November 17, 2011

The Honorable Thomas Frieden, MD, MHP
Director, Centers for Disease Control and Prevention
1600 Clifton Rd, N.E.
Mailstop A-07
Atlanta, Georgia, 30329

Re: Docket No. CDC-2011-0011: Public Health Service Guideline for Reducing Transmission of Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV) through Solid Organ Transplantation

Dear Dr. Frieden,

The American Society of Transplantation (AST), the largest society representing professionals engaged in the field of organ transplantation, is pleased to comment on "PHS Guidelines for Reducing the Transmission of Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV) through Solid Organ Transplantation." The stated goal of this guideline is to update the 1994 document*: PHS Guidelines for Preventing Transmission of HIV through Transplantation of Human Tissue and Organs.* AST agrees that updating the 1994 document is timely and appropriate. The overall safety of patients and the successful transplantation of the maximum number of patients with end-stage organ failure are both of high importance to AST. Our comments are in keeping with a long tradition of AST's collaborative work with federal agencies to develop policies promoting safe and successful solid organ transplantation. Unfortunately, the currently proposed draft guidelines depart from this tradition in terms of process, and there are major flaws in its conceptualization, development, methodology and conclusions. The draft document, without appropriate justification in terms of overall benefit, views the practice of solid organ transplantation from the sole perspective of minimizing the risk of unintended transmission of HIV, HCV and HBV.

General comments

1. The document fails to provide a reasonably conclusive estimate regarding the overall rate of confirmed transmission of HIV, HCV and HBV from donor to recipient (all agree this must be extremely low), the clinical impact of these transmissions or any assessment regarding the magnitude of the problem. The brief overview of the current data on unintended transmission (pages 22-24) lacks precise numbers and perspective.

2. There is no justification of the need to urgently reform existing guidelines. In fact, a substantial number of the recommendations in the draft revision are mere re-statements of practices currently mandated by the OPTN.

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3. Nowhere in the document is there analysis, modeling or even a logical projection of the anticipated clinical benefit in terms of reducing disease transmission. Similarly, there is no projection of the overall benefit to the practice of solid organ transplantation in the United States should the recommendations be implemented. Specifically, the draft guidelines completely ignore the impact on survival of those with irreversible organ failure resulting from a potential reduction in the number of solid organ donors due to the recommended screening strategies outlined. It is well known that the discard rate of donor organs categorized as "elevated risk" is higher than those that are standard risk. It is therefore highly likely this guideline, if implemented, will result in a net decrease in the number of available deceased donor organs and an increased number of deaths of waitlisted patients. Whether this would be offset by any reduction in infectious disease transmission is not addressed, nor do the provided data inform this concern.

4. The categorization algorithm utilized to rate recommendations is of questionable validity. Many practices are rated IB (Strong recommendation supported by low- to very low-quality evidence suggesting net clinical benefits or harms). It is difficult to understand how this level of evidence supports a "strong recommendation." These recommendations pervade this document.

5. In many instances, the purpose of proposed screening is uncertain, as no corresponding recommendations are made regarding application of the results of screening tests. For instance, the guidelines indicate specimens be examined for HCV, HIV and/or HBV, though it appears organ transplantation can occur prior to the availability of the results; is the goal epidemiologic research on the prevalence of these infections in the donor population? Collecting these data may be worthwhile, but it is unclear how such a policy will reduce the transmission of disease. If the goal is to inform decision making and prevent transmission, screening results must be available prior to transplantation.

6. There is mention in many recommendations regarding diagnostic testing for HIV, HCV and HBV "in compliance with FDA-approved package insert." There is a blurring of the distinction between testing approved for diagnosing and monitoring of infection and those tests approved and developed for screening infection in potential donors. In many instances, it appears the draft guidelines recommend diagnostic tests approved for monitoring be utilized for screening. These tests were not developed for this use, and they have not been adequately tested and validated.

7. While AST acknowledges representation on the expert panel involved in preparation of this draft document, virtually all members of the panel drawn from the transplant community (clinicians engaged on a daily basis in the care of transplant patients) chose to withdraw their names from the document due to serious objections with methodology and conclusions. Indeed, as stated on page 2, this is "...not a consensus document."

8. Although this is a "guideline" document, it appears intended to (and likely will) become a regulatory standard: "...intended for use by OPO staff, transplant staff including physicians, nurses, administrators and clinical coordinators; and laboratory staff responsible for testing and storing donor and recipient specimens; and persons responsible for developing, implementing, and evaluating infection prevention and control programs for organ procurement organizations and transplant centers." (Page 20). Category 1 recommendations have even more potentially

burdensome implications: “For policymakers: recommendations may be adopted as policy or is current federal and/or state statutes, regulation or standards.” Further, the impact of the scoring and overrating some recommendations is likely to result in to third-party payers and CMS making reimbursement policy dependent upon these “guidelines.” This is a document with very serious implications for patient care in the United States. As such, its recommendations should be based on the highest level of evidence and consensus.

