Changing standards of care in South Africa: considerations for HIV vaccine trials

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AIDS Vaccines 2011, Bangkok, Thailand
Outline

• Standard of care

• Review of efficacious/effective biomedical interventions

• Challenges in implementing biomedical interventions in HIV vaccine trials: experience from Phambili (introducing male circumcision)

• Impact on HIV vaccine efficacy measures

• Regulatory considerations
“Standard of Care”

• The term “standard of care” refers to the nature of the prevention and/or care that will be provided to participants in research.

• It has been used variously to refer to:

  the general care and treatment that investigators agree to provide all participants in clinical research.

• And more specifically to:

  the quality of care that should be provided to people in the control arm of a RCT- i.e. those that are not receiving the experimental intervention.
Can further placebo-controlled trials of antiretroviral drugs to prevent sexual transmission of HIV be justified?

Louise Kuhn, Ida Susser, Zena Stein

The Centre for the AIDS Programme of Research in South Africa (CAPRISA) 004 trial\(^1\) that was reported in July, 2010, assessed the efficacy of a gel containing the antiretroviral drug tenofovir, which can be used intravaginally to reduce the risk of sexual transmission of HIV from men to women. In 889 women at community sites in South Africa, the gel was associated with a 39% reduction in HIV incidence in women. After adjustment for reported adherence the reduction was 54%. The randomised, double-blind, placebo-controlled Preexposure Prophylaxis Initiative (iPrEx) study,\(^2\) which was published soon afterwards, assessed the efficacy of daily oral antiretroviral drugs (tenofovir plus emtricitabine) in reducing the risk of sexual transmission of HIV between men. In 2499 high-risk men who have sex with men and transgender women at sites in Peru, Brazil, Ecuador, Thailand, South Africa, and the USA, this drug

Our argument against placebo-controlled trials does not mean that further research is not needed. Many important issues do need further research, but they can be best addressed with study designs that do not use placebos. For example, one important question is how best to use antiretroviral drug products. Is oral administration easier and more effective than mucosal administration or vice versa? Is use targeted around anticipated sexual intercourse? And is use of the product before and after intercourse (ie, the original study of tenofovir gel) better or worse than daily consumption (ie, iPrEx and oral contraceptive pills)? Randomised trials comparing different antiretroviral drug strategies are the optimum designs to address these issues, and such comparisons render the use of placebo unnecessary. Safety is another relevant question for which further research is needed. Because the completed trials were

Gertrude H Sergievsky Center, College of Physicians and Surgeons, and Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY, USA (L Kuhn PhD); Department of Anthropology, Hunter College, and the Graduate Center, City University of New York, and Department of Sociomedical Sciences, Mailman School of Public Health, Columbia University, New York, NY, USA (I Susser PhD); and HIV Center for Clinical and Behavioral Studies, New York State Psychiatric Institute, New York, NY, USA (Prof 2 Stein M.D. B. 8)
The Abandoned Trials of Pre-Exposure in the early 2000’s
“Guideline 13 of UNAIDS/WHO guidance document”

“Researchers, research staff, and trial sponsors should ensure, as an integral component of the research protocol, that appropriate counselling 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.”

UNAIDS/WHO. Ethical considerations in biomedical HIV prevention trials, 2007
New HIV risk reduction methods should be added based on consultation:

1) As they are scientifically validated
2) Or as they are approved by relevant authorities and take into consideration feasibility, expected impact and the ability to isolate the efficacy of the biomedical HIV modality being tested, as other prevention activities improve.

“What is scientifically validated?”

1) Regulators: data from 2 well controlled trials before licensure
2) WHO/UNAIDS waited for 3 RCTs on male circumcision
3) WHO embraced male condoms based on plausibility and observational data
4) Generalisability across populations

“When is it clinically reasonable”?  

New modality should not be applied too early in its clinical development, nor too late! 

New modality should not be applied in a haphazard fashion.

