June 15, 2012

James Berger
Senior Advisor for Blood Policy
Office of HIV/AIDS and Infectious Disease Policy
Office of the Assistant Secretary for Health and Human Services
1101 Wooton Parkway, Tower Building, Suite 250
Rockville, MD 20852

RE: Transplant Community Questions and PHS Revised Guidelines for Reducing HIV, HBV, and HCV through Organ Transplantation

Dear Mr. Berger:

On behalf of the American Society of Transplantation (AST) and American Society of Transplant Surgeons (ASTS), representing the majority of professionals caring for people awaiting or receiving lifesaving organ transplants, we remain grateful for the opportunity to work closely with the U.S. Department of Health and Human Services (HHS) as the Agency updates the 1994 document *PHS Guidelines for Preventing Transmission of HIV through Transplantation of Human Tissue and Organs.* The overall safety of patients and ensuring the availability and success of transplantation as a treatment option is of the highest priority and importance to our organizations.

The safety of our organ supply is paramount. As you know, during our long history of collaborative work with HHS and other federal agencies, our primary goal has always been to achieve safe and successful transplantation. We know that HHS shares this goal and are encouraged by the recent revisions made to the PHS guideline document in response to our voiced concerns. We applaud the Agency and HHS Assistant Secretary for Health Dr. Howard Koh for engaging in a dialogue that will hopefully ensure that the revised document achieves its stated purpose of strengthening public health. We are hopeful that this dialogue will continue until these stated goals are realized in the final product.

Although each society has attached a separate document with suggested edits and comments regarding specific sections of the revised proposed PHS guidelines, we also have several shared, overarching concerns and questions regarding the document – concerns that we consider to be essential and that have yet to be addressed. In an effort to truly achieve the outcomes stated by HHS at the onset of this rulemaking process, ASTS and AST believe that it is imperative that the Agency consider these issues.

First, as we all have recognized throughout this process, there is a natural tension between seeking to ensure the absolute safety of the organ supply and reducing unnecessary organ wastage. Do the revised Guidelines strike the appropriate balance? The answer depends on two other questions:

> *What is the estimated effect that these guidelines would have, if implemented, on reducing donor-transmitted HIV, HCV, and HBV?*
>
> *What is the estimated impact on deceased donor organ availability and overall transplant and waitlist outcomes?*

It is only when the appropriate balance is achieved that this document will be ready to be published in final form, and achieving this balance necessarily requires close consultation with the transplant community.

Second, it is unclear to us whether the PHS has evaluated the significant cost (in addition to the potential impact on organ availability) associated with implementing the revised Guidelines, especially the cost of collecting, monitoring, and storing multiple donor and recipient specimens over a 10-year period for each transplant performed. We believe these costs should be quantified before the agency moves to the next stage of finalizing the Guidelines, especially since it appears likely that the Medicare program will bear a significant portion of these costs through organ acquisition centers. In light of the critical need to curb rising health costs in both the private and public sectors, we would hope that the agency will not move forward without a comprehensive impact analysis.

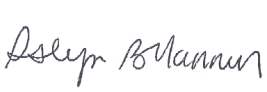
Third, although the Agency has indicated that this document is a "guidance tool," because the OPTN final rule requires OPTN policies to reflect CDC guidance, it highly likely that these guidelines will actually be binding on both OPOs and transplant centers. Under these circumstances, we urge PHS to ensure that there is a realistic plan and timetable for implementation of the Guidelines before the process proceeds further.

Fourth, although the Agency has stated in conference calls and meetings that the revision process will continue until a majority of the expert stakeholders in the transplant community are satisfied with the process and outcome, the Expert Panel has not been reconvened nor have there been any other opportunities for meaningful dialogue beyond a limited conference call and very brief future opportunity for final comment in mid-summer. What additional opportunities will there be for the Agency's expert panelists and transplant stakeholders to review the final guidance document? As concluded at the recent AHRQ conference supported by the AST and ASTS, consensus takes time and careful deliberation when there is such a broad spectrum of opinion regarding risk assessment.

