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Briefing Paper

Guidance on Explaining Risk Related to Use of U.S. PHS Increased Risk Donor Organs When Considering Organ Offers

OPTN/UNOS Ad Hoc Disease Transmission Advisory Committee

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Affected Policies: *None*
Sponsoring Committee: *OPTN/UNOS Ad Hoc Disease Transmission Advisory Committee*
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Executive Summary

In July 2013, the U.S. Public Health Service (PHS) published new guidelines for reducing human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV) transmission through organ transplantation. These new guidelines, called “increased risk” guidelines, replaced earlier guidelines from 1994 called “high risk” criteria. The phrase “increased risk” refers to the donor characteristics that could place the potential recipient at increased risk of disease transmission from one or more of these three viruses. The phrase is not a reference to organ quality, nor should it be interpreted to be a predictor of graft survival.

A potential organ donor may be labeled as increased risk for a variety of different exposures, and these exposures carry different risks of transmitting recent infection with HIV, HBV, or HCV. Helping transplant patients understand the potential risks of disease transmission from increased risk organs versus refusing an organ for transplant is an important, but challenging topic. The transplant community has requested assistance explaining relative risk of disease transmission involving increased risk organ donors to potential organ recipients. The OPTN/UNOS Ad Hoc Disease Transmission Advisory Committee (DTAC), in collaboration with the American Society of Transplantation (AST), the American Society of Transplant Surgeons (ASTS), and the North American Transplant Coordinators Organization (NATCO), together knowns as the Joint Societies, developed this document to inform and facilitate conversations between transplant team members and their patients. The guidance profiles recent peer reviewed literature and OPTN data to describe the risk of undetected disease transmission from PHS increased risk organ donors.

This guidance document will help transplant clinicians in decision-making upon receiving organ offers from OPOs, and allow them to consider the risk of undetected HIV, HBV, or HCV infection in the donor. This guidance also provides speaking points to transplant program staff for patient education. This will guide the patient’s decision-making process regarding whether the patient may want to consider an organ from an increased risk donor at the time of organ offer.

What problem will this proposal address?

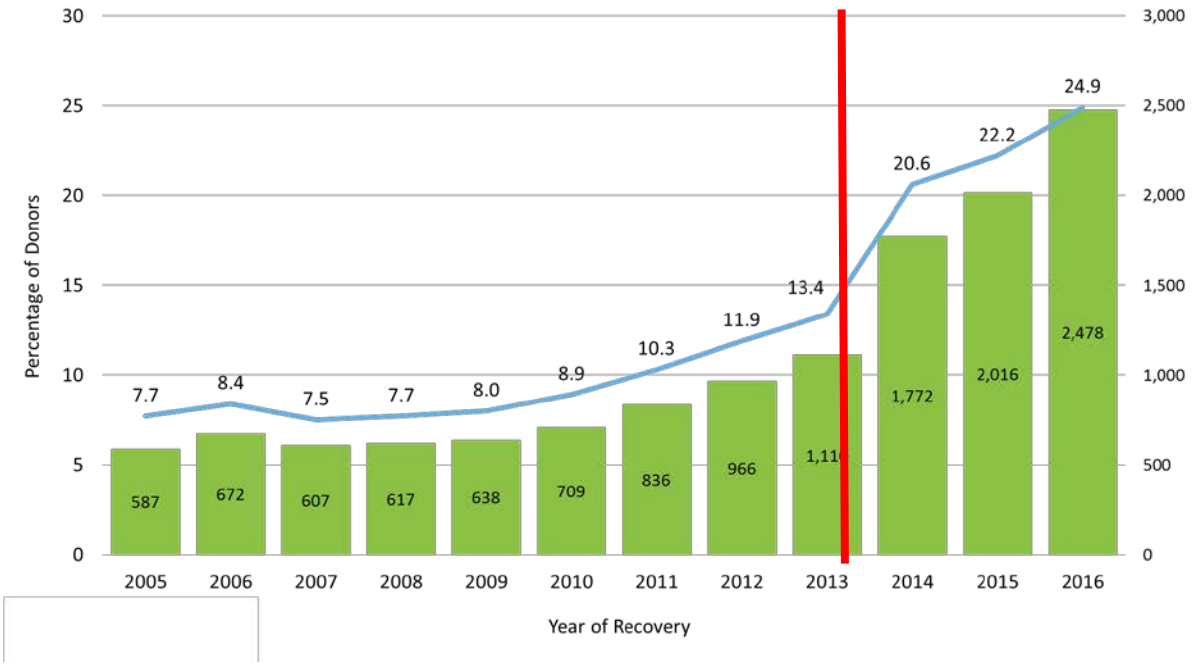
In July 2013, the U.S. PHS published new guidelines for reducing HIV, HBV, and HCV transmission through organ transplantation.[1] These new guidelines, called “increased risk” guidelines, replaced earlier guidelines from 1994 called “high risk” criteria. The phrase “increased risk” refers to the donor characteristics that could place the potential recipient at increased risk of disease transmission from one or more of these three viruses. The climbing prevalence of increased risk behaviors, and to some degree the change in increased risk guidelines, have resulted in more deceased organ donors over time that are labeled as increased risk for HIV, HBC, and HCV. Many transplant programs are reluctant to use organs from deceased donors that meet increased risk criteria due to perceptions that “increased risk” may translate to poor recipient or graft survival.[2]However, this label phrase is not a reference to organ quality, nor should it be interpreted to be a prediction of graft survival. This proposal will convey accurate information to the transplant community about the risk of HIV, HBV, and HCV in increased risk deceased organ donors. Additionally, the proposal will convey the risk of undetected HIV, HBV, or HCV infection in light of modern disease testing.

Why should you support this proposal?

Helping transplant patients understand the potential risks of disease transmission from increased risk donor organs versus refusing an organ for transplant is an important, but challenging topic. The transplant community has requested assistance how to best explain relative risk of disease transmission involving increased risk organ donors to potential organ recipients.[3] Data from the OPTN in Figure 1 illustrate the upward trend in increased risk (previously referred to as “high risk”) organ donors during the period of 2005 to 2016.[4]

[1] Seem, DL, Lee, I, Umscheid, CA, Kuehnert, MJ, "United States Public Health Service. PHS Guideline for Reducing Human Immunodeficiency Virus, Hepatitis B Virus, and Hepatitis C Virus Transmission Through Organ Transplantation," *Public Health Reports* 128, no. 4 (2013): 247-343.
[2] Volk, ML, Wilk, A, Wolfe, C, Kaul, DR, "The 'PHS Increased Risk' Label is Associated with Non-Utilization of Hundreds of Organs per Year," (presentation, American Transplant Congress. Boston, MA, June 11-15, 2016)
[3] Gordon, EJ, Mullee, J, Beauvais, N, Warren, E, Theodoropoulos, N, McNatt, G, et al, "Education and Informed Consent About Increased Risk Donor Kidneys: A National Survey of Non-physician Transplant Providers," *Transplant Infectious Disease* 16, no. 2 (2014): 251-260.
[4] Based on OPTN data as of April 7, 2017

Figure 1 – CDC High Risk and PHS Increased Risk Deceased Organ Donors Recovered 2005-2016



The OPTN/UNOS policy changes to include increased risk criteria were effective on October 1, 2013 (noted by red line). During the period between October 1, 2013 to February 1, 2014, OPOs could use either risk criteria so long as the transplant programs receiving offers were informed which criteria were used. Since February 1, 2014, OPOs must use the PHS increased risk criteria during deceased organ donor evaluations.

