UNAIDS (and other) Guidelines

Ethical Challenges for International HIV Prevention Research

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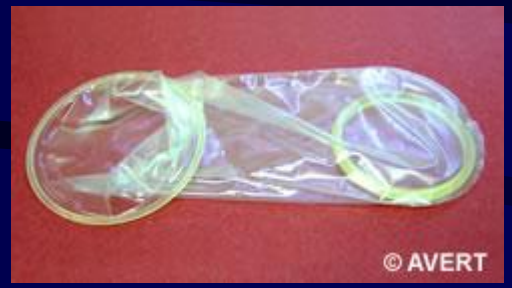
HIV Prevention Research

- Vaccines
- Microbicides
- PrEP
- Male circumcision
- Counseling

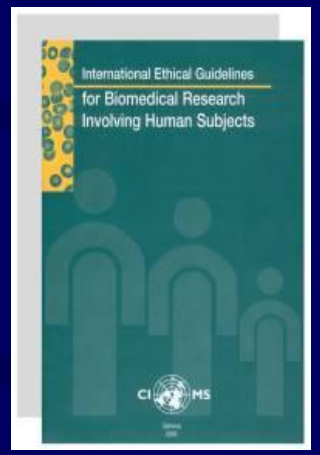
Methods of prevention

COUNSELING



Ethics guidelines

- **Guidelines or recommendations that address these concerns**
  - Declaration of Helsinki (2013)
  - CIOMS International Guidelines for Biomedical Research Involving Human Subjects (2016)
  - UNAIDS/WHO Ethical considerations in biomedical HIV prevention trials
    - 2007, additional guidance point added in 2012



Challenges for prevention, care and treatment

- How to identify and protect vulnerable populations?
- What should be provided to the control group in prevention trials studying efficacy of a new method?
- What methods to reduce risks should be provided to all participants in prevention trials?
- What should be provided to trial participants who acquire the “target disease” during the trial?

Vulnerable populations

- Purpose of guidelines on vulnerability
  - Assumption that special protections are needed for vulnerable persons being recruited for or enrolled in research
- Traditional approach has been to identify entire groups as vulnerable
- UNAIDS guidelines provide lists
  - Examples include children and adolescents, persons with mental or behavioral disorders, the elderly, members of hierarchical groups, poor people, women, prisoners, MSM, sex workers, the poor, homeless, transgender persons, and many others

CIOMS guideline 15

- Research involving vulnerable persons and groups
  - When vulnerable individuals and groups are considered for recruitment in research, researchers and research ethics committees must ensure that specific protections are in place to safeguard the rights and welfare of these individuals and groups in the conduct of the research.

Focus on characteristics

- CIOMS commentary accompanying the guideline avoids labeling entire groups as vulnerable
  - But identifies characteristics and situations that may render individuals vulnerable
- Commentary says
  - "In some cases, persons are vulnerable because they are relatively (or absolutely) incapable of protecting their own interests."

Specific characteristics

- The specific characteristics that make individuals vulnerable can aid in identifying special protections needed for persons who may have an increased likelihood of being wronged or of incurring additional harm
  - RECs can require such protections for groups to be recruited
  - Researchers recruiting and enrolling subjects must take individual characteristics into account

UNAIDS: Vulnerable populations

- The research protocol should describe…conditions for possible exploitation or increased vulnerability among potential trial participants, as well as the steps that will be taken to overcome these and protect the rights, the dignity, the safety, and the welfare of the participants.
  - UNAIDS/WHO GP7
- Vulnerable populations at risk for HIV infection pose challenges
  - Sexually active adolescents
  - People who inject drugs (PWID)
  - Gay men in some African and Caribbean countries

Children and Adolescents GP 10

- Since adolescents may be sexually active or injecting drugs, they should be enrolled in trials "in order to verify safety and efficacy from their standpoint."
  - Commentary: "It is imperative that trials are conducted in compliance with the protective laws and regulations applicable at the trial sites, including those related to legal age of consent…"
    - In most jurisdictions, parental permission will be required for enrolment of adolescents
    - Yet parents may be unaware of their adolescent's behavior
    - Adolescents may be at risk from their own parents who learn of their risk-taking behavior

Solution: recruit adolescents whose parents are aware

- Adolescents enrolled in drug treatment programs or treated at family planning or STD clinics
  - Adolescents could be approached in this setting for recruitment
  - They could be asked whether their parents are aware of their behavior, before involving parents in the consent process
  - To protect adolescents' confidentiality, a worker in the program or clinic would first have to ask adolescents if they would be willing to speak to the researcher

Challenges for prevention trials with PWIDs

- Involving community participation at all stages of planning and conducting HIV prevention trials
- Ensuring privacy and confidentiality of PWID during recruitment, conduct of the trial, and follow-up
- Addressing problems related to illegality of drug use
- Attitudes and behavior of police and other law enforcement agencies
- Difficulty or impossibility of adherence to ethical guidance on standard of prevention