Finally, and along similar lines, given that we all share the common goal of revising, improving, updating, and enhancing the guidelines to produce as strong a document as possible, why does there now appear to be such a fast-track and limited opportunity for review following the re-constituted Expert Panel (now termed "Technical Advisors") and review committee?

The ASTS and AST continue to believe strongly that this process should result in recommendations based on clearly stated goals, with comprehensive analysis of overall risk and benefit to transplant candidates and patients based upon current and accurate data. In the absence of data, we believe that gaining community consensus is the best path to reducing the risks of transmission of HIV, HCV, and HBV through organ transplantation. We recognize and very much appreciate the recent revisions made by PHS in response to the public comment. As leaders and stakeholders in the transplant community, we welcome the opportunity and look forward to continuing to work with you cooperatively and collaboratively to "get this right" and improve the health of our patients and the outcomes of those with end-stage organ failure. In this spirit, we thank you in advance for answering the concerns and questions we have summarized in this letter. We look forward to hearing from you in the near future. If you have any questions or require additional information, please do not hesitate to contact either of us directly.

Best Regards,



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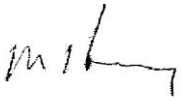

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AST Comments on the

"PHS Guideline for Reducing HIV, HBV and HCV Transmission through Solid Organ Transplantation"

Risk Factors and Recommendations

Factors associated with increased likelihood of recent HIV, HBV or HCV infection

	Version in Public Comment Document	Revisions per PHS Guideline Work Group
Intra-nasal	Intra-nasal use of an illicit drug (e.g., cocaine, heroin) in the preceding 12 months	Delete

AST Comment: Canadian and other data suggest that intranasal cocaine is a risk factor for prevalent HCV, although there does not appear to be adequate data regarding incident HCV in this sub-population of potential organ donors. We would recommend adding this to the questions for further study.

	Version in Public Comment Document	Revisions per PHS Guideline Work Group
Inmate	Inmate of a correctional facility (e.g., jail, prison, juvenile detention) >3 consecutive days in the preceding 12 months	Persons who have been in a juvenile correctional facility, lock up, jail or prison for more than 72 consecutive hours in the preceding 12 months

AST Comment: The language is unclear as to whether this refers ONLY to juvenile facilities or intends to refer to adult "lock-up, jail, or prison…" as well. Consider moving juvenile correctional facility to the end of the list to clarify that this is in addition to lock up, jail or prison for persons of any age.

Donor Risk Assessment

#7	Version in Public Comment Document	Revisions per PHS Guideline Work Group
Massive blood loss and intravascular volume replacement by infusion of crystalloid and colloid solution and transfusion of blood products can cause plasma dilution and result in unreliable test results for transmissible infections. Donors should	When a deceased potential organ donor's behavioral/medical history questionnaire cannot be obtained; behavioral and nonbehavioral risk factors cannot be determined; or the donor specimen is hemodiluted, the donor should be	

be considered at increased risk for harboring HIV, HBV and HCV when donor samples are determined to be diluted by an accepted plasma dilution algorithm and calculation method, such as provided by FDA, designed to evaluate volumes administered in the 48 hours before specimen collection, even when no risk factors are identified. (Category IB) (Expert Opinion - Question 3D)	considered at increased risk for HIV, HBV and HCV.

AST Comment: We would recommend a change in language from "at increased risk" to "potentially at increased risk" or "at unknown risk".

Donor Screening [change to Donor Testing (Living and Deceased)]

#3	Version in Public Comment Document	Revisions per PHS Guideline Work Group
Deceased potential organ donors also should be screened for HIV using NAT or the most sensitive test available regardless of risk of having HIV and regardless of time relative to procurement (i.e., Donor specimens should be obtained before procurement; however, NAT results should be obtained either before, if timing allows, or after procurement). (Category IB) (Question 3A)		All potential organ donors (living or deceased) should be tested for antibodies to HIV (e.g., anti-HIV 1/2 serology, Ag/Ab combination assay). All potential organ donors identified as being at increased risk for HIV infection additionally should be tested by NAT or for antigens to HIV (e.g., Ag/Ab combination assay). Donor specimens should be obtained before procurement. Antibody or antigen-antibody test results should be available before transplantation. (Refer to Table 3 for risk factors) Note: Address obtaining NAT results before or after transplantation as a footnote to the recommendation. For example "Optimally, all NAT results for deceased donors should be available before the transplant occurs; however, if this is not feasible, test results can be useful to guide recipient treatment."