9. Our final comments relate to the overall flow and ease of following the Draft Guideline document. Given the intent and importance of this document, we find it disappointing that it is so difficult to examine in any comprehensive fashion. The reader is frequently referred to questions and sections that are difficult to find and/or understand. Any revised or new document should be developed with specific attention to improving the flow (particularly of the portion of the document that follows the recommendations) so individual clinicians as well as transplant centers and OPOs are able to fully understand the intent, meaning and supportive evidence for the individual cases.

Specific comments on each recommendation follow below.

Donor Risk Assessment

General comments:

Many of the recommendations in this section refer to interviewing individuals regarding behaviors in themselves or family members that increase risk for acquiring HIV, HBV or HCV. For interviews to be effective, and for the utility of such an approach to be evaluable and of utility in epidemiologic studies, a standardized questionnaire is essential along with adequate training of personnel in administering it.

Specific comments by recommendation:

1. We agree with this and feel it should be standard practice.

2. We acknowledge the need to address this issue. We particularly agree with the need to perform this in a confidential manner. Our major concerns with this recommendation are lack of standardization of the questionnaire, training of personnel for its administration and the fact that we have not validated this questionnaire’s effectiveness in identifying those truly at risk. We are concerned that in the absence of a validated questionnaire, practices will vary widely, and there will be non-uniform categorization of potential donor risk, causing unnecessary loss of potential donors. Establishing a validated questionnaire is a critical area for research in the near future. Since this is difficult to do in organ donor populations in a timely manner, consideration should be given to studies interviewing both next of kin/partner/friend as well as individuals in both high- and low-risk non-donor populations as a surrogate for potential organ donors.

3. We are in general agreement with this recommendation. We would again recommend a standardized questionnaire and standardized training in how to provide counseling to limit subsequent risk. Additionally, we support developing studies to assess the efficacy of such counseling.

4. The recommendation is vague in several areas: What is the specifically intended age group? How would a potential pediatric donor be categorized as being at risk of maternal transmission of HIV, HCV or HBV if the father and/or mother have not been previously identified as being at risk for having acquired such infections themselves?

5. This recommendation again is vaguely worded: What is the reference age? By referring to "children," it is assumed the authors mean potential pediatric donors. What risk factors would be the basis of this distinction other than potential maternal transmission? Doesn't this apply to all potential donors—adult and pediatric? Is this recommendation really necessary?

6. We are in agreement with this recommendation, although it has important implications in terms of potentially reducing the availability of organs from a subset of donors (young children) where the pool is already extremely small.

7. This is current UNOS policy. We understand hemodilution may result in false negative serological and NAT testing. Guidelines regarding the use of organs from both average-risk and increased risk donors with negative but unreliable screens should be outlined. If organs are used, a standardized approach to quoting/communicating risk to potential recipients should be defined.

Donor Screening

General comments:

We have already expressed some general concerns over the use of Level 1 recommendations (per page 36 of the Guidelines, these could/should inform policy) when data are weak or potentially non-existent.

We have concerns with the recommendation that the "most sensitive test" should always be used. The "most sensitive" test may not be the right test in the organ donor setting when weighing risk/benefit, cost-effectiveness and logistics of implementation (Humar *et al*. *Am J Transplant*. 2010; 10: 889-899). NAT testing will almost always be more sensitive than antigen or antigen/antibody testing, but may be less effective in this setting due to specificity issues or delays in obtaining results that might impact organ quality or result in donor loss. The most sensitive test may result in an extremely marginal increase in yield (i.e. HIV, RNA and NAT versus fourth-generation HIV or Ag/AB screening) particularly when used in average-risk populations, but at an extremely large increment in cost. Should the most sensitive test be used regardless of cost-effectiveness? Cost-effectiveness estimates for the screening of low-risk populations using minipool NAT (blood donors) in the setting of previous screening using third generation anti-HIV and anti-HCV screening have been estimated to be $1,966,000/QUALY for HIV and $1,830,000/QUALY for HIV (personal communication MP Busch, Blood Systems). This stands in stark contrast with most commonly utilized medical and surgical procedures, including transplantation itself that cost less than $50,000/QUALY. Costs will likely be even higher in the setting of organ donation where "STAT" testing of individual donors (rather than less expensive batch minipool testing) is performed. We would suggest formal modeling of the cost-effectiveness of potential testing options prior to making recommendations, particularly as regards NAT testing of average-risk donors.

Specific comments by recommendation:

1. In general we find this recommendation to be appropriate. Since performance of these serologic screens is mandated by UNOS policy, shouldn't this recommendation be considered IC? However, we would like to take this opportunity to raise questions about the interpretation of screening results and the need for OPOs to develop processes and algorithms for confirming these results. Where possible, we believe these algorithms should be standardized across all OPOs (and perhaps Transplant Centers). Specific guidelines are needed regarding response to serology screens initially reactive (or repeat reactive) but suspected of being falsely positive based on immediate confirmatory testing or when confirmatory testing is not available but results are near the cut-off in an average-risk donor. Should such average or increased risk donors be utilized? Do these donors, if average-risk, become "high-risk" and require special informed consent when used? We also feel strongly that confirmation of positive results should take place regardless of whether or not transplant goes forward to better inform our understanding of the utility of the tests and the true prevalence of these pathogens in donors.

