Sexual Transmission of HIV: Advances in Prevention

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Persons in Low- and Middle-Income Countries Receiving Antiretroviral-Drug (ARV) Therapy, 2002-2005

Global Need for ARVs: 2006

70% of the total unmet need

(Number of people in millions)

Sub-Saharan Africa
Latin America and the Caribbean
East, South, South-East Asia
Europe and Central Asia
North Africa and the Middle East
“Between 2003 and 2005 . . . for each new person who got treatment for HIV, about 10 people became infected. Even during our greatest advance, we are falling behind.”

- Bill Gates
We are falling behind in prevention
Percentage of Individuals at Risk with Access to HIV Prevention

- 0.6% Adults with access to HIV testing
- 4% Harm reduction for injection drug users
- 9% Prevention of mother-to-child transmission
- 9% Condom access
- 11% Behavior change programs for men who have sex with men
- 16% Behavior change programs for commercial sex workers
Sexual Transmission of HIV

- Heterosexual transmission is the most common mode of transmission worldwide.
- Male to male transmission is the most common mode of transmission in many countries.
Worldwide, there are 42 million people living with HIV/AIDS. Of that population, 19 million are women.
Sexual Transmission of HIV depends on

- The infectiousness of the index case (HIV+ partner)
  - Plasma viral load (amount of virus in the blood)
  - Genital viral load (amount of virus in genital secretions)
- The susceptibility of the uninfected (HIV-) partner
  - Presence of (STIs) or other genital inflammation
  - Innate or acquired immunity of the exposed person
Correlation between seminal plasma and blood plasma HIV RNA

Coombs et al. JID .1998
## Relative Risk of Heterosexual Transmission: Rakai, Uganda Study

Quinn et al 2000

<table>
<thead>
<tr>
<th>HIV-1 RNA</th>
<th>Transmission/couple</th>
<th>Average sex/month</th>
<th>Adjusted rate (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1700</td>
<td>1 of 43</td>
<td>10.4</td>
<td>1.0</td>
</tr>
<tr>
<td>1700-12,499</td>
<td>11 of 45</td>
<td>9.4</td>
<td>16.1 (3.1-295.7)</td>
</tr>
<tr>
<td>12,500-38,499</td>
<td>11 of 42</td>
<td>8.0</td>
<td>19.9 (3.4-328.6)</td>
</tr>
<tr>
<td>&gt;38,500</td>
<td>15 of 44</td>
<td>8.0</td>
<td>27.7 (5.4-506.8)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GUD</th>
<th>Transmission/couple</th>
<th>Average sex/month</th>
<th>Adjusted rate (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>yes</td>
<td>4 of 19</td>
<td>7.6</td>
<td>2.58 (1.03-5.7)</td>
</tr>
<tr>
<td>no</td>
<td>34 of 155</td>
<td>9.2</td>
<td>1.0</td>
</tr>
</tbody>
</table>
Plasma Viral Load

Note spikes in viral load between weeks 0-12 (Acute or Primary Infection) and after year 7.
HIV Transmission and Acute Infection

Pilcher et al. JID 2004

The graph shows the probability of transmission per unprotected coital act over weeks from infection. The peak probability occurs around 4-5 weeks post-infection.
Detection of Acute HIV Infection
Pilcher et al. Jnl Clin Inv. 2004
Detecting Acute HIV Infection for Prevention/ Intervention

- Public Health Units in some areas of the USA now conduct HIV-RNA testing on pooled ELISA negative specimens to detect acute sero-converters.
- Acute sero-converters are contacted and counseled on HAART, safer sex and condoms.
- Recent sexual contacts of acute sero-converters are counseled and tested.
- Pilcher et al. have recently published on detection of acute infection in Malawi.

Prevention of Sexual Transmission: ABC

• Abstinence
• Be Faithful (Monogamy)
• Consistent Correct Condom use
Abstinence

• Effective for those who choose and practice it
• Many don’t want it: many others have no choices
• Problem is with “Abstinence Only” and abstinence as the population based prevention method
• Scientific data presented by groups pushing abstinence only is not rigorous and ideologically biased

A Glimpse of the Impact of HIV/AIDS on Married Women

- More than 40 per cent of new infections in Cambodia and Thailand are among women whose only sexual partner was their husband.

- In sub-Saharan Africa, 60 to 80 per cent of HIV-positive women report having had sexual relations only with their husbands.

- A study in India found that 90 per cent of HIV infected women were married, monogamous and had only one sex partner in their lives: their husbands.
Estimated Risks from 2 Acts of Unprotected Intercourse Per Week

Source: Cates, STD, 2002;29:350-52
But If Protected by Condoms

Source: Cates, STD, 2002;29:350-52
Female Condoms

- Shown to be as effective as male condoms in small studies
- Generally used to complement male condoms
- Are several times more expensive than male condoms
- Issues related to reuse are not totally defined
The ABC $D$ isaster

- The criticism of the content of AB is simple: the messages cannot be implemented by substantial parts of the population, they are not geared at real life. Abstinence is not an option for many (poor) women and being faithful does not protect against HIV/AIDS infection.

