

1 **Biomedical Prevention of HIV in Women: Microbicides and PrEP**

Sharon L. Hillier, Ph.D.
Professor

Department of Obstetrics, Gynecology and Reproductive Sciences, University of Pittsburgh Pittsburgh, PA
Magee-Womens Research Institute

2 **Estimated Number of Adults and Children Newly Infected with HIV During 2007**

3 **The Evolving Epidemic: Africa**

4 **Women and HIV: US**

- In 2004, teen girls represented 43% of AIDS cases in reported among people aged 13 to 19.
- AIDS is the leading cause of death of African-American women aged 25 to 34.
- African-American women are 24 times more likely to have AIDS than white women.
- African-Americans and Hispanics represented 25% of all women in the U.S. but they account for 82% of AIDS cases among women.
- 71% of women diagnosed with AIDS in 2005 contracted the disease through heterosexual sex.

5 **The Case for Pre-Exposure Prophylaxis to Prevent HIV in Women**

- Use of antiretroviral drugs has been proven to be effective in reducing mother to child transmission of HIV in the US and internationally
- Women are at increased risk of HIV due to biological and cultural factors
- Women cannot control condom use by their partners and have limited options for protecting themselves from HIV

6 **The HIV Prevention Spectrum**

7 **How Does HIV Invade?**

8 **Female-Initiated Barriers**

- Diaphragms and female condoms could allow women more control over sexual health
- Does not require active male participation
- Can be inserted in advance of sex
- Provides option if partner refuses male condoms
- Providing female increased protected sex acts from 31-65% in Brazil (Babosa et al 2000)
- In US, acts of protected sex increased from 44%-59% with female condoms (Choi et al 2003)

9 **MIRA (Gates Diaphragm Study)**

- Sites in South Africa and Zimbabwe (N=4948)
- Effectiveness of diaphragm with Replens gel in preventing heterosexual HIV acquisition in women
- All receive condoms, intensive safe sex counseling, STI treatment
- Randomization to condoms alone or condoms plus diaphragm used with Replens gel.

10 **Disappointment for a Gates Trial**

11 **MIRA Diaphragm Trial Results**

Results: No protective benefit from use of the diaphragm and lubricant gel compared to condoms alone

- 12 **The Ideal HIV Prevention Drug**
- PrEP = Pre-Exposure Prophylaxis
 - oral, vaginal, rectal
 - Potent activity against HIV
 - One dose daily – or less
 - Good tissue penetration at site of infection
 - Well tolerated, safe (including pregnancy)
 - Minimal drug interactions
 - Minimal resistance, preserve options
 - Affordable: drug cost and monitoring
- 13 **How Could Microbicides or Oral Drugs Prevent Infection?**
- 14 **Why Not Use Over the Counter Vaginal Products to Prevent HIV?**
- Nonoxynol-9 tested in three large studies including 2000 women:
 - N-9 sponge: increased HIV risk
 - N-9 film: not harmful or protective
 - N-9 gel: trend toward increased HIV among high frequency users
 - Outcome: N-9 recognized to be both irritating and ineffective at preventing HIV
- 15 **History of Microbicide Development**
- 16 **Why Not Develop Cheap and Safe Vaginal Products to Block HIV?**
- A microbicide is a product that can be applied to the vaginal or rectal mucosa with the intention of preventing or significantly reducing the transmission of sexually transmitted infections including HIV infection
- 17 **Microbicide Trial Design**
- 18 **Summary of Completed Non-Specific Microbicide Studies**
- 19 **BufferGel: A Carbopol Low pH Gel**
- The buffering action of BufferGel – acts by:
 - Enhancing the body's natural defences
 - Maintaining a low vaginal pH
 - Pre-Clinical Data
 - Sperm and many STD pathogens inactivated at pH less than 5
 - BufferGel has a well-documented safety record in mice, rats, dogs, rabbits, and macaques
 - Blocked HIV-PBL transmission in humanized-SCID mouse
 - Clinical Data
 - Phase I safety and acceptability established in both the US and several international sites
 - Phase III contraceptive trial showed good safety and contraceptive efficacy when used with diaphragm
- 20 **PRO 2000 Gel**
- PRO 2000 is a synthetic polyanionic polymer – acts by blocking attachment of HIV to the host cell
 - Formulation of 0.5% PRO 2000 Gel
 - Pre-clinical data
 - In vitro, PRO 2000 prevents HIV-1 infection and is active against HSV-2, *C. trachomatis* and *N. gonorrhoeae*

