Working group 3: Participant Education, Recruitment, & Informed Consent

Forum HIV Cure Project: Focus on The Regulatory Pathway
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Comments from co-chairs
David Evans and Timothy Henrich
Subgroups

- Informed Consent

- Recruitment Issues: Surveys Among Potential Trial Participants
Thanks to Working Group Members

Informed Consent
David Evans, Sam Garner, Sara Goldkind, Golf, Gail Henderson, George Hanna, Tim Henrich, Richard Klein, Bernard Lo, Deborah Persaud, Seema Shah, Jeremy Sugarman, Jeff Taylor, Mark Wainberg

Recruitment Issues: Surveys Among Potential Trial Participants
Rachael Anatol, Mike Cohen, Karine Dube, David Evans, Kevin Fisher, Cynthia Grossman, Timothy Henrich, Andy Kaytes, Damian Kelly, Diane Lawrence, Sandra Nusinoff Lehrman, Paris Mullen, Anna-Laura Ross, Seema Shah, Jeremy Sugarman
Informed Consent
Timothy Henrich

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Framing Risks & Benefits for Trial Participants

• “Cure” Language
  – How do we balance aspirational language with the reality of first-in-human trials and low chance of individual medical benefit?
  – How do we justify to prospective participants the need for potentially risky studies given current state of standard of HIV-1 care?
**Risk/Benefit Ratios for Trial Participants**

<table>
<thead>
<tr>
<th>Possible risks of participation in HIV cure oriented trials include, but are not limited to:</th>
<th>Possible benefits of participation in HIV cure oriented trials include, but are not limited to:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Risks involved with ART treatment interruption (see below for details)</td>
<td>• Reduction in the size of the HIV reservoir (although long-term benefit of this is unknown)</td>
</tr>
<tr>
<td>• Drug toxicities and adverse effects and potential for long-term toxicities</td>
<td>• Control of viremia in the absence of ART (a.k.a “functional cure”)</td>
</tr>
<tr>
<td>• Unknown drug toxicities in studies involving more than one experimental agent or strategy</td>
<td>• Absence of rebound viremia during an extended period of time</td>
</tr>
<tr>
<td>• Long-term toxicities related to fertility</td>
<td>• Preservation of immune function or reconstitution of immune function</td>
</tr>
<tr>
<td>• Oncogenic potential of drug</td>
<td>• Favorable alteration of the viral set point</td>
</tr>
<tr>
<td>• Development of drug resistance</td>
<td>• Decreased viral evolution and limited viral diversity</td>
</tr>
<tr>
<td>• No clear way to predict the timing of viral rebound when off ART (see above)</td>
<td>• Reactivation of latent replication-competent proviruses (e.g. latency-reversing agents) - followed by clearance of infected cells using combination agents/stategy</td>
</tr>
<tr>
<td>• Risks associated with chemotherapy and stem cell transplantation</td>
<td></td>
</tr>
<tr>
<td>• Highly invasive procedures required (e.g. gut biopsy, lymph node biopsy, lumbar puncture)</td>
<td></td>
</tr>
<tr>
<td>• Burdens related to study visits</td>
<td></td>
</tr>
<tr>
<td>• Inadequate protection of confidential or identifiable information</td>
<td></td>
</tr>
<tr>
<td>• Possible exclusion from future trial participation</td>
<td></td>
</tr>
</tbody>
</table>
Emerging Ethical Debates

• Analytic Treatment Interruptions
  – What is the tradeoff for participants when there is greater potential harm from experimental treatments vs. standard of care?

• Return of Results
  – Do participants have the right to know individual results of a curative therapy that may have had an impact on HIV-1 persistence or reservoir size?

• Reproductive Risks
  – Should standard practice for trial exclusion criteria be based on unknown factors or based on scientific evidence?

• Patient Centered Concerns & Privacy Issues
  – How do we ensure a participant-centered approach is represented in informed consent processes in HIV cure oriented trials?
  – How do investigators ensure privacy in the context of intense media attention related to HIV cure oriented trials?

