The Agony and the Ecstasy: The Dynamic field of HIV Prevention Research

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Family Health International

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March 26, 2007
September 2006 – Anticipated Prevention Trial Results

- Female Barrier - Diaphragm
- Microbicides - Carraguard
- Male Circumcision - Susceptibility
- Community VCT and HIV Support
- HSV-2 Treatment - Infectiousness
- Oral PrEP - IDU
- Microbicides
  - BG/Pro2000
  - CS – 1
  - CS – 2
  - Pro2000
  - TDF
- Oral PrEP
  - MSM
  - Heterosexual
- Vaccines - Prime/Boost
- Vaccines - Adenovirus1 Adenovirus 2
- Index Partner Treatment
- Oral PrEP - West Africa
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- HSV-2 Treatment – Susceptibility
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2006  2007  2008  2009  2010  ……  2012
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January 2007 – Anticipated Prevention Trial Results

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March 2007 – Anticipated Prevention Trial Results

- **Female Barrier**
  - Diaphragm

- **Male Circumcision**
  - Susceptibility

- **Microbicides**
  - CS-1
  - CS-2
  - Carraguard

- **Microbicides – CS-1 CS-2 Carraguard**

- **HSV-2 Treatment – Infectiousness**

- **Oral PrEP**
  - IDU

- **Vaccines**
  - Adenovirus-1
  - Adenovirus-2

- **Community VCT and HIV Support**

- **HSV-2 Treatment – Susceptibility**

- **Microbicides**
  - BG/Pro2000
  - Pro2000
  - TDF

- **Oral PrEP**
  - MSM
  - Heterosexual

- **Index Partner Treatment**

- **Oral PrEP – West Africa**

- **Male Circumcision – West Africa**

- **Female Barrier – West Africa**
Outline

- Current HIV Prevention Tools
  - Levels of evidence
  - Effective/ineffective tools
- Ongoing trials
  - What if they work?
  - What if they don’t?
Why New Prevention Tools?
Do the HIV Math

- Major success in ART access
  - 1.65 M on treatment, **BUT**
- 4.3 M new HIV infections
- We’re losing our fight against HIV
- We need better prevention tools
### Evaluation of Evidence

<table>
<thead>
<tr>
<th>Quality of Evidence</th>
<th>Strength of Recommendation</th>
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<tbody>
<tr>
<td><strong>I. Good evidence</strong></td>
<td></td>
</tr>
<tr>
<td>- large RCT</td>
<td></td>
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<tr>
<td>- clinical outcomes</td>
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</table>

**II. Fair evidence**
- smaller RCT
- observational studies
- surrogate outcomes

**III. Weak evidence**
- anecdotes
- expert opinion

**A. Stronger**
- important benefits
- broadly applicable

**B. Weaker**
- smaller benefit
- limited generalizability

**C. Insufficient evidence**
- expert opinion
Current HIV Prevention Approaches - Level I Evidence of Effectiveness

• ARTs Pre/Post exposure to prevent MTCT
• Male circumcision to prevent acquisition
• Treatment of curable STIs - 1 study
• Contraception to prevent MTCT
Effect of Current Contraceptive Use by HIV+ Women

- 577,000 unintended births averted annually in HIV+ women – implications for orphanage
- 30% vertical transmission if no ARTs
- 173,000 HIV+ births prevented annually
- If unmet need for contraception addressed, this number could be doubled.

Source: Reynolds, et al., 2005
Current HIV Prevention Approaches - Level I Evidence of Ineffectiveness

- Nonoxynol-9 sponge/film/gel
- Treatment of curable STIs – 4 studies
- Vaccines – VaxGen
- Behavior change - individual
Current HIV Prevention Approaches - Level II-III Evidence of Effectiveness

- Male condoms
- HSV suppression
- Partner reduction/selection
- Female barriers
- Malaria treatment
Ongoing HIV Prevention Trials

- 15 Phase IIb/III trials
- 8 complementary fields
- Dynamic process of review for effectiveness/safety
- A tale of two topics
  - Male circumcision
  - Cellulose sulfate
## Male Circumcision – 3 RCTs

