



BILLING CODE 4150-28

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Request for Information: Regarding Revisions to the PHS Guideline for Reducing Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV), and Hepatitis C Virus (HCV) through Organ Transplantation

AGENCY: Office of Infectious Disease and HIV/AIDS Policy, Office of the Assistant Secretary for Health, Office of the Secretary, Department of Health and Human Services.

ACTION: Request for information; notice.

SUMMARY: The Office of the Assistant Secretary for Health in the Department of Health and Human Services (HHS) seeks public comment regarding proposed revisions to the 2013 PHS Guideline for Reducing Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV), and Hepatitis C Virus (HCV) Through Organ Transplantation.

DATES: To be assured consideration, comments must be received at the address provided below no later than 5:00pm ET on **[INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER]**.

ADDRESSES: Electronic responses are strongly preferred and may be addressed to ACBTSA@hhs.gov. Written responses should be addressed to: U.S. Department of Health and Human Services, Mary E. Switzer Building, 330 C Street, SW, Room L001, Washington, D.C. 20024 Attn: ACBTSA – RFI.

FOR FURTHER INFORMATION CONTACT: Mr. James Berger, Designated Federal Official, Office of Infectious Disease and HIV/AIDS Policy, (202) 795-7608.

SUPPLEMENTARY INFORMATION:

I. Background

Since implementation of the Guideline in 2014,¹ the organ donation and transplantation community monitored the impact of the recommendations on provider and patient perceptions, organ utilization, and clinical outcomes. HHS conducted analyses to inform efforts to revise the Guideline recommendations. In April 2019, the Assistant Secretary for Health of the Department of Health and Human Services (HHS) received input from the Advisory Committee on Blood and Tissue Safety and Availability (ACBTSA) regarding revisions to the Guideline recommendations to reflect recent epidemiologic trends in clinical characteristics of deceased organ donors and scientific advances and improvements in testing for and treatment of HIV, HBV, and HCV infections.

HHS is asking respondents to review the proposed revisions to the current Guideline and provide assessments on updating the Guideline, whether these changes are achievable in the clinical setting, or if there are potential barriers to implementation. In addition, impact on organ allocation and utilization should be considered. Other comments pertinent to these proposed revisions are welcome.

¹ 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 (Washington, DC : 1974). 2013;128(4):247-343.

Since the emergence of the human immunodeficiency virus (HIV) epidemic, the U.S. Public Health Service (PHS) has made recommendations to reduce the risk of HIV transmission associated with organ transplantation.^{2 3} Historically, recommendations included identifying risk factors among organ donors associated with HIV infection to minimize risk of potential transmission to recipients. Recommendations also included laboratory screening of donors using anti-HIV antibody testing, with additional testing recommendations added as technologies such as nucleic acid testing (NAT) were developed. In 2013, based on donor-derived transmission events and reports of poor recipient outcome from hepatitis B (HBV) and C (HCV) transmission, the PHS released a revised guideline. The 2013 Guideline added organ donor screening recommendations for HBV (hepatitis B surface antigen (HBsAg) and total antibody to hepatitis B core antigen (anti-HBc)) and HCV (antibody to hepatitis C (anti-HCV) and NAT), in addition to HIV, to reduce the risk of unintended transmission through transplantation. This revised Guideline was enhanced by recommending specific recipient informed consent and post-

² CDC. Guidelines for preventing transmission of human immunodeficiency virus through transplantation of human tissue and organs. Centers for Disease Control and Prevention. MMWR Recommendations and reports : Morbidity and mortality weekly report Recommendations and reports / Centers for Disease Control. 1994;43(RR-8):1-17.

³ CDC. Testing donors of organs, tissues, and semen for antibody to human T-lymphotropic virus type III/lymphadenopathy-associated virus. MMWR Morbidity and mortality weekly report. 1985;34(20):294.

transplant recipient monitoring for evidence of possible disease transmission.

Per the 1994 guideline, donors with risk factors for HIV infection and transmission to recipients were designated “Centers for Disease Control and Prevention (CDC) High Risk” donors. The 2013 Guideline changed this terminology to “Increased Risk Donor (IRD)” and recommended HCV nucleic acid testing (NAT) for all donors and HIV NAT or p24 antigen testing for IRD. For living donors, testing was recommended to be performed as close as possible to the date of the organ recovery but at least within 28 days prior to surgery. For deceased donors, specimens for testing were to be obtained before procurement but with no specific recommendation on the timing of collection relative to organ recovery. The term “Increased Risk” was adopted over “High Risk” to convey the continued but small possibility of donor-derived disease transmission from donors with risk factors, even with use of the more sensitive NAT screening tests.

