Scientific and Ethical Challenges of HIV Prevention Trials

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HIV Prevention Challenges

• With the development of new HIV prevention tools, the HIV prevention field faces a number of challenges associated with the design of future trials.
  – Scientific;
  – Logistical; and
  – Ethical.
HIV Prevention Challenges (2)

- Complex clinical trial designs.
- Healthy volunteers - “at risk”.
- Results affected by user behavior.
- Sensitive issues (e.g. sex, power, gender).
- Stigma associated with HIV and sexual activity.
- Multiple trial sites and transnational collaborations.
Overlapping Frameworks

- Clinical Care
- Research
- Public Health
Researcher Roles

• Trial as a research endeavor: Investigator focused on delivering the highest quality research outcome.

• Trial as medical practice: Investigator as clinician.

• Trial as a public health initiatives Investigator assists community and helps build public health capacity.
The researcher is responsible for:

- Participants wellbeing
- Standard of Care (treatment)
- Referral
- GCP
- Adherence
- Loss to follow up
- SAE reporting
- NRA and Ethics reporting
- Protocol amendments
- Staff
- Research team
- Community partnership
- Community development

- Budgets
- Security
- Facilities
- Pharmacy
- Conference calls (at night)
- Network meetings
- Conference presentation
- Capacity building
- Paper writing
- Dissemination
- Access to product/intervention
- Sustainability
Core Ethical Principles

• The Belmont Report (1978):
  – Respect for Persons.
    • Autonomy.
    • Protection of vulnerable persons or those with diminished capacity.
  – Beneficence.
    • Maximizing benefits.
    • Minimizing harms.
  – Justice.
Other Articulations/Guidance

• Other ethical frameworks:
  – Standard of care.
  – Therapeutic obligation and equipoise.
  – Duty of rescue.

• Guidance documents:
  – Declaration of Helsinki.
  – CIOMS.
  – UNAIDS/WHO.
  – Nuffield Council.
• Guidance Point 20: People Who Inject Drugs (added 2012)

Researchers and sponsors should include people who inject drugs in biomedical HIV prevention trials in order to verify safety, efficacy, and effectiveness from their standpoint, including immunogenicity in the case of vaccines. As with other key populations at higher risk of HIV exposure, providing people who inject drugs with access to proven, effective HIV preventive interventions is a public health imperative. Researchers and trial sponsors should engage meaningfully with people who inject drugs and with other stakeholders to overcome the complex legal, ethical, and regulatory challenges to the participation in biomedical HIV prevention trials of people who inject drugs. Trial conduct that is ethical is informed by the latest scientific evidence on proven HIV prevention strategies and ensures that participants human rights, safety, and welfare are protected.
Consensus Ethical Principles

• Applied to HIV prevention trials, current ethical principles and guidance require:
  
  – Study participants be informed of the risks and benefits of participation;
  
  – Risks are minimized and benefits maximized (i.e. by providing an appropriate HIV prevention package to all participants); and
  
  – Trial participants and communities are not chosen solely for expedience.
Some Ethical Debates

• When does it become unethical to use a placebo in the control arm?

• Do researchers or trial sponsors have an obligation to provide life-long access to HIV treatment for seroconverters?

• What is the obligation to provide successful prevention tools to participants following a clinical trial in which they were enrolled?
More Ethical Debates

• What is the obligation to provide new HIV prevention tools to participants enrolled in planned or on-going clinical trials?

• Is it ever ethical to provide a less than “cadillac” standard of prevention to participants in HIV prevention trials?
Question 1

- When does it become unethical to use a placebo in the control arm?
- Do researchers or trial sponsors have an obligation to provide life-long access to HIV treatment for seroconverters?
- What is the obligation to provide successful prevention tools to participants following a clinical trial in which they were enrolled?
Use of Placebos

- Placebos control for the therapeutic aspects of a medicine not directly due to the intervention itself.
- Their use raises a number of ethical questions, including:
  - Can trial participants be randomized to receive a potentially inferior treatment?
  - Does delaying the use of a treatment or intervention harm participants?
The Hippocratic Oath obligates a physician to do what is best for the patient, without consideration of personal or social obligations.

If true, this obligation poses a challenge for physicians engaged in clinical research.
Clinical Equipoise

• Most clinical trials violate a researcher’s therapeutic obligation unless there is equipoise.

• Equipoise exists when there is “genuine uncertainty ... about the comparative therapeutic merits of each arm of a clinical trial.”
Study participants may randomized to receive a placebo control only when there is:

- No standard therapy;
- Standard therapy is no better than placebo;
- Standard treatment is placebo;
- There is doubt about the net therapeutic advantage of standard therapy; or
- Standard treatment is unavailable (e.g. because of cost or supply).
• When the study enroll participants who refractory to standard treatment.

Solomon (1995): “[I]t is more important to know ‘whether the treatment is better than nothing’ and will therefore offer an alternative for patients who do not have a response to the conventional treatment or cannot tolerate its adverse effects.

• When the placebo is added on top of standard treatment.

Gilbert (1995): “Patients are randomly assigned to receive a new drug or placebo, which is added to the existing treatment. Thus, patients in both the placebo and active treatment groups receive all medications that would normally be prescribed.”
Placebos may be used when:

- There is no established effective intervention;
- Withholding established intervention would expose subjects at most to temporary discomfort or delay in relief of symptoms; or
- Use of active control would not yield scientifically reliable results and subjects would not be put at risk of serious or irreversible harm.
A 1992 US study showed that the antiretroviral drug AZT – given orally to HIV infected mothers prenatally, intravenously during labor, and orally to the newborn – reduced perinatal transmission by two-thirds.

