American Society of Transplant Surgeons

National Office
2461 South Clark Street
Suite 640
Arlington, VA 22202
Phone: 703 414-7870
Fax: 703 414-7874
asts@asts.org
www.ASTS.org

President
Kim M. Olthoff, MD
University of Pennsylvania
Department of Surgery
3400 Spruce Street - 2 Dulles
Philadelphia, PA 19104
Phone: 215 662-6136
Fax: 215 662-2244
kim.olthoff@uphs.upenn.edu

President-Elect
Alan N. Langnas, DO
University of Nebraska
983285 Nebraska Medical Center
Omaha, NE 68198-3285
Phone: 402 559-8390
Fax: 402 559-3434
alangnas@unmc.edu

Secretary
Charles M. Miller, MD
Cleveland Clinic Foundation
9500 Euclid Ave.
Mail Code A-110
Cleveland, OH 44195
Phone: 216 445-2381
Fax: 216 444-9375
millerc8@ccf.org

Treasurer
Timothy L. Pruett, MD
University of Minnesota
Department of Surgery
420 Delaware Street
SE MMC 195
Minneapolis, MN 55455

Immediate Past President
Mitchell L. Henry, MD

Past President
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Sandy Feng, MD, PhD
John C. Magee, MD
Jean C. Emond, MD
Abhinav Humar, MD
Lloyd E. Ratner, MD, MPH

Executive Director
Kimberly Gifford, MBA
Kim.gifford@asts.org

September 12, 2012

James Berger
Senior Advisor for Blood Policy
Office of HIV/AIDS and Infectious Disease Policy
Office of the Assistant Secretary for Health
U.S. Department of Health and Human Services
1101 Wootton Parkway, Tower Building, Suite 250
Rockville, Maryland 20852

RE: ASTS Comments – PHS Revised Guidelines for Reducing HIV, HBV, and HCV through Organ Transplantation

Dear Mr Berger:

The American Society of Transplant Surgeons (ASTS) is pleased to have the opportunity to provide feedback on the revised *Guideline for Reducing Transmission of HIV, HBV and HCV Through Organ Transplantation* ("Draft Guidelines"). We very much appreciate the substantive changes made by the CDC in response to our prior comments and the comments of others, and the agency's willingness to continue to engage with us on this most important project.

This being said, it is with great regret and considerable reluctance that we must continue to take exception with the Draft Guidelines. While much needed changes were made in the definition of "increased risk" donors, and while we very much appreciate these changes, many of the deficiencies noted in our prior comments unfortunately remain. Specifically, the current draft:

- Continues to present HIV, HBV and HCV transmissions as a frequent event, and continues to intermingle transmissions of diseases other than HIV, HBV, and HCV with transmissions (or possible transmissions) of HIV, HBV, and HCV in a manner that is potentially misleading;

- Fails to provide objective and accurate estimations of the risks to better inform our patients of the potential risks for a given donor;

- Fails to provide a risk/benefit analysis for the Draft Guidelines;

- Will, as a practical matter, result in HCV, HIV, and HBV NAT testing for all donors;[1]

- Precludes the use of vessel conduits subsequent to the completion of the initial transplant;

- Continues to make sweeping recommendations based on weak or no evidence;

- Fails to address the issue of discordant test results and their impact on organ usage;

- Appears to ignore the existence of OPTN policies already in place to protect against transmissions;

- Dictates medical practice with respect to post-transplant testing of recipients of increased risk organs; and

- Recommends the collection and storage of specimens for 10 years, without adequate evidence and without consideration of the cost of such storage.

We are particularly concerned that the Draft Guidelines continue to overstate the risk of transmission and continue to cite to outdated data and data that includes transmissions of diseases other than HIV, HBV, and HCV. In this regard, the Executive Summary of the Draft Guideline states:

> Unexpected transmission of HIV, HBV, and HCV through organ transplantation is a critical patient safety and public health issue.

It is not until page 23 of the Draft Guideline, well into the Background section, that the reader learns that, in fact, since 1986, there have been six donors that "slipped through the cracks" of the existing screening protocols, resulting in unexpected transmission of HBV, HCV, or HIV.

