at least 5% of donors had bacteremia at the time of procurement [57]. However, there were no episodes of transmission from donor to recipient. Donors with bacteremia were more often febrile within 24 hours prior to transplant compared to donors who did not have bacteremia.

The impact of donor-derived bacterial infections on recipient outcomes have varied. Some recipients have developed sepsis or allograft dysfunction. In a review from China looking at 67

liver transplant recipients, the most common organisms isolated from donor blood cultures were gram positive organisms: coagulase-negative *Staphylococci* and *Staphylococcus aureus* [58]. However, no episodes of donor-derived infections were due to gram positive organisms. They were due to *Klebsiella pneumoniae* and *Enterobacter aerogenes*. Within 3 months of transplant, recipients with donor-derived infections had higher graft loss and mortality rates.

Donor-derived multidrug resistant organisms, including carbapenem-resistant Enterbacteriaceae (CRE), are becoming a more concerning challenge in transplant. CRE infections can have a high mortality rate in transplant recipients. Even patients who are hospitalized for less than 2 days are at risk for MDROs [59]. The optimal management of MDRO donor-derived infections is not clearly defined. However, in cases with known bacteremic donors, it is recommended that recipients receive a 7 to 14-day course of targeted antibiotics [60].

Cases of MDRO transmission are listed in (Table 1) [59, 61-66]. Mularoni et al 2015 reviewed the clinical course and outcomes of recipients who received organs from donors who were colonized/infected with carbapenem-resistant gram-negative organisms that were not known about at the time of procurement [59]. 10.5% (18 out of 750) deceased donors had colonization/infection with carbapenem- resistant gram-negative organisms. From these 18 donors, 30 organs were transplanted into 30 recipients. In recipients who received early antibiotic therapy that was appropriate, there was no transmission. A case of donor-derived carbapenem resistant *Acinetobacter baumanii* (CRAB) infection of the lungs and surgical wound was documented in a lung transplant recipient [64]. The isolate contained the bla_{OXA23} gene. Despite treatment with polymyxin B, the recipient died from sepsis on post-operative day 65.

The risk for donor-derived infections can be reduced by screening transplant donors and by using targeted antibiotic prophylaxis after transplant. Ideally, donors who are known to be infected should receive at least 24-48 hours of antibiotics with some degree of clinical response [60]. Rapid recognition of infection is critical; however, this depends on clinical suspicion for a donor-derived infection and the availability of donor cultures. It has been shown that a delay in communication of possible donor infection can contribute to disease transmission [59]. Ariza-Heredia et al reported 4 transplant recipients receiving organs from a donor found to have *Klebsiella pneumoniae* carbapenemase (KPC)-producing *Klebsiella pneumoniae* [62]. Only 2 patients had a donor-derived infection while the other 2 recipients were given tigecycline for prophylaxis. The cases were reported to OPTN which led to quick communication between different institutions and teams regarding the isolate's susceptibilities and likely lead to the early start of pathogen targeted antibiotics. Establishing protocols for communicating important donor information should be considered. Source control and draining infected fluid collections can also help to decrease the organism burden.

Table 1 Cases of donor-derived MDROs.

Reference [#]	**# of infected donors**	**# of recipients infected**	**Type of transplant**	**MDR organism**	**Recipient Site of infection**	**Antibiotics**	**Outcome**
Mularoni *et al* 2015 [59]	18	1	Right liver graft	CRKP	Abdominal drainage fluid	Tigecycline + colistin	Survived
		1	Double Lung	CRKP	BAL	Meropenem + colistin	Survived
		1	Liver	CRKP	Abdominal wound swab, peri-hepatic fluid	Meropenem + Vancomycin	Survived
		1	Kidney	CRKP	Peri-graft fluid, urine, blood	Meropenem + Ertapenem + colistin	Died 2 months post-transplant
Giani *et al* 2014 [61]	1	1	Kidney	OXA-48-producing *Klebsiella pneumoniae*	Bloodstream infection	Meropenem	Graft failure
		1	Liver			Meropenem → Ertapenem	Survived
Ariza-Heredia *et al* 2012 [62]	1	1	Liver-kidney	KPC-producing *Klebsiella pneumoniae*	Peritoneal fluid and peri-hepatic fluid	Tigecycline + Amikacin + Meropenem	Survived
		1	Vein graft		Preservative fluid for graft vessel	Amikacin + Tigecycline	Survived
Chung *et al* 2010 [63]	1	1	Kidney	MDR *E. coli*	Urine	N/A	Nephrectomy
		1	Kidney		Perinephric abscess, wound culture	Piperacillin/tazobactam	Nephrectomy
Martins *et al* 2012 [64]	1	1	Lung	CRAB (+bla_{OXA23})	BAL and surgical wound	Polymyxin B	Died on POD 65

Variotti *et al* 2016 [65]	1	1	Kidney-pancreas	CRKP	Duodenoileal anastomotic leak + abscess around right common iliac artery	Ertapenem + Meropenem + Tigecycline	Died on POD 195
Galvao *et al* 2018 [66]	1	1	Heart	KPC-producing *Klebsiella pneumoniae*	Bloodstream infection, pericardial fluid	Ertapenem + Meropenem + Amikacin	Died on POD 50

Abbreviations: BAL= bronchoalveolar lavage, CRAB= Carbapenem resistant Acinetobacter baumanii, CRE= Carbapenem Resistant Enterobacteriaceae, CRKP= Carbapenem resistant Klebsiella pneumoniae, KPC= Klebsiella pneumoniae carbapenemase, MDR= multi-drug resistant, POD= post-operative day

6. Conclusion

Opportunities to increase the donor pool are constantly being evaluated. Using IRDs may help to improve the shortage of organs for transplantation. An ongoing challenge is to address the concerns for transmission of infection as the number of IRDs and ODDs increase with the opioid epidemic While data from the South African experience with HIV to HIV positive kidney transplant has been favourable, data from the HOPE trial will help to show whether or not the same benefits will be generalizable to HIV positive recipients in the USA. Studies have shown that kidney and liver transplant recipients with HCV positive donors have comparable outcomes to patients with HCV negative donors, and DAA therapy can be used for treatment post-transplant. Organs infected with MDROs have been used, but with variable outcomes. Communication and notifying transplant centers and OPOs early when organs from a donor infected with a MDRO are used are critical to initiating therapy early. As the organ shortage persists, IRDs and donors with HIV, HCV, and MDRO can be utilized with careful consideration. The risk and benefit of using these organs should be tailored to each individual recipient. Further research should continue in order to improve the treatment and management of transplant recipients who receive organs from IRDs or donors with HIV, HCV, or MDROS.

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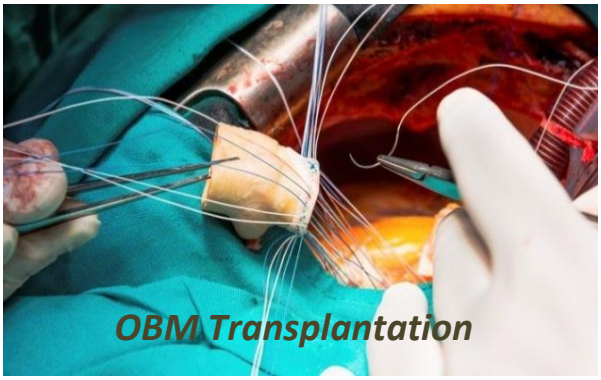

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