Ethical and Scientific Issues in Prevention Research

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Overlapping Frameworks

- Clinical Care
- Research
- Public Health
**Medicine**

- **Autonomy**
  - Right to decline care.
- **Non-maleficence**
  - Do no harm.
- **Beneficence**
  - Help patients.
- **Justice**
  - Provide equal care to all.

**Public Health**

- **Interdependence**
  - Individual actions affect others.
- **Participation**
  - Input from the public.
- **Evidence**
  - Facts, not beliefs or conjecture.
Research vs. Public Health

Research

- Respect for Persons
  - Get consent.
  - Protect the vulnerable.

- Beneficence
  - Maximize benefits.
  - Minimize risks.

- Justice
  - Fair subject selection.

Public Health

- Interdependence
  - Individual actions affect others.

- Participation
  - Input from the public.

- Evidence
  - Facts, not beliefs or conjecture.
HIV/AIDS is now a largely preventable disease as well as a chronic manageable condition.

- Behavioral interventions.
- New prevention modalities.
  - Pre-exposure prophylaxis; and
  - Treatment as prevention.
- Advances in treatment.
A global view of HIV infection
33.3 million people [31.4–35.3 million] living with HIV, 2009
HIV Prevention Trials

- 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.
• **Challenge 1**: HIV disproportionately affects vulnerable populations.

  – Generally, the people at greatest risk are also those who are:
    
    • Impoverished;
    
    • Less educated;
    
    • Stigmatized (drug users, sex workers, MSM);
    
    • Lack access to health care.
Challenge 2: Most HIV prevention research is done in resource-poor settings

- “Standard of care” in HIV trials has been the subject of intense debate:
  
  • What package of prevention services should be provided to participants in the control arm?
  
  • What types of ancillary care should be provided to trial participants?
• **Challenge 3: Infection with HIV is a necessary study endpoint.**

  – Many researchers and ethicists would argue that HIV infection occurs despite trial participation, not because of it.

  – Should these participants be offered lifelong access to HIV care and treatment?
Basic Trial Design

Recruitment

Screening Visit
- HIV Testing
- STI Testing/Treatment
- Pregnancy Testing

Enrollment Visit
- HIV Testing
- STI Testing/Treatment
- Pregnancy Testing

Randomization

Experimental Arm
- Condoms
- Counseling
- STI Testing/Treatment
- Other Prevention Tools + Product

Control Arm
- Condoms
- Counseling
- STI Testing/Treatment
- Other Prevention Tools + Placebo or Comparator

How Many Remain HIV-negative?
Scientific Issues

• Prevention packages don't address the needs of many participants, and may be unsustainable once a trial ends.

• Prevention packages make also it difficult to assess experimental interventions.
  – Social desirability bias.
  – Complications of poor measurement.
  – Attenuation of power.

• When does it become unethical to use a placebo?
Evaluating Efficacy vs. New Technology (Vaccine) + Effective Prevention (Condoms) + Effective Prevention (Gel) vs. Effective Prevention (PrEP) + Effective Prevention (Condoms) + Effective Prevention (Gel)
Sample Size

• Assumptions:
  – Background HIV rate: 4.5%
  – Effectiveness of standard package: 0%
  – Effectiveness of new intervention: 55%
  – 12 month follow-up with 10% attrition
  – 300 HIV endpoints required

Number of Participants: 10,218

Estimated Cost of Trial: $71m US
• Assumptions:
  – Background HIV rate: 4.5%
  – Effectiveness of standard package: 50%
  – Effectiveness of new intervention: 55%
  – 12 month follow-up with 10% attrition
  – 300 HIV endpoints required

Number of Participants: 20,435

Estimated Cost of Trial: $142m US
<table>
<thead>
<tr>
<th>Trial</th>
<th>Pre-Trial Estimate</th>
<th>During Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cameroon (1995-97)</td>
<td>14.0</td>
<td>6.7</td>
</tr>
<tr>
<td>Nairobi (2000-02)</td>
<td>6.0</td>
<td>3.7</td>
</tr>
</tbody>
</table>
• Assumptions:
  – Pre-trial HIV rate: 4.5%
  – Estimated HIV rate during trial: 2.0%
  – Effectiveness of standard package: 50%
  – Effectiveness of new intervention: 55%
  – 12 month follow-up with 10% attrition
  – 300 HIV endpoints required

Number of Participants: 50,731

Estimated Cost of Trial: $267m US
Sustainability

- Survey of condom use by participants enrolled in a randomized controlled trial of N-9 in Cameroon (Wong et al. 2005):