Moreover, the Draft Guidelines continue to exaggerate the potential risk of unintended disease transmission by including cases that were, in fact, caught be existing screening mechanisms and by including transmissions of infectious diseases other than HBV, HCV, and HIV. For example, in the section of the document misleadingly entitled, "Donor Derived Infections", the Draft Guidelines cite to a study of "potential organ donors" evaluated January 2004 to mid-2008 by 17 OPOs, and, based on the data in that study, the Draft estimate that the incidence of "undetected" viremia for normal-risk potential donors was 1 in 50,000 for HIV and 1 in 5,000 for HCV (1 in 11,000 for HIV and 1 in 1,000 for HCV for high risk donors). What the Draft Guideline does not say is that, of the anti-HIV-positive donors identified by the 17 OPOs involved in the study, none were transplanted. And of the anti-HCV-positive potential donors,

[1] While the Draft Guidelines purport to require HCV NAT testing only, NAT testing is generally performed for HCV,HBV and HIV at the same time.

36.0% did not have any organs recovered. Far from supporting the proposition that the incidence of HIV and HCV in the potential donor population is cause for alarm, as the Draft Guideline suggests, the article, read objectively, appears to suggest that current clinical judgment and screening mechanisms are in fact working relatively well.

Even more disturbingly, the Draft Guidelines continue to refer to data that intermingles HBV, HCV, and HIV unexpected transmissions with other disease transmissions. Specifically, on page 22, the Draft Guidelines cite to OPTN data from 2005-2007, and note, that:

> …of 80 potential donor-derived disease transmissions reported to UNOS, 30 cases were confirmed, although underreporting may have resulted in an underestimation of the true count."

What the Draft Guideline fails to note is that the 30 cases were not confined to HIV/B/C, but rather include all infection disease transmissions. It is unclear from the data cited whether any of the 30 cases constituted transmissions of HBV, HCV, or HIV.

More recent HBV, HCV, and HIV DTAC data for cases reported from 2008-2011 suggest that there was one recipient death due to transmission of HCV during this four year period, and none reported due to unexpected transmission of HIV or HBV. We believe that the Draft Guidelines utterly fail to put the issue of unexpected transmission of HBV, HCV, and HIV into context and for this reason, among others set forth at further length in the attached analysis, is fatally flawed.

We have numerous other comments on the Draft Guideline, which are set forth in greater detail in **Appendix A**. Underlying all of our concerns, however, is our genuine puzzlement regarding why the alarmist tone sounded in the Draft Guideline persists, in light of the relatively few cases involving transmission of HBV, HCV, or HIV that have occurred over the past decade. While we are most certainly dedicated to minimizing the risk of unexpected transmission of HBV, HCV, and HIV, we firmly believe that this goal is most likely to be achieved through an objective assessment of the efficacy of the screening mechanisms currently in place, a careful analysis of both the advantages and costs of adding additional precautionary measures, and genuine acceptance of the notion that "zero transmissions" is not an achievable goal.

We appreciate the tremendous effort by numerous experts to create more appropriate guidelines that properly reflect today's clinical practice and were encouraged last January when Dr. Cono assured us that the final product would be acceptable to the transplant community. Unfortunately, we firmly believe the Draft Guidelines are not ready for public release without further input and revision. ASTS remains committed to working with HHS to finalize an acceptable document and would be greatly disappointed to have come this far in the process and not be able to support the final product. We would very much appreciate the opportunity for further dialogue and revision that would allow ASTS to embrace the final product. In the absence of further dialogue

and revision, ASTS will regrettably request that our organization and our representative not be recognized within the document. We trust you will agree that further dialogue, focused on resolving the remaining key issues, is appropriate and ask you to contact ASTS Executive Director, Kim Gifford, via email, kim.gifford@asts.org, or phone, 703-414-1609, to arrange a mutually agreeable time to continue our discussions.

Sincerely,

Kim M. Olthoff, MD
President

Cc Ronald Valdiserri, MD
Deputy Assistant Secretary for Health, Infectious Disease
Department of Health and Human Services

Matthew J. Kuehnert, MD
Director, Office of Blood, Organ and Other Tissue Safety
Centers for Disease Control and Prevention

Debbie L. Seem, MPH, RN
Nurse Consultant, Division of Healthcare Quality Promotion
Centers for Disease Control and Prevention

APPENDIX A

Detailed Comments

I. Executive Summary.

In our view, there are a number of significant problems with the Executive Summary:

First, and most importantly, the Executive Summary sets an alarmist tone for the document by characterizing the unexpected transmission of HIV, HBV, and HCV as a "critical patient safety and public health issue" and, even further, raising the spectre of further transmission from infected recipients to others, which, to our knowledge, has never happened.

Second, the Executive Summary includes conflicting statements regarding the intent of the Guidelines. Two very different objectives are set forth: (1) to reduce the risk of transmission of HBV, HCV, and HIV and (2) to "maximize transplant recipient outcomes while preserving patient safety with regard to risk of HIV, HBV, and HCV transmission, keeping in mind that transplantation can never be free of this risk." There is a considerable differences between these objectives, which the document fails to recognize or reconcile.

