Implementing Federal Guidelines for Human Research: A Researcher’s Perspective

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HIV in 2011

- Declining HIV incidence in many African countries compared to 2007
- We may be at or nearing the ‘tipping point’
  - If we increase coverage of HIV testing, treatment, and other effective HIV prevention strategies
- Research has contributed to this decline, and can continue to be part of the public health response
Antiretrovirals for prevention

PrEP in HIV-uninfected persons:
- A gel or pill decreases HIV acquisition by 39%-42% in young South African women and MSM

ART for HIV-infected persons:
- Early ART in HIV+ persons decreases HIV transmission by 96%

I’m afraid you’ve had a paradigm shift.”
A preview of my conclusions

• International clinical research can and is being implemented to the highest ethical standards

• Substantial effort is required & there are multiple challenges & barriers to achieving this
  – Multiple layers of review; sometimes inconsistent recommendations
  – Conservative approach (medical vs public health perspective) leads to substantial delays
  – Collaborative, capacity-building research is essential

• Given high HIV incidence among women in sub-Saharan Africa, there is an urgent need to reevaluate barriers to including pregnant & breastfeeding HIV-women in research
## Introduction to perspectives: My research experience

<table>
<thead>
<tr>
<th>Year(s)</th>
<th>Project Description</th>
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</thead>
<tbody>
<tr>
<td>1989-94</td>
<td>Epidemiology of Sexually transmitted infections among men who have sex with men (MSM) in US &amp; Peru</td>
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<td>1995-03</td>
<td>HIV vaccine preparedness cohorts, phase II &amp; III HIV vaccine trials, &amp; behavioral intervention in MSM in US</td>
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<td>2002-08</td>
<td><strong>Phase III trial of suppression of genital herpes to prevent HIV acquisition</strong>: 3265 MSM in US, Peru &amp; women in Africa (9 sites; NIH funded)</td>
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<td>2003-09</td>
<td><strong>Phase III trial of suppression of genital herpes to prevent HIV transmission</strong>: 3408 heterosexual HIV serodiscordant couples in 14 sites in East &amp; southern Africa (sponsor: BMGF)</td>
</tr>
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<td>2007-present</td>
<td><strong>Phase III trial of antiretroviral pre-exposure prophylaxis (PrEP)</strong>: 4758 heterosexual HIV serodiscordant couples in Kenya &amp; Uganda (sponsor: BMGF)</td>
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<td>2007-present</td>
<td>Executive Committee, Microbicides Trial Network (MTN, NIH)</td>
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<td>2008-2012</td>
<td>Pilots of combination HIV prevention (home-based HIV testing, linkages to ART &amp; prevention (Uganda &amp; South Africa, NIAID funded)</td>
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<td></td>
<td>Pending proposal for community RCT in KwaZulu-Natal, So Africa</td>
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Principles & realities of international HIV prevention & vaccine research

- Test interventions that can be delivered, if effective
- Poverty levels, stigma, & access to quality health care
  - Research in ‘vulnerable populations’
- Understanding of consent by individuals with low literacy
- Multiple, sometimes inconsistent reviews: funder, US and international IRBs
- Insurance coverage
- Use of stored samples, esp for genetic studies
- Evolving standards of care: interpretations & expectations
  - Examples of male circumcision & earlier ART initiation
- Researchers obligations for providing services
  - Example of ART for HIV seroconverters during trial
- Post-trial access for effective interventions
HSV-2 Suppression to Prevent HIV Transmission: Partners in Prevention

3408 HIV-discordant couples with HIV+ partner also HSV 2-coinfected

Randomize HIV/HSV-2+ persons not eligible for ART by national guidelines (CD4 ≥250)

Acyclovir 400 mg twice daily

Placebo twice daily

Follow couples for 1-2 years

Primary endpoint: HIV infection in HIV-negative partner
Summary of Partners in Prevention HSV/HIV Transmission Study

• ~55,000 couples of unknown status HIV tested & pre-screened across 14 sites in East & southern Africa

• 6,543 HIV discordant couples screened

• 3,408 HIV discordant couples enrolled (3,007 ineligible)

• High retention at 24 months (92% HIV+ & 84% HIV- partners)

• High drug coverage (85%)
Partners in Prevention HSV/HIV Transmission Study
Community Outreach and Recruitment
Partners in Prevention HSV-HIV Trial: What it Took

- 1½ yrs to build a Coordinating Center at an academic center; prepare 14 sites, 7 of which were new to clinical trials
- 20 IRB reviews of initial protocol and protocol revision
- Translation & back-translation into 16 languages:
  - 6 ICFs (3 for HIV+, 3 for HIV- partner)
  - 304 case-report forms (CRFs) into 16 languages
- 579,000 CRFs faxed to Seattle; 617 QC reports (20,500 pgs)
- 2 million samples collected
  - ~750,000 specimens shipped to Seattle Central Repository
  - For HSV & HIV confirmation, HIV viral load, HIV sequencing of endpoints
- 100s of quarterly monitoring & site visits, & conference calls
Lesson Learned: HIV discordant couples are key

- A high proportion of new HIV cases in Africa occur in cohabitating HIV discordant couples (= in which one partner is HIV infected and the other is HIV uninfected)

- In a couple in which one member is HIV+, there is only a 50:50 chance that the other will be HIV+

- ~30% of HIV infections within serodiscordant couples come from an outside partner