Research on acceptance practices between 2005 and 2014 noted variation in the use of organs from deceased donors meeting increased risk criteria. Depending on organ type, between 7.4 to 16.4% of transplant programs did not use any increased risk donors. During the same period, between 16.4 to 42.3% of transplant programs performed transplants using increased risk donor organs in at least 10% of their recipients.[5] Other data demonstrated that the level of risk is not uniform across all increased risk organ donors. For example, the residual risk identified through HCV ELISA screening for donors with a history of intravenous drug use was 300.6 per 10,000 donors (3%), compared to only 0.26 per 10,000 donors (0.002%) with a history of hemophilia.[6] After reviewing these data sets, DTAC feels the need for guidance on this issue is greater than ever. DTAC believes that enhanced understanding of disease transmission risk involving organs from increased risk donors may lead to a greater number of organ transplants that may otherwise be discarded, or reduce the amount of time for organ allocation efforts.[7]

How was this proposal developed?

The DTAC formed a working group (the Joint Society Working Group-JSWG) with representatives from the American Society for Transplantation (AST), American Society of Transplant Surgeons (ASTS), and

[5] Ison, MG, "Risky Business: Does All Risky Behavior Increase Risk Equally," Presentation, American Transplant Congress, Philadelphia, PA, May 5, 2015.

[6] Kucirka, LM, Sarathy, H, Govindan, P, Wolf, JH, Ellison, TA, Hart, LJ, et al, "Risk of Window Period HIV Infection in High Infectious Risk Donors: Systematic Review and Meta-analysis", *American Journal of Transplantation* 11, no. 6 (2011):1176-1187.

[7] Volk, ML, Wilk, A, Wolfe, C, Kaul, DR, "The 'PHS Increased Risk' Label is Associated with Non-Utilization of Hundreds of Organs per Year," (presentation, American Transplant Congress. Boston, MA, June 11-15, 2016).

North American Transplant Coordinators Organization (NATCO) to develop this guidance document.[8] This is similar to the collaborative approach used to develop the *Guidance on Zika Virus* by AST, ASTS, OPTN, and the Centers for Disease Control and Prevention in 2016.[9]

DTAC members drafted guidance in the spring of 2016 and shared it with the JSWG. The JSWG and members of DTAC met by conference call on several occasions during the spring and summer of 2016 to review the document. Numerous enhancements were made to the document, including the addition of:

- Executive Summary with speaking points for transplant program staff.
    - Members of the JSWG felt "speaking points" for transplant program staff would be a valuable addition to the document. These speaking points were added to help guide discussions with transplant program staff and patients.
- Graphic renderings to describe the risk of disease transmission compared to the risk of death from other causes.
    - Members of the JSWG felt expressing the risk of disease transmission from an increased risk donor organ verses the risk of death in layman's terms was a valuable addition. This will help patients understand the relative risk of disease transmission in practical terms they may be already familiar.
- Risk of declining an organ from a donor that met PHS guidelines for increased risk of HIV, HBV and HCV infection versus remaining on the waiting list.
    - This is an important element of informed decision-making. Transplant staff and patients need to carefully weigh the risk of disease transmission versus continuing to wait for another organ offer, especially if the patient's severity of illness is increasing.
- Consequences of transmission of HIV, HBV, and HCV.
    - There are many misconceptions to HIV, HBC, and HCV infection. Much of this is due to historical understanding and stigma, and does not consider recent medical advances in the treatment and management of these viral infections.
- Risk of acquiring HCV on hemodialysis.
    - Hemodialysis carries its own risk of HCV transmission. Transplant staff and patients should carefully weigh this risk versus accepting an organ from an increased risk donor.
- Limitations of current screening technology.
    - Donor testing is not foolproof and subject to other possible errors. False negative results for Nucleic Acid Testing (NAT), while rare, have occurred. In addition, determining if a potential donor should be classified as actually having a risk behavior of interest is challenging. In the setting of deceased donation, information is typically obtained from family members or friends who know the donor. The information gathering is intended to be very thorough, but may be limited if individuals interviewed were unaware of the donor's behaviors.

Over the course of the JSWG's discussions, one member felt this guidance document was a good opportunity to define what "increased risk" is more specifically and simply. The JSWG discussed the accuracy and understanding of the phrase. Since the term "increased risk" is derived from the federal regulation, the JSWG ultimately decided that it was inappropriate to give an alternate definition at this time. Further, some members felt it was outside the purview of the OPTN to provide this definition. The JSWG deferred to the definition appearing in the PHS guidelines.[10]

Following a final review by the JSWG in November 2016, the group supported review by AST, ASTS, and NATCO. These societies reviewed the document in December 2016 and each supported the document without changes. DTAC reviewed this document in January 2017 and considered minor edits to clarify some elements of the document. These included clarifying the risk of undetected HIV, HBV, or HCV in the setting of donor death secondary to drug overdose. Edits were also made to display risk of undetected

[8] The purpose of the JSSC is to provide clinical input for OPTN projects with the potential to direct or prescribe medical care.
[9] https://optn.transplant.hrsa.gov/news/guidance-on-zika-virus/
[10] Seem DL, Lee I, Umscheid CA, Kuehnert MJ. "PHS Guideline for Reducing Human Immunodeficiency Virus, Hepatitis B Virus, and Hepatitis C Virus Transmission Through Organ Transplantation", *Public Health Reports* 128, no 4, (2013): 247-343.

disease transmission both as a ratio and as a percentage. DTAC unanimously supported moving forward to solicit public comment on this guidance (Yes - 13, No - 0, Abstain - 0).

How well does this proposal address the problem statement?

The intent of the U.S. PHS increased risk criteria is to identify *recently* infected organ donors that would appear negative on serologic testing, yet be capable of inadvertently transmitting the HIV, HBV, or HCV to transplant recipients. As shown in Figure 1, the number of deceased organ donors that meet U.S. PHS criteria for increased risk of disease transmission continues to rise. Additionally, the percentage of donors classified as increased risk donors who had organs procured increased from 12.3% to 19.5%, and exceeded 25% in 14 OPOs.[11] The exact reasons for these increases are unknown. The rise may be related to increased numbers of potential donors who died from opioid overdoses, or from the change in the criteria used to screen deceased organ donors. Additionally, the 2013 criteria are also designed to screen for HIV, HCV and HBV, whereas the 1994 criteria was designed to screen for only HIV.