Third, the Executive Summary mischaracterizes the current state of knowledge regarding the factors that may impact HIV, HBV and HCV transmission or the steps that can be taken to prevent it. For example, the Draft Guidelines indicate that these factors that may impact HIV, HBV, and HCV transmission are "known"; in fact, the Evidence Review in the Draft Guidelines itself suggests that there is very little or no data available regarding the factors known to be associated with increased likelihood of disease transmission by organ donors. The factors identified in the document to identify increased risk donors are based on expert opinion only. More generally, there is little or no data available to answer most of the questions posed in the Guidelines, and the Executive Summary should explicitly acknowledge this unfortunate fact.

Fourth, the Executive Summary fails to acknowledge that strict application of the 1994 Guidelines, as written, would significantly and unnecessarily limit the number of organs available for transplantation and that the1994 Guidelines need to be changed in this regard. In 2011, 10.3% of all deceased organ donors in the United States were identified as "high risk" using the 1994 definitions, and the 1994 Guidelines stated that irrespective of donor testing results, deceased donors that met the identified criteria should not be used as organ or tissue donors. In fact, a review of the OPTN experience over the past four years does not demonstrate differences in one and three year graft/patient survival for recipients of organs from standard or high risk donors. The incidence of malignancy and/or infection in these populations is no different. While eliminating the language from the 1994 Guidelines that precludes use of organs

from donors identified as being at higher risk is one of the major reasons for revising the 1994 Guidelines, the Draft Guidelines fail to state explicitly state that the 1994 Guidelines are being revised in this regard, and that a donor with the identified variables will not be excluded from donating. This needs specific clarification.

Fifth, the Grading system used in the document requires clarification in a number of respects:

- It is unclear to us on what basis the authors determine whether there evidence of "net clinical benefits or harms" or evidence of a "trade-off between clinical benefits and harms". In our view, virtually all of the questions posed in the document involve some "trade-off" between clinical benefits and harms, since there is a natural tension between minimizing the risk of disease transmission and preventing organ wastage. The critical issue is how these benefits and harms are to be balanced to determine whether any particular recommendation results in a "net benefit," or a "net harm," or whether the calculation is so complex or unclear as to be indeterminate.
- In our view, the paragraph on page 11, beginning "The evidence based recommendations were cross-checked" is fundamentally incomprehensible. So far as we understand it, Category ID recommendations are simply strong recommendations that the authors wish to make without reviewing whether or not they are supported by any evidence?
- The GRADE categories include categories for both strong recommendations and weak recommendations based on "high to moderate quality evidence". However, the Evidence Review suggests that there was no high or moderate quality evidence to support any recommendations. This should be explicitly noted in the Executive Summary.

Donor Risk Factors for Recent HIV, HBV, or HCV Infection.

It should be explicitly noted that "increased risk" donors are defined based on the views of "subject matter experts" and on studies of populations other than organ donors. We very much appreciate the revisions that have been made to this section of the document; however, we continue to believe that it is not appropriate to include men who have had sex with another man or women who have had sex with a man with a history of MSM behavior in the preceding 12 months in the definition of "increased risk" living donors. Also, throughout the document, care should be taken to use the terminology "engage in behaviors identified with increased risk" rather than using the terminology "donors at increased risk", since these factors have not been definitively associated with increased risk of disease transmission.

Donor Testing (Living and Deceased)

While the Draft Guidelines no longer call for NAT testing for HBV or HIV, they continue to call

for NAT testing of all organ donors for HCV. Since NAT testing generally is provided for all three viruses or not at all, as a practical matter, the retention of NAT testing for HCV means that all donors, regardless of risk, will be NAT tested for all three viruses. Furthermore, the Draft Guidelines does nothing to address the issue of discordant test results and their impact on the donor pool.

The basis for the recommendation for NAT testing for all organ donors is unclear. In fact, the Literature Review found moderate quality evidence demonstrating the sensitivity and specificity of second and third generation immunoassays for HCV, with test sensitivity of 100% and a specificity range of 94.4-99.9% for third generation assays. By contrast, the Literature Review found low quality evidence regarding the sensitivity and specificity of NAT assays for HCV. Moreover, it appears that the studies are inconclusive regarding the impact of receiving organs from HCV positive donors compared to HCV negative donors, even when recipients were negative before transplant.

We also believe that any reference to HIV antigen testing be eliminated from the Draft Guidelines since this form of testing has not been cleared by the FDA, and is not commercially available in the United States. It is clearly inappropriate for the CDC to recommend the use of a test that cannot be furnished legally in this country.