Compatible with other modalities

Jonathan Jay, manuscript in preparation
Current “Standard of Care” in HIV Vaccine Trials

- High quality VCT
- Condoms
- STD screening & RX
- Circumcision

“a la carte” approach as other modalities become available?
Competing considerations

- Belief that sponsors have an ethical obligation to provide care and treatment according to their resources

- A desire to achieve equity in care and treatment received by participants in sponsor and host countries

- Belief that participants deserve the best available care in light of the risks they have assumed for the larger good

**VS**

Concern by some that promising access to enhanced prevention/care to trial participants might create “undue inducement” to participate if these services are otherwise unavailable locally

- Concern that providing these services only to trial participants might exacerbate local inequities and create problems within families and communities
PREVENTION TRIALS

- HSV-2 Treatment - Infectiousness
- Vaccine - Prime/Boost Thailand
- Microbicide - BufferGel, PRO2000
- Microbicide - PRO2000
- Microbicide - Tenofovir Gel South Africa
- Oral TDF - MSM US (Ph II)
- Oral TDF, Truvada - Partners PrEP
- Oral TDF, Truvada - Heterosexual Botswana
- Oral Truvada - FemPrEP
- Oral Truvada - MSM (iPrEx)
- Oral Truvada - Heterosexual Botswana
- Vaccine - DNA Prime/Ad5 Boost US
- Additional trials of 1% TFV gel
- Oral TDF & Truvada & Tenofovir gel - VOICE
- Testing & linkage to care plus (TLC+)
- New Vaccine concept(s)
- Microbicide - Dapivirine ring

Emphasis now needed for combinations that provide the greatest impact on HIV incidence
### New biomedical intervention strategies

<table>
<thead>
<tr>
<th>Study</th>
<th>Effect size (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prime-boost HIV Vaccine (Thai RV144)</td>
<td>31% (1, 51)</td>
</tr>
<tr>
<td>1% tenofovir gel (Caprisa 004, Karim et al.)</td>
<td>39% (6, 60)</td>
</tr>
<tr>
<td>TDF/FTC oral-PrEP in MSM (iPrEx, Grant et al 2010)</td>
<td>44% (15, 63)</td>
</tr>
<tr>
<td>Medical male circumcision (MMC) (Orange Farm, Rakai, Kisumu)</td>
<td>57% (42, 68)</td>
</tr>
<tr>
<td>TDF/FTC oral-PrEP in heterosexuals (TDF2, CDC)</td>
<td>63% (22, 83)*</td>
</tr>
<tr>
<td>TDF oral-PrEP in serodiscordant Partner (Partners PrEP)</td>
<td>62% (34, 78)*</td>
</tr>
<tr>
<td>TDF/FTC oral-PrEP in serodiscordant Partner (Partners PrEP)</td>
<td>73% (49, 85)*</td>
</tr>
<tr>
<td>Immediate ART for positive Partners (HPTN052)</td>
<td>96% (82, 99)*</td>
</tr>
</tbody>
</table>

Efficacy

*Provisional
Topical Microbicides: CAPRISA 004

39% Efficacy

Karim, Science, 2010
Treating discordant couples

96% Efficacy

HPTN 052
Cohen M, NEJM, 2011

73% Efficacy

Partners Prep
Cellum, C. IAS 2011
PrEP to individuals

Efficacy (MITT) 44% (15–63%)
Infection Numbers: 64 – 36 = 28 averted

Time to Event Analysis of Seroconverter Data
Analysis using all 33 Seroconverters

63% Efficacy

iPrEX (MSM)  Botswana CDC (heterosexual)
Implementing interventions

Circumcision was offered to all men enrolling into Phambili/HVTN 503 (30% circumcised at baseline)
## Phambili Circumcision

