

Biomedical HIV Prevention: current status, challenges and future directions

Nancy S. Padian

Women's Global Health Imperative

University of California, San Francisco

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Overview

- Review of selected biomedical HIV-1 prevention technologies
 - HSV-2 suppression
 - PrEP
 - Microbicides
 - Female-initiated barrier methods
- MIRA results and methodological challenges
- Recommendations for future prevention research

Ongoing & recently completed large-scale HIV-1 prevention trials



PrEP



Microbicides



**Cervical barriers &
Female condom**



HSV-2 suppression

HSV-2 Suppression

Sponsor	<u>Trial</u> Population	Anticipated N =	Study sites (<i>Expected results</i>)
Gates Foundation	<u>Partners in Prevention</u> HIV-1 discordant couples, index is HSV2+ (transmission)	~3400 couples	Kenya, Tanzania, South Africa, Uganda, Rwanda, Zambia, Botswana (2008/2009)
NIAID	<u>HPTN 039</u> HIV-1-/HSV-2+ MSM and women (acquisition)	3277	USA, Peru, Zambia, Zimbabwe, South Africa (2007)
Wellcome Trust	<u>LSHTM/AMREF/NIMR</u> HIV-1 negative/HSV-2+ female sex workers	821	Tanzania (2007)

Pre-exposure prophylaxis (PrEP)

Sponsor	Trial/product population	Anticipated N =	Study sites (<i>Expected results</i>)
CDC	Tenofovir male & female IDUs	2000	Thailand (2008)
CDC	Truvada heterosexual men & women	1200	Botswana (2009)
CDC	Tenofovir MSM	400	USA (2009)
NIH	Truvada MSM	1400	Peru/ Ecuador (2010)

Microbicides

Sponsor	<u>Trial</u> Product Mechanism	Anticipated N =	Study sites (Expected results)
NIH	<u>HPTN 035</u> BufferGel & 0.5% PRO2000 <i>Acid buffer & entry inhibitor</i>	3220	Malawi, South Africa, USA, Zambia, Zimbabwe (2009)
CONRAD/ USAID	<u>CAPRISA 004</u> 1% Tenofovir gel <i>ARV-containing</i>	980	South Africa (2010)
DFID/ Indevus	<u>MDP</u> 0.5% and 2% PRO2000 <i>Entry inhibitor</i>	9673	South Africa, Tanzania, Uganda, Zambia (2009)
USAID/ Gates Foundation	<u>Population Council</u> Carraguard <i>Entry inhibitor</i>	6203	South Africa (2007)

Source: <http://www.microbicide.org>

Female Condom

- The only female initiated method for HIV and STI prevention
- Old concept, new designs
 - Female Health Company: second generation female condom (FC2) made of synthetic nitrile
 - PATH: seeking FDA clearance for commercial distribution of women's condom
 - Reddy: V-Amour latex condom
- No HIV trials expected or planned