Persons who developed HIV, HBV, or HCV several months prior to organ donation would be identified by serological (antibody) tests performed on virtually all potential donors.[12] NAT, which has been used with increasing frequency over the last decade, is now required in OPTN/UNOS policy (for HCV and HIV) for all increased risk donors.[13] The NAT window period is very short, so NAT testing becomes positive much closer to the time of infection compared to serological testing. Table 1 below describes the time from infection to detection associated with different serological or NAT methods.[14]

Table 1: Estimates of window period length for different testing methods*

Pathogen	Standard Serology	Enhanced Serology (fourth generation or combined antibody-antigen tests)	Nucleic Acid Testing
HIV	17-22 days (5-8)	~7-16 days (9, 10)	5-6 days (5,6)
HCV	~70 days (5, 8, 11)	~40-50 days (12-14)	3-5 days (5, 11)
HBV	35-44 days (15, 16)	Not applicable	20-22 days (8,15)

*Window period = time to detection of infection by a specific testing method. HIV, HCV, and HBV NAT data are listed for the most sensitive NAT currently used in blood-donor screening (Gen Probe TMA for HIV and HCV, and Roche Cobas MPX for HBV on individual donation); the window period will be longer if less sensitive NAT is used for donor screening. HIV- and HCV-antibody and HBV surface antigen data are for tests licensed and current used in blood-donor screening (enzyme immunoassays or chemiluminescent assays). Window period estimates for fourth generation assays are derived from more limited data and show substantial variation with different manufacturer's test kits.

With this in mind, the increased risk classification should be considered in context with the HIV, HBV, and HCV testing currently available. Table 2 below describes the estimated risk of window period infection (remote infection would result in a positive antibody test) expressed per 10,000 donors.[15, 16] The ELISA column refers to the number of donors in the serological window period based on serology (antibody) testing only; the NAT column refers to the number of donors with negative NAT who are in the NAT

[11] Kucirka, LM, Bowring,,MG, Massie, AB, Luo, X, Nicholas, LH, Segev, DL, "Landscape of Deceased Donors Labeled Increased Risk for Disease Transmission Under New Guidelines. "*American Journal of Transplantation* 15, no. 12 (2015): 3215-3223.

[12] Seem, DL, Lee, I, Umscheid, CA, Kuehnert, MJ, "United States Public Health Service. PHS Guideline for Reducing Human Immunodeficiency Virus, Hepatitis B Virus, and Hepatitis C Virus Transmission Through Organ Transplantation," *Public Health Reports* 128, no. 4 (2013)

[13] OPTN Policy 2.9 (*Required Deceased Donor Infectious Disease Testing*), https://optn.transplant.hrsa.gov/media/1200/optn_policies.pdf#nameddest=Policy_02

[14] Humar A, Morris M, Blumberg E, Freeman R, Preiksaitis J, Kiberd B, et al, "Nucleic Acid Testing (NAT) of Organ Donors: Is the 'Best' Test the Right Test? A Consensus Conference Report," *American Journal of Transplantation* 10, no. 4 (2010):889-899.

[15] Kucirka, LM, Sarathy, H, Govindan, P, Wolf, JH, Ellison, TA, Hart, LJ, et al, "Risk of Window Period Hepatitis-C Infection in High Infectious Risk Donors: Systematic Review and Meta-analysis," *American Journal of Transplantation* 11, no. 6 (2011):1188-1200.

[16] Kucirka, LM, Sarathy, H, Govindan, P, Wolf, JH, Ellison, TA, Hart, LJ, et al, "Risk of Window Period HIV Infection in High Infectious Risk Donors: Systematic Review and Meta-analysis", *American Journal of Transplantation* 11, no. 6 (2011):1176-1187.

window period. NAT reduces the risk of serological window period infection by about 10-fold for most exposures.

Table 2: Estimated risk of window period infection (per 10,000 donors)

Risk per 10,000 donors	HIV ELISA	HIV NAT	HCV ELISA	HCV NAT
Men who have sex with men	10.2 (0.10%)	4.2 (<0.1%)	32.5 (0.33%)	3.5 (<0.1%)
IV drug users	12.1 (0.12%)	4.9 (<0.1%)	300.6 (3%)	32.4 (0.32%)
Persons with hemophilia	0.086 (<0.01%)	0.035 (<0.01%)	0.26 (<0.1%)	0.027 (<0.01%)
Commercial sex worker	6.6 (<0.1%)	2.7 (<0.1%)	114.9 (1.2%)	12.3 (0.12%)
Sex with a partner in above categories	0.7 (<0.1%)	0.3 (<0.1%)	114.9 (1.2%)	12.3 (0.12%)
Blood product exposure	1.5 (<0.1%)	0.6 (<0.1%)	4 (<0.1%)	0.4 (<0.1%)
Incarceration	2.3 (<0.1%)	0.9 (<0.1%)	7.2 (<0.1%)	0.8 (<0.1%)

The Committee believes this guidance document will aid transplant program staff in two ways. The data analyzed for this guidance document will help transplant clinicians in decision-making during organ offers from OPOs, and allow them to consider the risk of undetected HIV, HBV, or HCV infection in the donor. This guidance document also provides speaking points to transplant program staff for patient education. This will guide the decision-making process whether the patient may want to consider an organ from an increased risk donor at the time of organ offer. This document is not intended to offer guidance on informed consent discussions or effective practices on disclosure of donor information by transplant programs.

Was this proposal changed in response to public comment?

Public comment was sought on this guidance document during a special 30-day period from March 27, 2017 to April 25, 2017. This proposal was widely supported in public comment, both in response to a national webinar in April 2017, and presentations to seven OPTN committees. Professional societies and individuals also submitted comments on the proposal online. Themes identified in public comment included:

- The guidance document responds to a significant community need.
- Add data regarding known donor-derived HIV, HBV, HCV cases.
- More prominently show the benefits of accepting an organ from a PHS increased risk donor as compared to the low risk of undetected disease transmission.
- Add pediatric-specific content.
- Clarify post-implementation monitoring questions regarding changes in use of PHS increased risk donor organs, and the comparison of outcomes between PHS increased risk versus non-PHS increased risk donor organs.
- Add the risk of death associated with remaining on the waitlist versus risk of death associated with organ transplantation from a PHS increased risk organ donor.

In response to the feedback, the DTAC made several modifications to the guidance document. First, the DTAC clarified that the overall risk window period infection is low, and the benefit of transplantation may outweigh the risk of undetected HIV, HBV, or HCV. The DTAC determined it was not feasible to add granular data on risk for individual organs in large part due to regional differences in waitlist mortality. Content was added to reflect national data on the risk of waitlist mortality for kidney transplant candidates, as these candidates comprise the largest portion of the waitlist.

DTAC also updated some figures and data used throughout the guidance document, including:

- Figure 1 to reflect 2016 data. These data were only available up through 2015 prior to public comment.
- Figure 1 in the guidance document for clarity, and to show only the risk of undetected HCV due to intravenous drug use (IVDU).
- Clarification that the risk of death from a traffic accident in Figure 2 is lifetime risk.