<table>
<thead>
<tr>
<th></th>
<th>VACCINE</th>
<th>PLACEBO</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncircumcised</td>
<td>161</td>
<td>152</td>
<td>313</td>
</tr>
<tr>
<td>Post enrolment circumcision</td>
<td>72 (44.7%)</td>
<td>70 (46.1%)</td>
<td>142 (45.2%)</td>
</tr>
<tr>
<td>Timing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 month</td>
<td>6 (8.3%)</td>
<td>12 (17.1%)</td>
<td>18 (12.7%)</td>
</tr>
<tr>
<td>&gt;1-3 months</td>
<td>14 (19.4%)</td>
<td>14 (20.0%)</td>
<td>28 (19.7%)</td>
</tr>
<tr>
<td>&gt;3-6 months</td>
<td>15 (20.8%)</td>
<td>10 (14.3%)</td>
<td>25 (17.6%)</td>
</tr>
<tr>
<td>&gt;6 months -1 year</td>
<td>8 (11.1%)</td>
<td>12 (17.1%)</td>
<td>20 (14.1%)</td>
</tr>
<tr>
<td>&gt;1 -2 years</td>
<td>14 (19.4%)</td>
<td>12 (17.1%)</td>
<td>26 (18.3%)</td>
</tr>
<tr>
<td>&gt;2 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relationship to unblinding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-unblinding</td>
<td>27 (37.5%)</td>
<td>24 (41.4%)</td>
<td>47 (33.1%)</td>
</tr>
<tr>
<td>Post-unblinding</td>
<td>45 (62.5%)</td>
<td>46 (58.6%)</td>
<td>95 (66.9%)</td>
</tr>
</tbody>
</table>
Circumcision uptake is variable and site dependent

<table>
<thead>
<tr>
<th></th>
<th>Soweto</th>
<th>Cape Town</th>
<th>KOSH</th>
<th>eThekwini</th>
<th>Medunsa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncircumcised at enrolment</td>
<td>118</td>
<td>15</td>
<td>122</td>
<td>28</td>
<td>30</td>
</tr>
<tr>
<td>Post-enrolment circumcision</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>68 (57.6%)</td>
<td>7 (47.7%)</td>
<td>44 (36.1%)</td>
<td>22 (78.6%)</td>
<td>1 (3.3%)</td>
</tr>
</tbody>
</table>
## Impact of adherence on effectiveness of tenofovir gel

<table>
<thead>
<tr>
<th></th>
<th># HIV</th>
<th>N</th>
<th>HIV incidence</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>TFV</td>
<td>Placebo</td>
</tr>
<tr>
<td>High adherers (&gt;80% gel adherence)</td>
<td>36</td>
<td>336</td>
<td>4.2</td>
<td>9.3</td>
</tr>
<tr>
<td>Intermediate adherers (50-80% adherence)</td>
<td>20</td>
<td>181</td>
<td>6.3</td>
<td>10.0</td>
</tr>
<tr>
<td>Low adherers (&lt;50% gel adherence)</td>
<td>41</td>
<td>367</td>
<td>6.2</td>
<td>8.6</td>
</tr>
</tbody>
</table>
Designing the next HIV Vaccine Efficacy Trials
Future trials investigating biomedical interventions

- Combined use of oral PREP and microbicides for intermittent dosing—optimal systemic and local drug levels (steady state and bolus)
- PrEP (oral, topical) for women combined with circumcision + oral PrEP for men
- T4P combined with ARV PrEP (microbicide or oral for women, oral for MSM) for the HIV-negative partner
- Vaccines plus ARV PrEP (microbicides or oral for women, oral for men & circumcision)
How do we optimise future HIV vaccine trials? Using Thai RV144 as an example…

- The vaccine appeared most effective (60% reduction) at 1 year post vaccination
- Infection may be reflective of suboptimal immune responses or exposure to a higher and/or more frequent infectious challenge
- Revaccination (annual/biannual) likely required to have a significant impact on incidence (Hontelez et al Vaccine June 2011)
- Co-implementation of PrEP (oral, microbicides) and/or MMC might provide conditions that could significantly increase vaccine efficacy
- This hypothesis could be explored in proposed ALVAC-protein prime-boost trials being proposed in Thailand and RSA
How might (VAX and PrEP) deliver better protection?

