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HIV Solid Organ Transplantation: Looking Beyond HOPE

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Introduction:

In 2015, the HOPE (Human Immunodeficiency Virus Organ Policy Equity) Act was approved in the United States\(^1\). This Act has allowed transplantation of organs from HIV positive donors into HIV positive recipients under the umbrella of research activities. The course that has brought us to this point has not been easy and in cases encumbered by the stigma of the disease not realized in the transplantation of individuals with Hepatitis C. The purpose of this article is to take us to today as regards the transplantation of HIV organs, and continue a conversation regarding at what point do we, or should we, consider transplanting HIV donor organs into non-infected recipients. This is a complex conversation involving strong ethical issues. However, as our technology and treatment improve what we would not have done before may be closer to a reality today. Ten years ago who would have thought organs from patients with Hepatitis C could be transplanted into negative recipients and then cured of the disease\(^2\). As with most decisions this comes down to understanding the risk and benefit to the patient.

In the United States the need for solid organ transplant continues to be high. UNOS (United Network for Organ Sharing) reports (https://www.unos.org/data/) that 115 thousand individuals are in need of a transplant and of those approximately 75 thousand are on the active waiting list. However, the pool of individuals willing to donate organs is not sufficiently large to cover the need resulting in approximately 20 individual who die each day while waiting for a transplant.

The number of individuals on the transplant list has increased over 5-fold from 1991 to the 2016 (https://www.organdonor.gov/statistics-stories/statistics/data.html), whereas, the number of organ donors have increased less than half that number. How these numbers fundamentally impact patient outcomes can be seen for those waiting for Heart transplantation. For those patients
in the sickest category the longer the time they wait for a transplant the higher the mortality [3]. Unfortunately over the past decade the median wait time for cardiac transplant candidates in both the highest and intermediate priority category have increased dramatically [4]. If one looks at the 90-day mortality for cardiac patients waiting for a transplant as a function of risk, those at the highest risk have almost a 20% mortality rate [5]. This indicates a growing need for more alternatives for these patients.

Evolving Ethics:

In 2002 a position paper was published from Halpern and colleagues [6] on the ethical considerations in performing transplants into HIV-infected recipients using non-infected organs. In this paper they asked for a “call for consistency” and re-evaluate organ transplantation in patients with HIV informed by arguments supported by the improvements in treatment thereby eschewing past ethical considerations not to transplant. This thinking has further evolved, along with the field, as evidenced recently by the work of Wispelwey and colleagues who evaluated the ethics of transplanting donor positive organs into negative recipients [7]. They argued that autonomy, beneficence/non-maleficence and justice supported such transplantation. Moreover, for them the bridge has been crossed in using HIV organs in transplantation of negative recipients as evidenced by the transplantation of cytomegalovirus positive organs into negative recipients [8]. Significant advances in the transplantation of Hepatitis C organs into negative recipients who are then cured with direct-antiviral therapy [2] further underline the progress in transplanting positive organs into negative recipients (albeit not fully analogous). For patients with HIV the improvements in treatment options have led to significant improvements in life expectancy [9] and quality of life.

The interplay between beneficence and non-maleficence, do good and do not harm, is clearly important. The concern about the transmission of a resistant viral strain is real but with over a decade of transplanting HIV positive organs into HIV positive patients this has not been a significant issue, and with newer robust
medications continues to diminish in countries that have access to them. The HOPE Act has addressed this concern directly in the safeguards guidance and added this as a potential risk in the informed consent.

