

# Global Prevention in 2007: Current status and challenges in prevention of heterosexual transmission of HIV

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Women's Global Health Imperative

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## Overview

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- Review of selected biomedical HIV-1 prevention technologies and their mechanisms of action
  - HSV-2 suppression
  - PrEP
  - Male circumcision
  - Microbicides
  - Female-initiated barrier methods
- Challenges in HIV prevention research
- Way forward

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



HSV-2 suppression



PrEP



Male  
circumcision



Microbicides



Cervical barriers &  
Female condom



## Ongoing HSV-2 suppression trials

Sponsor	Trial Population	Anticipated N =	Study sites (Expected results)
Gates Foundation	<u>Partners in Prevention</u> discordant couples; index is + for HIV-1 and HSV-2 (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)

Source: Nagot N, Delany-Moretlwe S, Mayaud P. *Future HIV Ther* (2007); 1:131-136.



## Recently completed HSV-2 suppression trials

Location (Citation)	Population/Intervention	N =	Results from ITT
Tanzania (Watson-Jones 2007)	<ul style="list-style-type: none"> <li>• HIV-1-/HSV-2 + women (acquisition)</li> <li>• 400mg oral twice daily acyclovir</li> </ul>	821	<u>Sero-conversions</u> Intervention: 30 (8%) Control: 33 (8%)  Rate ratio =1.01 (95% CI: 0.61-1.66)



## Ongoing PrEP trials

Sponsor	Population/Intervention	Anticipated N =	Study sites ( <i>Expected results</i> )
CDC	<ul style="list-style-type: none"> <li>• Male &amp; female IDUs</li> <li>• Tenofovir</li> </ul>	2000	Thailand (2008)
CDC	<ul style="list-style-type: none"> <li>• Heterosexual men &amp; women</li> <li>• Truvada</li> </ul>	1200	Botswana (2009)
CDC	<ul style="list-style-type: none"> <li>• MSM</li> <li>• Tenofovir</li> </ul>	400	USA (2009)
NIH	<ul style="list-style-type: none"> <li>• MSM</li> <li>• Truvada</li> </ul>	1400	Peru/Ecuador (2010)

Truvada = Tenofovir + emtricitabine

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



## Another type of PrE(I)P trial

Sponsor	Trial Population/Intervention	Anticipated N =	Study sites ( <i>Expected results</i> )
NIH	<p><u>HPTN 052</u></p> <ul style="list-style-type: none"> <li>HIV-discordant couples where the HIV-infected partner is ART naïve and has a CD4+ cell count of 350-550 cells/mm<sup>3</sup></li> <li>ARM 1: ART upon enrollment plus HIV primary care</li> <li>ARM 2: HIV primary care without initiation of ART until 2 consecutive CD4 ≤ 250</li> </ul>	1750 couples	Brazil, India, Malawi, Thailand, Zimbabwe (2012)

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



## Completed male circumcision trials

Location (Citation)	Population	N =	Results
South Africa (Auvert 2005)	18-24 year old uncircumcised men	3274	60% risk reduction (95% CI: 32%–76%)
Kenya (Bailey 2007)	18-24 year old uncircumcised men	2784	53% risk reduction (95% CI: 22%–72%)
Uganda (Gray 2007)	15-49 year old uncircumcised men	4996	60% risk reduction (95% CI: 30%–77%)



## Microbicide Candidates

Mechanism	Description	Examples
Surfactants	Disables the virus by breaking up the membrane surface	Savvy (C31G)
Vaginal defense enhancer	Maintain the normal microflora and acidity of the vaginal environment	BufferGel
Entry/fusion inhibitor	Attachment inhibitors prevent attachment of the virus to the white blood cell; fusion inhibitors prevent HIV from entering the cell	Carraguard, VivaGel (SPL 7013)
Viral replication inhibitor	Suppresses replication of HIV that enters the vagina or rectum during intercourse	Tenofovir, UC-781, Dapivirine

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



## Ongoing microbicide trials

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

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



## New developments in microbicides

- Application devices (longer acting, less frequent insertion, coitally independent)
  - Vaginal ring (w/ Dapirivine)
  - Duet Diaphragm (w/ BufferGel)
- Male Tolerance
  - Dapirivine
  - UC-781

*Summary as of September 2007; Alliance for Microbicide Development, [www.microbicide.org](http://www.microbicide.org)*



## Female Condom

- The only available 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



## Completed female condom trials

Location (Citation)	Intervention	N =	Results
USA (Macaluso 2007)	<ul style="list-style-type: none"> <li>• Cross-over RCT of women</li> <li>• MC vs. FC</li> <li>• Assessed semen exposure</li> </ul>	108	<ul style="list-style-type: none"> <li>• No difference in PSA exposure</li> </ul>
Thailand (Fontanet 1998)	<ul style="list-style-type: none"> <li>• RCT of female sex workers</li> <li>• MC vs. FC or MC</li> <li>• Assessed # unprotected sex acts and STIs</li> </ul>	504	<ul style="list-style-type: none"> <li>• No effect</li> <li>• Similar # of unprotected sex acts and STI incidence</li> </ul>
Kenya (Feldblum 2002)	<ul style="list-style-type: none"> <li>• Cluster RCT of women</li> <li>• MC vs. FC or MC</li> <li>• Assessed condom use and STIs</li> </ul>	1929	<ul style="list-style-type: none"> <li>• No effect</li> <li>• STI prevalence (12 mo): 18.2% FC vs. 18.4% MC</li> </ul>
USA (French 2002)	<ul style="list-style-type: none"> <li>• RCT of women attending STD clinics</li> <li>• MC vs. FC</li> <li>• Assessed condom use and STIs</li> </ul>	1442	<ul style="list-style-type: none"> <li>• No effect</li> <li>• OR for STD occurrence: 0.75 (95% CI: 0.56-1.01)</li> </ul>



