Public Comment Proposal

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

Prepared by: OPTN/UNOS Ad-hoc Disease Transmission Advisory Committee
UNOS Policy Department

Contents

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

Affected Policies: *None*
Sponsoring Committee: *OPTN/UNOS Ad-hoc Disease Transmission Advisory Committee*
Public Comment Period: *March 27, 2017 to April 25, 2017*

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. 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 Joint Society Steering Committee, 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 during 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 decision-making process whether the patient may want to consider an organ from an increased risk donor at the time of organ offer.

Is the sponsoring Committee requesting specific feedback or input about the proposal?

The Committee requests the following feedback:

- What challenges has your organization experienced with PHS increased risk organ donors, e.g.: inconsistent acceptance practices with increased risk donors, lack of clarity regarding appropriate disclosure of donor risk behaviors?
- What practice changes have you made at your organization in response to these challenges?

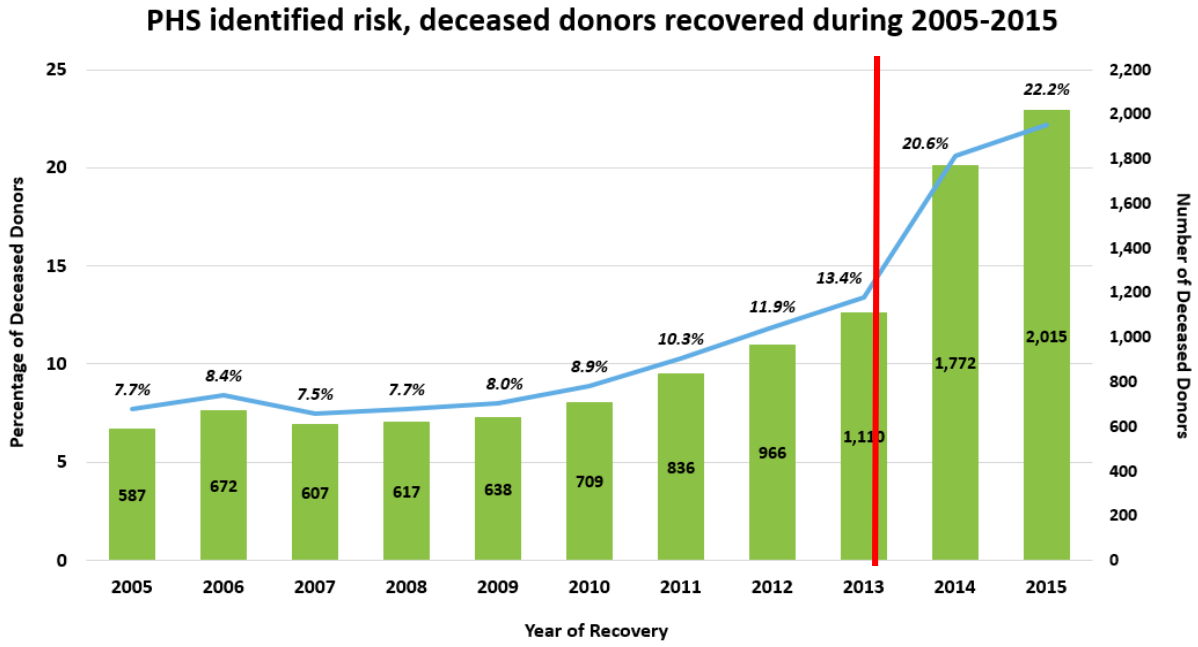
What problem will this proposal address?

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. This phrase is not a reference to organ quality, nor should it be interpreted to be a prediction of graft survival. However, 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]

Why should you support this proposal?

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 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 increase in increased risk (previously referred to as "high risk") organ donors during the period 2010 to 2015.[4]

Figure 1 – CDC High Risk and PHS Increased Risk Deceased Organ Donors Recovered 2005-2015



[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 May 27, 2016

The OPTN 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. After February 1, 2014, the PHS increased risk criteria were to be used 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 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 this with JSWG members. 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 Working Group 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 Working Group 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.

[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).
[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/

- 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/management of these viral infections.
- Risk of acquiring HCV on hemodialysis.
  - Hemodialysis carries its own risk of HVC transmission. Transplant staff and patients should carefully this risk versus accepting an increased risk donor organ.
- 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 Working Group's discussions, one member felt this guidance document was a good opportunity to define what "increased risk" is more specifically and simply. The Working Group discussed the accuracy and understanding of the phrase. Since the term "increased risk" is derived from the federal regulation the members of the Working Group 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 Working Group 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 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).

The Committee recognizes many entities are analyzing the current opioid epidemic and new data may be forthcoming. The Committee will amend the guidance document post-public comment to incorporate the most recent published literature on these deceased organ donors. An example of this will be an update to Figure One from colleagues at the U.S. Centers for Disease Control and Prevention to more clearly depict the risk of HIV and HCV infection from intravenous drug use.