FHC - Reality



PATH – women's condom

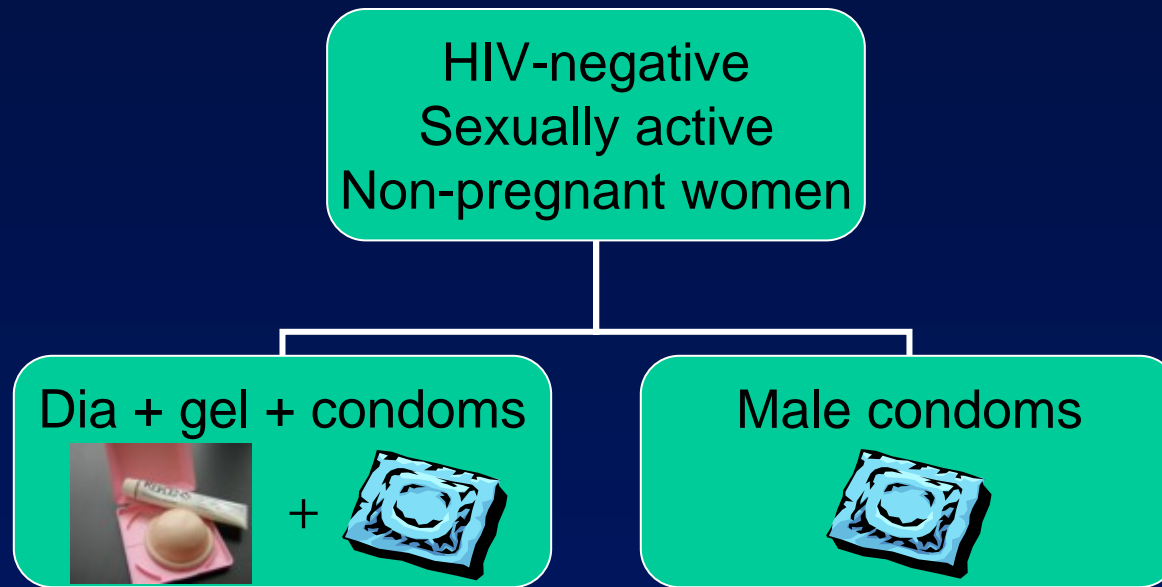


Reddy – V-Amour

Recognized challenges in HIV prevention trials

- Lower than anticipated HIV incidence
- High pregnancy rates
- Maintaining high retention rates
- Suboptimal product adherence
 - Prevention vs treatment

MIRA Study Design



All women receive risk reduction counseling, free male condoms and diagnosis and treatment of curable STIs

Women were followed quarterly for 12-24 months

MIRA Results from ITT (n=4948)

HIV	Incidence rate	Relative Hazard (95% CI)
All Sites	4.0	1.05 (0.84 – 1.32)
Harare	2.7	1.20 (0.83 – 1.74)
Durban	6.8	0.95 (0.69 – 1.31)
Johannesburg	3.4	1.05 (0.60 – 1.87)

MIRA study challenges

- Assessing multi-component interventions
 - Intervention tested in the context of a highly effective but perhaps not sustainable prevention package
- Open-label design
- Assessment of adherence/product use
 - Measurement of unobservable behavior