- 0.5% PRO 2000/5 Gel showed no evidence of toxicity in rats, rabbits or macaques
 - Showed protection in a macaque SIV challenge model
 - Clinical data
 - Phase I studies among 136 women from four countries showed no safety concerns and good acceptability
 - **No serious adverse events reported, and no evidence for systemic absorption or toxicity**
- 21 **HPTN 035 Study**
- To estimate the safety and effectiveness of BufferGel and 0.5% PRO2000/5 (P) when applied intravaginally by women at risk for sexually-transmitted HIV infection
 - Enrolled at 7 sites (1 US, 6 Africa) between Feb 2005 and August 2007
 - All women followed a minimum of 1 year; some women enrolled early in the study followed for a maximum of 30 months
 - Study completed in September 2008; Results presented at CROI 2-09
- 22 **HPTN 035 Study Sites**
- 23 **Retention & Adherence**
- 24 **HIV Incidence & Effectiveness**
- 25 **Effect of PRO 2000 on HIV infection by Frequency of Gel and Condom Use**
- 26 **MDP-301 Study of PRO2000/5 (P)**
- ✓ PRO 2000 0.5% and 2%
 - ✓ Sponsored by the Microbicide Development Programme (MDP) of the UK
 - ✓ Intended sample size: 9,590
 - ✓ First enrollment: 25 Oct. 2005
 - ✓ 16 years or older, except in S Africa and Zambia: 18years
 - ✓ Last SDMC meeting: Feb 2008 resulting in closure of 2% PRO 2000
 - ✓ Estimated complete enrollment: late 08, results early 2010
- 27 **History of Microbicide Development**
- 28 **Tenofovir Gel Study in Macaques**
- 29 **Efficacy evaluation of 1% tenofovir Gel Applied Vaginally in Macaques**
- 30 **Complete Protection by TFV or TFV/FTC Gel in Macaques**
- 31 **What are the comparative drug levels for oral vs. topical tenofovir?**
- 32 **CAPRISA-004 Study of 1% Tenofovir**
- ✓ Tenofovir 1% gel vs placebo
 - ✓ Proof-of-concept trial in 980 women in Durban
 - ✓ 18 years and older
 - ✓ Required to use contraception
 - ✓ Coitally dependent: gel use within 12 hours before and 12 hours after sex, max. 2 applications within 24 hours

- ✓ Fully accrued as of January 2009
- ✓ Study to be completed in January 2010

33 **Oral Pre-Exposure Prophylaxis**

- Premise: If women are willing to use contraceptive pills everyday to prevention pregnancy, maybe they would be willing to use drugs active against HIV prophylactically to prevent HIV infection

34 **Topical and Oral PrEP Agents**

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- Topical
 - Higher concentrations in genital tissues
 - Potential for long-acting formulations
 - Potential for combination products
 - Little systemic toxicity
 - Less monitoring
 - Use in pregnancy/BF

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- Oral
 - Systemic exposure
 - Potential for greater toxicity
 - Requirement for monitoring
 - More resistance?
 - Population impact
 - Limited to ART?
 - Overlap with treatment

35 **The VOICE Study**

- Safety and effectiveness study of tenofovir gel, tenofovir tablet and Truvada tablet for prevention of HIV infection in 4,200 women
- Randomized trial with 5 study groups. Women will use product for average of 21 months

36 **Why VOICE?**

Tenofovir Tenofovir Gel Truvada

- Which is safer?**
- Which is effective?**
- Which will women use?**

37 **Partners PrEP Study (Oral PrEP)**

38 **Partners PrEP: Design**

39 **FEM-PrEP: Trial Overview**

40 **State of the HIV Prevention Field for Women**

- Female barriers (diaphragm) and over the counter contraceptive products not effective at reducing acquisition of HIV in women

- First generation microbicide gels have been evaluated in efficacy studies; only PRO2000 showed some level of effectiveness.
- Potent antiretroviral microbicides and oral drugs (topical and oral PrEP) now in efficacy studies- linkages between HIV prevention and treatment programs will be critical
- Women urgently need (and deserve) prevention methods to reduce risk of HIV

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Ten years ago, 1 percent of women in South Africa had contracted HIV; today the number is 25 percent. These women are living a nightmare, but we in rich countries are the ones who have to wake up. We need to develop prevention tools that can give women a chance to defend themselves. We need to deliver them as soon as they're available, and we need to deploy now the prevention tools we already have.

Melinda French Gates, Newsweek, May 15, 2006