HIV Prevention Research: The Global Picture

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Outline

- Why the need for HIV prevention research?
- What constitutes evidence of efficacy?
- HIV prevention strategies – what works?
- Technologies under development to prevent sexual transmission of HIV
- Envisioning a future
- Conclusion
Global HIV epidemic, 2009

33.4 million living with HIV, 2.7 million new infections, 2 million deaths

Source: UNAIDS 2009
Modes of transmission

Unprotected sex with an infected partner

Sharing needles with infected persons
Transmission risk reduced by:
• needle exchange

Transmission from infected mother to fetus
Transmission risk reduced by:
• prevention of HIV in young women,
• contraception,
• abortion,
• ARVs,
• exclusive / avoid breastfeeding

Exposure to blood and blood products (occupational exposure)
Transmission risk reduced by:
• PEP,
• Universal precautions
Rising epidemics:
The HIV epidemic in South Africa

Source: Data from South African Department of Health Antenatal Surveys. www.doh.gov.za/
The HIV epidemic in Africa

Declining epidemics: Uganda

HIV prevalence rates in pregnant women in Uganda from 1985 to 2001

The evolving HIV epidemic in the USA

Providing AIDS treatment is important…
…so is providing AIDS prevention

Estimated number of people receiving antiretroviral therapy
2008 = 4M

Walking backwards on a treadmill…. 

By end 2009:

- People with HIV : 33.4 million
- People on ARVs : 4 million
- New infections (in 2008): 2.7 million
Need to scale-up proven prevention strategies

Global Access to existing HIV prevention methods, 2003

- 0.2% Adults with access to HIV testing
- 4% Harm reduction got injection drug users
- 8% Prevention of mother-to-child transmission
- 11% Behaviour change programs for men who have sex with men
- 16% Behaviour change programs for commercial sex workers
- 21% Condom access

Source: UNAIDS et al, 2004
Which interventions have been proven effective & warrant scale up for preventing sexual spread of HIV?
How do we decide if an intervention prevents HIV infection?

Then we concur: there is no causal link between HIV and AIDS!
The Evidence Pyramid

Criteria for evidence:
1. Randomized control trial
2. HIV endpoint
3. Repeatability
4. Biological plausibility
5. Observational data

Systematic reviews and meta-analyses
Why the fixation with RCTs: Vitamin A & pMTCT

- Several observational studies suggested that low serum vitamin A levels associated with increased Mother-To-Child-Transmission of HIV

- Low vitamin A levels in pregnant women - risk factor for mother-to-child-transmission of HIV in Malawi
  - Mean vitamin A concentration in 74 mothers who transmitted HIV to their infants was lower than that in 264 mothers who did not transmit HIV to their infants (0.86 [0.03] vs 1.07 [0.02], p < 0.0001).

Meta-analysis of 4 trials of vitamin A supplementation showed no effect on preventing mother to child transmission

Vit A, Fawzi, 2002 1.35 (1.10; 1.65)
Vit A, Couttsoudis, 1999 0.98 (0.73; 1.31)
Vit A, Kumwenda 2002 0.84 (0.65; 1.08)
Combined [random] 1.05 (0.78; 1.41)
Multivit, Fawzi, 2002 1.04 (0.82; 1.32)

What works for HIV prevention: Results from RCTs with HIV incidence

- Review: 37 HIV prevention RCTs on 39 interventions:
  - PrEP: 1
  - Behavioural: 7
  - Microbicides: 12
  - STI treatment: 9
  - Microfinance: 1
  - Diaphragm: 1
  - Male circumcision: 4
  - Vaccines: 4

- Only 5 RCTs showed a protective effect on HIV incidence in almost 3 decades of HIV research:
  - 3 medical male circumcision trials
  - 1 STD treatment trial (Mwanza)
  - 1 vaccine trial (Thai vaccine RV144 trial)

HIV prevention: Circumcision works

Criteria for evidence:

1. Randomized control trial ✓
2. HIV endpoint ✓
3. Repeatability ✓
4. Biological plausibility ✓
5. Observational data ✓

Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomised controlled trial

Robert C Bailey, Stephen Moses, Corette B Parker, Kawango Agot, Ian Maclean, John N Krieger, Carolyn F M Williams, Richard T Campbell, Jiecktori O Ndonga-Acholi

March 11, 2009

Summary

Male circumcision could provide substantial protection against acquisition of HIV infection. Our aim was to test whether male circumcision had a protective effect against HIV infection, and to assess safety and feasibility of the intervention.

