

# Microbicides Trials Update

**Overview of ongoing trials and newly emerging challenges  
in the conduct of microbicide trials in developing countries**

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ICRH



# ICRH

- A research centre established in 1994 in response to the International Conference on Population and Development (ICPD, Cairo, 1994)
- Multidisciplinary centre within Faculty of Medicine and Health Sciences at Ghent University.
- Focus on sexual and reproductive health research
- Satellite NGO in Kenya (ICRH-Kenya)
- Collaboration agreements with Mozambique, South-Africa, Ruanda, Nicaragua, China, Burkina Faso, and many European partners
- Networks all over the world
- Since April 2004, WHO collaborating centre for research on sexual and reproductive health

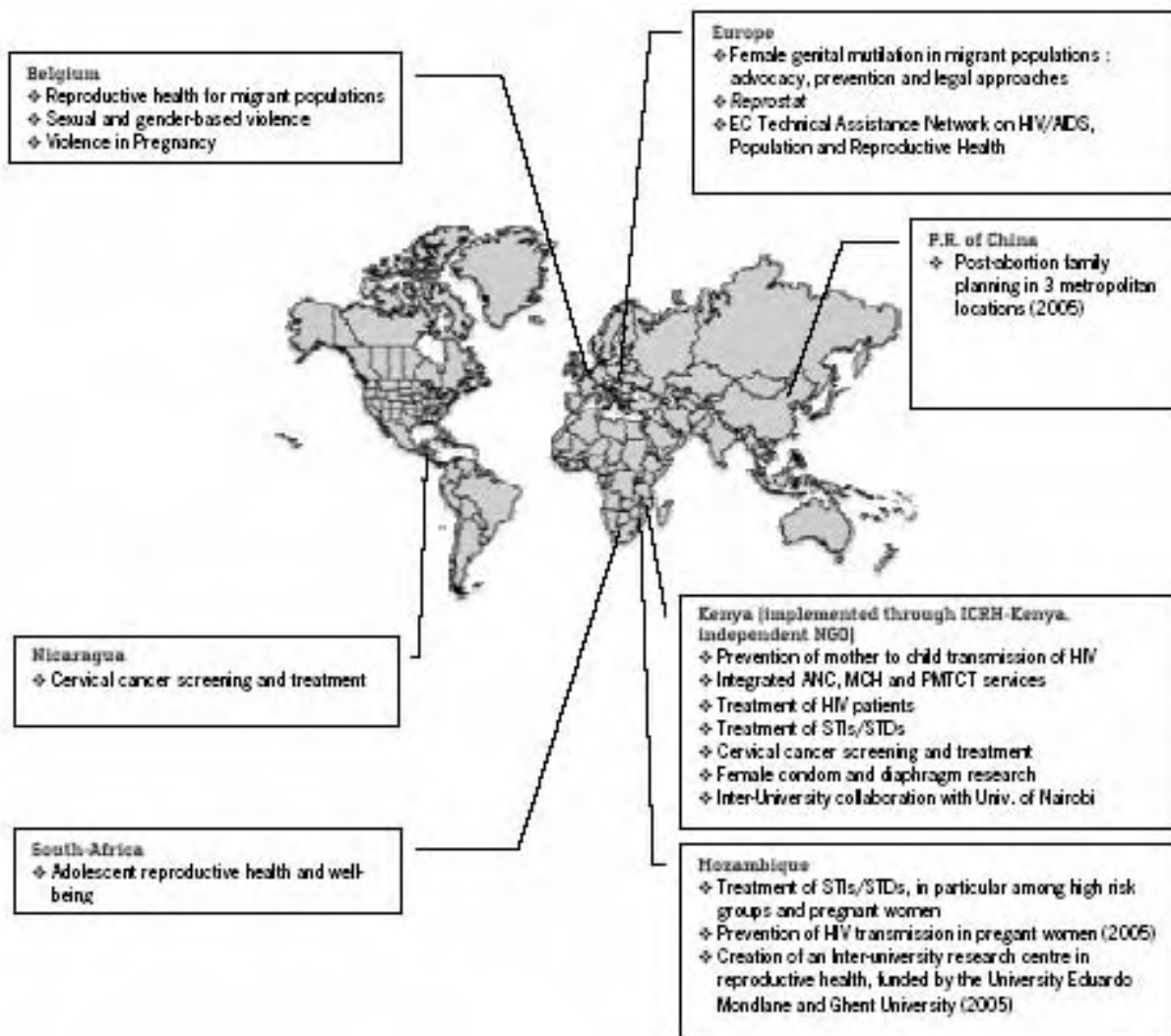


# Objectives and strategies

- To improve sexual and reproductive health in a broad sense
  - Safe motherhood
  - Family planning,
  - HIV/AIDS/STI, including cervical cancer
  - sexual and gender-based violence
  - discouragement of harmful practices such as FGM
- From a rights and gender perspective
- With particular attention to disadvantaged groups
- Through
  - Operational, clinical and policy research
  - Capacity building
  - Training
  - Advocacy



## Permanent missions



# ICRH 2007



# Responding to HIV

## ■ A sustainable response to HIV

- Comprehensive approach to HIV needed
- Prevention, treatment and care in an enabling environment
- Currently 6 new infections per person starting ARVs\*



## ■ Impact on Women

- In Sub-Saharan Africa, 74% of young adults (aged 15-24 years) living with HIV are female
- In South Africa: 1 in 4 women infected by age 22
- HIV infections also on the rise in women and girls in Eastern Europe, Asia, Latin America and the Caribbean



\*Global HIV Prevention Working Group, 2007

# Responding to HIV

- Current prevention methods are male controlled & contraceptive
- Women have no means to protect themselves if their male partners do not collaborate
- Abstinence and being faithful will not protect married women or those who are sexually coerced
- More effective HIV prevention must meet the needs of women

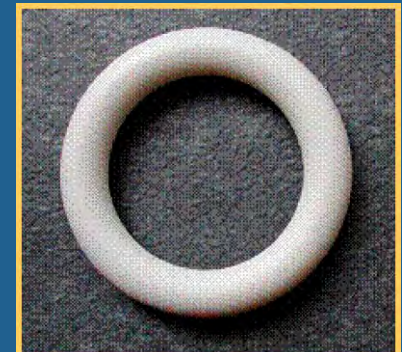


# What is a Microbicide?

- Vaginally applied substance that prevents or reduces transmission of HIV
- Could potentially be delivered in many forms:
  - gel
  - intravaginal ring
  - vaginal tablet
  - film
  - sponge
  - diaphragm



