Workgroup 1

Definition of Donors at Increased Risk of Transmission of HIV, HBV & HCV

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Workgroup I

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Aim 1: To Develop a consensus definition of donors at increased risk of transmission of HIV, HBV and HCV and Disseminate these findings to the transplant community

• Review current research findings and evidence-based information relevant to development of a standard definition and/or set of risk behaviors that will **appropriately** identify donors at increased risk of transmitting HIV, HBV & HCV and disseminate these findings to the transplant community

• To identify knowledge gaps needed to inform development of **appropriate** definition of donors at increased risk of transmission of HIV, HBV, and HCV and develop a rational research agenda or strategy to address these gaps
Introduction

• Existing PHS Guideline published in 1994 and was limited to prevention of transmission of HIV
  – Ongoing revision process whose goals include generation of updated set of evidence-based criteria which will identify donors at increased risk of transmitting HIV, HBV & HCV
  – PHS contracted with University of Pennsylvania for systematic assessment of available literature
  – Inherent limitations in accomplishing this goal due to general lack of relevant data in literature
    • Only 30 publications met criteria for inclusion in evidence review relevant to “new” definitions despite expansion of literature review to include potential tissue donors, blood donors and general population
    • Only 2 of the 30 included data on risk for infection with HIV, HBV or HCV in potential or actual organ donors
    • Only 2 of the studies specifically assessed children
Potential Philosophical Approaches to Defining “Increased Risk for Transmission”

• Minimize risk of transmission to lowest possible level by using list of criteria with HIGH sensitivity
  – Higher sensitivity can result in greater lack of specificity
  – Implementation of this approach likely results in uninfected donors being identified as being at increased risk of transmitting
  – Potential consequence of identification as “increased risk” on “acceptability” of organs
    • ? Longer periods on waiting list
    • ? Withdrawal from waiting list due to disease progression or death

• Maximally reduce risk of transmission
Potential Philosophical Approaches to Defining “Increased Risk for Transmission”

• Alternate approach would be to “maximize” specificity of definitions of which donors are at risk of transmission
  – Increased likelihood of missing presence of infection in some potential donors
    • Impact of unexpected transmission on recipient, the public and the Organ Donation Enterprise
  – More patients are likely receive organ in shorter period of time with potential to improve quantity and quality of life in recipients
Balancing Risks & Benefits of Sensitivity & Specificity

• In determining where to set the balance between sensitivity & specificity one needs to identify what the acceptable risk of transmission is?
  – Does this level of acceptable risk vary by which pathogen we are considering?
  – Does the increasing effectiveness & availability of targeted antiviral therapies impact decision making?
  – Current laws allow for use of HCV and HBV positive donors in certain circumstances while use of HIV + donors forbidden under NOTA
    • OPTN Policy calls for informed consent for use of donors known to have or to be at risk for HBV & HCV
Development of Definitions: Approach of the Workgroup

• Draft Update of PHS Guidelines included 14 “factors” identified in the literature to be associated with increased likelihood of recent HIV, HBV or HCV infection
• Workgroup developed 4 key questions to get at essential facts necessary to look at data relevant to each proposed “risk factor” in appropriate context of organ donation
• Each member of Workgroup asked to answer the 4 questions for 3 of the 14 factors
• Answers to questions for EACH proposed “risk factor” reviewed during Workgroup phone calls
  – General strengths and concerns relevant to each proposed risk factor discussed INCLUDING choice of relevant time period assigned for each
Table 3. Factors identified in the literature to be associated with increased likelihood of recent HIV, HBV or HCV infection (See Appendix I for more detailed information)

- Sexual Contact
  - Persons who have had sex with ≥2 partners in the preceding 12 months
  - Persons who have had sex with a person known or suspected to have HIV, HBV or HCV infection in the preceding 12 months
  - Men who have had sex with another man (MSM) in the preceding 12 months
  - Women who have had sex with a man with a history of MSM behavior in the preceding 12 months
  - Persons who have had sex in exchange for money or drugs in the preceding 12 months
  - Persons who have had sex with a person who had sex in exchange for money or drugs in the preceding 12 months
  - Persons who have had sex with a person who injected drugs by intravenous, intramuscular, or subcutaneous route for non-medical reasons in the preceding 12 months
- Birth to a mother infected with HIV, HBV or HCV (for infants ≤2 years of age)
- Persons who have injected drugs by intravenous, intramuscular, or subcutaneous route for non-medical reasons in the preceding 12 months
- Intra-nasal use of an illicit drug (e.g., cocaine, heroin) in the preceding 12 months
- Inmate of a correctional facility (e.g., jail, prison, juvenile detention) ≥3 consecutive days in the preceding 12 months
- Persons who have, or have been treated for, syphilis, gonorrhea, or genital ulcers in the preceding 12 months
- Persons who have been on hemodialysis in the preceding 12 months (for HCV only)
- Persons who have immigrated to the United States in the preceding 12 months from a country of intermediate or high hepatitis B prevalence (for HBV only)
Acknowledgement: Our work was made feasible in great part due to the recent efforts of the PHS & University of Pennsylvania