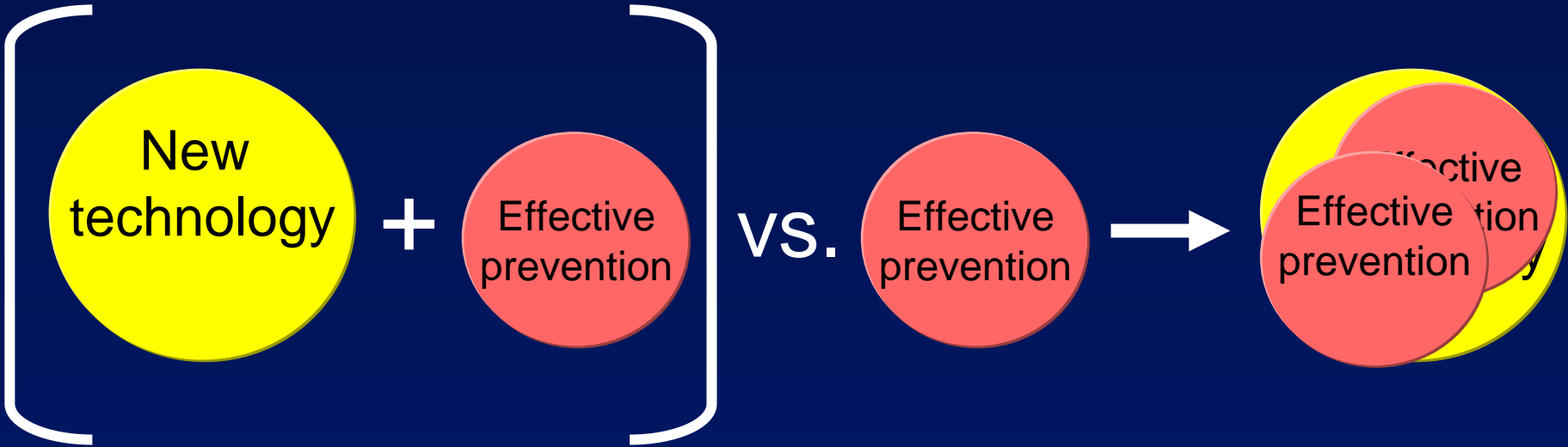


Evaluating new technologies

Intervention

Control

Attributable fraction



Maintaining effective prevention beyond the life of the study

- STD dx and tx
- VCT, education
- Sustainability of high levels of condom use beyond the trial
 - Survey of participants enrolled in an RCT of N-9 in Cameroon 14 months after study participation
 - Attributable to a change in behavior or a change in reporting?

	During study	Post-study
% of acts with condoms	82 - 84	57
% of ppts reporting consistent condom use	64 - 67	35

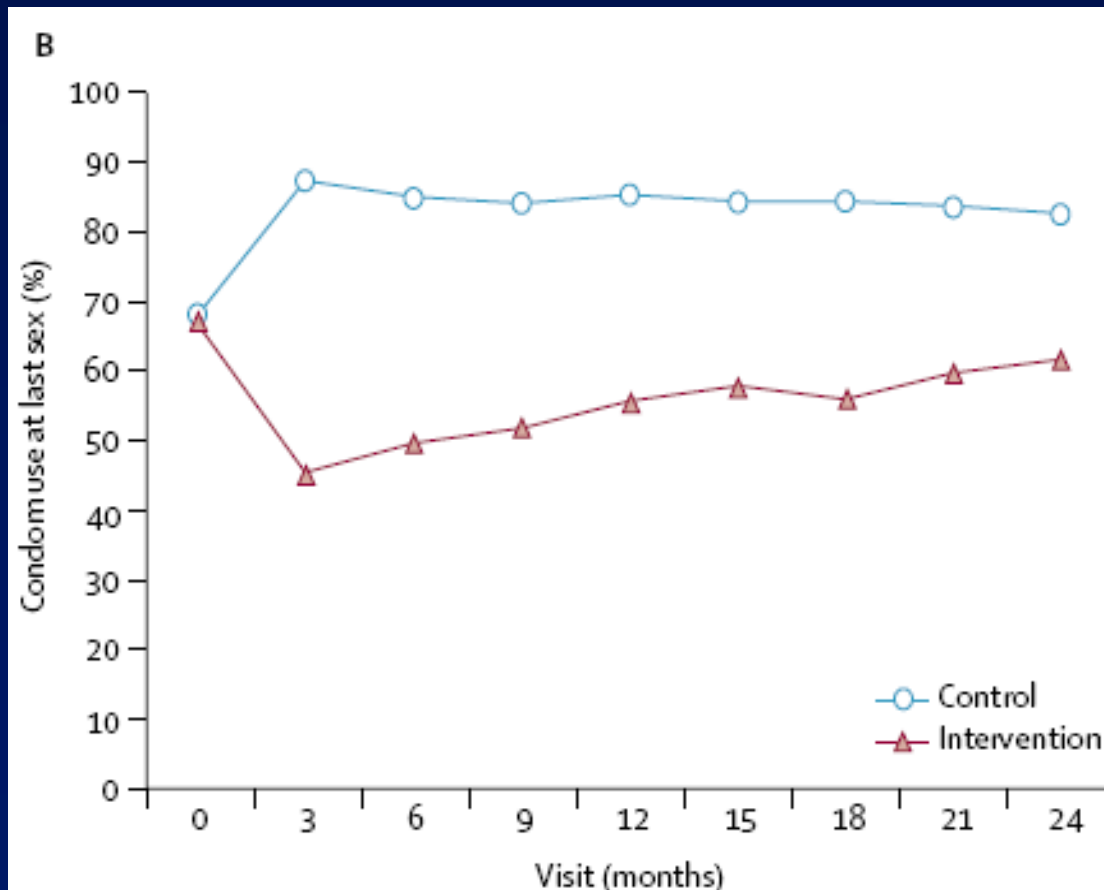
Source: Wong et al.