Vaginal applicator



Vaginal ring

- Ideally safe, effective, low cost and user-friendly



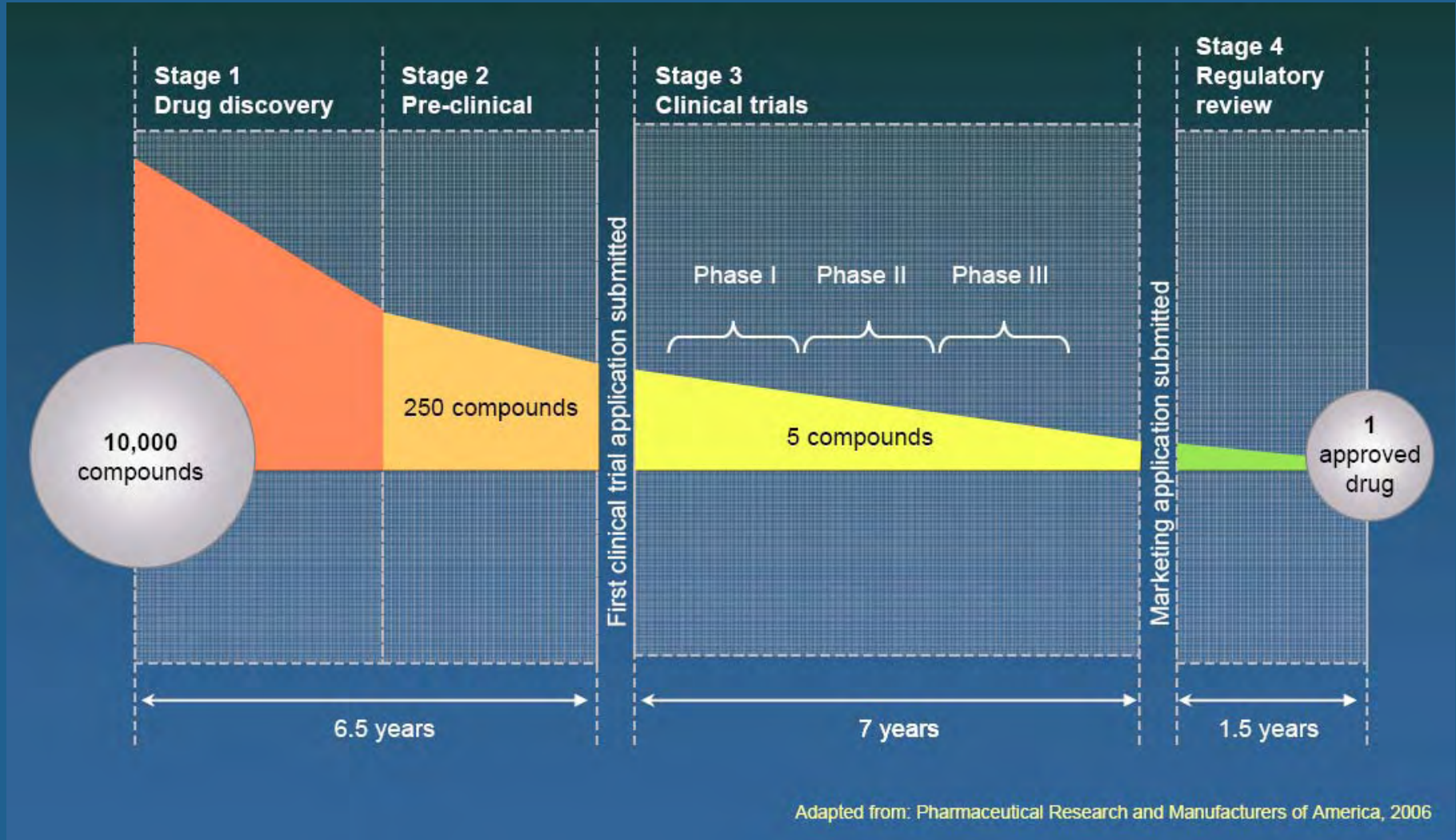
# Comprehensive Approaches to HIV/AIDS

Prevention		Treatment and Care
Prior to Exposure	Time of Exposure	
<ul style="list-style-type: none"> <li>■ Behavior change</li> <li>■ STI treatment</li> <li>■ Male circumcision</li> <li>■ Pre-exposure prophylaxis</li> <li>■ HIV vaccines</li> </ul>	<ul style="list-style-type: none"> <li>■ Male and female condoms</li> <li>■ Antiretroviral rx (mother-to-child)</li> <li>■ Post-exposure prophylaxis</li> </ul>	<ul style="list-style-type: none"> <li>■ Antiretroviral therapies</li> <li>■ Opportunistic infection therapies</li> <li>■ Basic care</li> </ul>
<b>Microbicides</b>		

