An Exception to the Rule or a Rule for the Exception? The Potential of Using HIV-Positive Donors in Canada

Alissa J. Wright, MD,[1] Caren Rose, PhD,[2] Maeghan Toews, JD, LLM,[3] Michel Paquet, MD,[4] Daniel Corsilli, MD,[4] Jean-François Le Cailhier, MD, PhD,[5,6,7] and John S. Gill, MD[2,8]

Abstract: Selected human immunodeficiency virus (HIV)-infected patients with end organ failure can safely receive an organ transplant from an HIV uninfected donor. Recent demonstration of the short term safety of organ transplantation between HIV-infected persons prompted a change in US American law to allow such transplantations. Prompted by the recent completion of the first organ transplantation between HIV-infected persons in Canada, we review Canadian law regarding the use of organs from HIV-infected donors, estimate the number of potential HIV-infected donors in Canada, and critically review considerations related to advancing organ transplantation from HIV-infected donors in Canada. Existing legislation allows organ transplantation from an HIV-infected donor under exceptional medical circumstances and therefore no change in legislation is required to increase utilization of organs from HIV-infected donors for transplantation in Canada. Among 335,793 hospital deaths between 2005 and 2009 in Canadian provinces excluding Quebec, 39 potential HIV-infected donors were identified. The actual number of HIV potential donors is estimated to be approximately 60% lower (3-5 potential donor per year), if the absence of viremia is required for transplantation. Although offering all Canadians the opportunity to donate organs is a laudable goal, further research to understand the need for HIV-positive donors and the willingness of HIV-positive recipients to accept organs from HIV-positive donors is needed to inform future policy regarding organ donation from HIV-infected persons in Canada.

(*Transplantation* 2017;101: 671–674)

Antiretroviral therapy (ART) has dramatically improved the life expectancy of patients infected with human immunodeficiency virus (HIV) such that end-stage kidney and liver disease now exceed opportunistic infections in treated HIV-infected persons in developed countries.[1,2] Persons who develop end organ failure with clinically stable HIV infection are eligible for organ transplantation and achieve comparable transplant outcomes to those achieved in HIV uninfected transplant recipients.[3-5]

The increasing gap between the supply and demand for transplantable organs together with recent evidence from South Africa confirming the short term safety of organ transplantations between HIV-infected persons prompted change to legislation in the United States to allow HIV-positive patients awaiting kidney and liver transplantation to receive organ transplants from HIV-positive deceased donors.[6,7]

Received 28 November 2016. Revision received 30 November 2016.

Accepted 10 December 2016.

[1] Division of Infectious Disease, University of British Columbia, Vancouver, British Columbia, Canada.

[2] Division of Nephrology, University of British Columbia, Vancouver, British Columbia, Canada.

[3] Health Law Institute, Faculty of Law, University of Alberta, Edmonton, Canada.

[4] Département de Medicine, Centre Hospitalier Universitaire de Montréal, Montreal, Canada.

[5] Research Centre of Centre Hospitalier de l'Université de Montréal (CRCHUM), Montreal, Quebec, Canada.

[6] Montreal Cancer Institute, Montreal, Quebec, Canada.

[7] Nephrology Division, CHUM and Department of Medicine, Université de Montréal, Montreal, Quebec, Canada.

[8] Centre for Health Evaluation and Outcome Sciences, Vancouver, British Columbia, Canada.

The authors received no specific funding for this paper. J.G. is funded by a Foundation Grant from The Canadian Institutes of Health Research. M.T. is jointly funded by Canadian Blood Services and the Canadian National Transplant Research Program.

A.J.W. has previously received educational support from a combined University of British Columbia-Pfizer and Sunovion Pharmaceuticals grant. She has also received honoraria for speaking at a conference from Astellas and participated on an advisory board for Merck. J.G. has served as a consultant and received grant support from Astellas, Canada and served as a consultant for Alexion, Canada.

All authors contributed to the design of this study, the writing of this article and the review of the statistics, legal commentary and case information. C.R. performed the statistical analysis. M.T. provided expert legal commentary.

Correspondence: John S. Gill, MD, Division of Nephrology, University of British Columbia Providence Building, St. Paul's Hospital, Ward 6a 1081 Burrard Street, Vancouver B.C., Canada V6Z 604-806-8970 1Y6. (jgill@providencehealth.bc.ca).

