Successful results of clinical trials

- Four clinical trials for HIV prevention in past two years showed different degrees of efficacy
  - HPTN 052 showed 96% reduction in HIV transmission from HIV infected men and women to uninfected partners
    - Early treatment of HIV-positive partner with oral ART
    - “Treatment as prevention” (2011)
  - iPrEx PrEP effectiveness trial
    - Once-daily pill reduced the risk of HIV infection in HIV-negative gay men and other men who have sex with men by 44% (2010)
      - HIV negative partner took drugs
Two more successful trials

- CAPRISA 004 microbicide trial had 39% fewer infections among women who received 1% tenfovir gel compared to women who received the placebo gel (2010)
  - More modest success than two oral ART trials
- Thai vaccine vaccine regimen reduced HIV risk by approximately 30 percent (2009)
  - Statistically significant
  - But too low to be considered for approval by regulatory agency
The Latest: July 13, 2011 announcement

- Partners PrEP study in Kenya and Uganda enrolled 4,758 heterosexual discordant couples
  > Results revealed that both tenofovir (TDF, marketed as Viread) and tenofovir plus emtricitabine (TDF/FTC, marketed as Truvada) taken daily can reduce the risk of HIV transmission among both men and women.
  > Daily oral TDF reduced HIV risk by an estimated 62 percent infections and daily oral TDF/FTC reduced HIV risk by an estimated 73 percent when compared to a placebo.
Also announced on July 13, a separate TDF2 study in Botswana enrolled just over 1,200 sexually active men and women.

Analysis of final data on numbers of infections in the active and placebo arms indicated that daily oral TDF/FTC reduced the risk of HIV infection in both men and women participants by an estimated 62.6 percent compared to those who received the placebo.
What next?

• 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 2008
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

- Previously called “risk reduction measures”
- 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.
Ethical quandaries

• What is the criterion for “state of the art”?
• What degree of efficacy of a preventive method warrants regulatory approval?
  > Oral ART at 96%
  > Vaginal microbicide gel at 39%
  > Injectable vaccine at 31%
• Is it ethically acceptable to wait for regulatory approval?
  > Can take two years or more for approval
  > Usual requirement is for confirmatory studies before approval
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
  > Gay men in some African countries
Adolescents in research

- Barriers to recruiting adolescents for preventive HIV/AIDS research
  - In most jurisdictions, parental permission is required by law up to the age of majority
  - Parents may be unwilling to subject their offspring to risks and burdens of serving as participants in phase I/II research
  - Phase III trials would require identifying adolescents engaged in high risk behavior
    - This could result in stigma
    - It would disclose to parents the adolescent’s high risk behavior
Solution: Avoid parental permission?

- Even if ethically acceptable, this is a bad idea
  > It breaks the law in most jurisdictions
  > It may be practically difficult for adolescents to maintain the secret
  > Parents would have to be notified in case of an adverse event
  > Discovery by parents or authorities could halt the research and have even worse consequences
Solution: Adolescents who lack parental supervision?

• Not ethically acceptable on grounds of justice and vulnerability
  > Some adolescents lacking adult supervision are street children, and therefore vulnerable because of their marginalized status
  > Some adolescents are married, and therefore not under parental supervision
    • Primarily adolescent girls married to older men, and therefore also vulnerable
    • Remaining group are emancipated minors who support themselves and do not live with parents
Solution: recruit adolescents whose parents are aware

- Phase III trials: Adolescents enrolled in drug treatment programs or treated at 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 PWIDs 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 with PWIDs

• 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)
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
“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?
Recruitment of Participants GP 7

- Commentary
  - “In some situations, voluntariness of participation may be compromise by factors such as social marginalization, political powerlessness, and economic dependence.”
  - Could such factors be a challenge in recruiting PWIDs for biomedical HIV prevention trials?
    - If so, how to overcome the challenges?
Dilemma of resource allocation

- Prevention vs treatment
  - Truvada (oral medication that showed 96% reduction in HIV transmission from HIV infected men and women to uninfected partners) is part of AIDS treatment cocktail
  - Cost is high, supplies are limited
  - One side argues that making this form of prevention widely available is a public health imperative
  - Opponents claim that AIDS patients have urgent needs for treatment, especially in Africa where many remain untreated
Resource allocation dilemma

• No agreement exists on what ethical principle should be used in priority setting in a variety of contexts in health policy because there are competing principles.