AST Comment: We recommend clarifying the language from "antigens to HIV" to "HIV antigens". It is difficult to comment on language that is noted as being "for example" (the "Note") as we do not know what the final proposed recommendation will be. That said, we are in agreement that it would be optimal if all NAT test results were available on all elevated risk donors prior to transplantation, but recognize that in certain urgent life-saving situations, this may not be possible, and that it would be acceptable to proceed with transplantation in the absence of NAT results under certain circumstances with appropriate consenting.

#4	Version in Public Comment Document	Revisions per PHS Guideline Work Group
Deceased potential organ donors also should be screened for HCV using NAT or the most sensitive test available regardless of risk of having HCV and regardless of time relative to procurement (i.e., Donor specimens should be obtained before procurement; however, NAT results should be obtained either before, if timing allows, or after procurement). (Category IB) (Question 1B)	All potential organ donors (living or deceased) should be tested for antibodies to HCV (anti-HCV) and by NAT. Donor specimens should be obtained before procurement. Antibody test results should be obtained before transplantation. Note: See recommendation #3 Note regarding NAT.	

AST Comment: Although we have reservations about this recommendation as expressed in the AST public comments response letter, we strongly recommend that an algorithm for confirmation of a positive HCV NAT in a donor with no known risk factors be clearly articulated. In addition, the added costs of testing and the impact of HCV NAT results on organ acceptance and discard should be monitored to assess the cost effectiveness of measuring HCV NAT in all donors regardless of identified risk factors.

#7	Version in Public Comment Document	Revisions per PHS Guideline Work Group
Only FDA licensed-screening tests or approved-diagnostic tests should be used to test blood samples from living or deceased organ donors for HIV, HBV or HCV. (Category I)	Delete, but place comparable language in Guideline text.	

AST Comment: We would be very interested in seeing the comparable language in the context that it is going to be placed in order to comment. We would strongly recommend language that is consistent with UNOS/OPTN policy.

	Version in Public Comment Document	Revisions per PHS Guideline Work Group
Algorithms to guide initial reactive serology and NAT results		Revise recommendation #12 under Recommendations for Further Research as follows: Develop standardized algorithms for real-time discrimination of initially reactive organ donor test results to separate true versus false positive results. Retesting reactive specimens can better inform on the utility of assays; confirmed prevalence in the potential organ donor population; and decisions by OPOs, transplant centers and transplant patients on organ suitability.

AST Comment: While this is now a "research" question, organs recovered from donors with initially positive, but subsequently negative tests are currently being used today. We recommend developing in more detail a recommendation regarding that the process of utilizing such organs, specifically addressing the responsibility of OPOs, and transplant centers regarding the use of such organs, and the attendant informed consent issues for recipients regarding the use of an organ from a donor with a non persistent positive result, especially if from a donor with known risk factors. We do not believe that the recipient can simply be told that the result is negative.

Recipient Testing (change to Pre- and Post-transplant Recipient Testing)

#1	Version in Public Comment Document	Revisions per PHS Guideline Work Group
Transplant candidates, for whom follow-up testing is planned post-transplant, should have a serologic assessment of their HIV, HBV, and HCV status at the time that they are admitted to the hospital to undergo the organ transplant but prior to implantation of the organ. (Category IB) (Expert Opinion - Question 2A)	Pre-transplant testing of transplant candidates for HIV, HBV and HCV should be conducted when the donor (living or deceased) meets any of the following conditions: 1) identified as being at increased risk for HIV, HBV and HCV infection*; 2) screening specimens are hemodiluted; or 3) the medical/behavioral history is unavailable. Transplant candidate testing should be performed during admission to the hospital to undergo the organ transplant, unless known through prior testing to be infected. *If the donor is only identified as being at risk for HCV infection (hemodialysis in the preceding 12 month), then testing for HCV only is recommended.	