ISSN: 0041-1337/17/10104-671

DOI: 10.1097/TP.0000000000001630

The generalizability of the South African experience to Canada is uncertain: HIV-positive deceased donors in South Africa without a history of ART have a low prevalence of primary resistance to ART (approximately 5%).[6] In contrast, the higher prevalence of primary HIV resistance (9.8%) and higher proportion HIV patients treated with ART in Canada may portend an increased risk of secondary resistance if these individuals are accepted as deceased donors.[8,9]

Prompted by the first case of organ transplantation from an HIV-positive donor in Canada, we review Canadian legislation related to the use of organs from HIV-infected donors for transplantation, and define the potential impact of routinely utilizing organs for transplantation from HIV-infected deceased donors by estimating the potential number of HIV-infected deceased donors in Canada.

The First Canadian HIV+ Donor/Recipient Renal Transplant

A HIV-positive adult with end-stage renal disease who met medical criteria for kidney transplantation including the absence of any active opportunistic infections, documented long-term compliance with ART, an undetectable viral load, and stable CD4 count greater than 200 cells/mm^3 [10] provided informed consent and underwent transplantation from a neurologically brain dead HIV-positive deceased donor who was a registered organ donor. The deceased donor had also received long-term ART with an identical regimen and had a stable CD4 count greater than 200 cells/mm^3 and no evidence of HIV replication or active opportunistic infections at the time of transplant. The physicians providing HIV care for both donor and recipient were contacted and were able to confirm that neither individual had clinical evidence of resistance to their current ART regimen (ie, they were virally suppressed). The recipient received basiliximab induction tacrolimus, mycophenolate mofetil, and corticosteroids in addition to ART that included abacavir, lamivudine and dolutegravir. At last follow-up more than 1 year post-kidney transplantation, the recipient was rejection free and enjoyed excellent kidney transplant function, had continued HIV viral suppression, and maintained a stable CD4 cell count greater than 200 cells/mm^3. Both the transplant recipient and donor family provided consent for the inclusion of the clinical information in this report.

Estimating the Number of Potential HIV-Infected Deceased Donors in Canada

We performed a retrospective analysis of in-hospital deaths recorded in the Discharge Abstract Database (DAD) from the years 2005-2009.[11] The DAD captures all in-hospital discharges from Canadian acute care facilities, with the exception of Quebec. Diagnostic and procedural information is coded using the International Statistical Classification of Diseases, 10th Revision, Canadian enhanced version and Canadian Classification of Health Intervention codes. Emergency room discharges are excluded from the DAD.

The primary outcome was the number of potential deceased donors who were infected with HIV. Donors were identified using a previously validated algorithm.[12] Briefly, we limited the analysis to persons who had a diagnostic code indicating HIV infection. Consistent with the current definition of a death eligible for donation, we limited potential donors to individuals 70 years or younger.[13] With the exception of HIV infection, we then excluded individuals who met absolute and relative contraindications to donation as defined by Canadian Standards Association.[14] Thereafter, potential donors were identified by having a cause of death compatible with donation.[15] Finally, potential donors were identified only among persons with a procedural code for mechanical ventilation. All analyses were performed using SAS 9.4 (Carey, NC). A internal review Board permission had been obtained.

Potential HIV-Infected Deceased Donors in Canada

There were 335,793 in-hospital deaths during the study period. Of these deaths, 1147 occurred in individuals with a diagnostic code for HIV infection and 97% of these deaths N = 1117 (97%) involved persons 70 years or younger. Among these deaths, n = 830 occurred among persons with contraindications to donation (excluding HIV infection). Among the remaining n = 287 persons, N = 69 (24%) had causes of death compatible with organ donation and of these only 57% were treated with mechanical ventilation leaving a total of 39 potential HIV-infected deceased donors with HIV over the 4-year study period.

The first reported case of organ transplantation between an HIV-infected donor/recipient in Canada was based on the efforts of healthcare providers with the awareness and expertise to support the donor's desire for organ donation as well as the recipient's ability to understand the potential risks while providing informed consent for the transplantation under emergent conditions.