• Some ethicists advocate a procedural approach to such questions.
  > Procedure must be fair, transparent, accountable, subject to revision based on accumulating evidence.

• But procedural approach could arrive at an ethically unacceptable solution.
Principles

- **Utilitarian** principle: choose the option that has the most overall beneficial consequences
  > Requires a wealth of empirical data, plus predictions: how effective will the preventive method be, overall? How many deaths can be averted by using resources for treatment rather than prevention?

- **Egalitarian** principle, or the principle of **equity**
  > Divide resources—equally or equitably between prevention and treatment
    * Too blunt an instrument; requires no analysis
Principles

• Principle of **urgent need**
  > For the many untreated AIDS patients at present, the decision would be to use the drug for treatment

• **Prioritarian** principle
  > Provide resources first to the **least advantaged**
    • Who are they?
      – The poorest people? The most vulnerable? The least empowered?
  > Not helpful for making choices between prevention and treatment
Principled resolution

- Best solution would be a combination of equity and urgent need
  - Bulk of scarce resources could be used for treatment of people who will sicken and die unless they receive treatment
  - Smaller share could go for prevention in the case of groups with “urgent need”
    - Those most likely to become infected if they lack effective preventive means
  - Scales could tip toward more for prevention once an efficacious vaccine is developed
Ongoing challenges

• Access to care
  > What level of care and treatment should be provided to participants in a preventive vaccine trial who acquire the disease the vaccine is designed to prevent?
  > 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?
Responses

• No one country, industrial sponsor, or agency will or should bear the entire burden of providing treatment

• Numerous mechanisms are now in place in many developing countries
  > GFATM
  > PEPFAR
  > Gates Foundation
  > Clinton Foundation
  > Other public-private partnerships
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 and microbicides, raising the “standard of care” issue
Benefits to the community

• What is owed to the community or country where research is conducted?
• “Distributive justice” requires a fair distribution of the benefits and burdens of research.
  > Risks of research should not be borne by groups or populations that will not receive the benefits of the research.
  > Those who share in the benefits of research should also share in the risks.
Post-trial obligations

- One position: no obligation exists
  - To provide successful products is beyond the ability of researchers
  - To require companies to provide products is unreasonable, as they are businesses that must realize a profit
  - Host countries lack resources to provide the products
  - If this were made a requirement, much important research could not be done in developing countries

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for the Fordham HIV Prevention Research Ethics Training Institute
Post-trial obligations

• Opposing view:
  > An obligation exists to make successful products of research “reasonably available”
    • to the research participants who still need them after the trial is over; and
    • to the community or even the country where the research is conducted
Critics’ response

- An absolute requirement to provide effective interventions would act as an impediment to finding sponsors willing to support research in developing countries.
- Beneficial research might therefore be delayed or avoided altogether, thus harming developing countries.
Reply to critics

• If there is little likelihood that successful research results will be implemented in the community or country where it is conducted, then the research is not truly responsive to the population’s health needs.

• Even if it is true that research might be delayed or prevented, the population has lost nothing because the benefits of the research would not be available to them anyway.
Reply to critics

• If there is little likelihood that successful research results will be implemented in the community or country where it is conducted, then the research is not truly responsive to the population’s health needs
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What do the guidelines say?

- World Medical Association, Declaration of Helsinki
  > 2008 revision
- CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects 2002
  > Ethical considerations in biomedical HIV prevention trials
• Before undertaking research in a population or community with limited resources, the sponsor and the researcher must make every effort to ensure that:
  > the research is responsive to the health needs and the priorities of the population or community in which it is to be carried out; and
  > any intervention or product developed, or knowledge generated, will be made reasonably available for the benefit of that population or community.
• Availability of Outcomes

> …During the initial stages of development of a biomedical HIV prevention trial, trial sponsors and countries should agree on responsibilities and plans to make available as soon as possible any biomedical HIV prevention intervention demonstrated to be safe and effective, along with other knowledge and benefits helping to strengthen HIV prevention, to all participants in the trials in which it was tested, as well as to other populations at higher risk of HIV exposure in the country.
What counts as benefits?

- What should count as “benefits” of research conducted in developing countries?
  - Successful interventions and knowledge only?
  - Contributions to building capacity and infrastructure—and beyond (e.g., roads)?

- Who should decide what should count as benefits
  - Host country
  - Sponsoring country/agency
  - International consensus
Global Campaign for Microbicides in India