- Providing protection during the immunization period
- Reducing infectious challenge and primary foci of infection
- Increase eclipse phase prior to systemic dissemination providing an extended opportunity for adaptive immunity to respond
- Boosting local immunity (virus/antigen)
- Broadening localized immunity through protected exposure to prevalent virus.
- Converting high risk challenge to low risk challenge (RV144)
- Coverage between potential re-vaccination campaigns as immunity wanes
- Providing immunological coverage of intermittent PrEP adherence, break through virus and resistance evolution
How do new HIV interventions impact on the design of future HIV Vaccine Trials?

Higher prevention standard will impact on HIV incidence (Increase sample size)

<table>
<thead>
<tr>
<th>Annual incidence placebo arm</th>
<th>Test: VE=52% vs. VE&lt;=20% VE(0-24)</th>
<th>Test: VE=58% vs. VE&lt;=30% VE(0-24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.0%</td>
<td>3450</td>
<td>3650</td>
</tr>
<tr>
<td>2.5%</td>
<td>2825</td>
<td>2950</td>
</tr>
<tr>
<td>3.0%</td>
<td>2350</td>
<td>2450</td>
</tr>
<tr>
<td>3.5%</td>
<td>2025</td>
<td>2125</td>
</tr>
<tr>
<td>4.0%</td>
<td>1800</td>
<td>1850</td>
</tr>
<tr>
<td>4.5%</td>
<td>1600</td>
<td>1675</td>
</tr>
<tr>
<td>5.0%</td>
<td>1450</td>
<td>1500</td>
</tr>
<tr>
<td>5.5%</td>
<td>1300</td>
<td>1350</td>
</tr>
<tr>
<td>6.0%</td>
<td>1200</td>
<td>1250</td>
</tr>
</tbody>
</table>

Courtesy: Peter Gilbert & Jim Kublin
How do new HIV interventions impact on the design of future HIV Vaccine Trials?

May complicate endpoint measurement

? Lower viral load set point

? Delay identification of acute infection

? Resistance

? Impact on natural history of HIV infection

? Impacts on genetic bottleneck

? Impacts on immune markers or correlates

ARV protection

Gel/cream:
- Physical barrier
- Lubrication

Maintenance of normal microflora

Prevention of other STDs

Viral disruption

Epithelium

Stroma

Inhibition of HIV uptake by dendritic cells (e.g. anti-DC-SIGN)

Inhibition of reverse transcriptase

Fusion/absorption inhibition (e.g. polyanions, co-receptor antagonists)
How do new HIV interventions impact on the design of future HIV Vaccine Trials?

• Increased complexity in trial implementation: increased visits, HIV testing, adherence counselling, safety assessments may increase

• Higher costs of trials
How do new HIV interventions impact on the design of future HIV Vaccine Trials?

• Interventions like Tenofovir gel may not be licensed or available in country.

• Procurement of intervention and who pays for the intervention?

• If submitted for licensure, company may not wish intervention to be used with another experimental intervention.
The landscape within which future HIV prevention trials will be run

- A limited window may exist for placebo (PrEP) controlled trials
- ARV PrEP combined with vaccines may create lower-risk conditions making a partially efficacious vaccines a viable option
- Additive or synergistic effects will stimulate incremental reductions in HIV incidence
- This in turn will raise the bar of evidence required for new approaches (cost-effectiveness and population impact) in RCT
- Decreasing incidence will necessitate larger and more costly trials with an increased emphasis on adaptive design
- Placing an intrinsic value on high incidence cohorts

*Summarized in: AIDS. Turning the tide against HIV. Science. 2011 Jul 1;333:42-3*
The landscape within which future HIV prevention trials will be run

Engaging stakeholders will be key

community, regulators and ethics committee
Pathway to reversing the epidemic
Seeing prevention research/funding as a continuum

A combined research strategy for biomedical interventions is likely to provide the fastest, most tangible impact on HIV transmission.

- Circumcision
- Treatment 4 prevention
- ARV PrEP (oral, microbicide)
- Partially effective vaccine
- Highly effective vaccine

Behavioral and structural interventions

Science. 2011;333:42-3
Clinical trials are fundamental to public health and medical innovation. They provide the evidentiary basis for diagnosis, treatment and prevention of disease.