- Addition of known donor-derived cases of HIV, HBV, and HCV. The most current data were added following presentation at the 2017 American Transplant Congress.

The DTAC also updated content to more clearly explain the risk of the window period for HCV infection. The document also now emphasizes that risk-benefit decisions should be individualized for each transplant candidate, and includes pediatric-specific guidance. Finally, the DTAC made a few non-substantive changes for style, clarity, and consistency.

Some commenters requested DTAC's recommendations on repeat donor testing to mitigate the risk of undetected HIV, HBV, or HCV infection from exposure in close proximity to procurement, and post-transplant recipient monitoring. DTAC did not feel there was consensus on either topic and such changes were outside the scope of this project. DTAC recommends that OPOs and transplant programs defer to their institutional protocols for repeat donor testing and post-transplant monitoring.

Several professional groups responded in public comment that Figure 2 of the guidance document (Risk of Death from a Traffic Accident) did not add value to the document. This graphic was added following recommendations from the JSWG. The OPTN/UNOS Patient Affairs Committee (PAC) felt strongly this graphic was a very informative. Further, PAC felt laypersons could easily understand this example of risk as compared to risk of undetected disease transmission from a PHS increased risk donor. As a result, the graphic was not excluded from the final document.

The OPTN/UNOS Transplant Coordinators Committees and PAC inquired if cases of HIV, HBV, and HCV transmission involving PHS increased risk donors were collected by the OPTN. Both groups were pleased to know this data has been collected by the OPTN since 2008 and will be considered when DTAC conducts its biennial review of this guidance document.

DTAC approved this guidance and recommended consideration by the OPTN/UNOS Board of Directors during its June 2017 meeting by an electronic vote (Yes - 14, No - 0, Abstain - 0).

Which populations are impacted by this proposal?

This guidance document will be an optional resource for transplant programs. Guidance documents from the OPTN are not required to be used, and do not carry the weight of policies or bylaws. The Committee hopes this guidance will lead to a decline in organ wastage, an increase the number organs transplanted, and change in acceptance practices at those transplant programs that do not routinely consider organs from increased risk donors.

How does this proposal impact the OPTN Strategic Plan?

1. *Increase the number of transplants:* Communicating the risk related to accepting an organ from an increased risk donor in a way that is easily understood and applied in everyday terms will help transplant candidates make more educated decisions based upon their own relative risk tolerance. This education may lead to an increase in the number of increased risk organs utilized when these offers are considered in conjunction with donor NAT results.
2. *Improve equity in access to transplants:* There is no impact to this goal
3. *Improve waitlisted patient, living donor, and transplant recipient outcomes:* There is no impact to this goal
4. *Promote living donor and transplant recipient safety:* There is no impact to this goal
5. *Promote the efficient management of the OPTN:* There is no impact to this goal

How will the OPTN implement this proposal?

Due to community interest of and the complexity surrounding this topic, an instructional program would be developed once the guidance is approved by the Board. UNOS anticipates that there will be questions from the community related to information within the guidance, and thus will provide an opportunity for

subject matters experts to speak on the topic and answer those questions. UNOS will communicate this new information through TransplantPro and the OPTN website.

How will members implement this proposal?

Transplant Hospitals

Transplant hospitals may elect to use this as a resource for staff at their transplant programs. Use of this document is optional and is intended to provide information that can be used in discussions with patients and when considering organ offers. A small amount of resources may be required to disseminate this information to transplant program staff.

The Fiscal Impact Advisory Group reviewed this proposal and determined there is no substantial financial impact, as any changes can be completed within normal operations. Implementation is estimated at 1-2 months for most programs, and is likely to include staff time to adjust protocols for patient discussions and to update any existing education. Staff time is variable dependent on the size of the transplant program and existing protocol. Additionally, the number of transplants may go up if programs accept a greater number of increased risk organs, but costs are expected to be reimbursed by insurance.

Organ Procurement Organizations

As a result of this guidance, OPOs may see a small increase in the number of organs recovered for transplant. This may be useful in those Donation Service Areas (DSAs) with higher numbers of increased risk deceased organ donors. The Fiscal Impact Advisory Group reviewed this proposal and determined the guidance would have minimal to no impact for OPOs.

Will this proposal require members to submit additional data?

No additional data submission will be required at this time.

How will members be evaluated for compliance with this proposal?

Guidance from the OPTN does not carry the weight of policies or bylaws. Therefore, members will not be evaluated for compliance with this document.

How will the sponsoring Committee evaluate whether this proposal was successful post implementation?

It will be challenging to establish causation of a change in organ acceptance practices based on this guidance document and corresponding education/outreach. In order to assess if the guidance and related education/outreach has positively impacted organ donation and transplantation, the Committee will monitor the number of organs recovered and transplanted from deceased organ donors that meet U.S. PHS increased risk criteria. UNOS staff will report this information to the Committee at six month intervals following approval by the Board. The Committee will also review this guidance every two years, or more frequently if pertinent discoveries in transplant infectious disease are encountered, to ensure clinical relevance of this guidance. This guidance will be updated as needed based on review by experts in the field.

Guidance Document

RESOLVED, that the guidance document entitled *Understanding the Risk of Transmission of HIV, Hepatitis B, and Hepatitis C from U.S. PHS Increased Risk Donors*, as set forth below, is hereby approved, effective June 6, 2017.

Understanding the Risk of Transmission of HIV, Hepatitis B, and Hepatitis C from U.S. PHS Increased Risk Donors

Summary and Goals

In July 2013, the U.S. Public Health Service (PHS) published new guidelines for reducing human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV) transmission during organ transplantation.[17] The federal regulation governing the operations of the Organ Procurement and Transplantation Network (OPTN Final Rule) requires that the OPTN/UNOS Board of Directors develops policies that are consistent with the recommendations of the Centers for Disease Control and Prevention (CDC) regarding testing potential organ donors and following transplant recipients to prevent donor-to-recipient transmission of infection. Subsequently, the Board voted to modify existing OPTN/UNOS policies defining which groups qualify as increased risk donors, and to require nucleic acid testing (NAT) of all donors for HCV. Additionally, the Board required NAT or antigen/antibody (Ag/Ab) combination HIV testing for increased risk donors.

Since implementation of the new policies, the number of potential deceased donors classified as increased risk has increased to almost one in five donors nationally.[18] Research studies have demonstrated that organs from donors classified as increased risk are less likely to be used than organs from non-increased risk donors.[19,20] This finding persists despite the fact that post-transplant graft and patient survival with increased risk organs is equal to or better than that with non-increased risk organs.