Unlike the situation in the United States before the HIV Organ Policy Equity Act,[7] Canadian law does not preclude deceased donation from HIV-positive donors. Provincial and territorial legislation only require valid consent (either from the donor or his/her substitute decision maker) for the removal of organs and tissues for transplantation. In this case, the donor family agreed to donation with the knowledge that only a single kidney transplant would be performed. The safety of the recipient is governed by Federal regulations that require determination of donor suitability according to standards established by the Canadian Standards Association.[14,16] Canadian Standards Association standards consider HIV infection as a contraindication for organ donation and organs from HIV-infected persons cannot be used for transplantation unless requirements for "exceptional distribution" have been met. Exceptional distribution of organs for transplantation is not uncommon and occurs when: (a) an organ that has been determined to be safe by Canadian Standards is not immediately available, (b) the transplant physician authorizes the transplant using his or her clinical judgment, and (c) the patient provides informed consent to receive the organ transplant.[17]

In this case, the criteria for exceptional distribution were met; the recipient was not anticipated to receive a living or deceased transplant for many years. The median time that kidney transplant recipients required dialysis treatment prior to receiving a deceased donor transplant in Canada was 3.78 years between 2010 and 2014, and approximately 5% of waitlisted patients either die waiting or develop medical contraindications to transplantation during the waitlist period.[18] These risks may be higher in HIV-infected transplants candidates and therefore the first requirement for exceptional distribution was fulfilled.[19,20] The most important medical

considerations with organ transplantation between HIV-infected persons include the risk of infecting the recipient with a distinct strain of the HIV virus that leads to more rapid HIV disease progression (due to differences in viral sub-type or resistance to ART).[21-23] Although testing for viral strains is available, these tests are expensive and too time consuming to be done in the context of organ transplantation. Information about the type and response to ART in both donor and recipient were available and sufficient for the physician to authorize transplantation. The patient's ability to provide informed consent to proceed with the transplantation under emergent conditions was the most difficult exceptional distribution criteria to fulfill and was achieved in this case based on the patient's education level, an existing therapeutic relationship and a high level of trust with the transplant physician. Similar circumstances are likely to be uncommon and formal patient education prior to an offer for organ transplantation from an HIV-infected donor would ideally be provided in future cases.

Our results indicate that the number of potential donors gained by utilizing organs from donors with HIV infection in Canada is small. Our analysis excludes deaths in the province of Quebec but overestimates the number of potential donors by a factor of approximately 1.5 among deaths involving persons younger than 50 years (the majority (69%) of HIV-infected in-hospital deaths in the study were among persons younger than 50 years).[12] Therefore, we estimate a maximum annual potential of 8 to 10 HIV-infected organ donors in Canada. This estimate does not account for subsequent exclusion of donors with viremia. Approximately 25% of HIV-infected Canadians may be unaware of their diagnosis.[24] Assuming a similar proportion of potential donors would be unaware of their HIV infection and that all such individuals are viremic may reduce the number of potential donors by 25%. Furthermore, a significant proportion of potential donors with a known HIV diagnosis will be viremic. Based on data from British Columbia, 29% of known HIV-infected persons are not treated with ART and likely viremic, and 22% of HIV-infected persons receiving ART are not virally suppressed.[8] Therefore, if the absence of viremia is used as a criteria for donation (representing the initial proposed approach in the United States), the number of potential HIV-infected donors would likely be reduced by 60% or more—with only 3 to 5 potential HIV-infected donors annually in Canada.[25,26] Of note, the absence of donor viremia does not exclude the risk of transmission of resistant virus as the transplanted organ may serve as a reservoir for latent virus.[22]

Even after accounting for a 10-fold difference in population between the United States and Canada, our estimate of potential HIV-infected donors in Canada is much lower than the recent estimate of 500 potential donors per year in the United States.[27] In our analysis, 7.7% of all in hospital deaths among HIV-negative persons < 70 years were identified as potential donors compared to only 3.2% of in hospital deaths among HIV-infected persons.[12] This difference is due to a lower proportion of deaths due to causes compatible with donation and higher proportions of contraindications to donation among HIV-infected persons. There are several reasons why our estimate of potential HIV-infected donors in Canada is lower than that in the United States including a higher proportion of deaths with contraindications to donation in Canada (72% vs 62%), and fewer deaths due to causes compatible with donation (24% vs 29%).[27] In addition the US estimate of potential donors was not limited to persons treated with mechanical ventilation,[27] whereas our algorithm excluded 43% of otherwise eligible deaths that occurred in patients without mechanical ventilation.

Our findings that there may be only 3 to 5 potential HIV-infected donors in Canada per year bring into question whether routinely offering deceased organ donation to severely brain injured HIV-infected persons is warranted. There is no reliable information about the number of HIV-infected patients with end organ failure who might benefit from transplantation due to limitations of existing national waitlist data, privacy regulations, and probable disparities in referral of HIV-infected persons with end organ failure for transplantation. Determination of the number of such patients as well as assessment of their willingness to accept organs from HIV-infected donors should be prioritized to better understand the potential impact of routinely expanding organ donation services to HIV-infected persons. Understanding this information is also important from a cost perspective because HIV-positive donors may infrequently be multiorgan donors.