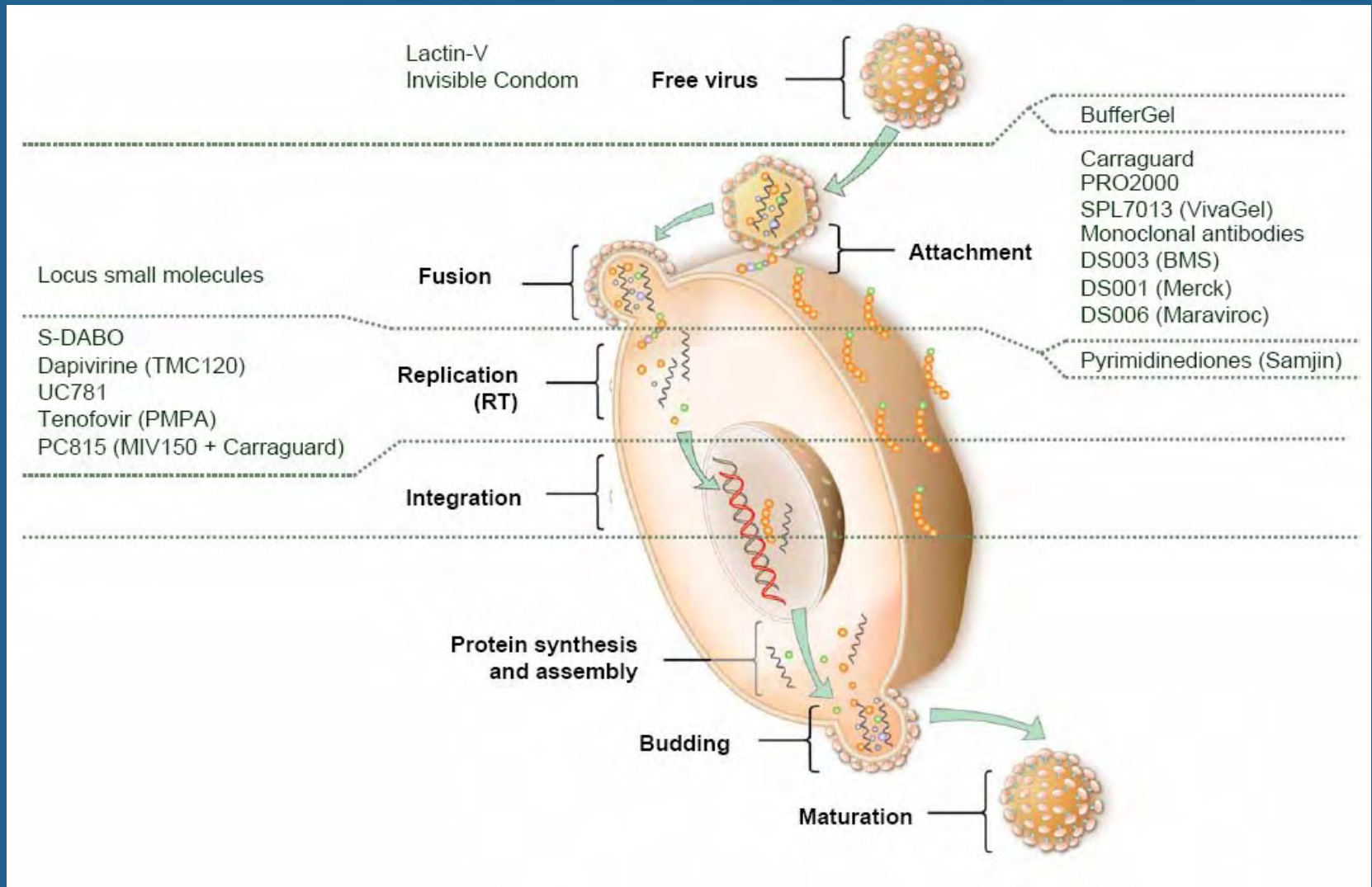
*Microbicides would offer a woman-initiated method to reduce HIV transmission*