Open-label design

- Challenges
 - Study arm can influence behavior
 - Increased possibility of lack of independence between condoms and diaphragms
- Utility and Strengths
 - If a true placebo doesn't exist, there may be no alternative
 - For microbicide trials, condom-only arm distinguishes the effect of the placebo from that of study product
 - Biological effect
 - Behavior that might change with product use

Differential condom use in MIRA

Figure 3. Proportion of women reporting condom use at last sex, by visit



Potential reasons for differential use

- Therapeutic misconceptions
- Partner more likely to refuse condoms if he knew his partner was using a diaphragm
- Using “two” products less appealing

Effect of adherence + differential condom use

Post-trial simulations, with levels of diaphragm and condom use equivalent to that observed in our study sample:

- 70% diaphragm use (in intervention arm)
- 50% condom use in the intervention arm
- 85% condom use in the control arm



Power to detect a 33% reduction in incidence is $< 25\%$.

Measurement of self-reported behaviors

- Adherence
 - Not a problem for vaccines, circumcision or DOT
 - No DOP for condoms or test products
 - Poor biological markers of use
 - Need novel methods of self-report
 - Electronic diaries, etc..
 - Devices with computer chips that register use (e.g. body heat)
- Confounders or effect modifiers
 - Condom use
 - Sexual behavior of participant or partners

MIRA bottom line

In the context of a comprehensive HIV prevention package offered to all participants, the trial found **no additional protective benefit against HIV infection** from providing the diaphragm plus lubricant in the intervention arm.

What MIRA could not assess...

- Whether the cervix is most vulnerable
 - Characteristics in common with the foreskin
- Whether a diaphragm is as good as a condom
- Whether a diaphragm is better than nothing
- Whether other cervical barriers might have worked better
 - Coitally independent
 - Infrequent insertion
- Whether a barrier would be more effective with a microbicide

Future directions in prevention research

- Behavioral research and biomedical interventions
- New study designs
- New research directions

Behavioral research and biomedical interventions

Behavior

**Biomedical
prevention**



Need for basic behavioral research is as important as new biomedical technologies

- Adherence
 - Motivation
 - Context
 - Male partner involvement (or not)
- Measurement of self-reported behavior (for adherence, confounding or effect modification)
 - Understanding the value added for individuals **not** to say what we want to hear: better ways to assess and control social desirability bias
 - Order and type of questions
 - Innovative confidential or anonymous tools

Future directions in design

- Pre-randomization study (run-in)
 - Select non-condom users
 - Select good adherers
- Post randomization: adaptive designs
- Reconsider standards of condom counseling
 - Community standard vs bells and whistles?
 - Head-on comparison (true equivalence)?

Future research directions: Technological hierarchy of HIV prevention

Vaccines



Microbicides



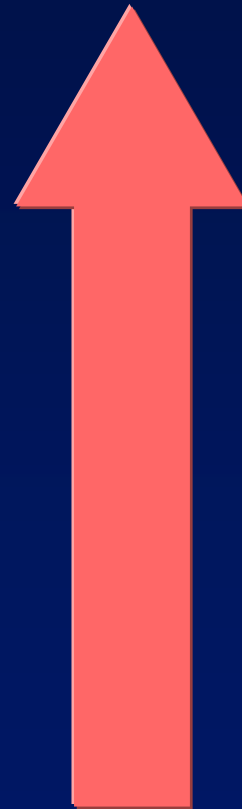
Cervical Barriers



Structural interventions for gender equity

Making the best of available evidence

- Male circumcision
- STD tx for HIV
- Male condom*
- Female condom*
- Abstinence*
- Reducing # of sex partners (absolute and concurrent)*
- Postponing sexual debut *



More evidence

Less evidence

* No HIV trial evidence: biological plausibility, laboratory data and evidence from observational studies

All scientific work is incomplete - whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time.

-- Bradford Hill, 1965

Acknowledgments

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