Solid Organ Transplantation and the Probability of Transmitting HIV, HBV, or HCV: A Systematic Review to Support an Evidence-based Guideline

Evidence-based Practice Center
ECRI Institute
Plymouth Meeting, Pennsylvania
April 14, 2010

Additional literature search performed by members of the Working Group
Question 1

How feasible is it to identify donors who actually fall into the risk group?

– Does the donor exhibit a behavior which is considered to put them at increased risk?

– Can you objectively confirm the presence of the behavior?
  - If the risk group is "sex with >1 partner in the last year", how feasible would it be, based on family report and/or any tests or medical records available, to determine if this donor actually had sex with >1 partner in the last year)

A. **Very Strong** = Effects of the behavior are detectable by lab tests, physical exam, etc (for example, tox screen and track marks might identify an IDU)

B. **Strong** = The behavior can be documented in a medical record (for example, previous STI)

C. **Weak** = The behavior can only be identified by report from family members, and they are likely to know this information

D. **Very Weak** = The behavior can only be identified by report from family members, but they are unlikely to know this information
Question 2

Are the estimates of risk (from the literature) for this group reliable?

- in other words, are there studies of people with this behavior which reliably estimate HIV, HBV and HCV seroconversion rates?

A. **Very Strong** = Studies of actual organ donors (in other words, a study that looked at, for example, 10,000 potential donors who were IDUs and quantified what % of them had an undetected infection at the time of organ offer)

B. **Strong** = Population-based studies of incidence (for example, an ongoing study of IDU's drawn from the general population -- not necessarily those that are organ donors -- that estimates seroconversion rates)

C. **Weak** = Population-based studies of prevalence (for example, a cross-sectional study of IDU's to see what proportion of them are seropositive)

D. **Very Weak** = No good studies
What is the estimated risk, and is it high enough to warrant screening beyond that of universal screening?

- Quantify the estimated risk, based on whatever best literature is available,
- Conference Workgroup to determine threshold beyond which the risk is high enough to warrant additional screening

A. 1:1,000 or more common (in other words, of 1000 donors, 1 will carry a window period infection by nucleic acid testing)
B. Between 1:1,000 and 1:10,000
C. Between 1:10,000 and 1:100,000
D. 1:100,000 or less common
E. Cannot tell (because estimates in the literature are too weak)
Question 4

What proportion of donors would be expected to fall into the risk group and thereby require additional screening? (based on literature or educated guess)

A. <1%
B. 1-5%
C. 5-10%
D. >10%
Caveat

- For questions whose answers include the terms: “Very Strong”, “Strong”, “Weak”, “Very Weak”
  - While the term itself MAY be “subjective” the definition resulting in assigning this answer is based on “objective” criteria
  - The Consensus Conference Working Group may choose to adjust these terms though they will still need to acknowledge declining level of evidence in support of given proposed Risk Factor
Risk Factor 1: Persons who have had sex with \( \geq 2 \) partners in the preceding 12 months

How feasible is it to identify donors who actually fall into the risk group?

**D-Very Weak:** Behavior can only be identified by report from family members but they are unlikely to know this information.
Risk Factor 1: Persons who have had sex with 2 partners in the preceding 12 months

Are the estimates of risk (from the literature) for this group reliable?

*Weak* = Population-based studies of prevalence (for example, a cross-sectional study of IDU's to see what proportion of them are seropositive)
Risk Factor 1: Persons who have had sex with 2 partners in the preceding 12 months

What is the estimated risk, and is it high enough to warrant screening beyond that of universal screening?

Cannot tell - estimates in the literature felt to be too weak to inform decision
Risk Factor 1: Persons who have had sex with 2 partners in the preceding 12 months

What proportion of donors would be expected to fall into the risk group and thereby require additional screening?