## Diaphragms

- Diaphragms approved for use: latex by Ortho-McNeil (1,2) and Miletex (3); silicone by Semina (4)

1



2



3



4



- Diaphragms in development: SILCS by SILCS Inc. (5) and BufferGel Duet (diaphragm + microbicide) by ReProtect (6)

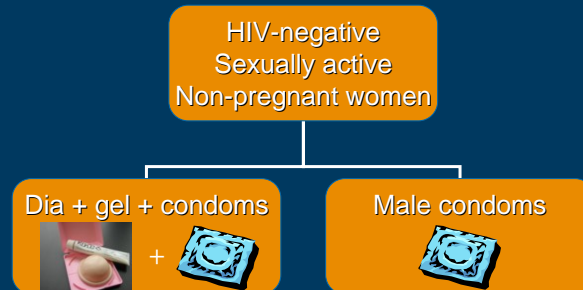
5



6



# MIRA Study Design



- All women received 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)
<b>All Sites</b>	<b>4.0</b>	<b>1.05 (0.84 – 1.32)</b>
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 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.

## RCT scorecard

Intervention	Individual or community RCT	No effect	Positive effect	Negative effect	Stopped due to futility
		N	N	N	N
STD Treatment	I-RCT	2	0	0	0
	C-RCT	3	1	0	0
Circumcision	I-RCT	0	3	0	0
Microbicides	I-RCT	4	0	2	2
Cervical barriers	I-RCT	1	0	0	0
	Total completed	No effect	Positive effect	Negative effect	Stopped due to futility
<b>All interventions</b>	<b>16*</b>	<b>10</b>	<b>4</b>	<b>2</b>	<b>2</b>

Effectiveness based on results from ITT analysis

\*2 microbicide trials stopped due to futility – not included in total completed

## Previously recognized challenges in HIV prevention trials

Challenge	Expected in MIRA	Observed in MIRA
1. Low HIV incidence	4.0%	4.0%
2. High pregnancy rates	Not pre-specified	13% annual incidence
3. High retention rates	≥90%	92.5%
4. Suboptimal product adherence	80% of sex acts	73% at last sex; 58% “always”

## Adherence

### HSV-2 suppression trial adherence by tablet count

Adherence <sup>1</sup>	N	%
<25%	20	1.5
25–49%	42	3.2
50–74%	227	17.4
≥75%	950	72.8
Unknown <sup>2</sup>	64	4.9
<b>Total</b>	<b>1305</b>	<b>100</b>

<sup>1</sup> Censored at earliest of date of first positive pregnancy, or date of last follow-up  
<sup>2</sup> Women who did not attend after randomisation round

*N* = number of women

Watson-Jones 2007

[www.hptn.org/web%20documents/HPTN039/WSMMeeting/MwanzaHSVtalkforJoBurg180507.pdf](http://www.hptn.org/web%20documents/HPTN039/WSMMeeting/MwanzaHSVtalkforJoBurg180507.pdf)

## Novel methods of self-report: Better ways to control social desirability

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- Cell phones, electronic diaries, etc..
- Innovative biological markers:
  - Markers of unprotected sex
  - Drug concentration in hair specimens
  - Drug metabolites in breath specimens
  - Devices (barriers, applicators) with computer chips or dye that register use (body heat, pH)

## Ways forward: Improved study design

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- Pre-randomization study (run-in)
  - Select non-condom users
  - Select good product adherers (using biomarkers)
- Post randomization: adaptive designs
- Reconsider standards of condom counseling
  - Community standard vs. enhanced counseling?
- Nature of control arm
  - Need for a non-intervention arm? (community incidence)
  - Head-on comparison of intervention to condom (true equivalence)?

## Alternative methods of analyses

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Moving beyond traditional intent-to-treat (ITT):

- Direct effects - uses counterfactuals that model estimated effects of the intervention while maintaining randomization and controlling for causal intermediates
  - For example, analyze data as if all women did (or did not) use condoms or diaphragms
  - Allows evaluation of the direct effects of the intervention

## Little progress in HIV Prevention

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- Disappointing results in biomedical research interventions

*and*

- Poor coverage and scaling up of what we know works (VCT, MTCT, knowing your status, stigma)

## Future research directions: Technological hierarchy of HIV prevention

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Vaccines



Microbicides



Cervical Barriers



Structural interventions for gender equity

## Making the best of available evidence

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- 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

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# MIRA team

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