Challenges for prevention trials

- Providing access to treatment for individuals found to be HIV-positive during screening
  - When they become medically eligible for treatment
- Providing access to treatment for individuals who become HIV-positive during the trial (UNAIDS/WHO GP 14)
  - When they become medically eligible
- Making successful biomedical HIV preventive interventions available to participants in the trials and to other populations at high risk of HIV exposure when research is concluded (GP 19)

UNAIDS, CIOMS, DoH

- Ethics guidelines call for effective products to be used as comparators in clinical trials
  - The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:
    - The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists
      - Declaration of Helsinki 2013

UNAIDS/WHO Guidance 2007

- 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 (Guidance Point 15)

Ethics guidelines: UNAIDS/WHO 2007

- Participants in both the control arm and the intervention arm should receive all established effective HIV risk reduction measures. 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.
  - How to interpret ‘the type being studied’?
  - Which populations are “comparable”?

Standard of Prevention

- UNAIDS/WHO Guidance Point 13
  - 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. 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.
    - No “double standards” permitted
    - One for rich countries, another for LMIC

Researchers' challenge and reply

- 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
- Implementation of this recommendation must be consistent with scientific design and feasibility

Proper prevention package

- What should be provided in a biomedical prevention trial to reduce the risk of participants becoming HIV-infected as a result of their behavior, not the experimental product itself?
  - 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
    - UNAIDS/WHO ethical guidance

Community Participation: GP2

- "…researchers and trial sponsors should consult communities through a transparent and meaningful participatory process which involves them in an early and sustained manner in the design, development, implementation, and distribution of results of HIV prevention trials."
  - Transparency may reveal the identity of persons actively using illegal drugs, thus placing them at legal risk
  - Identifying appropriate representatives or spokespersons from PWID community

GP 2 Commentary

- "Defining the relevant community for consultation and partnership is a complex and evolving process that should be discussed with relevant local authorities."
  - Who are the relevant local authorities appropriate for consultation in trials involving PWIDs?
  - How to implement this recommendation when the local authorities may place potential trial participants at risk?
  - What should be the involvement of governmental or other authorities in recruiting and enrolling PWIDs as participants?

Ongoing challenges

- Access to care
  - What level of care and treatment should be provided to participants in a preventive HIV vaccine trial who acquire HIV in the course of the study?
  - What care and treatment should be provided for other diseases participants acquire during a prevention trial?

Access to care & treatment

- Challenging questions remain
  - Who bears the responsibility to provide treatment for individuals who become HIV infected in the course of a prevention trial?
  - Why should participants in HIV prevention trials be singled out for treatment if family members and others in the community are not receiving needed ARV treatment?

What opponents argue

- Research is not therapy
  - Obligations of researchers are not those of physicians treating patients
- Treatment would not be financially affordable
  - "Double standards" are ethically acceptable based on economic considerations

UNAIDS/WHO Guidance

- Strong statement in Guidance Point 14, Care and treatment
  - 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
    - Substantive and procedural ethical considerations

Undue Inducement

- Some argue that promising ART to potential participants in preventive HIV vaccine trials is an "undue inducement" to enroll
- However
  - Trial participants are healthy and do not currently need treatment
  - If promise of possible treatment would be an undue inducement, then why not a vaccine or PrEP, with possible efficacy?

Ongoing ethical challenges

- Ethical challenges remain and will continue as more HIV prevention research goes forward
- The main current challenges are a result of successes
  - Successful treatment of HIV/AIDS, posing the “access” questions
  - The prospect of increasing numbers of efficacious vaccines, PrEP and microbicides, raising the “standard of care” issue

Confidentiality GP18

- Researchers and research staff must ensure full respect for the entitlement of potential and enrolled participants of information disclosed or discovered in the recruitment and informed consent processes, and during conduct of the trial….
  - Commentary: Legal exceptions to the duty to maintain confidentiality might exist, for example, where disclosure is mandated by a court order or where there is a duty to report to public health authorities.
    - Are there reporting laws regarding drug use in jurisdictions where trials might be done?
    - Responsibility of researchers to find out

Loss to follow up

- Steps should be taken to ensure that efforts to follow up participants who do not show up for trial visits are done with prior consent of participants
  - At enrollment, participants should be asked to name a trusted person who can be contacted in case they do not show up for a scheduled trial visit

Incarceration during trial

- Some participants might be jailed or imprisoned while participating in the trial
  - How can their continuation in the trial be ensured
    - In a way that protects their confidentiality while they are incarcerated?
- What steps must be taken in advance to ensure they can be contacted without breach of confidentiality?
  - All trial participants should be asked at enrollment for the name of a trusted individual who might be contacted

Conclusions

- UNAIDS/WHO Guidance document contains a variety of obligations on the part of researchers
  - These may be difficult to fulfill
  - Do the same obligations exist when the research is social and behavioral, in contrast to biomedical?
    - Social and behavioral researchers could partner with biomedical researchers in addressing this question