We require a new paradigm to efficiently conduct large scale efficacy trials while at the same time we explore correlates of protection.
Acknowledgements

- Jim Kublin
- Peter Gilbert
- Slim Karim
- Connie Celum
- Mike Cohen
- Robin Shattock
- Ian McGowan
- Jonathan Jay
- Magda Sobieszyk
- Ken Mayer
“RCT and use of placebo”

• Declaration of Helsinki & WMA

Extreme care must be taken in making use of a placebo-controlled trial and the methodology should only be used in the absence of existing proven prophylaxis or drug therapy.
Combination prevention

Coates et al., Lancet 2008
Undue Inducement

Does offering circumcision:
Lead to both bad judgement and exposure to unreasonable risks?
Does it lead to substantial, prospective risk of serious harm?

Anything that has a favourable risk benefit ratio cannot be an undue inducement!
<table>
<thead>
<tr>
<th>Definition</th>
<th>Classic example</th>
<th>Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Undue Inducement</td>
<td>Offer of a desirable good in excess such that it compromises judgement and leads to serious risks that threaten fundamental interests</td>
<td>“I'll pay you a million dollars to…….”</td>
</tr>
<tr>
<td>Traditional solution: reduce the quantity of the desirable good. Actual Solution: Reduce risks or improve risk:benefit ratio</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coercion</td>
<td>Threats that make a person choose an option that necessarily makes him or worse off and that he or she does not want to do</td>
<td>“Your money or your life”</td>
</tr>
<tr>
<td>Prevent or remove the threat</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exploitation</td>
<td>Unfair distribution of burdens and benefits from an interaction</td>
<td>“that deal is unfair, you are charging too much (or you aren’t giving me enough)”</td>
</tr>
<tr>
<td>Increase benefits to the party receiving the inadequate level of benefits</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injustice</td>
<td>Unfair distribution of resources before any interaction</td>
<td>Lack of access to ARV drugs because of poverty</td>
</tr>
<tr>
<td>Redistribute resources, increase resources of worst off before interaction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deception</td>
<td>Intentional withholding or distortion of essential information to mislead or create a false impression</td>
<td>“this won’t hurt at all”</td>
</tr>
<tr>
<td>Disclose accurate information</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inadequate disclosure</td>
<td>Providing insufficient information</td>
<td>Disclose all relevant information</td>
</tr>
<tr>
<td>Misunderstanding</td>
<td>Inadequate comprehension of essential information</td>
<td>“I did not know I might get placebo”</td>
</tr>
<tr>
<td>Improve comprehension through more discussion between researcher and participant</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Emanuel, Lancet 2005
## Orange Farm Trial (ANRS 1265) of Male Circumcision of 18-24 year old: Incidence over time (4664 person years of follow up)

<table>
<thead>
<tr>
<th></th>
<th>M0-M3</th>
<th>M4-M12</th>
<th>M13-M21</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intervention</strong></td>
<td>2</td>
<td>7</td>
<td>9</td>
<td>18</td>
</tr>
<tr>
<td><strong>Control</strong></td>
<td>9</td>
<td>15</td>
<td>27</td>
<td>51</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>11</td>
<td>22</td>
<td>36</td>
<td>69</td>
</tr>
</tbody>
</table>

Incidence Rates:
- **Intervention**: 0.77 (0.49-1.23)/100 py
- **Control**: 2.2 (1.7-2.9)/100 py

U RR: 0.35 (0.2-0.6)  
**p=0.00013**

Source: Auvert B, et al, IAS 2005
Opportunities for biomedical interventions

Prior to exposure
- Male circumcision
- Oral pre exposure prophylaxis (daily PrEP)
- Topical PrEP (daily gels or intra-vaginal rings (microbicides)
- Preventive Vaccines

Exposure (pre-coital/coital)
- Oral pre exposure prophylaxis (intermittent PrEP)
- Coitally dependent topical PrEP (microbicides)

Exposure (pre-coital/coital)
- Oral post exposure prophylaxis (PEP)

After infection
- Anti-retroviral therapy
- Immediate treatment of positive partners in discordant couples
- Treatment for prevention in all who test positive for HIV (T4P)

All have a behavioral and structural components