2. We agree all living donors should undergo serologic screening for HIV, HBV and HCV. However, we are concerned about the lack of data supporting the recommendation to perform NAT for <u>all</u> prospective living donors for HIV, HBV and HCV, independent of whether or not they are at increased risk for being infected with one of these viruses. That said, we agree that when performed, NAT testing should be repeated as close as is practical to the actual transplant, and AST supports the use of NAT for HIV and HCV in potential donors at increased risk for these pathogens. Screening potential donors many months prior to the date of transplant could indeed allow donation to proceed from a donor infected subsequent to the remote screening process. However, we are concerned the recommendation to screen all potential live donors within seven days of the intended date of surgery may not be feasible: a seven-day time period may not be adequate to obtain the results of these tests in time to inform decisions regarding the operation, particularly if a given donor is part of a multi-patient "chain." While its theoretical basis is admirable (in reducing the window period), not only may results be unavailable, but the short time frame limits adequate evaluation of a potentially false-positive result. We recommend reconsidering this timeline in light of laboratory logistics and transplant scheduling; it should be extended by at least several days. We are also puzzled by (and have strong reservations regarding) the statement, "Test results should be obtained before organ recovery occurs, if feasible." In the living donor situation, there is no delay between organ procurement and organ implantation, and thus this suggests transplantation may proceed without knowledge of the NAT screening results, an unreasonable proposition in the living donor setting. Why perform NAT testing and proceed with organ recovery and transplantation prior to availability of results in this setting? If the purpose of the use of NAT testing to minimize risk of transmission in what is clearly an "elective" procedure as regards timing, then NAT screening must be performed sufficiently in advance to guarantee these results will be available in time to inform a decision about going forward or not. Again, is recommendation of NAT testing in this context to support epidemiologic research or perhaps to inform early treatment interventions rather than prevent transmission of HIV and HCV? We further believe decisions regarding the need to perform NAT screening of live donors for HIV and HCV can be stratified based on the presence or absence of risk, reserving NAT for those with risk factors. This is particularly applicable to those found to be seronegative for exposure to HIV and HCV earlier in the donor evaluation process. With repeated serologic screening more proximal to the day of surgery, in the continued absence of identified risk factors, the use of NAT is unlikely to be of benefit. There is

no published evidence that NAT in this circumstance would be of significant net benefit when weighed against the disruption and delays associated with potential false positive results. (See cost-effectiveness comments in general comments above). While in the living donor setting false positive results are less likely to result in donor loss, they nonetheless delay surgery, add attendant costs and disrupt multi-patient chains. As an alternative, we support the development and implementation of standardized algorithms to interpret and respond to positive screening results in potential living donors that incorporate repeat testing and follow up to confirm initially reactive results. (See discussion below under item 3). Specifically, guidelines should outline confirmatory and follow-up testing requirements for the donor, including the timeframe when testing should take place to provide sufficient proof the initial reactive NAT screen is a false positive result, and therefore that donation can proceed. Consideration should be given to using or adapting algorithms developed by transfusion services in several countries, including the US, to allow re-entry of blood donors who have initially reactive or repeat reactive individual donor (ID) NAT screens but in whom follow up testing fails to confirm infection (Weusten Transfusion 2011;51:203). Among potential living donors without a previous history of HBV immunization or natural immunity, the use of accelerated or standard HBV immunization strategies might offer protection from window period infections, be of benefit to the donor and obviate the need for NAT screening for HBV. Finally, we are also uncomfortable with Level I assignment for this set of recommendations. The recommendation appears to be a disproportionate response to a single case of HIV transmission from a living donor known to be in an increased risk category (MMWR 2011; 60:10) without adequate consideration of potential implications of broadly implemented testing, particularly in low-risk populations. Although there is theoretical benefit of window period reduction with NAT testing, there is no direct evidence to support significant benefit in average-risk living donor populations, and there is the potential for both harm and significantly increased costs.