Male circumcision was performed on 2784 men aged 18–24 years in Kisumu, Kenya. Men were randomly assigned to a circumcised group (n=1391) or a control group (delayed circumcision, n=1393). Men in the intervention group were circumcised at enrolment, and behavioural interviews during follow-ups at 1, 3, 6, 12, 18 and 24 months. The median follow-up was 24 months. Follow-up was complete for 22 men in the intervention group and 47 in the control group. The 2-year HIV incidence was 2.1% (95% CI 1.2–3.0) in the circumcision group and 3.2% (95% CI 1.8–5.7) in the control group (p=0.0065); the relative risk of HIV infection in circumcised men was 0.68 (95% CI 0.43–1.06). The difference in HIV incidence between the two groups did not reach statistical significance. The 95% confidence interval for the difference did not exclude the null value of zero. There were no deaths or serious adverse events related to the intervention. This trial is registered with the World Health Organization International Clinical Trials Registry Platform as www.who.int/trialsearch/trial.aspx?ref=NCT0059371.

Does STD treatment reduce HIV incidence?

Impact of improved treatment of sexually transmitted diseases on HIV infection in rural Tanzania: randomised controlled trial


Summary
A randomised trial was set up to evaluate the impact of improved sexually transmitted disease management at primary health care centres on the incidence of HIV infection in rural Tanzania. The incidence was compared in 12 intervention villages and six pair-matched control villages in a cohort of about 1000 adults followed for 6 years. The incidence of adult HIV infections rose to an all-time high rate of 2.1% per year in the late 1990s, and is projected to reach 3.0% per year by the year 2000. Most new infections are occurring in the developing world and are among young women. Large numbers of infections were acquired in central and western Saharan Africa, the region most severely affected by the first decade of the epidemic. The epidemic has begun to spread rapidly in the last 5 years. The incidence of HIV infection has been significantly reduced in the intervention villages compared with the control villages (rate ratio 0.54, 95% CI 0.38 to 0.79). The results of this study indicate that prevention of HIV infection can be achieved through improved management of sexually transmitted diseases.
Does the Thai vaccine reduce HIV incidence?

Vaccination with ALVAC and AIDSVAX to Prevent HIV-1 Infection in Thailand

Criteria for evidence:
1. Randomized control trial ✓
2. HIV endpoint ✓
3. Repeatability X
4. Biological plausibility X
5. Observational data X
Preventing sexual spread of HIV: what works?

- Existing accepted proven HIV prevention strategies - AB CCC:
  - Abstinence
  - Behaviour
  - Condoms
  - Counselling and Testing
  - Circumcision

Note - STD treatment: Jury is out on its impact on HIV but it is an intervention in its own right for STD control
Abstinence, Behaviour (Be faithful), Condomise

Criteria for evidence:
1. Randomized control trial ×
2. HIV endpoint ×
3. Repeatability ✓
4. Biological plausibility ✓
5. Observational data ✓

Source: http://www.hivaidssearch.com/
Does VCT reduce HIV incidence?

Efficacy of voluntary HIV-1 counselling and testing in individuals and couples in Kenya, Tanzania, and Trinidad: a randomised trial

The Voluntary HIV-1 Counseling and Testing Efficacy Study Group*

Summary

Background Our aim was to determine the efficacy of HIV-1 voluntary counselling and testing (VCT) in reducing unprotected intercourse among individuals and sex-partner couples in Nairobi (Kenya), Dar es Salaam (Tanzania), and Port of Spain (Trinidad).

Methods Individual or couple-assigned HIV-1 VCT or placebo were offered at baseline, and follow-up (mean 7·3 years' follow-up). Information participants were offered VCT, and the proportion of infections were diagnosed. The second follow-up (mean 7·3 years) involved only behavioural change. Participants were again offered VCT.

Findings 3120 individuals and 1838 couples were included in the study. The proportion of individuals who reported unprotected intercourse with non-primary partners declined significantly.