<table>
<thead>
<tr>
<th></th>
<th>Orange Farm</th>
<th>Rakai</th>
<th>Kisumu</th>
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<tbody>
<tr>
<td>Population</td>
<td>Semi-urban</td>
<td>Rural</td>
<td>Urban</td>
</tr>
<tr>
<td>MC Rate</td>
<td>20%</td>
<td>16%</td>
<td>10%</td>
</tr>
<tr>
<td>HIV Incidence</td>
<td>1.6%</td>
<td>1.0%</td>
<td>1.6%</td>
</tr>
<tr>
<td>Age Range</td>
<td>18-24 yrs</td>
<td>15-49 yrs</td>
<td>18-24 yrs</td>
</tr>
<tr>
<td>Sample size</td>
<td>3,128</td>
<td>4,996</td>
<td>2,784</td>
</tr>
<tr>
<td>RR – ITT</td>
<td>0.40</td>
<td>0.49</td>
<td>0.47</td>
</tr>
<tr>
<td>RR – PP</td>
<td>0.24</td>
<td>0.45</td>
<td>0.40</td>
</tr>
</tbody>
</table>
Modeling the Impact of Circumcision on HIV Prevalence/Incidence

• In SSA, 100% uptake of MC could avert 2 million new infections and 300,000 deaths over ten years

• In Soweto, 50% uptake of MC could avert 32,000 – 53,000 new infections over 20 years

• Prevalence would decline from 23% to 14%

Sources: Williams et al., 2006; Mesesan et al., 2006
Male Circumcision “Worked” – So What?

- Differential endpoints
- Regulatory approval
- Level of impact on individuals and populations – adherence, access
- Effect on current and future trials
- Ability to scale up
Differential Endpoints

- HIV acquisition - proven
- HIV transmission – concern if sex before healing
- HIV disease progression – unlikely for circumcision, but for other technologies (vaccines, oral PrEP)
Regulatory Approval

- Unnecessary for circumcision
- But for other technologies
  - How many trials?
  - What level of significance?
  - What if inconsistent results?
  - What if toxicity/resistance issues?
<table>
<thead>
<tr>
<th>Level</th>
<th>Efficacy</th>
<th>Effectiveness</th>
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</thead>
<tbody>
<tr>
<td>Individual</td>
<td>Perfect Use</td>
<td>Typical Use</td>
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<tr>
<td>Population</td>
<td>Clinical Trial Setting</td>
<td>Scale-Up</td>
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HIV Prevention Tools - Infection Rates

- Abstinence
- Microbicides
- Diaphragm
- Female condom
- Male condom
- Oral Acyclovir
- Oral ARV
- Male circumcision
- Vaccines

Percent of Persons Infected after a Decade of Use

Rate during perfect use
Rate during typical use
Percentage at Risk Globally with Access to HIV Prevention Tools

- 0.6% HIV testing
- 4% Harm reduction for injection drug users
- 9% Prevention of mother-to-child transmission
- 9% Condom access
- 11% Men who have sex with men
- 16% Commercial sex workers

Source: UNAIDS, 2006; USAID et al., 2004
Amplification of Effectiveness – Population-Level

- Multiplicative dynamics of ID epidemiology
- RCTs examine only one generation of HIV transmission
- Scale up – if successful – amplifies the causal association and the public health impact

Source: Koopman and Longini, 1994
Male Circumcision: Impact on Other Prevention Trials

- How we counsel participants about the benefits and risks of MC?
- Must we offer MC to all participants (or their partners)?
- Require controls to be circumcised?
- Stratify enrollment by MC status?
- By how much will MC affect our power?
Scale Up in Real World

- Key to PH impact
- Requires immediate investment
- Need for trained personnel/supplies
- Phase IV surveillance for safety and disinhibition?
- Continued search for better technologies
Cellulose Sulfate – “Doesn’t Work” – So What?

- CS Trials
- DSMB coordination/decision
- Communications plan
- Operational follow-up
Conclusion

• Dynamic field
• Broad lessons learned
• Stay tuned for implications
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Years:
- 2006
- 2007
- 2008
- 2009
- 2010
- 2012