3. AST has concerns regarding the recommendation to obtain HIV NAT for all potential deceased donors. We acknowledge that, based on window period incidence modeling in organ donors, HIV NAT has the potential to reduce the incidence of undetected HIV infection during the window period from 1.72 to 0.55 per 100,000 donors in average-risk donors and 8.54 to 2.72 per 10,000 donors in high-risk donors (Ellingson Am J Transplant 2011;11:1201). Despite this potential benefit, we are concerned about the impact of false positive NAT screens that result in exclusion of appropriate donors and an increased number of deaths of those awaiting life-saving transplants. In average-risk donors, the vast majority of reactive ID NAT screens would represent false positive results (Challine Lancet 2004; 364:1611). Extensive experience in the blood system using FDA licensed donor screening NAT assays indicate false positive rates for initially reactive tests as follows:

    i. Roche MPX assay (tested in minipools) 0.07%- 0.70% (~1/150 -1/1500) S*chmidt Vox Sanguinis 2010 98:37.*

    ii. Genprobe Ultrio assay (tested in minipools 0.069 % (~ 1/1500) *Stramer (ARC) personal communication.*

    iii. False positive rates for ID NAT screening as will be performed in organ donor testing has poorer specificity than minipool NAT. Estimated false positive rates for ID NAT (Ultrio assay) are 0.13% - .85% (1/117- 1/769) *Kleinman* ISBT Science Series 2008;3:191.

Limited data modeling of the benefits versus risks (donor loss from false positive tests) in average-risk donors suggested over a wide range of extremely conservative false positive rates (1 in 500 to 1 in 5,000), NAT testing would result in a net loss of quality adjusted life years for transplant recipients. This modeling is based on the assumption that all donors whose initial screening test is reactive will not be used (Humar *et al*. *Am J Transplant*. 2010; 10: 889-899). To date, there are no data demonstrating use of NAT testing for potential donors *not* identified as at increased risk will actually lead to a net savings in lives; this document provides no such estimates. A recent consensus conference did not support universal HIV NAT (Humar *et al*. *Am J Transplant*. 2010; 10: 889-899). In the scenario of performing NAT on potential donors who are not at increased risk for HIV, we believe universal donor testing will increase the frequency of confusing scenarios, such as when a reactive HIV NAT is suspicious of being a false positive (e.g. NAT result with a very low copy number with repeat negative tests in a patient unlikely to be at risk [such as a toddler]). At the present time, we are aware some OPOs have offered organs in scenarios such as this, and they have been transplanted. For organ donors, clear standardized guidelines based on initial and confirmatory testing results are needed with respect to when organs should or should not be used, when results require the reclassification of average donors as high-risk donors requiring special consent and when results should be communicated to the donor/donor family and to public health. There should also be clarity on whether the response to testing results with respect to organ use should differ in average-risk versus increased risk donors and in living related versus deceased donors. Guidelines may need to be specific for each analyte (HIV, HCV and HBV). Response to the following NAT testing results should be included in the guideline: a) initially reactive, negative on repeat testing; b) initially reactive, negative on discriminatory testing; and c) initially reactive, positive on discriminatory testing. (Note that this profile has only a 35% PPV for true positivity in US blood donors using the Ultrio triplex assay [*Stramer N Engl J Med 2011:364:236*] who have follow up testing and only a 50% PPV for true HIV positivity in higher risk blood donors in South Africa [*Vermeulen M Transfusion 2009; 49:1115*]). Guidance should also be developed for use of organs when serology results are positive for either HIV or HCV and NAT results are negative. Based on experience in the blood system, NAT testing once implemented in average-risk donors will be difficult to discontinue even if its cost-effectiveness is questioned when alternative testing becomes available. Studies in the US public health system suggest in relatively low-risk settings, there is no significant yield associated with HIV NAT testing for the purpose of identifying acutely infected HIV patients when fourth-generation HIV testing is in place. It has been suggested that after fourth-generation HIV Ag/Ab screening, NAT testing should be used only in high-risk populations for the detection of window period infections in seronegative subjects. (*Patel Arch Intern Med 2010;170: 66*). Fourth-generation HIV testing has recently received FDA licensing for diagnostic testing in the US. These assays will reduce window period infections and will likely be significantly less costly than NAT. They will be more rapid with respect to result generation and less likely to result in donor loss (as we would be replacing a test with comparable specificity rather than adding a test). Consideration should be given to either delaying or removing the recommendation for NAT testing of average-risk donors and working towards implementation of fourth-generation Ag/Ab HIV testing as an alternative. Even in high-risk settings, fourth-generation HIV testing has been estimated to reduce the HIV NAT yield by 46% (*Vermeulen M Transfusion 2009; 49:1115*). We are again puzzled by the statement: "…NAT results should be obtained either before, if timing allows, or after procurement." For heart, lung and liver transplantation, there is very little time between organ procurement and implantation, and surgery may begin simultaneously on donor and recipient. Is it the intent of the authors that transplantation may occur prior to obtaining the results of NAT testing? If so, how will

performing NAT impact the transmission of HIV to recipients with results not available prior to implantation? Do the authors recommend a national effort to create infrastructure that allows for results to be available prior to procurement? Finally, the evidence ranking in support of this Level I recommendation is only B. For donors at increased risk, we support the use of NAT screening for HIV. In average-risk donor populations, we recommend more careful monitoring, particularly on risk of donor loss, to define the potential impact of this recommendation.