# Drug discovery, development and review



# Locus of action for microbicides in development



# Overview of ongoing clinical trials

## MICROBICIDE CANDIDATES IN ONGOING CLINICAL TRIALS: SUMMARY AS OF OCTOBER 2007\*

<i>Phase</i>	<i>Candidate Name and Formulation</i>	<i>Mechanism of Action</i>	<i>Sites by Country</i>
<b>3</b>	Carraguard® gel†	Entry/fusion inhibitor	South Africa
	0.5% and 2% PRO 2000/5 gels	Entry/fusion inhibitor	South Africa, Tanzania, Uganda, Zambia
<b>2B</b>	1% Tenofovir gel ("CAPRISA 004")	Replication inhibitor	South Africa
<b>2/2B</b>	0.5% PRO 2000/5 gel (P) and BufferGel® ("HPTN 035")	Entry/fusion inhibitor and Vaginal defense enhancer	Malawi, South Africa, United States, Zambia, Zimbabwe
<b>2</b>	1% Tenofovir/PMPA gel	Replication inhibitor	India, United States
<b>1/2</b>	Dapivirine (TMC120) vaginal ring†	Replication inhibitor	Belgium
	Dapivirine (TMC120) gel†	Replication inhibitor	Rwanda, South Africa, Tanzania
	Invisible Condom™ gel	Entry/fusion inhibitor	Cameroon
<b>1</b>	Dapivirine (TMC120) vaginal ring	Replication inhibitor	Belgium
	Dapivirine (TMC120) gel†	Replication inhibitor	South Africa
	1% Tenofovir/PMPA gel	Replication inhibitor	Dominican Republic, United States
	0.1% UC-781 gel	Replication inhibitor	United States
	0.1% and 0.25% UC-781 gel	Replication inhibitor	United States
	0.1% and 0.25% UC-781 gel	Replication inhibitor	Thailand
	3% VivaGel™ (SPL7013 gel)	Entry/fusion inhibitor	Puerto Rico, United States
	3% VivaGel™ (SPL7013 gel)	Entry/fusion inhibitor	Kenya, United States
<b>N/A</b>	Vaginal ring safety and acceptability study	Placebo ring‡	Kenya, South Africa, Tanzania

Source: Alliance for Microbicide Development ([www.microbicide.org](http://www.microbicide.org)).