AST Comment: We recommend clarifying the language to indicate that this testing should be done just prior to transplant.

#3	Version in Public Comment Document	Revisions per PHS Guideline Work Group
Where the donor (living or deceased) was infected with HBV or HCV, post-transplant recipient testing should be done, unless recipient infection has been documented pre-transplant. (Category IB) (Expert Opinion - Question 2C)la	Pre-transplant testing of transplant candidates for HBV or HCV should be conducted when the donor (living or deceased) is infected with HBV or HCV. Patient testing should be performed during admission to the hospital to undergo the organ transplant, unless known through prior testing to be infected.	

AST Comment: We recommend clarifying the language to indicate that this testing should be done just prior to transplant.

Recipient Informed Consent

#2	Version in Public Comment Document	Revisions per PHS Guideline Work Group
Patients should be allowed opportunities to discuss with clinicians issues related to organ and associated risk acceptance at any time while on the waiting list. (Category IB) (Expert Opinion - Question 1C)		The transplant candidate, or medical decision maker, should have opportunities to discuss with clinicians issues related to organ and associated risk acceptance while on the waiting list.

AST Comment: The language is unclear as written. We recommend clarifying it, such as: "…issues related to the risks associated accepting or turning down organs"

Donor and Recipient Specimen Collection and Storage

	Version in Public Comment Document	Revisions per PHS Guideline Work Group
Rec. #1	For initial deceased donor screening, consider collecting separate ethylenediaminetetraacetic acid (EDTA) plasma specimens for NAT rather than using serum samples for serologic assays. When an alternate specimen is not available and a previously assayed serum is used for NAT, documentation should be provided. (If only one specimen tube is feasible, all FDA licensed-screening tests and/or FDA-approved tests are licensed for use with serum or EDTA plasma specimens.) (Category IIB) (Expert Opinion - Question 3B)	Create two recommendations for blood specimen collection and storage: 1) deceased donors and 2) living donors, transplant candidates and recipients: For deceased donors, collect two blood specimens for HIV, HBV and HCV testing prior to organ recovery, when possible – an ethylenediaminetetraacetic acid (EDTA) plasma specimen or serum specimen for serologic assays and a separate EDTA plasma specimen for NAT. Additionally, collect two blood specimens for archiving, when possible. If it is only feasible to collect one specimen, a plasma specimen collected in EDTA is optimal. For living donors, transplant candidates and recipients, two blood specimens should be collected when HIV, HBV or HCV testing is planned – an EDTA plasma specimen or serum specimen for serologic assays and a separate EDTA plasma specimen for NAT. Additionally, two blood specimens should be collected from living donors during admission to the hospital for organ recovery and from transplant candidates during admission to the hospital for organ transplantation for archiving. Note: In the Guideline text, provide rationale for collecting two separate

		samples and preference of plasma over serum if only feasible to collect one tube of blood.

AST Comment: We recommend clarifying that the first two specimens are for "real time screening or testing" and that the second two specimens (or only one where only this is feasible) are those being saved for archiving. In addition, we are concerned about the logistical issues associated with saving one or two specimens in a -70 freezer for 10 years. There are several unanswered questions that should be addressed: What would be the estimated cost and who would assume this cost? Who would be responsible for monitoring the freezers? Are two specimens really necessary: wouldn't EDTA/Plasma only be sufficient? Could these specimens be stored for a lesser period of time? Is this care or research? Would it be necessary to obtain informed consent from living donors as well as the recipients that specimens are being archived? Would additional consent be required to access the "biobank" and who would control access to these archived specimens?

Tracking and Reporting of HIV, HBV and HCV

3. When a transplant center receives information that a recipient of an organ or blood vessel conduit from a deceased donor is newly infected with HIV, HBV or HCV post-transplant, the transplant center should notify 1) the OPTN; 2) the OPO that procured the organs and any blood vessel conduits; and 3) public health authorities where the transplant took place in accordance with state requirements for reporting notifiable infectious diseases.

AST Comment: We recommend that the language be clarified to indicate clearly that this refers to "a recipient of……from any deceased donor is newly infected at any time post-transplant with ….." We also suggest adding a recommendation that all information obtained in investigating the source of infection in newly infected recipients be shared completely between public health authorities and the OPTN.