4. The rationale for universal NAT for HCV is the exceptionally long window period until serologic testing becomes positive for HCV. Studies of HCV window period modeling demonstrate a reduction in residual risk of infection from 19.9 to 1.99 per 100,000 donors in average-risk donors and 104.9 to 10.5 per 10,000 in increased risk doors (Ellingson K, et al. *Am J Transplant* 2011;11:1201). As with NAT testing for HIV, this recommendation should likely be considered separately for donors identified as average-risk compared to those identified as increased risk. For those donors at increased risk for HCV, the previous consensus conference supported the use of NAT testing (Humar *et al*. *Am J Transplant*. 2010; 10: 889-899). However, for low-risk donors, there were concerns that universal NAT testing would lead to the unnecessary exclusion of suitable donors which will result in morbidity and mortality among potential recipients. (See discussion above regarding expected false positive rates and need for guidelines for interpretation and response to test results.) The predictive positive value of the "duplex" or "triplex" NATs even when paired with confirmatory individual NAT in a low prevalence population is 35%. Even in a high prevalence area, the predictive positive value was only 50%. We recommend performance of more careful modeling to fully determine the impact of this recommendation. Of note, recent studies in both US (Zou S, et al. *Transfusion 2010;50:1495)* and Canadian blood donors *(*O'Brien SF, et al *Transfusion 2007;47:316)* found actual HCV NAT yield was significantly lower than that predicted using incidence-window period modeling. This suggests the window period reduction with NAT compared to serology is likely less than original estimates. Since similar modeling has been performed to inform HCV NAT screening recommendations in organ donors, perhaps these models should be revisited particularly in average-risk donors to better inform risk/benefit ratios. Once again, we are puzzled by the statement: "…NAT results should be obtained either before, if timing allows, or after procurement." For heart, lung and liver transplantation, there is very little time between organ procurement and implantation, and surgery may begin simultaneously on donor and recipient. Is it the intent of the authors that transplantation may occur prior to obtaining the results of NAT testing? If so, how will NAT impact transmission of HCV to recipients if the results are unavailable prior to implantation? Do the authors recommend a national effort to create infrastructure that allows results to be reported prior to organ recovery and implantation?

5. The AST is not certain there is sufficient data to indicate HBV NAT testing will have a significant impact on recipient safety if used in either average-risk or high-risk organ donors. Although we acknowledge the theoretical window period (WP) reduction associated with NAT screening relative to HBsAg screening (20-25 days versus 36-44 days), we are unaware of any reported cases of HBV transmission from a window period organ donor lacking all serologic markers for HBV infection to a recipient. Moreover, modeling of risk/benefit for HBV NAT has not been undertaken, and the quality of incidence data from the current vaccine era necessary for modeling in even high-risk populations is poor. Significant issues that should be considered include universal childhood immunization (in place for several decades) along with targeted immunization of high-risk groups (impacting donor risk) and targeted catch-up HBV immunizations and boosting (although sometimes with a suboptimal response) of recipient

populations. Some recipient populations (HCV infected) often already have a high prevalence of prior HBV infection and the low levels of infectious virus present in WP donors may be neutralized by antibody present in blood products given to recipients. Most programs already have procedures in place for handling anti-HBc positive organs including the use of HBV NAT testing in this setting (ref: AST hepatitis guidelines), so the benefit of NAT would be largely derived from its ability to detect WP rather than occult infection. Experience in the blood system suggests donors with HBV infection are less likely to have risk factors identified by the social/behavior questionnaire compared to HCV and HIV positive donors. Current criteria to identify increased risk donors have not been validated for utility in identifying incident HBV disease in the current vaccine era.

We note that the implementation of NAT for HBV has only recently been recommended in the blood system based on data from a clinical trial by Stramer et al in 2008 (N Engl J Med 2011;364:3) who observed immunization was protective and almost all WP infections were subclinical, transient, non- A2 (vaccine) infections in previously immunized individuals with low levels of immunity, transmitted by sexual or healthcare exposure in this low-risk setting. It was unclear whether these donors were infectious (Vermeulen M, et al. Transfusion 2011 in press). NAT yield was low (8 per 3,117,918 donations) and subsequent follow up data (2009-2010) found an unexplained eightfold lower yield (2 per 6,459.047) [Stramer Transfusion 2011;51:2012]. It is not clear that the same decision would have been made to implement HBV NAT in the blood system had this cumulative data been available for review. HBV viral loads in WP donors are also often extremely low, creating greater problems in differentiating true positive from false positive results. The issue of false positive results (discussed above) exists with respect to HBV NAT testing. According to data presented at the above-referenced consensus conference, NAT screening would pick up an additional positive donor in North America once every 9.7 years. Thus, it is not certain that implementation of this recommendation will result in any net benefit to potential recipients. Finally, if NAT testing for HBV is implemented, we agree that having results available after recovery and transplantation might positively impact recipient care as preemptive treatment with antiviral therapy might prevent or modify infection and clinical disease. However, from a patient safety perspective, greater net benefit may be derived from using resources that would have been used for NAT testing for HBV vaccine programs that would improve immunization rates and effectiveness in patients with organ failure and high-risk populations.