Criteria for evidence:

1. Randomized control trial ✓
2. HIV endpoint X
3. Repeatability X
4. Biological plausibility ✓
5. Observational data ✓

Introduction

More widespread HIV-1 voluntary counselling and testing (VCT) in less-developed countries is advocated on the grounds that it provides an opportunity for education and behaviour change, and that knowledge of serostatus allows individuals to plan, make important decisions, and seek information and support.1,2 But VCT in isolation compared with health education is not a particularly effective counselling intervention, and has potentially negative social and psychological effects including family and social disintegration, sexual violence, stigma, and blame.3-6 An important role for VCT is as a prevention strategy to reduce the incidence of HIV, particularly in less-developed countries.7-9 A recent systematic review of VCT concluded that it significantly reduces risk for persons who acquire serodiscordant couples.10 However, all but a few studies were observational in...
Preventing sexual spread of HIV: what works?

- Existing accepted proven HIV prevention strategies - ABCCC:
  - Abstinence
  - Behaviour
  - Condoms
  - Counselling and Testing
  - Circumcision

Note - STD treatment: Jury is out on its impact on HIV but it is an intervention in its own right for STD control
Age & gender distribution of HIV infection in South Africa

**HIV prevalence in Vulindlela 2005-08**

<table>
<thead>
<tr>
<th>Age Group (Years)</th>
<th>HIV Prevalence (%) (N=1237)</th>
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<tr>
<td>≤16</td>
<td>10.6</td>
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<td>17-18</td>
<td>21.3</td>
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<td>19-20</td>
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<td>44.3</td>
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<td>23-24</td>
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Globally, AIDS prevention needs all three of the following approaches:

- Implement known proven prevention strategies with greater commitment
- Combine AIDS treatment & AIDS prevention
- Invigorate the search for new & better prevention tools
Technologies under development to prevent sexual transmission of HIV

- Microbicides
- Pre-exposure prophylaxis (PrEP)
- Vaccines
- Extending ART for prevention
- Behavioural
- Combination Prevention
Recent technologies no longer under development to prevent sexual transmission of HIV

- Diaphragm
- HSV-2 suppressive therapy
- Polymer microbicides
Microbicides

- A microbicide is a product that can be applied to the vaginal or rectal mucosa with the intention of preventing the transmission of sexually transmitted infections including HIV.

- Mathematical modeling impact: 2.5 million HIV infections could be averted over 3 years with 60% effective microbicide in 73 low-income countries.
Past & Current Microbicide Clinical Trials

1st class: Surfactants
eg. N9, SAVVY
- Kenya N-9 sponge trial
- FHI N-9 film trial
- UNAIDS COL-1492 trial
- FHI SAVVY trial

2nd class: Polymers
eg. PRO2000, Carraguard, Cellulose Sulfate (CS)
- CONRAD CS trial
- FHI CS Trial
- PopCouncil Carraguard trial
- HPTN PRO2000 & BufferGel trial
- MDP 0.5% PRO2000
- 2% PRO2000

3rd class: ARVs
eg. Tenofovir gel, Dapivirine gel/ring
- CAPRISA Tenoforv gel trial
- MTN 003 VOICE trial
- IPM Dapivirine gel & ring trial

Zena Stein publishes seminal article “HIV prevention: the need for methods women can use”

'90 '92 '98 '00 '03 '04 '05 '07 '09 '11

Safe but not effective  Increased HIV infection  Stopped for futility  Planned
Pre-exposure prophylaxis (PrEP)

- Pre-exposure prophylaxis (PrEP) is an experimental HIV prevention strategy that uses antiretroviral agents prior to exposure, to prevent HIV acquisition.

- PrEP for HIV prevention builds on the concept that medications can be used by healthy people to prevent infections:
  - Mefloquine prophylaxis for malaria
  - INH prophylaxis for tuberculosis
  - AZT for prevention of MTCT of HIV

- Mathematical modeling impact: 2.7 - 3.2 million new HIV infections could be averted in southern Africa in 10 years by targeting PrEP (if 90% effective) to those at highest behavioral risk.