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 One on page two of this document, the number of deceased organ donors that meet U.S. PHS criteria for increased risk of disease transmission continues to rise. Additional data noted the percentage of donors classified as increased risk donors who had organs

[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.

procured, increased from 12.3% to 19.5%, and exceeded 25% in 14 organ procurement organizations.[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 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. The table 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
HCV	~70 days (5, 8, 11)	~40-50 days (12-14)	3-5 days (5, 11)

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

[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.

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
IV drug users	12.1 (0.12%)	4.9 (<0.1%)	300.6 (3%)	32.4 (0.32%)
Commercial sex worker	6.6 (<0.1%)	2.7 (<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%)

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. A future project may be considered based on community feedback during public comment.

Which populations are impacted by this proposal?

This guidance document will be an optional resource to 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 in pediatric and adult transplant candidates, 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:* DTAC believes 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 be expected to 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. The OPTN 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. The OPTN will communicate this new information through TransplantPro and the OPTN website.

How will members implement this proposal?

Transplant Hospitals

OPTN member 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.

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.

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 consideration 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.

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 through 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 develop 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 the use of NAT or antigen/antibody (Ag/Ab) combination testing for HIV among 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.

The use of NAT markedly shortens the “window period” between infection and seroconversion. 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) provides this guidance document to help transplant professionals to better understand the actual risk of window period infection present in PHS increased risk donors.

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[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.

This resource tool is intended to give educational support for Organ Procurement Organizations (OPOs) and transplant centers and is for voluntary use by members. This resource is not an 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 PHS increased risk classification.

- 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, becomes 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. Incarceration or sexual practices are generally much lower risk than donor 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 (< 1%).
- Ultimately, with appropriate counselling and informed consent, we aim to maximize organ availability.

Window Period with Nucleic Acid Testing

The concept of “increased risk” (previously referred to as “high risk”) donors was created to

identify 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. This period between infection and the development of antibodies is called the "serological window period." 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. NAT, 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. The NAT window period is very short, so NAT testing becomes positive much closer to the time of infection compared to serological testing.

The behavior 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 below describes the time from infection to detection associated with different serological or NAT methods.[23]

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
HCV	~70 days (5, 8, 11)	~40-50 days (12-14)	3-5 days (5, 11)

*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 guidelines, the 1994 guidelines were used and were intended to identify risk factors for HIV only. The table 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 Guidelines	2013 Guidelines
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

[23] 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 Guidelines	2013 Guidelines
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
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 guidelines occurred between August 2013 and February 2014. Beginning in February 2014, only the new guidelines 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.[24] The exact reasons for this increase are unknown, but may be related to increased numbers of potential donors who died from opioid

[24] 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.

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. The table below describes the estimated risk of window period infection (remote infection would result in a positive antibody test) expressed per 10,000 donors, or as a percentage.[25, 26] 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 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)

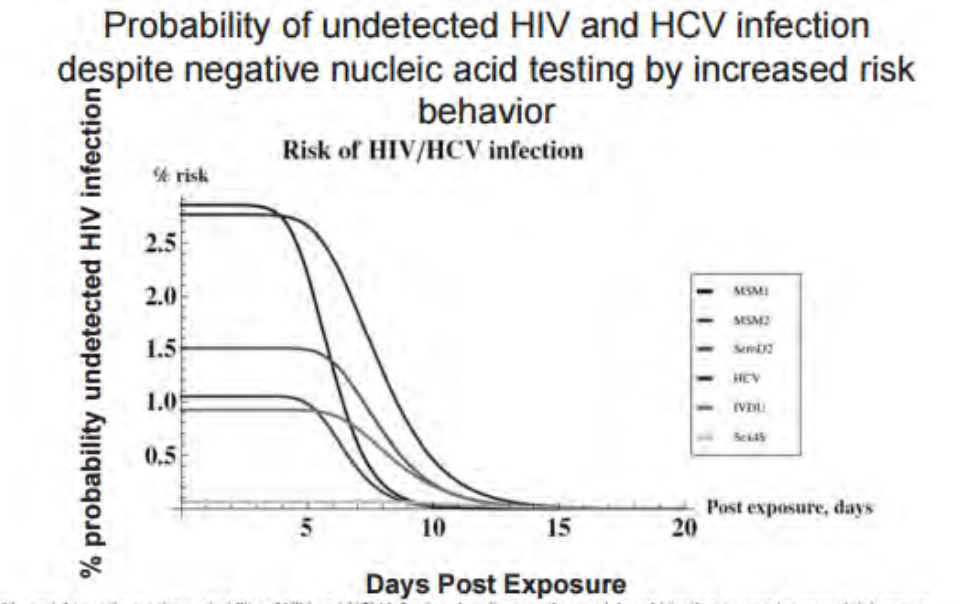
Risk per 10,000 donors	HIV ELISA	HIV NAT	HCV ELISA	HCV NAT
IV drug users	12.1 (0.12%)	4.9 (<0.1%)	300.6 (3%)	32.4 (0.32%)
Commercial sex worker	6.6 (<0.1%)	2.7 (<0.1%)	114.9 (1.2%)	12.3 (0.12%)
Blood product exposure	1.5 (<0.1%)	0.6 (<0.1%)	4 (<0.1%)	0.4 (<0.1%)

Even with the increased sensitivity offered by NAT, this testing may not detect an HIV, HBV, or HCV exposure that occurred within the three to five 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 One illustrates the probability of undetected HIV or HCV infection despite negative NAT results.