Although we support offering all potential organ donors the opportunity to donate, there are significant uncertainties and challenges with routinely offering organ donation to HIV-positive persons. Uncertainties include a lack of information about the long-term transplant outcomes and the potential to accelerate HIV infections in the recipient due to a superinfection with a resistant or more aggressive viral strain remains a consideration even with the use of nonviremic donors because the transplanted organ may serve as a reservoir for latent virus. Other challenges include the potential risk of allowing HIV-infected organs into the general organ pool and the need for safeguards to prevent accidental disease transmission, as well as the need to ensure that recipients receive appropriate informed consent regarding the risk and benefits of accepting an organ from an HIV-infected donor. Although there are web-based tools to help understand the risk and benefits of accepting an HIV-infected organ for a HIV-infected transplant candidate, it still will be challenging to ensure that patients understand the risks and uncertainties of transplantation of an organ from an HIV-infected donor.[28] The decision to proceed with organ donation from an HIV-infected donor in Canada remains a medical decision and there may be select cases where transplantation of an HIV-infected organ by exceptional distribution is warranted as in our case. Further research to understand the need for organ transplantation among HIV-infected Canadians, the amount of potential organs, and the willingness of recipients to accept HIV-infected organs appears relevant to inform Canadian and Institutional policy makers.

REFERENCES

1. Deeks SG, Phillips AN. HIV infection, antiretroviral treatment, ageing, and non-AIDS related morbidity. *BMJ*. 2009;338:a3172.
2. Samji H, Cescon A, Hogg RS, et al. Closing the gap: increases in life expectancy among treated HIV-positive individuals in the United States and Canada. *PLoS One*. 2013;8:e81355.
3. Stock PG, Barin B, Murphy B, et al. Outcomes of kidney transplantation in HIV-infected recipients. *N Engl J Med*. 2010;363:2004–2014.
4. Trullas JC, Cofan F, Tuset M, et al. Renal transplantation in HIV-infected patients: 2010 update. *Kidney Int*. 2011;79:825–842.

5. Kumar MS, Sierka DR, Damask AM, et al. Safety and success of kidney transplantation and concomitant immunosuppression in HIV-positive patients. *Kidney Int*. 2005;67:1622–1629.
6. Muller E, Barday Z, Mendelson M, et al. HIV-positive-to-HIV-positive kidney transplantation–results at 3 to 5 years. *N Engl J Med*. 2015;372:613–620.
7. HIV organ policy equity act. 2013;PL 113–151.
8. HIV monitoring quarterly report for British Columbia: First quarter 2016. http://www.cfenet.ubc.ca/publications/centre-documents/hiv-monitoring-quarterly-reports-first-quarter-2016. Updated 2016.
9. Public Health Agency of Canada. Chapter 12: Primary HIV antiretroviral drug resistance in Canada (2010). http://www.phac-aspc.gc.ca/aids-sida/publication/epi/2010/12-eng.php. Updated 2010.
10. Blumberg EA, Rogers CC, AST Infectious Diseases Community of Practice. Human immunodeficiency virus in solid organ transplantation. *Am J Transplant*. 2013;13(Suppl 4):169–178.
11. Canadian Institute for Health Information. Data quality documentation for external users: Discharge abstract database. 2010–2011… 2011.
12. Rose C, Nickerson P, Delmonico F, et al. Estimation of potential deceased organ donors in Canada. *Transplantation*. 2016;100:1558–1563.
13. Organ procurement and transplantation network policies. https://optn.transplant.hrsa.gov/media/1200/optn_policies.pdf. Updated 2016.
14. Canadian Standards Association. CAN/CSA-Z900.1-12 - cells, tissues, and organs for transplantation: General requirements. 2012;1.
15. American Medical Association. International classification of diseases, 9th revision, clinical modification. 1997.
16. Safety of human cells, tissues and organs for transplantation regulations. 2015;SOR/2007-118.
17. Health Canada. Guidance document for cell, tissue and organ establishments - safety of human cells, tissues and organs for transplantation. http://www.hc-sc.gc.ca/dhp-mps/brgtherap/reg-init/cell/cto_gd_ld-eng.php#a210. Updated 2012.
18. Canadian Institute for Health Information. Canadian organ replacement register. 2014.
19. Trullas JC, Cofan F, Barril G, et al. Outcome and prognostic factors in HIV-1-infected patients on dialysis in the cART era: a GESIDA/SEN cohort study. *J Acquir Immune Defic Syndr*. 2011;57:276–283.
20. Ragni MV, Eghtesad B, Schlesinger KW, et al. Pretransplant survival is shorter in HIV-positive than HIV-negative subjects with end-stage liver disease. *Liver Transpl*. 2005;11:1425–1430.
21. Kouri V, Khouri R, Aleman Y, et al. CRF19_cpx is an evolutionary fit HIV-1 variant strongly associated with rapid progression to AIDS in Cuba. *EBioMedicine*. 2015;2:244–254.
22. Hong FF, Mellors JW. Changes in HIV reservoirs during long-term antiretroviral therapy. *Curr Opin HIV AIDS*. 2015;10:43–48.
23. Cornelissen M, Pasternak AO, Grijsen ML, et al. HIV-1 dual infection is associated with faster CD4+ T-cell decline in a cohort of men with primary HIV infection. *Clin Infect Dis*. 2012;54:539–547.
24. Public Health Agency of Canada. Summary: Estimates of HIV prevalence and incidence in Canada, 2011. http://www.phac-aspc.gc.ca/aidssida/publication/survreport/estimat2011-eng.php. Updated 2012.
25. Boyarsky BJ, Durand CM, Palella FJ Jr, et al. Challenges and clinical decision-making in HIV-to-HIV transplantation: Insights from the HIV literature. *Am J Transplant*. 2015;15:2023–2030.
26. Richterman A, Blumberg E. The challenges and promise of HIV-infected donors for solid organ transplantation. *Curr Infect Dis Rep*. 2015;17:471. -015-0471-z.
27. Boyarsky BJ, Hall EC, Singer AL, et al. Estimating the potential pool of HIV-infected deceased organ donors in the United States. *Am J Transplant*. 2011;11:1209–1217.
28. Johns Hopkins IRD kidney transplant calculator. http://www.transplantmodels.com/ird/. Updated 2012.