Source: Abbas UL, PLoS ONE 2(9): e875. doi:10.1371/journal.pone.0000875
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<td>FHI (West Africa)</td>
<td>CDC 4323 (US)</td>
<td>CDC 4370 (Thailand)</td>
<td>CDC 4940 (Botswana)</td>
<td>iPrEx (multi-country)</td>
<td>CAPRISA 004 (SA)</td>
<td>Partners PrEP (Kenya &amp; Uganda)</td>
<td>FEM-PrEP (multi-country)</td>
<td>VOICE/MTN 003 (multi-country)</td>
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- **FHI** - Phase II, daily tenofovir disoproxil fumarate (TDF) in 936 high-risk women in Cameroon, Ghana and Nigeria *(funded by Gates Foundation)*
- **CDC 4323** - Phase II, daily TDF among 400 MSMs in US *(funded by CDC)*
- **CDC 4370** - Phase II/III, daily TDF among 2,400 IDUs in Thailand *(funded by CDC)*
- **CDC 4940** - Phase III, daily TDF + emtricitabine (FTC) among 1,200 heterosexual men and women in Botswana *(funded by CDC)*
- **iPrEx** - Phase III, daily TDF+FTC among 3,000 MSM in Brazil, Ecuador, Peru, South Africa, Thailand, US *(funded by NIH and Gates Foundation)*
- **CAPRISA 004** - Phase IIIb, pre- and post-coital 1% tenofovir gel among 980 women in South Africa *(funded by USAID and LIFElab, with support from FHI and CONRAD)*
- **Partners PrEP** - Phase III, daily TDF, TDF+FTC among 3,900 serodiscordant heterosexual couples in Kenya and Uganda *(funded by Gates Foundation)*
- **FHI FEM-PrEP** - Phase III, daily oral TDF+FTC in 3,900 high-risk women in Kenya, Malawi, South Africa *(funded by USAID and Gates Foundation)*
- **MTN 003/VOICE** - Phase IIb, daily tenofovir gel, oral daily TDF or oral TDF/FTC in 4,200 women in South Africa, Malawi, Uganda, Zambia, Zimbabwe *(funded by NIH)*
Questions raised about topical or oral PrEP

- Is it safe to give ARV drugs to uninfected people?
- Will those who get infected have HIV that is resistant to the PrEP antiretrovirals? Will this affect their subsequent care and choice of ARV treatment?
- Will healthy people be willing to take medication everyday for long periods for prevention?
- Is this an affordable and practical HIV prevention strategy for scale-up if it is efficacious?
HIV vaccine

- A safe and effective HIV vaccine remains a critically important goal
- Historically, vaccines have been central to the prevention of viral infections
- Mathematical modelling impact: 50% effective vaccine decreases HIV by 29% in adolescents
Challenges to vaccine development

- Lack immune correlate of protection
- High mutation and recombination in HIV
- Different Clades of HIV
  - Vaccine for Clade A may not necessarily work for Clade C
- HIV integrates into helper T cells
- HIV vaccine aims to stop infection – vaccines (e.g. measles) prevent disease & cannot stop infection

Global HIV vaccine trial sites
Extending ART for prevention: epidemiological basis for this strategy

VIRAL LOAD AND HETEROSEXUAL TRANSMISSION OF HUMAN IMMUNODEFICIENCY VIRUS TYPE 1

Thomas C. Quinn, M.D., Maria J. Wawer, M.D., Nelson Sewankambo, M.B., David Serwadda, M.B., Chuanjun Li, M.D., Fred Wawire-Mangen, Ph.D., Mary O. Meehan, B.S., Thomas Lutalo, M.A., and Ronald H. Gray, M.D. for the Rakai Project Study Group

Abstract

Background and prevalence of viral load in the heterosexual transmission of human immunodeficiency virus type 1 (HIV-1) was studied in 16,127 people. We identified 415 HIV-1-positive partners and followed them. The incidence of HIV-1 transmission among the initial partners in relation to HIV-1 RNA levels is shown. Male-to-female transmission was not significantly different from female-to-male transmission (p = 0.11). The predominant mode of transmission was through heterosexual contact by this means of communication and educational programs. The risk of transmission was increased in the presence of condom use and in the absence of other risk factors. The understanding of the factors that influence the transmission of the virus is essential for the prevention of HIV-1.
Extending ART for prevention: mathematical modeling impact

Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model

Reuben M Granich, Charles F Gilks, Christopher Dye, Kevin M De Cock, Brian G Williams

Summary

Background Roughly 3 million people worldwide were receiving antiretroviral therapy (ART) at the end of 2007, but an estimated 6.7 million were still in need of treatment and a further 2.7 million became infected with HIV in 2007. Prevention efforts might reduce HIV incidence but are unlikely to eliminate this disease. We investigated a theoretical strategy under which the HIV epidemic might be controlled or even reversed.

