EMERGING ETHICAL ISSUES

Challenges for HIV vaccine research

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Ethical considerations

- Vaccine trials have ethical requirements in common with other biomedical studies involving human participants
  - Minimize risks to participants
  - Ensure that participants understand what they are told during informed consent process
  - Provide adequate protection for participants' confidentiality
  - Make provision for care and treatment

Preventive HIV vaccine trials

- Must be conducted on healthy individuals
  - Risk of potential harm, discomfort, inconvenience not otherwise present
  - Phase III HIV trials may stigmatize even healthy individuals because the trials typically recruit people engaged in high-risk behavior
  - Participants in some vaccine trials likely to test HIV positive even when uninfected
  - Scientific need for long-term follow-up

Ethical challenges

- Many potential participants in phase III HIV prevention trials are engaged in high-risk behavior or come from marginalized or stigmatized groups
  - Need to protect privacy and confidentiality in process of recruitment and conduct of trial
  - Potential participants from some groups may be engaged in illegal activity
  - Some participants may be jailed during trial

New challenges from STEP trial

- Disturbing finding that a subgroup of participants in experimental arm had higher incidence of HIV infection than participants in placebo arm
  - Knowing causal factors is critical in order to avoid similar results in future vaccine trials
  - Poses questions about ethically acceptable design of future trials

Threshold Questions

- Do the STEP trial results mean that HIV preventive trials in humans should not continue?
  - Some have argued that more preclinical research is needed before proceeding
  - Does the finding of enhanced susceptibility among participants who received the vaccine mean that current vaccine approaches are too risky (and therefore unethical)?

Designing future trials

- The ethically best course of action is to avoid future trial designs that include the probable suspected causes of enhanced susceptibility as emerged from review of the STEP data
  - Yet uncertainties remain
  - Vaccine scientists should use all available evidence when making decisions under risk and uncertainty
  - Potential tension between ethics and methodology

Emerging challenge

- Given what the trend showed regarding greater number of infections among uncircumcised men in the vaccine group
  - Should future trials have exclusion criterion for uncircumcised men?
  - Should circumcision be
    - Required for potential participants?
    - Encouraged for potential participants?
    - Offered free of charge for potential participants?

Standard of Prevention

- UNAIDS/WHO Ethical Guidance 2007
  - Researchers, research staff, and trial sponsors should ensure, as an integral component of the research protocol, that appropriate counseling and access to all state of the art HIV risk reduction methods are provided to participants throughout the duration of the biomedical HIV prevention trial.
    - Ethical Considerations in Biomedical HIV Prevention Trials
      - Guidance Point 13

Guidance Point 13 (cont'd)

- New HIV risk-reduction methods should be added, based on consultation among all research stakeholders including the community, as they are scientifically validated or as they are approved by relevant authorities.

Researchers' challenge

- Do you really mean *all* state of the art prevention methods?
  - Would that include a partially effective vaccine or microbicide when such methods become available?
  - This requirement will make it difficult, if not impossible, to analyze the results of HIV prevention trials
  - Researchers may not be able to provide *all* state of the art HIV risk reduction methods

Care and Treatment

- UNAIDS/WHO 2007 Guidance Point 14
  - Participants who acquire HIV infection during the conduct of a biomedical HIV prevention trial should be provided access to treatment regimens from among those internationally recognised as optimal. Prior to initiation of a trial, all research stakeholders should come to agreement through participatory processes on mechanisms to provide and sustain such HIV-related care and treatment.
  - This guidance point does not address treatment or compensation for trial-related harm

Care and treatment

- Enhanced susceptibility to HIV infection demonstrated in STEP trial
  - It is unquestionably a "trial-related harm"
  - It calls for enhanced obligation to participants for follow-up, monitoring of viral loads, and ARV treatment when medically appropriate
    - No time limit for period of providing ART
    - But no obligation to provide monetary compensation unless stipulated in advance

Informed Consent

- What must be disclosed in informed consent process in future trials?
  - Facts regarding enhanced susceptibility of participants in the STEP trial
  - Say whether the vaccine product and other risk factors in a future trial are similar to or different from those in the STEP trial
    - In what way or ways

Future challenge: control groups

- The use of a placebo control arm is ethically acceptable in a biomedical HIV prevention trial only when there is no HIV prevention modality of the type being studied that has been shown to be effective in comparable populations.
  - UNAIDS/WHO 2007 Guidance Point 15

Control groups

- How to interpret 'the type being studied'?
  - Is the "type" any preventive HIV vaccine?
  - Or is it a specific type of vaccine?
- What are criteria for comparability among populations?
  - Different racial or ethnic groups?
  - Different geographic locations?
  - Different nutritional or health status?
  - Differences in risk behavior?

Response to challenge

- How to respond to this challenge, from a scientific and methodological point of view?
  - Negotiations [among all research stakeholders, including the community] should take into consideration feasibility, expected impact, and *the ability to isolate the efficacy of the biomedical HIV modality being tested, as other prevention activities improve.*
    - UNAIDS/WHO GP 15 Commentary

Conclusions

- The new recommendation on standard of prevention (GP 13) is ethically commendable but poses a challenge for interpreting results of future prevention trials
- The new recommendation on control groups (GP 15) is ethically sound but requires interpretation and could provoke scientific and ethical controversy

Conclusions

- Ethical challenges in HIV preventive vaccine research should be addressed as soon as they are recognized
  - All stakeholders should be involved in discussing ethical problems and reaching consensus on their resolution
- Community engagement should take place "in an early and sustained manner" and "through genuine, transparent, meaningful participatory processes"
  - UNAIDS/WHO GP 2
  - UNAIDS/AVAC 2007 Good Participatory Practice Guidelines for HIV Biomedical Prevention Trials

The UNAIDS documents

- http://data.unaids.org/pub/Report/2007/jc1399-ethicalconsiderations_en.pdf
- http://data.unaids.org/pub/Report/2007/jc1364-gpp_en.pdf