6. The same considerations and concerns apply here as in recommendation five. In the absence of any history permitting risk evaluation, the risk in this population is at most equal to and highly likely to be less than in a known increased-risk cohort.

7. This recommendation requires clarification, as it raises numerous questions. Does this statement mean one can use FDA-licensed diagnostic tests as opposed to assays licensed for donor screening for screening living and deceased donors? This would be a change in national policy and would represent an off-label use of the former tests. Would this allow use of the fourth-generation serologic tests (HIV already approved in the US)? A similar question would apply to the use of quantitative NAT assays. These tests, currently used in the diagnostic sector for HIV, HCV and HBV patient monitoring, are not approved as screening assays in either the diagnostic or donor screening setting. The current generation of these assays often has comparable analytic sensitivity to those used in the blood donor setting. Many clinical laboratories that perform organ donor screening already have these assays in place, and the

implementation of NAT screening may be logistically easier if use of these assays were permitted. We support approving a broader range of tests, if the sensitivity and specificity of the assays are comparable.

How is it recommended that we deal with evolving data and newer tests? Donor screening assays are validated in extremely low-risk populations and have never actually been validated in the organ donor setting where specificity and donor exclusion are a significantly greater problem. Both the average-risk and increased-risk organ donor populations much more closely resemble the mixed populations screened in the diagnostic setting than an average blood donor population. Since the two types of tests have not been directly compared in the same sample set, it is not clear that donor licensed tests are actually more sensitive and diagnostic tests are more specific as claimed. A side-by-side evaluation of screening and diagnostic tests would be useful. Significant logistical issues and reagent waste is associated with the implementation of donor-licensed assays that are highly automated systems designed for high-throughput batch testing while what is needed in the donor screening setting are rapid stat testing of single samples.

8. Serologic results should be available in a timely fashion, and, accordingly, we do not think one should go forward with transplantation without such results. As regards NAT testing, results would clearly not protect the recipient if not available pre-transplant, although they might inform early treatment for HIV and HBV. Since most recipients of heart, lung and liver transplants are in situations of life-threatening illness, this recommendation raises questions regarding the purpose of this entire guideline, which, as noted in our introductory comments, has not been clearly articulated.

9. Accurate confirmation of initially reactive serologic results usually requires not only repeat testing as outlined by the manufacturer, but also sequential performance of other assays for viral markers, immunoblots, Western blots and NAT assays as well as performing alternate manufacturer's assays for the same analytes. These types of algorithms are not outlined in the manufacturer's instructions but should be standardized to allow accurate determination of true and false positive results in the transplant setting, as rapidly as possible so as to avoid donor loss. Donor licensed NAT assays are designed for use in low-risk blood donor settings, and the confirmatory algorithms and result interpretation are designed from that perspective. It is not clear that they are always appropriate when screening high-risk populations. Even when following the manufacturer's instructions one will be left with a significant number of difficult to interpret results (i.e. repeat reactive but non-discriminated). Follow up testing is not possible in deceased donors; if these donors are not used, alternate algorithms will be needed in order to resolve these cases for accurate surveillance and assessment of donor loss. Further input from individuals with laboratory expertise to review these issues and outline optimal algorithms and result interpretation would be useful. (See additional discussion in section 3 above).

Table 3. Comments:

Sexual Contact: We believe that the risk factor of "persons who have had sex with $\geq$ 2 partners in the preceding 12 months" does not have specificity and would lead to large proportion of the donor population being classified as being at increased risk resulting in the requirement for special informed consent from a large proportion of recipients. Further, this population has

been stable, and we are unaware that this risk factor alone has resulted in significant increase in transmission. The quality of data supporting this recommendation is poor. A review of the data tables that accompany the proposed guidelines indicates this risk was not identified for all three of the viruses, and further that the studies evaluated risk-based sexual partners in a six-month (rather than a 12-month) time period and was much more impressive for a larger number of sexual contacts in the six month time period. Again, modeling should be done as to the impact that this is likely to have on organ donation and transplantation. We accept all of the other bullets under sexual contact.

Maternal transmission: We agree with restricting this to infants $\leq$ 2 years old and birth to a mother infected with HIV, HBV or HCV.

Parenteral injection of drugs in last 12 months: We agree with this recommendation.

Intranasal use of illicit drug in last 12 months: We agree with this recommendation.

Inmate in a correctional facility: The time limit of > 3 days seems a bit arbitrary but appears reasonable. We agree that for potential donors who are out of a correctional institution more than 12 months are not at increased risk for recent infection.

STD treatment in the preceding 12 months: We agree with this recommendation.