4. When a donor recovery center receives information before organ recovery that a living potential donor is infected with HIV, HBV or HCV, the donor recovery center should notify 1) the OPTN; 2) the transplant center to receive the organ; and 3) public health authorities where the potential donor lives in accordance with state requirements for reporting notifiable infectious diseases.

AST Comment: We suggest clarifying this recommendation to indicate that if the organ transplant is NOT going to happen, then only mandated PHS/State reporting should take place. If a potential living donor is found during routine donor evaluation to be infected with HCV, HBV or HIV, in most circumstances the donation will not occur and there is no reason to notify the OPTN. If the transplant is still going to proceed, then we would agree with language as written.

5. When a donor recovery center receives information after organ recovery that a living donor is infected with HIV, HBV or HCV or that an organ recipient infection with HIV, HBV or HCV is suspected of being donor-derived, the organ recovery center should notify 1) the OPTN; 2) the transplant center that received an organ from the donor; and 3) public health authorities where

the organ recovery took place in accordance with state requirements for reporting notifiable infectious diseases.

<u>AST Comment</u>: We recommend clarifying the language to indicate that this section refers specifically recipients of live donor organs: "….or that a live donor organ recipient infection…" We recommend a similar change in 2. (above) regarding recipients of deceased donor organs, which would read: "….or that a deceased donor organ recipient infection…"

	Version in Public Comment Document	Revisions per PHS Guideline Work Group
Rec. #10	Prospective living donors should be notified if they are found through the screening process to be HIV, HBV or HCV infected. (Category I)	A living donor whose blood specimen is positive for HIV, HBV or HCV when tested by the donor recovery center should be notified by the donor recovery center of his or her infectious disease status. WG

<u>AST Comment</u>: We would recommend changing the language to "A prospective living donor…"

	Version in Public Comment Document	Revisions per PHS Guideline Work Group
Rec. #3	Data on the results of pre- and post-transplant bloodborne pathogen infection assessments in recipients should be collected nationally and analyzed on a regular basis to inform policy decisions and future screening recommendations. Nationally aggregated data on donor-derived infections should be disseminated to allow the transplant community to have access to the data. (Category IB) (Expert Opinion - Question 2G)	Move revised recommendation to Recommendations for Further Research, recommendation #15. On an annual basis, collect, analyze and report national data on HIV, HBV and HCV infection transmission rates based on donor and recipient testing to inform policy decisions and future screening recommendations

<u>AST Comment</u>: We would recommend that this specifically state that the OPTN would collect, analyze, and report these data on annual basis.

<u>Recommendations for Further ~~Research~~ Study</u>

<u>AST Comment</u>: In general, we would recommend collection and analysis of the National NAT data as an important additional topic for Study.

	Version in Public Comment Document	Revisions per PHS Guideline Work Group
#9	Evaluate transplant candidate and recipient outcomes if organ donors with behavioral or nonbehavioral risk factors were excluded from donating. This process may also require comparing incidence of infection among population subsets within risk factors.	Leave as is

<u>AST Comment</u>: This recommendation touches on a broader concern we have with these proposed guidelines. We strongly urge that there be modeling data available on the projected impact of these guidelines on organ donation, disease transmission, organ transplant outcomes, and costs PRIOR to, or at the time of publication of these proposed guidelines rather than saying that this is important question for further study after the guidelines are published.

	Version in Public Comment Document	Revisions per PHS Guideline Work Group
#11	Evaluate the rate of false positive immunoassay and NAT results for HIV, HBV and HCV among potential organ donors and the percentage of cases where donors are declined due to such results stratified by organ type.	Evaluate the rate of false positive test (e.g., immunoassay and NAT) results for HIV, HBV and HCV among potential organ donors and the percentage of cases where donors are declined due to such results stratified by organ type.

<u>AST Comment</u>: We strongly agree with collecting national data on performance of these donor and recipient testing including NAT, and specifically the results of confirmatory tests related to any positive result – NAT or immunoassay (including those found to be false positive tests).

June 15, 2012

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