Methods We used a long-term dynamical model of HIV transmission in a population where a large fraction of adults living with HIV was taking ART. We considered various scenarios, including universal voluntary HIV testing and immediate ART in all adults living with HIV.

Findings The model predicts that universal voluntary HIV testing and immediate ART could reduce HIV incidence by 50% within 5 years and by 90% within 10 years.

Conclusion Universal voluntary HIV testing and immediate ART could be a powerful tool for controlling the HIV epidemic in populations with high HIV prevalence and high rates of ART adherence.
Extending ART for prevention: clinical trial evaluation of strategy

HPTN 052

A Randomized Trial to Evaluate the Effectiveness of Antiretroviral Therapy Plus HIV Primary Care versus HIV Primary Care Alone to Prevent the Sexual Transmission of HIV-1 in Serodiscordant Couples

What is HPTN 052?

HPTN 052 is a Phase III, two-arm, multi-site, randomized trial to determine the effectiveness of two treatment strategies in preventing the sexual transmission of HIV in HIV-serodiscordant couples.

Based on data collected in Africa and Thailand, there is a correlation between HIV viral load (blood levels) and HIV transmission. Specifically, the higher the viral load in the blood, the more likely the chance for transmission. Antiretroviral therapy (ART) reduces the viral load in the blood, as well as in genital secretions (for both men and women), and the drugs can be detected in semen and vaginal and cervical secretions. All of this information strongly suggests that ART may make HIV-infected people less contagious. HPTN 052 compares the HIV–infection rates of two groups of HIV-serodiscordant couples. The index case of the first group starts taking ART as soon as the couple is enrolled in the study, while the index case of the second group starts taking ART when he or she has two consecutive measurements of a CD4+ cell count within or below the range of 200-250 cells/mm³, or when he or she develops an AIDS-defining illness. Both groups will receive HIV primary care and couples counseling sessions to teach them how to reduce their risk of transmission.
Empirically HIV acquisition can be reduced by:
- ↑ age of sexual debut
- ↓ sexual frequency
- ↓ partner change
- ↓ concurrent partners
- ↑ condom use

Hypothesis: knowledge of HIV status → ↓ HIV
- HPTN043 – Project ACCEPT

Hypothesis: cash incentives → ↓ HIV risk behaviour
- CAPRISA 007: Reducing HIV in Adolescents (RHIVA) trial
Combination Prevention

Title: Methods for Prevention Packages Program (MP3) (R01)

Announcement Type:
This is a replacement of RFA-AI-08-018 which was previously released on February 21, 2008 and withdrawn on March 24, 2008 per NOT-AI-08-043.

Update: The following update relating to this announcement has been issued:

- March 19, 2010 - This RFA has been reissued as (RFA-AI-10-005).

NOTICE: Applications submitted in response to this Funding Opportunity Announcement (FOA) for Federal assistance must be submitted electronically through Grants.gov (http://www.grants.gov) using the SF424 Research and Related (R&R) forms and the SF424 (R&R) Application Guide

APPLICATIONS MAY NOT BE SUBMITTED IN PAPER FORMAT.

This FOA must be read in conjunction with the application guidelines included with this announcement in Grants.gov/Apply for Grants (hereafter called Grants.gov/Apply).

A registration process is necessary before submission and applicants are highly encouraged to start the process at least four weeks prior to the grant submission date. See Section IV.

Request for Applications (RFA) Number: RFA-AI-08-044
Envisioning a future.....

**Community level impact on HIV**

- Widespread HIV testing
- Improved diagnostics and treatment for STDs
- Scale up of circumcision for men
- High coverage of ARV microbicide in young women
- High coverage of oral PrEP in high risk populations
- Extending coverage of ART & positive prevention
Envisioning a future: Community level impact on the HIV epidemic in South Africa

Current epidemic trajectory

Desired future projections

Implementing combined community level HIV prevention programme

Source: Data from South African Department of Health Antenatal Surveys. www.doh.gov.za/
Acknowledgements

• A special tribute to the many thousands of people who participate in HIV prevention trials