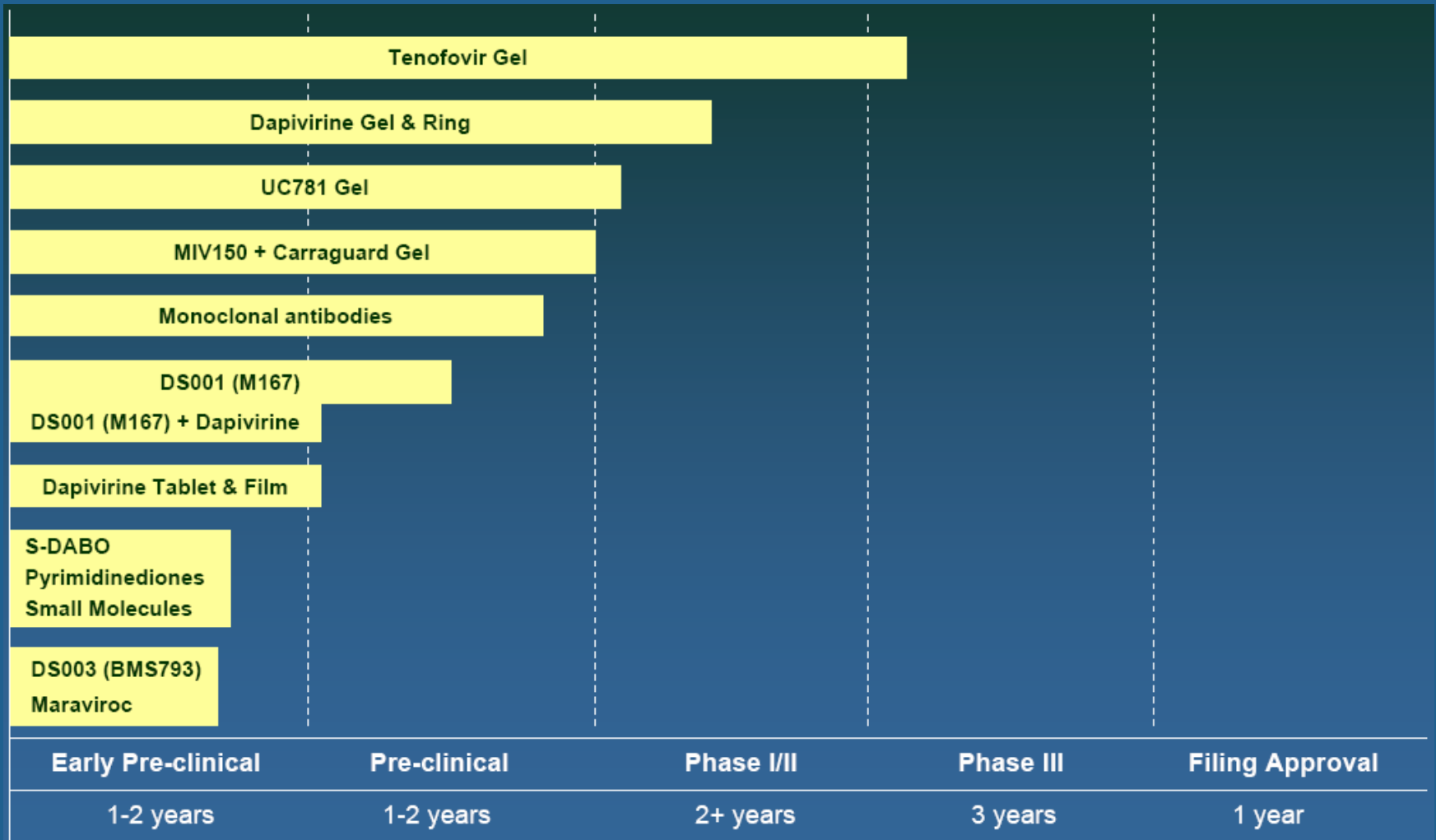


# Next Generation Microbicides

- Based on drugs used successfully for AIDS treatment
- Timing of use is more flexible, with products offering sustained protection
- May combine active ingredients that work in different ways
- Phase 2b trial of tenofovir gel initiated May 2007
- Additional candidates/delivery mechanisms in safety trials