Hemodialysis in the preceding 12 months: The evidence here appears to be acceptable. For dialysis patients, antibody screening may not be valid, but they are not frequently donors. Should this be expanded to individuals undergoing other medical procedures in outpatient settings such as endoscopy or receiving intravenous therapy for HCV risk? Recent data from the US blood system suggests an unexplained increase in the incidence of HCV infection, largely in Caucasians of both sexes older than the age of 50. The speculation is this might be endoscopy-related nosocomial infection as has been described in other countries as a risk factor for acute HCV (Zou Transfusion 2010; 50:1495). Consideration should be given to collecting this information and perhaps, as well, data on persons with >2 partners so that data would be available for retrospective analysis, rather than at this time having them considered risk factors.

Persons who have immigrated to the US in last 12 months from high or intermediate prevalence area (HBV only): We support this recommendation. More specific information on areas considered high incidence areas (i.e. what is the cut off defining high incidence areas?) would be useful. Risk factors vary geographically and temporally and can change quickly in an outbreak setting. Closer links among organ procurement groups, the blood system and public health surveillance groups as well as ongoing coordinated vigilance and review of new data would be useful for monitoring risk factors of concern and modifying guidelines in a timely manner.

HBV-Infected Donors and Transplantation by Specific Recommendation

We feel this section is fairly straightforward and not controversial. We think clarifying the definition at the beginning is the most important area of this section requiring change. Our major questions are: What does being HB core IgG positive alone mean in terms or risk of transmission for recipients of

organs other than the liver? Does this not mean non-hepatic organs from these donors should be used only with special consent?

1. We have no concerns.

2. We have no real concerns. The intervention recommendations are only recommendations.

3. We have no concerns though this should be with informed consent as described in 4.

4. We agree with consenting and prophylaxis.

5. We are comfortable using these organs, but would still consider these as potentially infected. Accordingly, we would consent these recipients and recommend monitoring and documentation of HBV status following transplantation.

6. The issue is whether or not there is benefit for doing all of these tests.

HCV-Infected Donors and Transplantation by Specific Recommendation

Definition of infected donor or candidate: agree with definition as written.

1. We are in agreement with this recommendation. It is surprising the level of evidence here is considered level IIB. There are substantial data regarding long-term follow-up in kidney transplant recipients documenting risk and benefit. HCV + kidney are routinely transplanted into HCV + recipients.

2. We are in agreement with this recommendation. It is surprising this practice is strongly recommended and considered to be IB.

3. We are in agreement with this regarding the need for consenting and risk reduction strategies.

Recipient Informed Consent by Specific Recommendation

1. This is appropriate. We would recommend use of standardized approach to this consenting process. We think general discussion of risk (including infectious risk) of both accepting and refusing an organ should be included in this initial consenting process.

2. We agree with this recommendation.

3. It is often not known whether or not an additional vessel will be required until the surgery is underway. This makes implementation of the second half of this recommendation somewhat difficult.

4. As in 1, we would recommend the development and use of standardized approach to the consenting process, with certain defined key elements to be included.

Recipient Testing by Specific Recommendation

1. We are concerned that HCV testing by antibody alone may be problematic for at least some organ candidates. They may require NAT to accurately establish their baseline. We would favor the following language: "Baseline testing for which recipients are previously negative should be repeated by either serology or NAT at the time of admission to undergo transplantation, but prior to implantation according to individual patient's clinical circumstances. For example, dialysis patients would require HCV NAT while someone who was previously positive for HCV would not necessarily need HCV NAT testing (or any additional HCV testing)."

2. We are in agreement with the four criteria listed for post-transplant testing and for post-transplant testing in general.

3. We are in agreement with this recommendation.

4. We agree with this recommendation and with this choice of tests. There should also be exclusion for patients who have received the HBV vaccine and have a documented anti-HBV response. This eliminates the six-month time point recommended by consensus conference.

5. Do we need to do antibody testing if you are doing NAT or fourth-generation on everyone? Is this a research question? With regard to timing, we think one month is a good idea as donor-derived transmission should be positive at one month. There could be rare cases of negative at one month due to donor-derived infection, but this would be rare. What is of concern is classifying infection as donor-derived if testing is negative at one month but positive at three months. Consideration should be given to this issue and recommendations articulated.

6. HCV antibody testing is probably not needed if NAT testing is being done. We agree HCV NAT testing is indicated.

Donor and Recipient Collection and Storage by Specific Recommendation

The recommendations in this section seem to offer what would be best and optimal. However, there are logistic concerns and a lack of infrastructure for implementation of all these recommendations at the current time.

1. While getting both types of specimens would be the ideal, there are concerns that some OPOs may not be able to obtain both serum and EDTA tubes. This is particularly true when trying to find specimens that do not meet the criteria of hemodilution, and we fear this recommendation might result in the creation of a regulatory standard some OPOs will be unable to meet. Separate from the concern with potential regulatory consequences, we also feel the first line should be reworded to state that an EDTA specimen is preferred for NAT. Accordingly, where possible, a separate EDTA specimen should be obtained in addition to usual serum specimens.