When a person becomes infected, it takes some time for the infection to be detected in the body; this is called the “window period”. The use of NAT markedly shortens the window period. Survey data have demonstrated that most non-physician transplant providers would like further education regarding the risk of infection associated with increased risk donors. Survey data also show that patients have limited understanding and many misconceptions regarding the definition and implications of the increased risk designation.[21, 22] Accordingly, the OPTN/UNOS Disease Transmission Advisory Committee (DTAC), the American Society of Transplantation (AST), the American Society of Transplant Surgeons (ASTS), and the North American Transplant Coordinators Organization (NATCO) provide this guidance document to

[17] Seem, DL, Lee, I, Umscheid, CA, Kuehnert, MJ, "United States Public Health Service. PHS Guideline for Reducing Human Immunodeficiency Virus, Hepatitis B Virus, and Hepatitis C Virus Transmission Through Organ Transplantation," *Public Health Reports* 128, no. 4 (2013): 247-343.
[18] Kucirka, LM, Bowring, MG, Massie, AB, Luo, X, Nicholas, LH, Segev, DL, "Landscape of Deceased Donors Labeled Increased Risk for Disease Transmission Under New Guidelines,” *American Journal of Transplantation* 15, no. 12 (2015): 3215-3223.
[19] Duan, KI, Englesbe, MJ, Volk ML, "Centers for Disease Control 'High-Risk' Donors and Kidney Utilization," *American Journal of Transplantation* 10, no. 2 (2010):416-420.
[20] Volk, ML, Wilk, A, Wolfe, C, Kaul, DR, "The 'PHS Increased Risk' Label is Associated with Non-Utilization of Hundreds of Organs per Year," (presentation, American Transplant Congress. Boston, MA, June 11-15, 2016).
[21] Gordon, EJ, Mullee, J, Beauvais, N, Warren, E, Theodoropoulos, N, McNatt, G, et al, "Education and Informed Consent About Increased Risk Donor Kidneys: A National Survey of Non-physician Transplant Providers," *Transplant Infectious Disease* 16, no. 2 (2014): 251-260.
[22] Gordon, EJ, Reddy, E, Ladner, DP, Friedewald, J, Abecassis, MM, Ison, MG, "Kidney Transplant Candidates' Understanding of Increased Risk Donor Kidneys: A Qualitative Study," *Clinical Transplantation* 26, no. 2 (2012):359-368.

help transplant professionals better understand the low risk of window period infection present in PHS increased risk donors.

This resource tool is intended to give educational support for Organ Procurement Organizations (OPOs) and transplant hospitals and is for voluntary use by members. This resource is not OPTN policy, so it does not carry the monitoring or enforcement implications of policy. It is not an official guideline for clinical practice, nor is it intended to be clinically prescriptive or to define a standard of care.

CONTENTS

Executive Summary

The following summary is provided to help transplant professionals accurately counsel potential organ transplant candidates on the relative risks associated with donors classified as PHS increased risk.

- The increased risk donor classification serves principally to identify those donors most at risk of having recent infection with HIV, HBV, or HCV.
- Increased risk donor classification does not mean that the organ is of lower quality.
- Choosing to accept an organ from an increased risk donor entails balancing donor and recipient characteristics. In many cases, the risks of declining such an organ offer may be greater than the risk of donor-derived viral infection.
- The risk of window period infection with HIV, HBV, or HCV, and therefore the risk of virus transmission from donor to recipient, is extremely small if a risk behavior occurred more than three weeks prior to NAT.
- There is wide variation in viral transmission risk even within donors classified as increased risk donors. Donors with a history of incarceration or less safe sexual practices are generally much lower risk than donors with a history of intravenous drug use (IVDU).
- Even under the highest risk behavior, the risk of HIV, HBV, or HCV transmission from a NAT negative donor organ is low (around 1% or less).
- Ultimately, with appropriate counselling and informed consent, we aim to maximize organ availability.

Window Periods with Serologic and Nucleic Acid Testing

Persons who had developed a HIV, HBV, or HCV infection several months prior to organ donation would be discovered by the routine serological (antibody) tests performed on all potential donors. However, there is the chance that exposure to HIV, HBV, or HCV in the days immediately prior to death could not be detected by serological (antibody) tests due to insufficient amount of antibodies against a specific virus. Additionally, substantial blood loss and hemodilution can also create an environment for false negative serological test results.

The concept of "increased risk" (previously referred to as "high risk") donors was created to identify such a population of deceased or living donors potentially at risk for ***recent*** acquisition of HIV or viral hepatitis. These recently infected donors would therefore be capable of inadvertently transmitting the virus to recipients, yet would appear negative on serologic testing. Importantly, most increased risk donors will be truly negative for each of these infections, and the classification does in no way reflect the quality of the organs donated.

Nucleic Acid Testing, which has been used with increasing frequency over the last decade, is now required by OPTN Policy (for HCV and HIV) for all increased risk donors.[23] The NAT window period is very short, so NAT testing can result positive much closer to the time of infection compared to serological testing. Behaviors resulting in transmissible infection would have had to occur within ***5-6 days*** (HIV) or ***3-5 days*** (HCV) before blood samples were obtained for disease screening. The window period for HBV (***20-22 days***) is longer than for HIV and HCV. The Table 1 below describes the time from infection to detection associated with different serological or NAT methods.[24]

Table 1: Estimates of window period length for different testing methods*

Pathogen	Standard Serology	Enhanced Serology (fourth generation or combined antibody-antigen tests)	Nucleic Acid Testing
HIV	17-22 days (5-8)	~7-16 days (9, 10)	5-6 days (5,6)
HCV	~70 days (5, 8, 11)	~40-50 days (12-14)	3-5 days (5, 11)
HBV	35-44 days (15, 16)	Not applicable	20-22 days (8,15)

*Window period = time to detection of infection by a specific testing method. HIV, HCV, and HBV NAT data are listed for the most sensitive NAT currently used in blood-donor screening (Gen Probe TMA for HIV and HCV, and Roche Cobas MPX for HBV on individual donation); the window period will be longer if less sensitive NAT is used for donor screening. HIV- and HCV-antibody and HBV surface antigen data are for tests licensed and current used in blood-donor screening (enzyme immunoassays or chemiluminescent assays). Window period estimates for fourth generation assays are derived from more limited data and show substantial variation with different manufacturer's test kits.

Changes to Increased Risk Donor Definition

Prior to the 2013 PHS guideline, the 1994 guideline was intended to identify risk factors for HIV only. Table 2 below summarizes the differences between the 1994 and 2013 increased risk donor guidelines criteria:

Table 2: Comparison of 1994 CDC High Risk and 2013 U.S. PHS Increased Risk Guidelines

1994 Guideline	2013 Guideline
MSM* in the preceding 5 years	MSM in the preceding 12 months
Non-medical injection drug use in preceding 5 years	Non-medical injection drug use in preceding 12 months
Sex in exchange for money/drugs in preceding 5 years	People who have had sex in exchange for money or drugs in the preceding 12 months
People who have had sex with a person known or suspected to have HIV infection in the preceding 12 months	People who have had sex with a person known or suspected to have HIV, HBV, or HCV infection in the preceding 12 months
Women who have had sex with a man with a history of MSM behavior in the preceding 12 months	Women who have had sex with a man with a history of MSM behavior in the preceding 12 months
People who have had sex with a person who had sex in exchange for money or drugs in the preceding 12 months	People who have had sex with a person who had sex in exchange for money or drugs in the preceding 12 months

[23] OPTN Policy 2.9 (*Required Deceased Donor Infectious Disease Testing*)

[24] Humar A, Morris M, Blumberg E, Freeman R, Preiksaitis J, Kiberd B, et al, "Nucleic Acid Testing (NAT) of Organ Donors: Is the 'Best' Test the Right Test? A Consensus Conference Report," *American Journal of Transplantation* 10, no. 4 (2010):889-899.