D. >10%
<table>
<thead>
<tr>
<th>Risk Factor in last 12 months*</th>
<th>Ability to Identify Risk Factor?</th>
<th>Strength of Risk for Infection?</th>
<th>What is estimated Risk?</th>
<th>Proportion of Donors Affected?</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 2 Partners</td>
<td>Very Weak</td>
<td>Weak</td>
<td>Cannot Tell</td>
<td>&gt; 10%</td>
</tr>
<tr>
<td>Sex with known of suspected infected partner</td>
<td>Very Weak</td>
<td>Weak</td>
<td>Cannot Tell</td>
<td>1-5%</td>
</tr>
<tr>
<td>Men who had sex with MSM</td>
<td>Weak</td>
<td>Strong</td>
<td>1:1000 - 1:10000</td>
<td>1-5%</td>
</tr>
<tr>
<td>Women who had sex with MSM</td>
<td>Very Weak</td>
<td>Very Weak</td>
<td>Cannot Tell</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td>Sex in exchange for $$ or drugs</td>
<td>Very Weak</td>
<td>Weak</td>
<td>≥ 1:1000</td>
<td>1-5%</td>
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<tr>
<td>Sex with someone who had sex in exchange for $$ or drug</td>
<td>Very Weak</td>
<td>Weak</td>
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<tr>
<td>Sex with someone who injected drugs for non-medical reasons</td>
<td>Very Weak</td>
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<td>Cannot Tell</td>
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<td>Infants ≤ 2 years born to infected mother*</td>
<td>Very Strong</td>
<td>Strong</td>
<td>≥ 1:1000</td>
<td>&lt; 1%</td>
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<td>Very Strong</td>
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<tr>
<td>Intranasal use of illicit drug</td>
<td>Very Weak</td>
<td>Weak</td>
<td>1:10,000 – 1:100,000</td>
<td>1-5%</td>
</tr>
<tr>
<td>Inmate for ≥ 3 Days*</td>
<td>Strong vs Weak?</td>
<td>Strong</td>
<td>1:1000-1:10,000</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td>Person treated for syphilis, gonorrhea or genital ulcers</td>
<td>Very Weak</td>
<td>Weak</td>
<td>Cannot Tell</td>
<td>&gt; 10%</td>
</tr>
<tr>
<td>Person on hemodialysis</td>
<td>Very Strong</td>
<td>Strong</td>
<td>≥ 1:1000</td>
<td>1-5%</td>
</tr>
<tr>
<td>Immigration to US from country with higher HBV prevalence</td>
<td>Very Strong/Strong</td>
<td>Weak/Very Weak</td>
<td>Cannot Tell</td>
<td>&lt; 1%</td>
</tr>
</tbody>
</table>
Summary Stratified On Ability to Reliably Identify Risk Factor?

- **A very strong** reliability of identifying presence of Risk Factor found for 4/14
  - Reliability of link between presence of risk factor and infection Very Strong in 3 of 4
  - Risk of Infection ≥ 1:1000 in 3 of 4
  - Affects < 5% of potential donors for all 4

- **A very weak** reliability of identifying presence of risk factor found for 7/14
  - Reliability of link between presence of risk factor and infection weak/very weak for 7/7
  - Cannot tell estimated risk of infection due to lack of evidence in 4/7
  - 2 of 7 Risk Factors would affect > 10% of potential donors
  - Despite this, our working group voted to include 2 of these 7 risk factors despite lack of definitive evidence
Next Step: Use the Analysis to make recommendation regarding specific proposed Risk Factor

- Endorse proposed Risk Behavior
- Endorse proposed Risk Behavior but with recommendations for consideration (e.g. Adjusting the time period associated with a given risk)
  - “Modify”
- Recommend against inclusion of Risk Behavior
- Identification of “key” knowledge gaps necessary to determine whether even modified Risk Behavior criteria would be of benefit
## Preliminary Recommendations
(12/14 possible votes)

<table>
<thead>
<tr>
<th>Risk Factor in last 12 months</th>
<th>Endorse</th>
<th>Modify</th>
<th>Exclude</th>
<th>Abstain</th>
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Gaps in Knowledge

• Decision analysis studies of risks and benefits of organs with higher infectious risk.
• Incidence studies of people in various putative risk groups, particularly those where high-quality incidence studies do not currently exist.
• Expanded national data collection on the specific risk factors underlying "CDC high risk" designation.
• Studies of patient attitudes, concerns, and priorities regarding infectious risk and the specific categories used to define higher infectious risk.
• Improvements in efficiency, accuracy, and availability of nucleic acid testing.
• Better quantification of false-positive rates of nucleic acid tests.
• National consensus and homogeneity among OPO's regarding nucleic acid testing methods.