<table>
<thead>
<tr>
<th></th>
<th>During Study</th>
<th>Post-Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of acts with condoms</td>
<td>82 - 84%</td>
<td>57%</td>
</tr>
<tr>
<td>% of participants reporting consistent condom use</td>
<td>64 – 67%</td>
<td>35%</td>
</tr>
</tbody>
</table>
Established and Proven

• If we accept the argument that researchers should provide all state-of-the-art interventions to study participants, we must ask:
  – When is something “proven” to be effective?
  – Once proven effective, when does it become an “established” intervention?
Established Preventions

• Does an intervention become an established when it is:
  – Recommended by a normative agencies?
  – Added to a national prevention strategy?
  – Available in the community?
  – Common practice?
Ethics and Placebo Controls

• Study participants may be randomized to receive a placebo control only when there is (Freedman 1987):
  – 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).
• Study participants may also randomized to receive a placebo control if:
  
  – The study only enroll participants who refractory to standard treatment (Solomon 1995); or
  
  – When the placebo is added on top of standard treatment (Gilbert 1995).
Given that PrEP has been shown to work, can we test the effectiveness of other formulations using a placebo-controlled trial design?
• If we want to test new formulations of PrEP against Truvada, we have to use one of two study designs:
  - Test if the new formulation of PrEP is superior to Truvada (a superiority trial)
  or
  - Test if the new formulation is equivalent or not worse (by an amount X) than Truvada (a non-inferiority trial)
Studies Using Active Controls (2)

- Superiority
- Non-inferiority
- Equivalence

Truvada Superior

New PrEP formulation superior

Difference in HIV Rates

Non-Inferiority Margin

$\Delta M_0$
• Problems with superiority trials:
  – We may end up rejecting an effective prevention tool.

• Problems with non-inferiority trials:
  – Determining the margin of allowable inferiority.
  – Sample size.
  – “Biocreep”.
  – Observed effectiveness in the past may no more be valid (constancy assumption)
Non-Inferiority

EFFECTIVENESS

Truvada

New PrEP formulation

Placebo

Non-Inferiority Margin (X)

Amount of Effect to be Retained (R)
## Non-Inferiority and Sample Size

<table>
<thead>
<tr>
<th>Active Control Effectiveness</th>
<th>Amount of Effect to be Retained</th>
<th>Number of HIV Endpoints Required</th>
<th>Required Resources</th>
</tr>
</thead>
<tbody>
<tr>
<td>60%</td>
<td>40%</td>
<td>~120</td>
<td>Average size of current trials (10,000 participants)</td>
</tr>
<tr>
<td>60%</td>
<td>50%</td>
<td>~1200</td>
<td>~10 times the size of current trials (100,000 participants)</td>
</tr>
</tbody>
</table>
“Biocreep”

**EFFECTIVENESS**

- **Truvada**
  - 60%
  - Non-Inferiority Margin (10%)

- **First new PrEP formulation**
  - 50%
  - Non-Inferiority Margin (10%)

- **Second new PrEP formulation**
  - 40%

- **Placebo**
  - 0%

New Amount of Effect to be Retained ($R - 10$)
What we assume:

1. New PrEP formulation non-inferior to Truvada.
2. Both are superior to a placebo pill.
What may be the case:

1. New PrEP formulation non-inferior to Truvada.
2. Both are not superior to a placebo pill.
Core Research Ethics Principles

• Respect for persons
  – Voluntary informed consent.
  – Protection of vulnerable persons.

• Beneficence
  – Maximize benefits and minimize harms.
  – Some frameworks break this principle into beneficence, non-maleficence and utility.

• Justice
  – Non-exploitation and equitable selection.
  – Individuals and groups that participate in trials should benefit from participation.
When applied to HIV prevention trials, these three principles require that:

1. Participants be informed of the risks and benefits of participation;
2. Risks minimized and benefits maximized by providing an appropriate HIV prevention package and other services; and
3. Trial participants and communities are not chosen solely for expedience or cost, and are not denied services to which they are normally entitled.
The principle of beneficence requires that trial participants be treated in an ethical manner “not only by respecting their decisions and protecting them from harm, but also by making efforts to ensuring their well-being. Two general rules have been formulated as complementary expressions of beneficent actions: 1) do no harm, and 2) maximize possible benefits and minimize potential harms” (Belmont Report 1979, §B2).
HIV Prevention Trial Ethics

• All trial participants should have information about proven and established HIV prevention services.

• It is not obligatory, however, to always provide or ensure access to the full range of proven and established prevention tools.

• The prevention package in a trial can vary in the type of services are provided so long as it:

  1) Is developed in consultation with the community; and

  2) Addresses the specific needs of the community.
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