**Brief History of HIV Transplantation:**

Prior to combination anti-retroviral therapy (cART) individuals with HIV that were transplanted had dismal outcomes because of the inability to mitigate HIV progression and immunologic demise \[^{10}\]. With the introduction of cART graft survival improved dramatically in HIV renal patients transplanted with organs from non-infected individuals \[^{10}\]. A study from Stock and colleagues of 150 HIV+ patients using uninfected organs \[^{11}\] bolstered earlier work that demonstrated efficacy for renal transplantation of uninfected organs into HIV individuals. The positive outcomes in patient survival, improved understanding of drug-drug interactions, maintenance of HIV immunologic control, supported making donor negative to recipient positive patients thereby putting much of the controversy about doing such transplants effectively to rest. During the time of Stock's study Muller led a group in South Africa where kidneys from HIV-infected donors were transplanted into HIV-infected recipients \[^{12}\]. The motivation for this was two-fold. First dialysis was not routinely available to all patients and many would be sent home to die, and second was that the donor pool was low. In a later paper they looked at 5-year outcomes in a larger transplanted cohort \[^{13}\]. Graft survival and patient survival after 1 and 5 years was comparable to patients with HIV that received an organ from an uninfected donor. Over a decade before this work transplantation of Hepatitis C positive organs into Hepatitis C positive recipients was being done, and in Spain was de rigueur \[^{14}\]. In Muller's studies and others it had been shown that organs transplanted into patients with HIV had a 2-3x increase in rejection when compared to uninfected recipients \[^{11,15}\]. However, since the advent of integrase inhibitor containing cART a number of studies have provided evidence that protease inhibitor containing cART has a poorer long term outcome than non-PI containing regimens \[^{16-18}\]. For renal transplant patients, this resulted in better graft survival and patient survival over a 3-year period.
Efforts to grow the Donor Pool:

As described earlier the need for solid organs to transplant is great with considerable wait times that translate into higher mortality for many. Numerous efforts are underway to enhance the availability of organs for transplantation. Improvements in technology may allow current restrictions on transplantation of certain organs to become more relaxed enhancing availability of organs previously discarded. There are data suggesting some hearts that previously did not meet the standard criteria for transplantation may produce comparable outcomes to those hearts held to the current standard [17, 19]. Progress in xenotransplantation has moved considerably ahead since the early 2000’s bringing a group of international experts together to publish a position paper proposing consideration by the regulatory bodies for activities and samples after xenotransplantation in humans once such transplantation is supported by preclinical data [20]. In non-human systems long-term engraftment [21], and inactivation of the pig retrovirus [22] have been achieved diminishing barriers raised against such transplantation. However, there continue to be hurdles to overcome [23]. An available organ pool also exists in the form of deceased or living HIV positive donors. It is estimated that at least 500 organs from HIV deceased donors are available annually in the United States [24].

Immunologic considerations:

The history above demonstrates that with new discovery comes new perspective. It is important to recognize that viewed immunologically, HIV infected individuals transplanted with an organ from a sero-negative donor may be considerably different than a sero-negative recipient transplanted with an organ from a positive donor if started on cART. Since transplantation of HIV organs into non-HIV recipients has been accidental, recipients have not, in general, been on early therapy and HIV has generally been diagnosed well after the primary HIV infection occurred in the host resulting in immunologic compromise [25, 26]. In one case report [27], identification of a positive donor occurred 5 days after
transplantation of various organs into multiple negative recipients who were placed on antiretroviral treatment with positive outcomes.

An individual infected with HIV has loss of CD4+ T-cells in the gut and disruption of the gut mucosa resulting in increased microbial translocation that adds to the chronic cell activation [28]. This cell activation, although diminished on cART, may persist chronically impacting on long-term outcomes in HIV-infected individuals. An HIV sero-negative individual transplanted with an HIV organ would most likely not have any significant microbial translocation if antiretrovirals are provided at the time of transplantation and the viral load is low or non-detectable [29]. The second difference would be in the establishment of viral reservoirs [30]. These reservoirs generally consist of a latent pool of virus that is in a non-active state. Since current treatments require viral replication for efficacy a fraction of these latent reservoirs will be able to produce replication competent virus once activated and the individual off antiretrovirals. The reservoir pool for a transplanted HIV organ is not known but HIV has been identified in pathologic samples from numerous tissue compartments [31]. In a recent study [32] the replication competent virus and latent virus in Rheseus macaques was evaluated and showed that >99% of all replication competent virus resided in lymphoid tissue (including gut and lung). Interestingly in this study when the SHIV infectious model was used no recoverable virus was found in the heart or kidney. The important take-a-way from this is that the viral reservoir burden transferred to a sero-negative recipient will be significantly lower than in an HIV infected patient. In organs from infected donors the tissue culprits that will, most likely, contribute to HIV transmission to a non-infected host are the passenger cells [33]. These cells consist of long-term resident cells and cells that reside in the organ transiently. Ex vivo organs for transplant are generally perfused and some may undergo multiple rounds of perfusion to improve viability [34, 35]. In a recent study ex vivo perfusion of porcine kidneys resulted in a significant removal of immune cells from the organs [36].