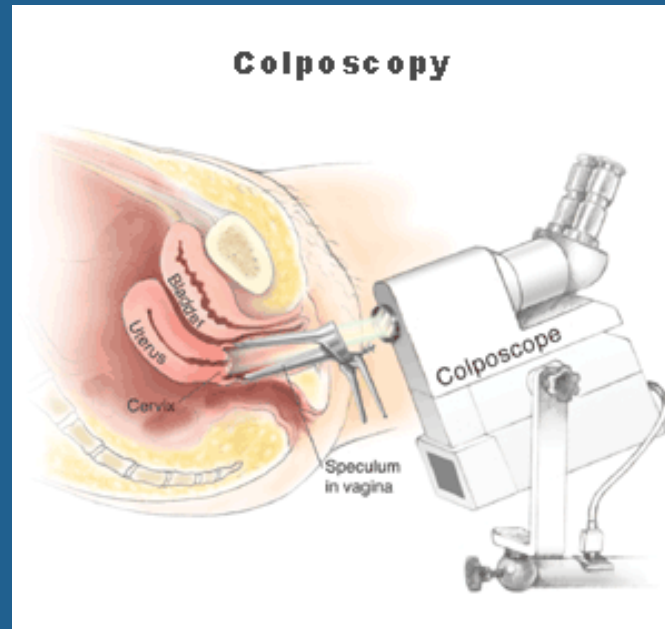


# Next generation product development



# Assessment of microbicide safety

## Colposcopy



### Constraints include:

- Inter-observer variability
- Unable to detect markers of increased susceptibility invisible to the naked eye



# Assessment of microbicide safety

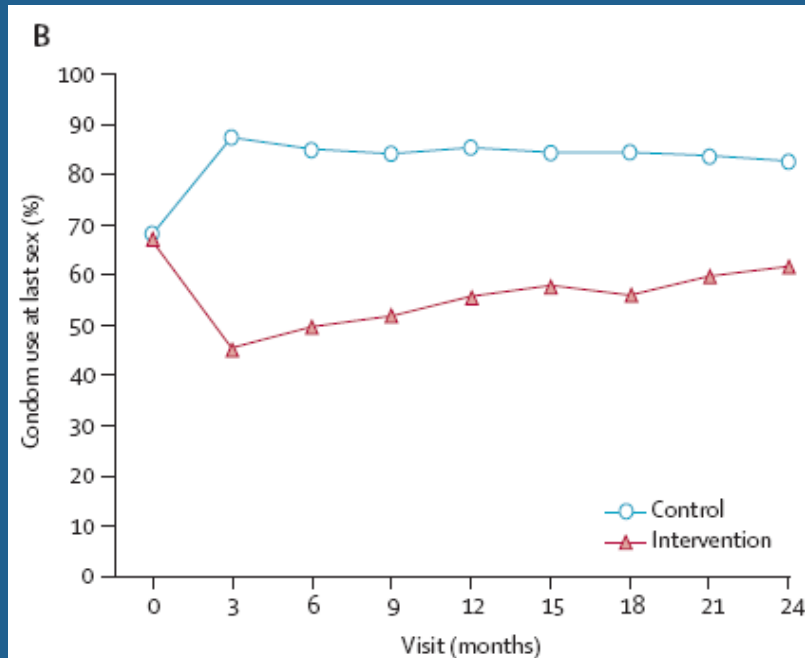
## Constraints include:

- Validation of existing models and biomarkers
- Assessment of impact of reproductive hormones, microflora and seminal plasma on microbicide-mucosa interactions
- Determination of microbicide effects on mucosal inflammation and innate immunity
- Identification of new biomarkers and models of microbicide-induced mucosal alteration that correlate with relevant in vivo properties



# Uptake and adherence

- Suboptimal adherence to regimen  
(~ RCT Diaphragm: use at last sex 73% of the time)
- Evidence of condom replacement



Padian et al. Diaphragm and lubricant gel for prevention of HIV acquisition in southern African women: a randomised controlled trial. *Lancet* 2007; 370: 251 – 261



# Uptake and adherence

- High incidence of pregnancy among HIV negative women in HIV incidence studies

How will pregnancy interfere with adherence and efficacy of microbicides?

- Co-enrolment of participants in multiple (microbicides- trials)

Many trials and interventions are concentrated in a limited number of sites

Mandatory fees to participants per visit in South Africa



# Microbicide Modelling

- Models use different approaches and report impact in different ways
- Assumptions based on early generation products
  - Duration of protection
  - STI efficacy
- Limited data on likely coverage and uptake rates
- Modelling must be iterative
  - Advances in product development
  - Understanding of likely use patterns
  - Changes in local conditions, HIV prevention mix and epidemiology



# Issues for Microbicide Use

- Integration into sexual practice
  - Risk perception
  - Other practices – eg. vaginal practices
  - Negotiation with partners
- Condom replacement
  - Potential to reduce positive impact in populations with high condom use
- Enabling environment for prevention
  - Microbicides not a panacea



# Microbicide Access Challenges

- Timing and product profile unclear
- First-in-class product
  - No historical demand data
  - No simple analogue
  - Product use understood from trials
  - Limited operational research
- Unit costs vary by formulation
- Partial effectiveness
  - Perfect use and ‘normal’ use



# Microbicide Access Challenges

- Association with HIV
  - Female Condom experience
- Gender roles
  - ‘Empowerment’ a key issue but how to include male partners?
- Demonstrating impact
  - Attribution as part of method mix
  - Dynamic HIV-prevention field
  - Time taken to show population effects



# Concurrent vaginal practices (VP)

- Everybody practises some type VP (mostly cleaning)
- How do products like talc, toothpaste, household detergents, cleaning products (Dettol, Omo) and natural substances interfere with microbicides?
- VP are likely to be associated with bacterial vaginosis and disruption of genital mucosa
- Association with HIV incidence is unclear, data from microbicides trials may help to clarify



# Insertion



Traditional and “modern” products in Mozambique

GSVP project 2007



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# South African Market: “Pantyhose” Insertions,



# Statistical and logistical considerations

Preparatory incidence studies and the trial itself as

an intervention: declining HIV incidence → **sample size** ↑↑

Trial	HIV Incidence/Per 100 p-y		
	Pre-Trial Estimate	During Trial	Post-Trial
Cameroon (1995-97)	14.0	6.7	3.7
Nairobi FSWs (2000-2002)	6.0	3.7	1.6

Source: Roddy (1998), Ngugi (2007)



# The diaphragm





Ik wou zelf m'n lichaam onderzoeken.





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dan zou ze het verklappen.  
Niemand wist het.



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- Luchters S et al. Acceptability of the diaphragm in Mombasa Kenya: A 6-month prospective study. Eur J Contracept Reprod Health Care. 2007
- Schroth A et al. Use of self home-made diaphragm for protection against pregnancy and sexually-transmitted infections: case report. East Afr Med J. 2007 Jan;84(1):35



Thank you!



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