The 2013 Guideline specifically outlines 12 medical or social history criteria resulting in IRD designation if these risk factors occurred within the 12 months prior to organ recovery. The 12 criteria are:

1. Sex with a person known or suspected to have HIV, HBV, or HCV infection.
2. Men who have had sex with men (MSM).
3. Women who have had sex with a man with a history of MSM behavior.
4. Sex with a person who had sex in exchange for money or drugs.
5. Sex with a person that has injected drugs by intravenous, intramuscular, or subcutaneous route.

6. Injecting drugs by intravenous, intramuscular, or subcutaneous route for nonmedical reasons.
7. Incarceration for > 72 consecutive hours.
8. Syphilis, gonorrhea, chlamydia, or genital ulcers.
9. Child (age ≤ 18 months) born to a mother known to be infected with, or at increased risk for HIV, HBV, or HCV.
10. Child breastfed within the preceding 12 months by mother known to be infected with, or at increased risk for HIV infection.
11. Hemodialysis (only increased risk for HCV).

Deceased donors for whom medical or social history are unavailable at the time of organ recovery are designated IRD. Donors are also designated as IRD if the organ-donation serum specimen used for HIV, HBV, or HCV testing meets criteria for hemodilution due to the donor receiving crystalloid or colloid infusion prior to specimen collection, based on hemodilution calculations described in FDA guidance (<https://www.fda.gov/media/73072/download>). The 2013 recommendations were not intended to restrict transplantation (or exclude specific donors) but to facilitate appropriate donor laboratory screening, enhance informed decision making by recipients and families, and ensure prompt recognition and treatment of donor-derived disease transmission events.

The following issues regarding the perceived impact of the 2013 Guideline

on organ utilization and allocation, clinical decision-making, and recipient outcomes have been reported in the scientific literature or communicated directly to relevant federal agencies, including CDC and the Health Resources and Services Administration (HRSA):

1. As a result of the national substance abuse and overdose epidemic, an increasingly larger number and proportion of organ donors are designated as IRD. These donors are often younger and have better organ quality compared with non-IRD standard risk donors (SRD).
2. Organs from IRD are underutilized compared with organs from SRD.
3. The “IRD” label may discourage organ acceptance and utilization by transplant physicians and transplant candidates:
 - a. The label may result in a perception that the risk is higher than the true risk for disease transmission and resultant morbidity and mortality of using these organs.
 - b. The label may convey a perception that IRD organs are of poorer quality despite scientific evidence that demonstrates these donors are often younger and have higher-quality organs.
 - c. Due to misperceptions related to disease transmission risk or organ quality, candidates may opt to decline an IRD organ offer and choose to wait for another organ, resulting in preventable morbidity and mortality had they accepted receipt of the IRD organ.

4. Not all criteria for current IRD designation are actually associated with a significant risk of HIV, HBV, and HCV infection and/or transmission and some of the criteria should be removed.
5. The 2013 Guideline recommendation designates donors as IRD if risk factors occur within 12 months prior to donation. Because organ procurement organizations (OPOs) have universally implemented screening of organ donors for HIV, HBV, and HCV by NAT, the 12 month timeframe should be shortened.
6. Because all organ donors are universally screened by NAT and the risk of unexpected donor-derived disease transmissions has decreased, donor risk designation and informed consent requirements should be modified.
7. Because the number of organ donors with risk factors has increased and effective suppression of HIV and HBV and a cure of HCV infection are available, all recipients should be screened for HIV, HBV, and HCV post-transplant, including recipients of organs from donors without recognized risk factors due to inherent uncertainty of questionnaire responses provided by donor next of kin.

HHS conducted additional data analyses in order to better understand the impact of the PHS Guideline recommendations on organ utilization, allocation, and recipient outcomes. The following analytic activities were undertaken by HHS with associated findings summarized:

1. A descriptive analysis of Organ Procurement and Transplantation Network (OPTN) data to calculate the total numbers and proportions of organ donors classified as IRD by year (since 2010) and further stratify by viral bloodborne pathogen screening

results was conducted. This analysis found that the percentage of adult donors classified as IRD has increased from 9.3% (2010) to 26.2% (2017), with higher percentages in some geographic regions. The percentage of deceased donors with drug intoxication as the mechanism of death increased from 4.3% (2010) to 12.6% (2016); approximately 60% of these donors have a history of nonmedical injection drug use (IDU). Additionally, the number of HCV-infected donors identified via NAT has increased among IRD since 2014.