- Over the years, the A and B of the ABC tend to get a lot more emphasis than the C.

- Pedro Chequer
What is Effective?

- Abstinence
- Be Faithful (Monogamy)
- Consistent Correct Condom use
- Circumcision
RCT of Male Circumcision and HIV acquisition: South Africa 2005

- > 3000 uncircumcised men 18-24 years of age randomized to intervention or control with 21 mos. follow-up.
- Trial was stopped at interim analysis when mean follow up was 18.1 mos. due to decreased HIV incidence in the intervention group.
- RR corresponds to a protection of 60% (95% C. I. 32%-76%)
Validation of Circumcision Effect

- RCTs in Kenya and Uganda were halted in late 2006 after interim analysis of data showed circumcision significantly reduces men’s risk of HIV infection
- A reduction of risk of about 50% was found in each trial
Male circumcision and HIV: keratinization, Langerhans cells

Figure 4. Representative photomicrograph of H&E-stained foreskin tissue from the outer surface (left) and the inner surface (right) of the foreskin. The extent of the keratin layer is identified by the black and white arrows.
Beyond Circumcision: HIV and Penile Hygiene
JAIDS (43), Sept 2006

Association Between HIV and Subpreputial Penile Wetness in Uncircumcised Men in South Africa

Nigel O’Farrell, MD, FRCP,*† Linda Morison, MSc,† Prashini Moodley, MB, ChB, PhD,‡
Keshree Pillay, MB, ChB,‡ Trusha Vamnali, MB, ChB,‡ Maria Quigley, MSc,†
Richard Hayes, MSc, DSc,† and A. Willem Sturm, MD, PhD‡

Independent Association of Hygiene, Socioeconomic Status, and Circumcision With Reduced Risk of HIV Infection Among Kenyan Men

Amalia S. Meier, PhD,*∥ Elizabeth A. Bukusi, MBChB, M Med(ObGyn), MPH,‡§
Craig R. Cohen, MD, MPH,∥ and King K. Holmes, MD, PhD∥§
Expanding on the ABCs: Advancing Prevention Technologies

- Female controlled methods-
  - diaphragm and microbicides
- Suppression of Genital Herpes
  Will not discuss
- Pr-EP (Pre-exposure Prophylaxis)-
  Dr. Martinez
Female Controlled Methods

- Diaphragm
- Microbicicides
The Diaphragm: Rationale for Exploration

• Female initiated and controlled
• Worn inside the vagina- unobtrusive
• Creates a physical barrier over the cervix- site believed to be most vulnerable to HIV infection
• If effective, could be combined with an effective microbicide

Moench et al. AIDS 2002
Vaginal Diaphragm Clinical Trial

- Mira Vaginal Diaphragm with Replens
- Over 5000 women enrolled in Africa
- 32% HIV seroprevalence baseline
- Results should be available mid 2007

Gita Ramjee, XVI IAC.2006
Microbicides

- Drugs or biologic products, for use primarily by women, that can be applied to the vagina prior to intercourse in order to reduce the transmission of HIV
- May or may not have spermicidal activity
- May be available as gels, intravaginal rings, or in other forms
- May be coitally dependent or provide continuous protection
- Potentially may be protective for rectal use as well
MICROBICIDES: POTENTIAL FOR HIV PREVENTION


Microbicides Phase III trials

• Four products are currently in phase III efficacy trials in South Africa and Asia
• Over 10,000 women enrolled
• Unexpectedly high pregnancy rates, lower than expected HIV incidence rates are challenges
Microbicides Phase III trials

- Phase III trial of Ushercell, a surface active microbicide, was halted January 2006
- Women randomized to Ushercell had a higher incidence of HIV than controls
- Trials of Savvy were halted in 2006 due to a lower than expected HIV incidence which would make proof of efficacy impossible
ARV Containing Vaginal Rings

- Could provide more specific, longer acting agents, including ARVs that enter genital tissues, but not the plasma
- Could provide coverage for 30 days or longer
- Would be unobtrusive, easy to use

Gita Ramgee. XVI IAC.2006
STIs as Cofactors of HIV infection

- STIs increase genital HIV RNA concentration in the HIV+ partner
- STIs increase abrasions and the number of cells receptive to HIV infection in the HIV- partner
- Genital Ulcer Disease (GUD) (Herpes, syphilis, chancroid) increases HIV acquisition up to 10 fold in the HIV- partner

Fleming and Wasserheit 1999
Treatment of STDs for HIV Prevention: Mwanza vs. Rakai

- Community randomized trials
- Mwanza-Improved management of symptomatic bacterial STDs
- 40% reduced HIV incidence over two years
- Rakai- Mass treatment for bacterial STIs q 6 months
- No significant reduction in HIV Incidence

Grosskurt et al. 1995.
Why the Difference?