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## Analytic Treatment Interruptions (ATIs)

**Table 1: Type of Analytical Treatment Interruption and Potential Risk to Participant**

<table>
<thead>
<tr>
<th>ART Re-Initiation Criteria</th>
<th>Immediate ART Re-Initiation after Rebound</th>
<th>Delayed ART Re-Initiation after Rebound</th>
</tr>
</thead>
<tbody>
<tr>
<td>Example</td>
<td>Restart immediately after viral rebound or at specified interval if no rebound</td>
<td>Restart after specified interval regardless of viral rebound or after VL reaches stable set-point</td>
</tr>
<tr>
<td>Potential Major Risks to Participant</td>
<td>ART resistance acute retroviral syndrome</td>
<td>ART resistance acute retroviral syndrome decrease in CD4 T cell counts opportunistic infections extensive cellular reservoir seeding disease progression</td>
</tr>
<tr>
<td>Benefit to Participant</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Scientific Benefit</td>
<td>Tests potential for strategy to eradicate virus or lead to prolonged ART-free remission</td>
<td>Allows inter-patient comparisons of viral rebound kinetics/evolution and immune dynamics; may inform on peak and set-point VL during ATI</td>
</tr>
<tr>
<td>Limitations and Logistical Issues</td>
<td>Requires frequent monitoring; does not inform on differences in immune control of virus or VL peak/nadir during ATI</td>
<td>Potential need for management of AEs and retroviral syndromes, OIs, etc.</td>
</tr>
</tbody>
</table>
### Table 2. Theoretical Risks of Returning Results to Patient in HIV Cure Oriented Studies: Surrogate Endpoints

<table>
<thead>
<tr>
<th>Type of Result</th>
<th>Result</th>
<th>Potential Risks</th>
<th>Duration of Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quantitative measure of reservoir (e.g. SCA, CA-DNA or RNA, VOA)</td>
<td>Significant decrease in reservoir measure</td>
<td>Patient independently stops ART leading to viral rebound; decreased medication adherence; Patient induced by result to participate in next step of tiered study (e.g. ATI)</td>
<td>Long-term</td>
</tr>
<tr>
<td></td>
<td>Significant increase in reservoir measure</td>
<td>Patient anxiety; ART change or intensification when not otherwise indicated</td>
<td>Long-term</td>
</tr>
<tr>
<td></td>
<td>Inaccurate, insensitive or unspecific results from experimental assays</td>
<td>Patient anxiety; ART change or intensification when not indicated; Patient induced by result to participate in next step of tiered study (e.g. ATI)</td>
<td>Long-term</td>
</tr>
</tbody>
</table>

SCA = single copy RNA assay; CA = cell associated; VOA = viral outgrowth assay
Informed Consent Strategies to Support Investigators & Participants

- **“Cure” Language**
  - Create semantic parallels with known disease lexicons to describe goals of potential therapeutic strategies to patients & avoid misunderstanding or undue influence.

- **Institutional Review Boards**
  - Early cross talk during design phase of trials may streamline study design & facilitate handling of controversial.

- **Streamline and Increase Readability of Consent Forms**

- **Controversies Related to Risks/ Benefits**
  - Administer a separate evaluation of risk/ benefit understanding; consider including written agreements to not participate in conception process for trial period.

- **Return of Research Results**
  - Clearly indicate return of results policy for the study. Ensure return of future research results are treated separately from study results.
How To Portray Potential Risks of Participation and Differentiate Likelihood, Nature, Magnitude, & Severity*

- Risks of genetic and other study interventions
- Risks of combinations of experimental agents
- Risks of highly invasive procedures
- Reproductive risks
- Risks of analytic treatment interruptions
- Risks of antibody formation, viral drift, mutagenesis, and blood cancer
- Risk of being ineligible for future trials or treatments
- Risk of lost of privacy or confidentiality of personal information

*Gail Henderson  www.hivforum.org
How to Portray Uncertainty*

“There may be unknown risks associated with this clinical trial, including death.”