1994 Guideline	2013 Guideline
People who have had sex with a person who injected drugs by intravenous, intramuscular, or subcutaneous route for nonmedical reasons in the preceding 12 months	People who have had sex with a person who injected drugs by intravenous, intramuscular, or subcutaneous route for nonmedical reasons in the preceding 12 months
A child who is ≤18 months of age and born to a mother known to be infected with, or at increased risk for HIV infection (should not be used)	A child who is ≤18 months of age and born to a mother known to be infected with, or at increased risk for HIV, HBV, or HCV infection
A child who has been breastfed in the past 12 months by a mother known to have or at risk for HIV infection	A child who has been breastfed within the preceding 12 months and the mother is known to be infected with, or at increased risk for, HIV infection
Inmates of correctional systems	People who have been in lockup, jail, prison, or a juvenile correctional facility for more than 72 consecutive hours in the preceding 12 months
Persons whose history or physical, exam, medical records, or laboratory reports indicate sexually transmitted disease	People who have been newly diagnosed with, or have been treated for, syphilis, gonorrhea, Chlamydia, or genital ulcers in the preceding 12 months
Not listed	People who have been on hemodialysis in the preceding 12 months (hepatitis C only)
Not listed	When a deceased potential organ donor's medical/behavioral history cannot be obtained or risk factors cannot be determined, the donor should be considered at increased risk for HIV, HBV, and HCV infection because the donor's risk for infection is unknown
Persons who cannot be tested for HIV infection because of refusal, inadequate blood samples (e.g. hemodilution that could result in false-negative tests), or any other reasons	When a deceased potential organ donor's blood specimen is hemodiluted, the donor should be considered at increased risk for HIV, HBV, and HCV infection because the donor's risk for infection is unknown

*MSM=men who have sex with men

The transition from the 1994 to 2013 guideline occurred between August 2013 and February 2014. Beginning in February 2014, only the new guideline could be used. The percentage of donors classified as increased risk donors who had organs procured increased from 12.3% to 19.5%, and exceeded 25% in 14 OPOs.[25] The exact reasons for this increase are unknown, but may be related to increased numbers of potential donors who died from opioid overdoses.

Risk Associated with Specific Exposures

As described above, a potential donor may be labeled as increased risk for a variety of different exposures, and these exposures carry very different risks of transmitting recent infection with HIV, HBV, or HCV. For example, a potential donor who was in a county jail 10 months ago for a period of 3 days would be at much lower risk of acquiring HCV or HIV in the preceding week as compared to a potential donor whose cause of death was opioid overdose from IVDU. Table 3 below is based on modeling data and describes the estimated risk of window period infection (both as risk per 10,000 donors and as a

[25] Kucirka, LM, Bowring, MG, Massie, AB, Luo, X, Nicholas, LH, Segev, DL, "Landscape of Deceased Donors Labeled Increased Risk for Disease Transmission Under New Guidelines. "*American Journal of Transplantation* 15, no. 12 (2015): 3215-3223.

percentage). The table is designed to estimate the average risk irrespective of when the test was completed (remote infection should result in a positive antibody test).[26, 27] The ELISA columns refer to the number of donors in the serological window period based on serology (antibody) testing only; the NAT columns refer to the number of donors with negative NAT who are in the NAT window period. NAT reduces the risk of serological window period infection by about 10-fold for most exposures.

Even with NAT, there is still some risk of transmission. However, not all donors with the PHS characteristics carry the same risk of window period infection. For example, donors with recent IVDU with negative serological testing still have a risk of undetected HCV of 300.6 per 10,000 donors (3%). Having both negative serology and negative NAT reduces this risk to 32.4 out of 10,000 donors (0.3%). In contrast, donors with a history of incarceration within the previous 12 months and negative NAT and serology testing would have only a 0.8 per 10,000 donors (0.008%) risk of infection with transmissible HCV.

Table 3: Estimated risk of window period infection (per 10,000 donors)

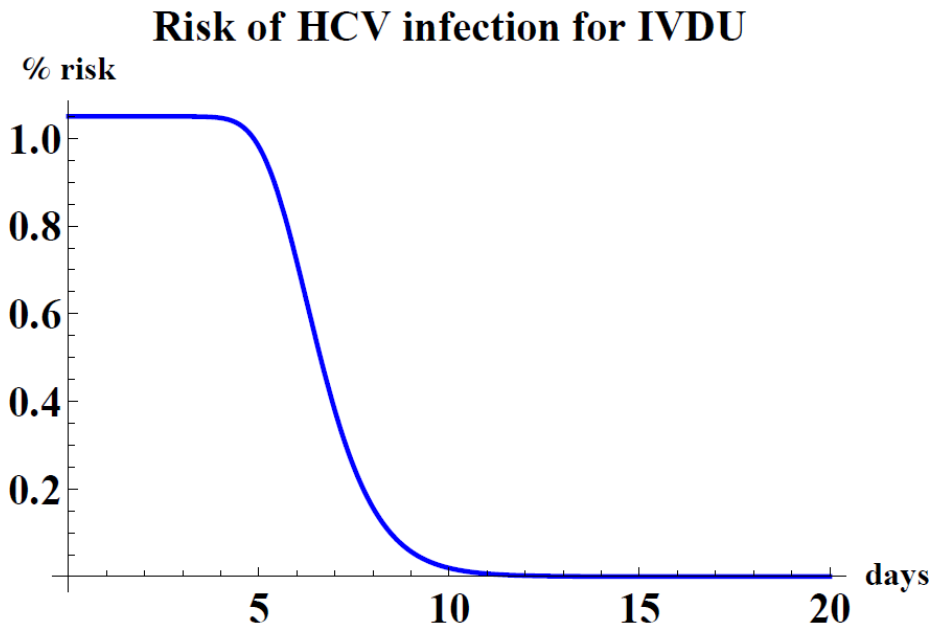
Risk per 10,000 donors	HIV ELISA	HIV NAT	HCV ELISA	HCV NAT
Men who have sex with men	10.2 (0.10%)	4.2 (<0.1%)	32.5 (0.33%)	3.5 (<0.1%)
IV drug users	12.1 (0.12%)	4.9 (<0.1%)	300.6 (3%)	32.4 (0.32%)
Persons with hemophilia	0.086 (<0.01%)	0.035 (<0.01%)	0.26 (<0.1%)	0.027 (<0.01%)
Commercial sex worker	6.6 (<0.1%)	2.7 (<0.1%)	114.9 (1.2%)	12.3 (0.12%)
Sex with a partner in above categories	0.7 (<0.1%)	0.3 (<0.1%)	114.9 (1.2%)	12.3 (0.12%)
Blood product exposure	1.5 (<0.1%)	0.6 (<0.1%)	4 (<0.1%)	0.4 (<0.1%)
Incarceration	2.3 (<0.1%)	0.9 (<0.1%)	7.2 (<0.1%)	0.8 (<0.1%)

Even with the increased sensitivity offered by NAT, this testing may not, for example, detect an HCV exposure that occurred several days prior to testing. Accordingly, a donor that died with an immediate needle exposure has a risk significantly higher than NAT may reflect, possibly as high as 3% for HCV, although lower for HBV and HIV. Figure 1 illustrates the probability of undetected HCV infection after a known IVDU exposure, despite negative NAT results.