• Different Prevalences of Genital Herpes and bacterial STIs
  38% of GUD in Rakai due to HSV
  <10% of GUD in Mwanza due to HSV
  Higher rates of bacterial STIs in Mwanza

• Genital Herpes was not affected by the antibiotics used in the trials
Genital Herpes Infection (HSV)
HSV-2 Seroprevalence in Various Countries

Figure 1. HSV-2 Seroprevalence in Different Populations

- Males over 12 years of age: 10%
- All over 12 years of age: 22%
- Females over 12 years of age: 26%
- HIV-seronegative men who have sex with men: 26%
- All adults between 30 and 39 years of age: 28%
- Low-income women between 18 and 29 years of age: 35%
- Blacks: 46%
- Cameroon men, all ages: 27%
- Cameroon men, all ages: 35%
- Cameroon men, all ages: 35%
- South Africa young adults: 35%
- Zimbabwe: 40%
- Male factory workers (majority HIV-seronegative), all ages: 51%
- Cameroon women, all ages: 54%
- Cameroon HIV-seronegative pregnant women: 55%
- Zimbabwe men, 35 years and older: 62%
- Kenya women, all ages: 68%
- Cameroon women, 35 years and older: 74%
- Thailand high risk HIV-seronegative men and women: 77%
- Kenya women, older than 30 years: 84%
HSV-2 and HIV

- HSV-2 may \( \uparrow \) susceptibility to HIV by
  - Disruption of normal barrier (ulcer breaks skin)
  - Recruiting inflammatory cells (CD4+) to site of viral activity, \( \uparrow \) HIV targets
  - Directly promoting growth of HIV

- HSV-2 may increase infectiousness of HIV by
  - \( \uparrow \) HIV-1 shedding at mucosal surface
  - \( \uparrow \) recurrence rates and severity of symptomatic HSV-2


Probability of HIV Acquisition per Sex Act by HSV-2 in HIV-Negative Partner and Viral Load of the HIV-Positive Partner

Risk of HIV acquisition \( \uparrow \) when HIV-positive partner is HSV-2 seropositive, even when control HIV viral load in HIV-positive partner is controlled.
HIV Seroconversion associated with HSV-2 infection

Can the use of Acyclovir and other anti-virals with activity against HSV suppress HSV shedding and reactivation decrease HIV transmission?
Reduction of Genital Shedding of HSV-2 and HIV With Valacyclovir\textsuperscript{[1]}

ANRS 1285

- Proof-of-concept, double-blind randomized trial
- 1285a: Women not eligible for HAART
  - Valacyclovir 500 mg BID vs placebo
  - 70 pts per arm
- 1285b: women on HAART
  - Valacyclovir 500 mg BID vs placebo
  - 30 pts per arm

Women not taking HAART (1285a)
- 0.5 log decrease in HIV-RNA in serum and genital secretions
- 65% reduction in genital HSV-2 shedding

Women on HAART (1285b)
- No decrease in plasma RNA, but a 0.7 log reduction in genital shedding
- Very little HSV-2 shedding, but further reduced by 70%

In separate study, HSV-2 was cause of 58% of genital ulcers in Malawi\textsuperscript{[2]}

## HSV-2 Suppressive Therapy: Clinical Trials

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<tr>
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<th>HPTN 039 (NIH)</th>
<th>Partners in Prevention (Gates Foundation)</th>
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<tbody>
<tr>
<td><strong>Objective</strong></td>
<td>Effect of HSV-2 on HIV susceptibility</td>
<td>Effect of HSV-2 on HIV infectiousness</td>
</tr>
<tr>
<td><strong>Study Design</strong></td>
<td>• Daily Acyclovir or placebo</td>
<td>• Daily Acyclovir or placebo</td>
</tr>
<tr>
<td></td>
<td>• HIV-, HSV2+ MSM &amp; women</td>
<td>• HIV discordant couples (HIV+ partner is HSV-2+)</td>
</tr>
<tr>
<td></td>
<td>• 9 sites (US, Peru, Africa)</td>
<td>• 14 sites in Africa</td>
</tr>
<tr>
<td><strong>Sample size</strong></td>
<td>3277 participants</td>
<td>3000 HIV discordant couples (6000 participants)</td>
</tr>
<tr>
<td><strong>Primary endpoint</strong></td>
<td>HIV acquisition</td>
<td>HIV transmission</td>
</tr>
<tr>
<td><strong>Status of enrollment</strong></td>
<td>100% (3277 participants)</td>
<td>70% (2100 couples)</td>
</tr>
<tr>
<td><strong>Anticipated completion</strong></td>
<td>2007</td>
<td>2008</td>
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A: Abstain
B: Be Faithful
C: Condomise
  Counselling
  & Testing

C: Circumcision
D: Diaphragm
E: Exposure prophylaxis (pre- and post)
F: Female-controlled microbicides
G: Genital tract infection control
H: HSV-2 suppressive treatment
I: Immunity
The End