2. A descriptive analysis was performed of all CDC-led outbreak investigations (2014-2017) of donor-derived HBV/HCV transmissions, including a summary of clinical outcomes and antiviral treatment of infected recipients. CDC investigated 9 potentially donor-derived transmission events of HCV, involving 31 HCV-negative recipients, of whom 20 developed HCV infection. During this period, CDC also investigated 7 potentially donor-derived transmission events of HBV, involving 15 HBV-negative recipients, of whom 7 developed HBV infection. No recipient died of either HCV- or HBV-related complications. In these cases, identification of organ donors with risk factors for viral bloodborne pathogen infection and IRD designation led to early diagnosis and treatment of recipient infection, which possibly averted graft failure or death.
3. Logistic regression analyses were conducted of national OPTN donor and recipient data to quantify the impact of IRD designation on organ utilization and thereby determine whether or not IRD designation was associated with organ underutilization, and if so, then to what extent. After adjusting for variables that may have impacted organ acceptance decisions (including donor HBV/HCV serostatus), there was no

observed underutilization of livers or hearts from IRD donors. IRD designation appeared to be associated with underutilization of adult kidneys but the magnitude was smaller than previous estimates and this association appeared attributable to low use by a subset of transplant centers, rather than broad underutilization by all U.S. transplant programs.

4. Mathematical modeling was performed using Monte Carlo simulation to estimate the current probability of undetected HIV, HBV, or HCV infection in an IRD donor for whom all recommended NAT testing was negative. These analyses were conducted to identify a shorter, but safe timeline during which risk behaviors result in IRD designation. The probability of undetected infection in donors with high-risk behaviors 30 days after the most recent potential risk behavior was $<1/1,000,000$ for HIV and HCV and near $1/1,000,000$ for HBV. The time period during which high risk behaviors lead to donor classification as increased risk can be safely reduced from 12 months to a shorter interval. HHS conducted an assessment of the current criteria that result in IRD designation to determine which criteria have been previously implicated in a donor-derived transmission of HIV, HBV, or HCV and are therefore associated with significant epidemiological risk of transmission. Criteria that were not previously implicated in cases of transmissions from IRD-designated organs included being a woman who had sex with a man with a history of same-sex sexual contact or having been newly diagnosed or have been treated for syphilis, gonorrhea, chlamydia, or genital ulcers, and hemodialysis.

In April 2019, HHS convened the Advisory Committee on Blood and Tissue Safety and Availability (ACBTSA) to receive expert input on whether, and if so, how, the current PHS

Guideline recommendations should be revised (<https://www.hhs.gov/oidp/advisory-committee/blood-tissue-safety-availability/meetings/2019-04-15/index.html>). Additionally, HHS solicited input from this committee on specific changes to current recommendations. The committee voted in favor of the following recommendations:

1. Continued recognition and designation of a category of potential organ donors with an augmented chance of transmission of HIV, HBV, and HCV.
2. Screen all organ donors for HIV, HBV, and HCV using NAT in addition to serology.
3. Shorten the current 12-month risk factor timeframe to 3 months.
4. Test all recipients, regardless of donor risk profile, for HIV, HBV, and HCV using NAT between 2 and 4 weeks after transplantation. Repeat testing, particularly for HBV, to be considered in future discussions.
5. Change the current “increased risk donor” terminology to reduce cognitive bias and improve decision making among clinicians and patients.
6. Remove the following as medical/social criteria:
 - a. Women who have had sex with a man with a history of same-sex sexual contact;
 - b. Newly diagnosed or have been treated for syphilis, gonorrhea, chlamydia, or genital ulcers;
 - c. Hemodialysis;
 - d. Hemodiluted blood specimen used for infectious disease testing;

- e. Child (age \leq 18 months) born to a mother at increased risk for HIV, HBV, or HCV;
 - f. Child breastfed within the preceding 12 months by mother at increased risk for HIV infection.
7. Continue the following criteria that would result in augmented donor risk designation:
Sex with a person known or suspected to be HIV, HBV, or HCV infected; Man who has sex with men; Sex in exchange for money/drugs; Sex with a person who had sex in exchange for money/drugs; Non-medical injection of drugs; Sex with person who has engaged in non-medical drug injection; Incarceration for $>$ 72 hours; Unknown medical/social history; Child born to a mother with HIV.
8. Support the development and use of tools and processes to educate transplant providers and enhance the process of transplant candidate counseling in order to enhance organ utilization.

II. Potential revisions to the 2013 Guideline

HHS has reviewed the ACBTSA recommendations and other available information and is considering the following revisions to current recommendations in the 2013 Guideline:

1. Test all organ donors for HIV, HBV, and HCV using serological tests (including total antibody to hepatitis B core antigen [total anti-HBc], hepatitis B surface antigen [HBsAg], and hepatitis C antibody [anti-HCV]) and NAT.