[26] Kucirka, LM, Sarathy, H, Govindan, P, Wolf, JH, Ellison, TA, Hart, LJ, et al, "Risk of Window Period Hepatitis-C Infection in High Infectious Risk Donors: Systematic Review and Meta-analysis," *American Journal of Transplantation* 11, no. 6 (2011):1188-1200.

[27] Kucirka, LM, Sarathy, H, Govindan, P, Wolf, JH, Ellison, TA, Hart, LJ, et al, "Risk of Window Period HIV Infection in High Infectious Risk Donors: Systematic Review and Meta-analysis", *American Journal of Transplantation* 11, no. 6 (2011):1176-1187.

Figure 1: Probability of Undetected HCV Infection despite Negative Nucleic Acid Testing due to isolated IVDU Increased Risk Behavior[28]



Days Post Exposure

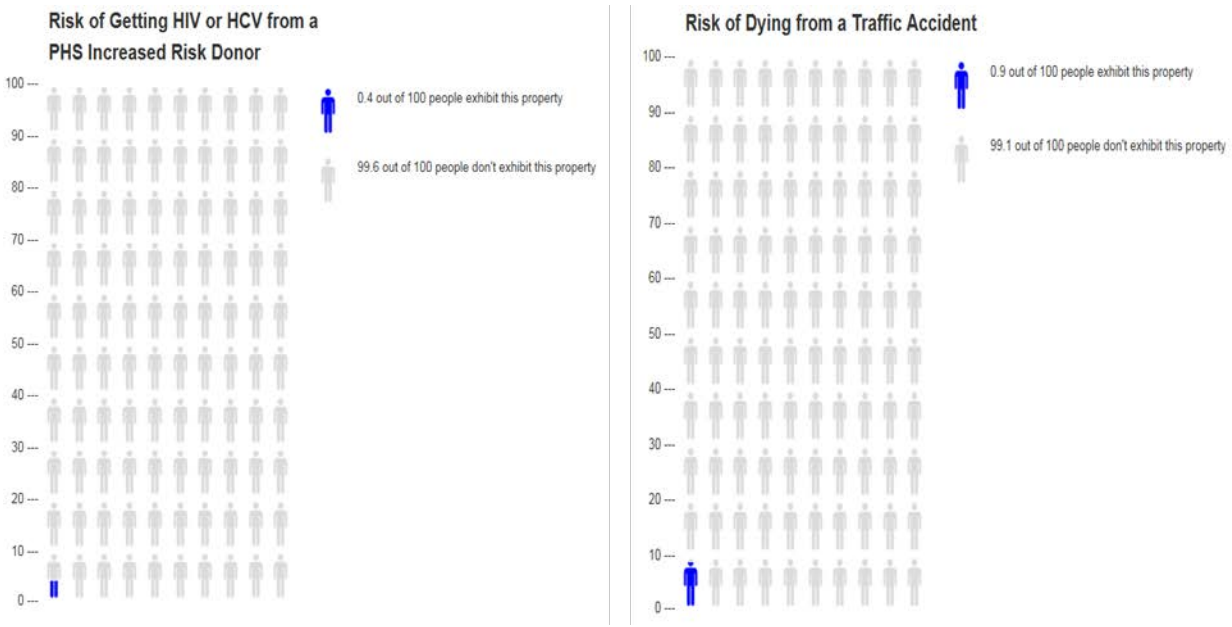
Disclosure of the donor's risk behavior is currently up for debate.[29] Even without disclosing the specific behavior of the donor that results in the increased risk designation, the actual comparative risk associated with that behavior should be communicated by the transplant team when informing a transplant candidate about the various risks associated with accepting an offered organ to optimize recipient's informed consent.

Risk can also be explained to patients relating to everyday concepts, as well as by using resources available. Figure 2 below, as well as a link to the National Safety Council provided in the footnotes, outlines the lifetime risk of death in a traffic accident. This information can help laypersons understand the relative risk of undetected disease transmission.

[28] Annambholta PD, Gurbaxani BM, Kuehnert MJ, Basavaraju SV, "A Model to Estimate the Probability of Human Immunodeficiency Virus and Hepatitis C Infection Despite Negative Nucleic Acid Testing Among Increased-risk Organ Donors," Transplant Infectious Disease, (2017), doi: 10.1111/tid.12676. Amended with permission from the author.

[29] Gordon, EJ, Beauvais, N, Theodoropoulos, N, Hanneman, J, McNatt, G, Penrod, P, Jensen, S, Franklin, J, Sherman, L, Ison, MG. "The Challenge of Informed Consent for Increased Risk Living Donation and Transplantation," *American Journal of Transplantation* 11, no. 12 (2011):2569-2574.

Figure 2: Risk of getting HIV or HCV from a "PHS increased risk" organ versus lifetime risk of dying from a traffic accident[30, 31, 32]



The InformMe website provides further animations and graphics to allow patients to understand the risk associated with accepting an organ from a donor bearing the PHS characteristics associated with higher risk of HIV, HBV or HCV infection.[33] Further, recipients who receive organs from donors with these characteristics should be informed that they will be monitored post-transplant for infection with HIV, HBV, and HCV.

Consequences of Transmission of HIV, Hepatitis B, and Hepatitis C

As treatments for HIV, HBV, and particularly HCV, have improved, the medical consequences of donor-derived infection have lessened. Solid organ transplantation of organs from donors who have screened negative for HIV into selected recipients living with HIV infection prior to transplant has become standard. Overall graft and recipient survival in HIV mono-infected recipients is similar to HIV negative recipients. Current treatments for HCV have demonstrated high cure rates in the post-transplant setting in those infected with HCV pre-transplant. HBV, if chronic infection develops, can be successfully suppressed. Nonetheless, the psychological consequence of donor-derived infection, particularly HIV, may have significant impact on recipient quality of life. Finally, if appropriate monitoring is not conducted after

[30]Kucirka, LM, et al, Risk of Window Period HIV Infection in High Infectious Risk Donors: Systematic Review and Meta-Analysis", *American Journal of Transplantation* 11, no 6 (2011): 1176-1187. Images created by Iconarray.com. Risk Science Center and Center for Bioethics and Social Sciences in Medicine, University of Michigan. Accessed November 22, 2016.