Research Highlights

Fadi Issa, MRCS, DPhil[1]

Interspecies Chimerism With Mammalian Pluripotent Stem Cells

Jun Wu, Aida Platero-Luengo, Masahiro Sakurai, et al. *Cell*. 2017;168(3):473–486.e15.

One of the most significant challenges in transplantation is the shortage of donor organs. Strategies addressing this issue have focused on increasing donation rates, improving transplanted organ longevity, and alternative sources such as xenotransplantation. However, none of these approaches are able to overcome the immune barrier. An ideal alternative would be to replace diseased organs with autologous functioning tissues or organs. Tissue engineering techniques have been investigated extensively in this regard, attempting to use biological scaffolds seeded with autologous stem cells, such as induced pluripotent stem cells from the patient.[1] However, this approach has had limited success, principally because it is challenging to produce three-dimensional vascularized organs composed of multiple tissues. In addition, there are limits to the use of nonembryonic stem cells that may not have the full capacity for multiple cell differentiation.

A more successful approach may be to use the same regenerative medicine techniques to grow organs de novo directly from stem cells within host animals, without the use of a scaffold. One possible method is interspecies blastocyst complementation, which is currently used in order to create animal models that can model human diseases, facilitate drug metabolism investigations, or create organs and tissues. The introduction of cultured pluripotent stem cells into a developing embryo is possible but is highly dependent on timing of chimera formation and species restriction. Consequently, the majority of reported models that have focused on mice or rats as hosts have been largely unsuccessful due to biological and immunological differences between humans and rodents. The study from Wu and co-workers aimed to address this gap in knowledge by assessing ungulates as host species, in particular focusing on the potential for human stem cells to create chimeras within pigs and cattle.[2] The authors propose a platform based on CRISPR-Cas9–mediated zygote genome

Received 7 February 2017. Revision received 8 February 2017.

Accepted 9 February 2017.

[1] Nuffield Department of Surgical Sciences, University of Oxford, John Radcliffe Hospital, Oxford OX3 9DU, United Kingdom.

The author declares no funding or conflicts of interest.

Correspondence: Fadi Issa,MRCS, DPhil,Nuffield Department of Surgical Sciences, University of Oxford, John Radcliffe Hospital, Oxford OX3 9DU, United Kingdom. (fadi.issa@nds.ox.ac.uk).

ISSN: 0041-1337/17/10104-671

DOI: 10.1097/TP.0000000000001687