Under suppressive cART therapy the virus from the transplanted organ is less likely to spread infectious virus to the host to any large degree. Indeed,
depending on the HIV burden transferred it may be possible for these recipients to remain antibody negative. Two lines of thinking support this idea. First comes from work done in the pediatric field. In a study of vertical HIV transmission in children started on antiretroviral therapy months after birth a child <3m of age started on cART had a 30% chance of testing HIV antibody negative and remain so. From the Mississippi baby report and later studies, see for example and references therein, we know that viral reservoirs are established early so in these cases the latent pools or low replication that might occur is not immunologically seen even as the child's immunity becomes more developed. Indeed, children treated early in life may become HIV sero-negative if suppressed over time. No doubt the development of the immune system over time in infants modulates the development and timing of the antibody response. In the adult population one can draw upon the work performed in Thailand. In this study frequent blood sampling of participating individuals allowed the researchers to follow development of the HIV antibody response as well as impact on various immunologic host parameters from initial infection. Specific focus for these immunologic variables was during the early Fieberg I stage of infection where individuals were HIV-RNA+, p24Ag- and HIV IgM- compared to later stages. In these cases there was less CD8 T-cell activation, and less recoverable virus from gut and CSF in early infection compared to later stages of infection. In another paper these researchers demonstrated in the same Thailand study population that those participants, Fieberg I stage, had dramatically lower viral reservoirs when treated early compared to treatment at later stages of infection. It would follow that a negative host under HIV suppressive therapy could have even less immunologic perturbations and viral reservoirs when transplanted with a positive heart or kidney compared to those treated early in acute infection. It becomes arguable that those individuals transplanted with an HIV-positive organ may have significantly improved outcomes when compared to an HIV-negative organ transplanted into an HIV-positive recipient.

**Conclusion:**
The need for organs for transplantation is high. The pool of those in need of a transplant continues to grow unmatched by the availability of organs resulting in longer wait times and increasing mortality. The improvements in treatment for those individuals infected with HIV and in the field of transplantation layered upon a growing need for organs continues to modulate the ethical landscape regarding the use of HIV donor organs. Whether opening this door in transplanting positive HIV organs into negative recipients is a modern day sword of Damocles is certainly important to discuss, but fundamentally, decisions should be made on best available information and circumstances. It may be time to further evaluate the highest risk populations for death against using an organ from an HIV infected individual with knowledge that HIV infected people can now have long lives on suppressive therapy.

References:


34. Kollmann D, Selzner M. **Recent advances in the field of warm ex-vivo liver perfusion.** *Curr Opin Organ Transplant* 2017; 22(6):555-562.


Please find the modified manuscript file (AIDS-D-18-00387) attached for resubmission with the edits as described below.

The author would like to thank the reviewers for their comments.

Response to reviewer #1:

1. Reviewer comments (in my opinion this comparison is not perfectly appropriate): I agree and added a parenthetical comment-pg3 in the Evolving Ethics Section third line from bottom of the 1st para.
2. Changed antiretroviral to direct-antiviral : pg3 in the Evolving Ethics Section 4th line from the bottom of the 1st para.
3. Changed anti-retrovirals to antiretrovirals pg 6, 8th ln from the top
4. Ex Vivo was changed to Ex vivo pg 6 first para 6 Ins from bottom (begins a sentence)
5. I added the reference and a sentence p5, last sentence first para of Immunologic Considerations

Response to Reviewer #2:

1. Changed that to than p5, 4th sentence 1st para Immunologic considerations
2. The reference to xenograph transplantations does not meaningfully contribute to the essay: Most likely I was not clear as regards why this was included. From the standpoint of need for donor organs numerous avenues are being explored. This is one of them. I added a sentence in the Efforts to grow the donor pool section, 2nd sentence first para.
3. The third point of the reviewers comment speaks to the purpose of the article that is fundamentally to start this discussion regarding transplantation. The comments are cogent but open many doors. At the end of the Evolving Ethics section I added a short paragraph that speaks to the question of transferring a resistant virus.
4. The 4th point is interesting. I state in numerous parts of the article that ethics are critical to the discussion. However, the point of the article is not for me to proffer my opinion that a well-informed patient should be offered the option to receive an HIV positive organ but provide sufficient information in the text for the reader to make that conclusion or refute it. I do add a sentence in the conclusion indicating that making the decision to transplant is difficult and should be based on the available information and circumstances.