In Africa, AZT treatment of HIV-infected mothers was unavailable because of cost and the lack of prenatal care.

18 studies were begun in these countries to test an alternative regimen. In these trials, some of the participants were randomized to receive no drug.
Points to Consider

- Can active control always be a scientifically acceptable substitute for placebo control?

- Do the ethics of a placebo-controlled trial depend on the consequence of remaining untreated?

- Must a known effective agent be used as a control, even if it cannot be implemented for financial and logistical reasons in studying a new agent?
You are designing a phase III randomized placebo-controlled trial of a vaginal gel containing 1% dapivirine among heterosexually-exposed women in Rwanda and Malawi.

The results of the CAPRISA 004 trial are released, showing that a gel containing 1% tenofovir reduced HIV acquisition among South African women by 39%.

Are you obligated to re-design your study in light of these results by providing a tenofovir-containing gel to participants in the control (comparator) arm?
Question 2

• When does it become unethical to use a placebo in the control arm?

• Do researchers or trial sponsors have an obligation to provide life-long access to HIV treatment for seroconverters?

• What is the obligation to provide successful prevention tools to participants following a clinical trial in which they were enrolled?
Infection with HIV is a necessary study endpoint – current trials are designed with 100-300 infections among participants.

Most researchers and ethicists would also argue, however, that HIV infection occurs despite trial participants, not because of it.

Given this, should participants who seroconvert during a trial be offered life-long access to care and treatment?
Ten years ago, it was considered morally praiseworthy but not ethically obligatory to provide some treatment.

Individuals who seroconverted during a trial (or screened out) were referred to local health care services for counseling.

No viable government-run treatment programs existed in most resource-poor countries where trials were occurring.
• Current consensus is that some access to HIV treatment and care should be provided.

• UNAIDS/WHO 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 recognized as optimal, and any deviation from this standard must be justified.”
Increased Challenges

• Ensuring long-term access to care in the face of political and financial instability, and restrictive donor policies.

• Demolishing barriers to access.
  – Many existing programs are overburdened (long waiting times).
  – Many existing programs are underutilized (stigma).

• Treatment for 'screen-outs'?

• Concerns that guaranteeing access to treatment could be an 'undue' inducement for trial participation.
• Ethical guidelines often raise concerns about inducements, particularly with respect to payment or provision of medical services.

• An inducement is 'undue' when it causes a person to assume risks that they would ordinarily consider to be unacceptable.

• There is considerable debate within the research ethics community and in existing guidance about what level of compensation or medical care constitutes an undue inducement.
• CIOMS’ International Ethical Guidelines for Biomedical Research:

“All payments, reimbursements and medical services provided to research subjects [... should not be so large or] so extensive as to induce prospective subjects to consent to participate in the research against their better judgment.”

• NBAC’s Ethical and Policy Issues in International Research:

“... the provision of medical care, by its very nature, cannot and does not create undue inducement to participate in clinical trials.”
Challenge Question 2

- Using a SBIR grant from the NIH, a small biotech company plans to conduct a phase II safety and immunogenecity study of a new HIV vaccine among IDUs in Baltimore.

- Participants will receive monthly HIV counseling and testing, and be paid $100 for each visit they attend. Seroconverters will be referred to an (overburdened) public HIV clinic for treatment. A one-time unrestricted $10K grant will be provided to cover costs.

- Local activists are outraged, arguing that the study is unethical because it does not provide state-of-the-art care for seroconverters, and demand that the company pay for lifelong treatment (including psychosocial support, TB prophylaxis, etc.)

- The company argues that provision of long-term HIV treatment in such an economically-depressed community will create a two-tier standard of care and would thus unduly induce study participation.

- Who is correct? What should be provided for HIV treatment? By whom?
Question 3

• When does it become unethical to use a placebo in the control arm?

• Do researchers or trial sponsors have an obligation to provide life-long access to HIV treatment for seroconverters?

• What is the obligation to provide successful prevention tools to participants following a clinical trial in which they were enrolled?
• Even once a trial demonstrates a new HIV prevention tool is safe and effective, it can take years to make it available in the larger community:
  – Additional requirements for confirmatory studies for licensure and approval;
  – Drafting local, national and international guidelines for implementation; and
  – Finding the resources for roll-out to the community.
Donor policies also generally restrict the provision of all care and services (not just new prevention tools) once a trial ends.

Some research-based solutions to making these tools available to study participants include:

- Bridging studies;
- Acceptibility studies; and
- Follow-up safety studies.
Post-Trial Access (3)

- Research-based solutions to making these tools available to community have consequences, including:
  - Unexpected impacts of introducing a new technology to the community;
  - Trial sites might be only community source of technology;
  - Sustainability issues;
  - Unplanned research expenditures; and
  - Governments do not like researchers pre-empting their policy role.
• Your NIH-funded phase III trial of 1% dapivirine gel showed that it decreased rates of HIV acquisition among heterosexually-exposed women in Rwanda and Malawi by 32% (95% CI = 8% - 54%).

• Neither Rwanda nor Malawi have regulatory mechanisms in place to approve this gel for use. Instead, they rely on the US FDA for this determination, which requires at least two RCTs for licensure.

• Thus, it is likely that it will be 3 years or more before this gel is approved for use in these countries, and even likely will be available only to those with the money to purchase the gel.

• What is your obligation to make this gel available to the trial participants? To the larger trial community? How are you going to achieve that?