Recipient Informed Consent

It is unclear to us why the Draft Guidelines include specific recommendations regarding Recipient Informed Consent, a topic which is addressed in a myriad of other sources, including OPTN Policies Medicare certification requirements; and state law. We do not believe that this is a subject that is appropriate to be addressed by CDC Guidelines: Informed consent has no role in minimizing the risk of disease transmittal or in clarifying the trade off between minimizing the risk of disease transmittal and minimizing organ wastage. In short, it is unclear what problem in the current informed consent process, if any, the inclusion of these recommendations is intended to address, and we suggest that all of the recommendations included in the Draft Document be eliminated.

These recommendations generally either reiterate current practice or require the transplant team to provide information to the potential organ recipient that is unknown or unknowable. For example,

- **Recommendation 10**: This recommendation mirrors current practice insofar as it requires that patients be counseled to consider potential risks of both accepting and rejecting organs from donors known to be infected or donors carrying the identified behavioral factors. However, this recommendation fails to indicate that this counseling should be included as part of the overall informed consent process, and put into the overall risk profile context.

- **Recommendation 12 and 13**:The Draft Guidelines require an additional informed consent discussion that "includes more specific information regarding the potential for increased risk of HIV, HBV or HCV transmission based on the donor information available at that time to enable the potential candidate or medical decision maker to better understand the risk." Likewise, Recommendation 13 indicates that the transplant center team is to have an informed consent discussion with the transplant candidate or medical decisionmaker prior to transplantation "regarding the probability of disease transmission." However, as the CDC's own literature review makes clear, there is little or no data currently available to share regarding the "potential for increased risk" or the "probability of disease transmission" beyond the fact that, as stated in recommendation 14, no screening question or laboratory test can completely eliminate the risk for transmitting these infections (or any other infection.)

Pre and Post-transplant Recipient Testing

While we concur that pre-transplant testing is appropriate, and that recipients of organs from the donors specified in the recommendations should be tested post-transplant, the scientific basis for requiring testing at certain specified intervals (one to three months post-transplant and at 12 months post transplant) is unclear to us.

Donor and Recipient Specimen Collection and Storage

We urge PHS to clarify that the recommendations relating to specimen collection and storage 24 apply only to donors that have been identified as engaging in behaviors that place them at increased risk, and not all donors**.** We also urge the agency to reconsider the recommendation for 10 year storage of organs and tissues from living donors and from recipients. While the OPTN does require OPOs to store certain specimens for 10 years, these recommendations would extend these requirements to transplant centers by making the 10 year storage requirements applicable to recipient specimens and specimens from living donors. Transplant centers, unlike OPOs, do not have the facilities to effectuate this recommendation.

Moreover, Recommendation 24 extends further than imposing onerous new storage requirements on transplant centers by precluding use of vessel conduits subsequent to completion of the initial transplant. The rationale for this recommendation is unclear.

Finally, we wish to comment on the accuracy of the Draft Document with regard to "Key Question 10: "What is the impact of false positive tests on the organ donor pool?

In this regard, the Draft guidelines state: "Our search did not identify any studies that estimated the number of donors or organs excluded from recovery due to false positive results for HIV, HBV, or HCV."

This seems to be quite odd as licensing data exists within the FDA regarding the sensitivity and specificity of all FDA approved tests and these could be used, discussed and applied to the numbers of donors assessed, as was done in **"***Nucleic acid testing (NAT) of organ donors: is the 'best' test the right test? A consensus conference report"* Am J Transplant 2010 Apr;10(4):889-99. In addition, the application of multiple tests to assess donors and discordant test results has been addressed. See *"Zero risk tolerance costs lives: loss of transplantable organs due to human immunodeficiency virus nucleic acid testing of potential donors.***"** Prog Transplant. 2011 Sep;21(3):236-47, stressing that more people have been denied organ transplantation and experienced an increased risk of death due to the use of NAT and antibody tests than diseases prevented. The lack of discussion of the impact of discordant/false positive testing upon the overall availability of organs for the nation's recipients is wrong: This is too big of a concern to be ignored. See *"A consolidated biovigilance system for blood, tissue and organs: one size does not fit all."* Am J Transplant. 2012 May;12(5):1099-101. In the event that there is no reliable data, then efforts should have been made to somehow address the issue. We believe that the time is ripe for an open and transparent discussion of the acceptable threshold of transmissible disease within our donor supply. See *Feces in our food, viruses in our organs: donor surveillance, organ transplantation and the risk for disease transmission.*