[31] Kucirka, LM, "Risk of Window Period Hepatitis-C Infection in High Infectious Risk Donors: Systematic Review and Meta-Analysis", *American Journal of Transplantation* 11, no 6 (2011): 1188-1200. Images created by Iconarray.com. Risk Science Center and Center for Bioethics and Social Sciences in Medicine, University of Michigan. Accessed November 22, 2016.

[32] http://www.nsc.org/learn/safety-knowledge/Pages/injury-facts-chart.aspx, Images created by Iconarray.com. Risk Science Center and Center for Bioethics and Social Sciences in Medicine, University of Michigan. Accessed November 22, 2016.

[33] Gordon EJ, Sohn MW, Chang CH, McNatt G, Vera K, Beauvais N, et al, "Effect of a Mobile Web App on Kidney Transplant Candidates' Knowledge About Increased Risk Donor Kidneys: A Randomized Controlled Trial, " *Transplantation* (2016).

transplantation and donor-derived infection is not recognized early, significant clinical consequences may occur and treatment of the infection may be less efficacious.

Risk of Declining the Organ from a Donor with the PHS Characteristics for Increased Risk of HIV, HCV or HBV Infection and Remaining on the Waiting List

In communicating the risk of donor-derived infection from any donor, including those associated with donors bearing the behavioral risk factors identified by the PHS, it is important to consider the risks to the potential recipient of *not* accepting that organ and continuing to wait for another offer. This risk-benefit calculation should be individualized, based on organ type, underlying disease, and patient factors, such as blood type and immunologic profile. Local organ wait times also vary. For example, the Scientific Registry for Transplant Recipients (SRTR) reported that waiting list mortality rates varied by DSA from approximately two to eight deaths occurring per year for every 100 candidates on the kidney transplant waitlist in 2015.[34]

The Johns Hopkins Increased Risk Donor Tool uses model-based predictions to calculate risks based on particular recipient characteristics.[35] In one analysis of candidates on the kidney waiting list, accepting or declining an increased risk donor organ resulted in five year survival differences that varied from 6.4% to +67.3% depending on specific recipient characteristics.[36] The risks of continuing to wait are likely even greater for liver or heart candidates.[37] Given the recent availability of highly effective HCV treatments, older estimates may overestimate mortality associated with HCV transmission. The InformMe website (https://informme.cbits.northwestern.edu) provides further context to help potential recipients weigh the risks and benefits of accepting organs from donors with increased risk behavioral characteristics, and an online calculator is available.[38]

Risk of Acquiring Hepatitis C While on Dialysis

Declining an organ bearing a risk of disease transmission will prolong time on dialysis for a patient with kidney failure, and, as hemodialysis is a risk for HBV and HCV, may paradoxically result in an increased risk of acquiring viral hepatitis. Vaccination, however, can substantially reduce the risk of HBV. No vaccine is available for HCV, and the incidence of HCV on hemodialysis is estimated to be 0.34% per year, or 1 in 3,000.[39] This risk is roughly similar to the one-time risk of acquiring HCV from an organ donor with active IVDU (the highest risk category). Therefore, in some instances, the risk of acquiring HCV can be greater by declining an organ from an increased risk donor.

Limitations to Current Screenings

Donor screening cannot detect all transmissible infections. DTAC review of reported data between 2008 and 2016 revealed 15 cases of donor-derived HCV. Four cases were likely related to human or testing error. The remaining 11 occurred as window period infections; four in the serologic window period and seven increased risk donors in a NAT window period. Intravenous drug use was identified as the cause of

[34] Hart, A, Smith, JM, Skeans MA, Gustafson SK, Stewart, DE, Cherikh, WS, Wainright, JL, Kucheryavaya, A, Woodbury, M, Snyder, JJ, Kasiske, BL, Israni, AK, "OPTN/SRTR 2015 Annual Data Report: Kidney", *American Journal of Transplantation* 17, S1 (2017): 21–116, DOI: 10.1111/ajt.14124, Rates are computed per patient-years on the waiting list. A patient on the list for only half a year contributes 0.5 patient years, for example.

[35] http://transplantmodels.com/ird/

[36] Chow, EK, Massie, AB, Muzaale, AD, Singer, AL, Kucirka, LM, Montgomery, RA, et al, "Identifying Appropriate Recipients for CDC Infectious Risk Donor Kidneys", *American Journal of Transplantation* 13, no. 5 (2013):1227-1234.

[37] Freeman, RB, Cohen, JT, "Transplantation Risks and the Real World: What Does "High Risk" Really Mean?", *American Journal of Transplantation* 9 (2009): 23-30.

[38] https://informme.cbits.northwestern.edu

[39] Schweitzer, EJ, Perencevich, EN, Philosophe, B, Bartlett, ST, "Estimated Benefits of Transplantation of Kidneys from Donors at Increased Risk for HIV or Hepatitis C Infection," *American Journal of Transplantation* 7, no. 6 (2007):1515-1525.

death in four of these 15 donors; three from 2016, and one from 2012[40]. There have been no cases of HIV transmission since the PHS Increased Risk guidelines were changed in 2013.

In addition to the limitations associated with laboratory testing, determining if a potential donor should be classified as actually having a risk behavior of interest is challenging. In the setting of deceased donation, information is typically obtained from family members or friends who may have limited knowledge of donor behaviors. Consequently, patients should be made aware that no transplant is truly risk free, yet the benefits of transplant often outweigh these risks.

Pediatric Organ Transplant Considerations

There may be unique considerations when evaluating an increased risk pediatric donor. The benefits of accepting an increased risk donor organ should be weighed against pediatric specific organ, and disease mortality and morbidity data, where possible. Though in smaller numbers as compared to adult deceased donors, OPTN data does note an increase in pediatric deceased donors that met increase risk guidelines during the period of 2005-2016.[41] During the same period, there was an increase in transplants performed on pediatric recipients using organs from increased risk deceased donors, up from 4.5% to 10.6%. There have been no reported transmissions involving HIV, HBV, or HCV from pediatric organ donors. Furthermore, no cases of donor-derived HIV or HCV have been identified in pediatric recipients.[42] Having said this, less is known about treatment options, particularly for HCV infected pediatric transplant recipients, should infection occur.

Conclusion

Through this guidance, transplant professionals can better understand and communicate the risk of window period infection present in PHS increased risk donors compared with the benefits of transplant to our community. This guidance will be reviewed periodically to ensure clinical relevance and currency.

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[40] Kaul, D, Clark, M, Michaels, M, Tlusty, S, Wolfe, C, “Deceased Donors with a History of IV Drug Use and Donor Derived Hepatitis C Virus,” (presentation, American Transplant Congress. Chicago, IL, April 29 - May 3, 2017).
[41] Based on OPTN data as of April 7, 2017
[42] Green, M, Taranto, S, Covington, S, Michaels, M, Wolfe, C, Kaul, D, “Pediatrics & Donor Derived Disease Transmission: The US OPTN Experience [abstract]. *American Journal of Transplantation 15*, suppl 3 (2015).