2. A major concern is the potential logistic problem of separation of samples into aliquots. While perhaps ideal, minimizing the risk of contamination and freeze-thaw injury, it is not clear this is widely feasible, and, accordingly, should not be a minimum standard. The 10 year storage is current OPTN/UNOS policy and AOPO best practice. It is unclear what the last sentence in this recommendation means: "If only one specimen..." (See "3" below)

3. It seems this is what item 2 was trying to say. It actually reads better and is more conditional in terms of stating when capacity exists and when there is adequate specimen volume. Could this just replace number 2?

4. The purpose of this recommendation seems to be you should store at -20C or colder. However, to preserve the possibility of NAT in the future, specimens should be stored at

   -70C. If this is indeed to be the recommendation, OPOs should move towards saving at -70C.

5. This recommendation addresses creating an archival bank from living donors. This would require the development of infrastructure by transplant centers to fulfill this recommendation. Is 10 years really necessary for HBV, HIV and HCV? Would not a significantly shorter period of storage be adequate for this purpose? If you want to answer future questions, it would be optimal to treat living donor specimens the same as deceased donor specimens. However, unlike the case with deceased donors, it will not enhance the safety of multiple recipients from the same donor. We support this concept though we recognize that some transplant centers may object to the creation of new mandates with associated cost and infrastructure requirements.

6. This is OPO policy. No comment on intent. No comment on wording.

7. We are aware an effort was made to implement this recommendation as OPTN policy. This was recently rejected by the OPTN board based on major concerns raised during the public comment period for this proposed OPTN policy. We are in support of this recommendation though we recognize that there is clearly a vocal opposition to this recommendation within the transplant community.

Tracking and Reporting of HIV, HBV and HCV by specific recommendation

Much of what is being recommended in this section has already been adopted by the transplant community and is part of current clinical practice and policy. We are supportive of these existing practices and appreciate the current document reflecting these practices.

1. We support a requirement for the OPO to report to the transplant center if information becomes available that a deceased donor was infected with HIV, HCV, HBV, or any other potentially transmissible agent. This is consistent with current practice.

2. We support a recommendation that information obtained by the transplant center that an organ transplant recipient has acquired a new infection with HIV, HBC or HCV that might be donor-derived should be reported back to the OPTN. We suggest establishing criteria to define this more precisely. For example, a recipient who has serial negative testing up to one or two

years following transplantation, but then tests positive for HIV, HBV or HCV many years later, the transmission was unlikely to derived from the donor. This should not necessarily be reported back to the OPTN, although it does require reporting the appropriate public authorities as per current local requirements and laws. We would also suggest reporting should be based on confirmed positive testing and would like to suggest that PHS put forward an algorithm that can be standardized for confirmation testing.

3. We recommend clarification as to whether PHS is asking for all data (negative and positive) on pre- and post-transplant assessments to be submitted into a national database. Does this refer only to HIV, HCV and HBV? We support having nationally aggregated data on screening and donor-derived infections in the recipients, which can inform the transplant community over time. We would strongly recommend this remain under the purview of DTAC. In addition, we again would suggest having standardized algorithms to help with determining confirmation of true positives and in defining true positives.

4. This is consistent with current policies and practices followed as per OPTN policies. We would suggest this section be worded to be consistent with the language of current OPTN policy. Ideally, the tracking system should be able to link all tissues, organs or vessels that came from the same donor. We also believe this to be Category 1C rather than Category 1, since this is already OPTN policy.

5. This is consistent with current policies and practices followed as per OPTN policies. We also believe this to be Category 1C rather than Category 1, since this is already OPTN policy.

6. This appears to be the same as #2 in this section and can be deleted. If it differs from #2, please clarify in what way.

7. We are in agreement and would add that this recommendation is already current policy and clarify that this is not intended to modify that policy.

8. We are in agreement. We believe this is current policy and therefore should be Category IC.

9. We are in agreement.

10. We are in agreement.

11. We are in agreement.

12. We are in agreement.

After careful review of the document, AST reiterates its strong objections to the draft "PHS Guidelines for Reducing the Transmission of Human Immunodeficiency Virus, Hepatitis B Virus and Hepatitis C Virus through Solid Organ Transplantation." We recommend the draft document be withdrawn and a renewed and truly collaborative effort be established to update the 1994 guidelines *(PHS Guidelines for Preventing Transmission of HIV through Transplantation of Human Tissue and Organs)* to more accurately reflect prudent practice and the constructive concerns we have detailed in this response. Such an effort should result in recommendations based on clearly stated goals, with comprehensive

analysis of overall risk and benefit to transplant candidates and patients as we have noted. AST looks forward to the opportunity to actively participate in development of a guideline document that addresses not just the risk of inadvertent infectious disease transmission, but the entire process required to ensure patients in need receive timely transplantation of donated organs commensurate with the most effective standards possible in the current environment.

Sincerely,

Robert S. Gaston, MD
AST President

Cc: AST Board of Directors