[25] 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.

[26] 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 HIV and HCV Infection despite Negative Nucleic Acid Testing by Increased Risk Behavior[27]



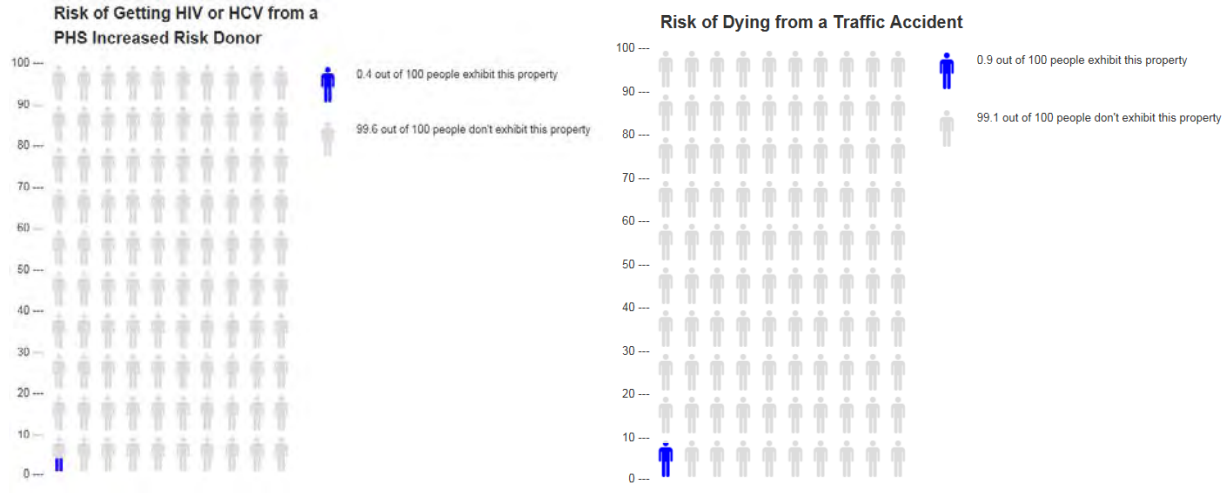
A model to estimate the probability of HIV and HCV infection despite negative nucleic acid testing among increased risk organ donors", Pallavi Annambhotla, Brian Gurbaxani*, Matthew Kuehnert, Sridhar Basavaraju (under review, *Transplant Infectious Diseases*)

Disclosure of the donor's risk behavior is currently up for debate.[28] 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 utilizing resources available. Figure one below, as well as a link to the National Safety Council provided in the footnotes, both discussed the odds of dying from some other causes. This information can be helpful to laypersons understanding relative risk of undetected disease transmission.

[27] Michaels, MG, PHS Increased Risk Donors: Putting it All in Perspective (presentation, Association of Organ Procurement Organizations Annual Meeting. Austin, TX, June 20-23, 2016).
[28] 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 risk of dying from a traffic accident[29, 30, 31]



The InformMe app 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.[32] Further, recipients who receive organs from donors bearing 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 with HIV infection prior to transplant has become standard with overall graft and recipient survival (in HIV mono-infected recipients) similar to HIV naive 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. Further, the possibility of difficult to treat multidrug resistant HIV infection exists. Finally, if appropriate monitoring is not conducted after transplantation and donor-derived infection is not recognized early, significant clinical

[29]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.

[30] 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.

[31] 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.

[32] 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).

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 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. The Johns Hopkins Increased Risk Donor Tool uses model-based predictions to calculate risks based on particular recipient characteristics.[33] 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.[34] The risks of continuing to wait are likely even greater for liver or heart candidates.[35] Given the recent availability of highly effective HCV treatments, older estimates may overestimate mortality associated with HCV transmission. The InformMe app 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.[36]

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.[37] 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 Screening Strategy

Donor testing is not foolproof and subject to other possible errors. False negative results for NAT, while rare, have occurred. An analysis of DTAC data of donor-derived HCV demonstrated that despite testing (although not always including NAT), eight donors (only one of whom was increased risk) transmitted HCV to at least one recipient. In three of these donors, testing was positive but human error resulted in a failure to recognize the positive tests. Four donors were in the window period and in three of those donors, NAT was not performed. The fourth donor was in the window period for NAT. One of the eight donors had a false negative serology and NAT was not performed.

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.

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

[34] 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.

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

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

[37] 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.