“There may be adverse effects that are presently unknown and unforeseeable.”

“Unknown frequency or theoretical risks’…insertion of the vaccine DNA into your body’s DNA which possibly lead to cancer, or into the DNA of bacteria or virus in your body (which has unknown consequences). This can be serious, but is expected to be rare if it ever occurs.”

*Gail Henderson

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How to Portray Potential Benefits of Participation & Differentiate Likelihood & Nature*

**Benefit Sections:** Minimize likelihood of direct medical benefit

“Not the study purpose,” “Very unlikely,” “Should not expect to benefit”

**Background & Study Purpose Sections:** Present study goals including:

- Surrogate endpoints: “modify CCR5 protein,” “viral load changes”
- Clinical endpoints: “improve the body’s ability to fight infection,” “remain healthy.”

These may be interpreted as the nature of benefit to be expected

*Gail Henderson*
Recruitment Issues:
Surveys Among Potential Trial Participants
David Evans
Mapping Potential Uses for HIV Cure Oriented Research Surveys

- Gauge willingness to participate in HIV cure oriented research
  - Specific motivations to participate (e.g., altruism, monetary compensation, perceived health benefit)
  - Explore willingness to participate across different populations (e.g., age, gender, income, geographic location, stage of disease, prior trial experiences)

- Assess medical literacy to guide clinical trial informed consent processes & reduce misconceptions

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Perceptions and Barriers to Participation in HIV Cure Trials

• Potential Factors Associated with Willingness to Participate
  – Desire to derive personal benefit
  – Unwilling to stop ARV therapy for clinical trial
  – Funding of trial
  – Degree to which trial will be available in the public domain
  – Randomization design for trial
  – Institutional Review Board approval

• Populations with Potential Systematic Barriers to Participation
  – Women
  – Ethnic/Racial Minorities
Applying Decisional Sciences to HIV Cure Oriented Research Surveys

- Bias in Decision-Making
  - Regardless of education
  - Can differ by age, location & other demographics
- Information presented first has more weight
- Individuals prefer to evaluate their own risks & benefits
- Individuals report more altruism than they display
Strategies to Mitigate Bias in Survey Design

• Conduct survey research within all target populations
• Create cognitive maps to identify gaps in knowledge that may hinder informed decision-making
• Tailor surveys according to familiarity with HIV cure oriented research
• Lessons learned from related disciplines
  – Oncology, Rheumatology, HIV prevention & treatment
Themes from Related Survey Literature Predicting Trial Participation*

• *Hope* for therapeutic benefit and altruism frequently embedded in decision-making process

• HIV treatment & prevention literature
  – Barriers included: safety concerns, fear/mistrust of physician, pragmatic obstacles, discrimination

• Cancer literature
  – Factors promoting participation included: trusting relationships between researcher and patient & positive communication processes (including informed consent)

* Karine Dube  www.hivforum.org
**WG Recommendations and Action Items**

- **Informed Consent Guidance Document**
  - Risk/ Benefit Language
  - Return of Results
  - Data Sharing & Electronic Medical Records
  - Reproductive Risks

- **Survey Research Recommendations for Potential Trial Participants**
  - Survey Design Considerations
  - Target Populations for Survey Research
  - Funding Priorities and Next Steps
Panel Discussion

- David Evans (PI), moderator
- Tim Henrich (HMS), moderator
- Nikos Dedes (EMA Managing Board)
- George Hanna (BMS)
- Gail Henderson (UNC)
- Richard Klein (OTC/FDA)
- Jeremy Sugarman (JHMI)
Panel Discussion

• As HIV cure oriented research evolves to the next generation of trials, what are the major bioethical challenges moving forward?

• There have been suggestions of language that should not be used to avoid coercion of trial participants. Are there specific suggestions of language that should be used?

• How can investigators improve participant education on the risks and benefits of HIV cure oriented research?