- a. For living potential donors, testing should continue to be performed as close as possible to the surgery, but at least within the 7-day time period prior to organ recovery.
 - b. For deceased donors, the donor specimen should be collected within 72 hours prior to organ recovery with results of these screening tests available at the time of organ recovery. If the donor sample used for testing was collected more than 24 hours prior to organ recovery, an additional donor specimen should be collected in the immediate 24 hours prior to organ recovery and tested for HIV, HBV, and HCV by NAT. Results of these screening tests should be made available as soon as possible, even if these results might not be available at the time of organ recovery.
2. Regardless of donor risk profile for HIV, HBV, or HCV, transplant programs should test all organ recipients:
- a. Before transplantation for HIV, HBV, and HCV using NAT and serologic tests including total anti-HBc, HBsAg, anti-HCV, and hepatitis B surface antibody (anti-HBs);
 - b. At 4-6 weeks following transplantation for HIV, HBV, and HCV (with NAT); and
 - c. At 12 months following transplantation for HBV (with NAT).
3. OPOs should ascertain whether any of the following medical or social risk criteria were present in potential organ donors within 30 days prior to organ recovery:
- a. Sex with a person known/suspected to be HIV, HBV, or HCV infected

- b. Being a man who has had sex with another man
- c. Sex in exchange for money/drugs
- d. Non-medical drug injection
- e. Sex with a person with history of non-medical drug injection
- f. Incarceration for > 72 consecutive hours
- g. Child breastfed by a mother with HIV
- h. Child born to a mother with HIV, HBV, or HCV

OPOs should identify donors for whom medical and social history is unknown at the time of organ recovery, which is also considered a risk criterion.

4. When donors with ≥ 1 of the criteria as specified under #3 are identified, OPO's should communicate this information to the appropriate transplant centers. Transplant centers should discuss this information with transplant candidates and families as part of transplantation-related informed consent discussions. Transplant centers should make efforts to contextualize these discussions and should include the following:
 - a. The risk of undetected HIV, HBV, or HCV infection is very low
 - b. Recipients are universally tested for HIV, HBV, and HCV after transplantation and should transmission occur, effective therapies are available

- c. Recipients may have a higher chance of survival by accepting organs from donors with risk factors for HIV, HBV, and HCV compared with waiting for an organ from a donor without recognized risk factors
5. Remove any specific label (e.g., “increased risk donor”) to describe donors with risk factors for undetected HIV, HBV, or HCV infection, with inclusion of additional strategies to enhance recipient safety
6. No requirement for specific informed consent with recipients who are considering acceptance of these organs, though recipients would still be informed of certain donor risk factors
7. All organ transplant candidates should be vaccinated for HBV per previous recommendations (<https://doi.org/10.1111/ctr.13563>)
8. HHS proposes no additional substantive changes to the following sections of the 2013 PHS Guideline:
 - a. Collection and/or storage of donor and recipient specimens
 - b. Tracking and reporting of HIV, HBV, and HCV infection in donors or recipients

HHS recognizes that the elimination of a specific label, (e.g. “increased risk donor”) to designate a separate group of organ donors with specific characteristics associated with a relatively small increased risk of donor-derived transmission of HIV, HBV, or HCV is a change to one of the ACBTSA recommendations for Guideline revision. HHS also acknowledges the diversity of opinions expressed during the deliberations of this committee regarding whether or not to continue to use any label to designate this group of organ donors. HHS has evaluated the

potential advantages and disadvantages of using such a label for a specific subset of all organ donors and proposes the approach outlined above for several reasons:

1. Designating a subset of organ donors does not necessarily prevent or reduce the risk of transmission of disease (HIV, HBV, or HCV).
2. Next-of-kin interviews used to identify risk factors may be unreliable.
3. For transplant candidates with end-stage organ disease, the risk of severe morbidity or mortality associated with HIV, HBV, or HCV transmission as a result of accepting an IRD organ is less than the risk of mortality while remaining on the wait list for another organ offer.
4. The risk of morbidity or mortality from HIV, HBV, or HCV transmission from an IRD organ is less than other risks of organ transplant-related complications, including organ rejection, and infections resulting from immune suppression.
5. Use of a label to specify an organ donor group with small risk of disease transmission (e.g., HIV, HBV, HCV) can detract from the recognition of other known clinical attributes in some donors that can place recipients at even greater risk for morbidity and mortality.

We seek informed feedback regarding this proposed approach to revising the recommendations in the 2013 Guideline, including the feasibility of the recommended timing of testing for living and deceased donors.

Dated: August 8, 2019.

Tammy R. Beckham,

Director, Office of Infectious Disease and HIV/AIDS Policy.

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