- Even with intensive risk reduction counseling, HIV risk is high for HIV-uninfected partners in discordant couples, particularly in couples desiring children
## Ongoing PrEP efficacy studies

<table>
<thead>
<tr>
<th>Location</th>
<th>Sponsor/ Funder</th>
<th>Population</th>
<th>N</th>
<th>PrEP Agent</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thailand</td>
<td>CDC</td>
<td>IDU</td>
<td>2400</td>
<td>TDF</td>
<td>Fully enrolled Results 2012</td>
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<tr>
<td><strong>Bangkok Tenofovir Study</strong></td>
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<tr>
<td>Kenya, Uganda</td>
<td>UW / BMGF</td>
<td>HIV discordant couples</td>
<td>4758</td>
<td>TDF, FTC/TDF</td>
<td>Fully enrolled Results 2012</td>
</tr>
<tr>
<td><strong>Partners PrEP Study</strong></td>
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<tr>
<td>South Africa, Uganda, Zimbabwe</td>
<td>MTN / NIH</td>
<td>Women</td>
<td>5000</td>
<td>TDF, FTC/TDF, Vaginal tenofovir gel (daily)</td>
<td>93% enrolled Results 2013</td>
</tr>
<tr>
<td><strong>VOICE / MTN 003</strong></td>
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- Safety, efficacy, resistance & costs will inform choice of drugs for PrEP roll-out
- Full spectrum of safety & efficacy will not be known among:
  - Pregnant and breastfeeding women
  - Adolescents (highest HIV incidence in young African women)
4758 HIV discordant couples (HIV+ partner does not yet qualify for ART)

Randomize HIV partners (normal liver, renal, hematologic function; not pregnant/breastfeeding)

TDF once daily

FTC/TDF once daily

Placebo once daily

All receiving HIV prevention services

Follow couples for 24-36 months

1° endpoint: HIV infection in HIV-negative partner

Co- 1° endpoint: Safety
International, collaborative research can be high quality & truly capacity building

- Human subjects, clinical (GCP) & laboratory (GCLP) training
- Monitoring visits every 6 weeks
- Durable capacity building
  - Mentoring young investigators
  - Clinical & laboratory infrastructure
  - Couples counseling programs

Dr. Nelly Mugo, Univ of Nairobi

Couples counseling: Mbale, Uganda
4 of 9 Partners PrEP sites were new to clinical research ...

Tororo site renovation: February to Nov 2008

Eldoret data room

Nairobi pharmacy
Imperative for finding new biomedical HIV prevention strategies for pregnant women

- Risk of HIV acquisition is high for women during pregnancy
- Risk of *perinatal* HIV transmission is high during acute HIV infection
- Pregnant & breastfeeding women are one of largest under-represented populations in HIV prevention research
- Generalizability concerns if pregnant & breastfeeding women are excluded from studies
- Ensures a delay in obtaining critical safety data
- Relegates pregnant women & providers to either choosing new interventions without sufficient safety data
- Lack of harmonization between federal agencies with review authority
Relevance of studying biomedical HIV prevention strategies in pregnant & breast feeding women

• ~60% of HIV infections in subSaharan Africa are in women

• During pregnancy, women have high risk of HIV acquisition
  – 13% in recent study in western Kenya

• Partners in Prevention HIV/HSV Transmission Study
  – 2-fold increased HIV \textit{acquisition} in HIV-negative pregnant women
  – 2-fold increased HIV \textit{transmission} from pregnant HIV-infected women to their HIV-negative male partners
Issues to consider for prevention research in HIV-negative pregnant women

• What constitutes minimal risk?

• Is evidence of efficacy in non-pregnant adults (e.g. FDA approval) required before a drug is studied in pregnant women?

• If so, how will safety data in pregnancy be acquired once a product is approved and used widely in the population?

• Balance caution with need to proactively obtain safety data for products which, if shown effective in other populations, will be used without safety data by:
  – Non-contracepting young women at high risk of pregnancy & HIV
  – Pregnant women at high risk for HIV
Barriers to Enrolling HIV-infected Pregnant Women in Clinical Research

- 45 CFR 46.204e requires paternal and maternal consent for enrollment of pregnant women
  - When intervention is of potential benefit to fetus but not the mother

- Paternal consent for enrollment of HIV-infected pregnant women into trials requires disclosure of maternal HIV status

- Partner notification is encouraged, must be done carefully, and is not always possible immediately
  - Thus, may hinder enrollment of HIV-infected pregnant women

- Regulation changed in end of Clinton administration but then overturned with change of administration

- Recommend re-evaluation of ethical issues regarding paternal consent for enrollment of pregnant women into trials
Summary of my conclusions

• International clinical research can and is being implemented to the highest ethical standards

• Substantial effort is required & there are multiple challenges & barriers to achieving this
  – Efficient, coordinated IRB reviews for multi-center studies
  – Feasibility of joint or external IRB review for int’l research
  – Needs assessment of international IRBs
  – Collaborative, capacity-building research is essential

• Evaluate barriers to including pregnant & breastfeeding HIV- women in research
  – Harmonization of federal agencies involved in review
International clinical means overcoming challenges

“Motto: Endeavour to Excel”
Kisumu, Kenya January 2009
Thank you to my many partners on the road long-travelled for HIV-1 prevention

If you want to go fast, go alone.
If you want to go far, go together.
– African proverb