Group 4: Recipient Evaluations
Background

- Focused attention on the optimal evaluation of recipients of organs from donors at increased risk of HIV, HBV, and HCV transmission.
- It is likely that infectious disease transmission occurs more often with transplantation than is recognized or reported.
- This topic merits broader evaluation:
  1. Transplantation cannot be performed without some risk of transmission of infection.
  2. The potential list of pathogens is broad. Assays do not exist, may not be universally available (locally or in a timely fashion) for many potential pathogens.
  3. A goal is to develop standardized assessment protocols so as to identify transmission events and to facilitate therapy, if available.
  4. Long term: to refine the screening and data analysis of potential organ donors. The development of data will facilitate optimization of the informed consent process and facilitate the post-transplant evaluation of recipients of organs from such donors.
Core Questions

- What is the time to recognition (clinical) and diagnosis (assay, NAT or serology) after a known exposure to virus? (These are distinct.)
- What is the benefit of "early" intervention (e.g., altered viral set points?) on the outcome of infection for HIV, HBV, HCV?
- What are optimal assays, at which frequency or intervals? (e.g., pre-transplant samples, and at 1, 3, 6 or 12 months?)
- Is the cost of routine testing of recipients of organs from potentially increased risk donors likely to be overwhelming? (Cost modeling)
- Can we consider a trial in which all such donors and recipients are tested for a period (e.g., 2 years + follow up)? And who will develop and perform these studies (Research agenda)?
Data in the area of documented transmission events and risk factors are limited. There are no prospective studies of disease transmission in transplantation. Thus, the baseline incidence of infection in the general and “increased risk” populations must be imputed from studies of blood transfusion and epidemiologic studies.

Most data relevant to transmission events and diagnostic assays have been well summarized in the recent background document for the Draft 2011 Public Health Service (PHS) Guideline for Reducing Transmission of HIV, HBV, and HCV through Solid Organ Transplantation.
General Conclusions

- **Diagnostic tests** must be used (as opposed to screening assays) – these will, in general, be FDA licensed. **Nucleic acid tests (NAT) are preferred** given the potential for delayed or absent seroconversion in immunosuppressed transplant recipients.

- In the immunosuppressed host, viral replication and disease progression are generally more rapid than in immunologically normal hosts. **It is important conceptually and in developing trials, to distinguish between a virologic diagnosis (i.e., viremia) and clinical or symptomatic disease (hepatitis or AIDS).** Can asymptomatic (viral) transmission of HIV, HCV and HBV can be recognized in advance of symptomatic disease? Reported transmission events have generally resulted in clinical disease (and thus viremia) early in the post-transplant course; generally within 1-2 months. **Early time points are informative.**

- Are later time points informative? Although some late HBV disease has been reported (two years) it is not known when detectable viremia occurred. Clinical disease for HIV, HCV, and HBV is expected to occur by 6 months after transplantation – with the expectation that viremia is established earlier. (Unnown)
General Conclusions - II

- There are no data (in non-transplant populations) to indicate that “early therapy” (weeks to months) is clinically advantageous with the exceptions that:
  - Therapy for HBV and HCV must be initiated before the development of cirrhosis
  - HAART (for HIV) should precede development of opportunistic infection and AIDS.
  - One potential advantage to early diagnosis might be avoidance of inadvertent transmission to uninfected social and sexual partners.

- A reasonable testing paradigm would include testing of recipients of organs from “donors at increased risk for transmission of infection” pre-transplantation (baseline) and at 1 and 3 months after transplantation using a diagnostic NAT assay with high sensitivity (10-25 IU/ml cutoff). Testing at later time points (6-12 months) would identify asymptomatic late infections. It is not known when these individuals become viremic. Research studies should include these later time points. There is some risk that acquisition of new disease outside of the transplant exposure may confound analysis of later time points.

- Caveat: Risk remains to recipients from unknown or uncommon pathogens (not HIV, HCV, HBV, herpesviruses) or organisms resistant to antimicrobial prophylaxis (azole-resistant yeasts).
Future Directions & Research

Agenda: Recipients

Discussions centered on the development of a prospective study of transmission of infection with organ transplantation. While most concerns focus on “increased risk donors”, the changing epidemiology of infection, increased travel and the growing population of asymptomatic carriers of HCV, possibly HBV, and other unknown infections makes broader study desirable. One possibility would be to design a study in which all donors and recipients were tested (or samples banked, or both) for a fixed period (e.g., 2-3 years). Possible variables include:

- Who should be tested?
  - All deceased donors vs. “increased risk” donors
  - Recipients of all organs vs. recipients of “increased risk” donors
  - Geographically (OPO’s) -- e.g., funding provided to assess risk for infection in e.g., a few dispersed and different OPO’s

- Which assays? i.e., those currently in use at the OPOs or specified assays for investigation?
  - High risk and common infectious concerns (HIV, HBV, HCV)
    - Diagnostic assays FDA approved/licensed
    - NAT, serologic (ELISA)
    - Samples reserved for research testing (e.g., high throughput sequencing, multiplex PCR, other) – frozen per standard protocol (-80 degrees)
    - Where are samples maintained?

- Which clinical data are needed?
  - How will clinical data of donor and recipient be linked (while preserving confidentiality)?
  - Standardized clinical data and questionnaires? Those data used at present to make clinical decisions? Or more detail?
  - Online/internet-based data collection tools?
  - Who controls the data?