

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

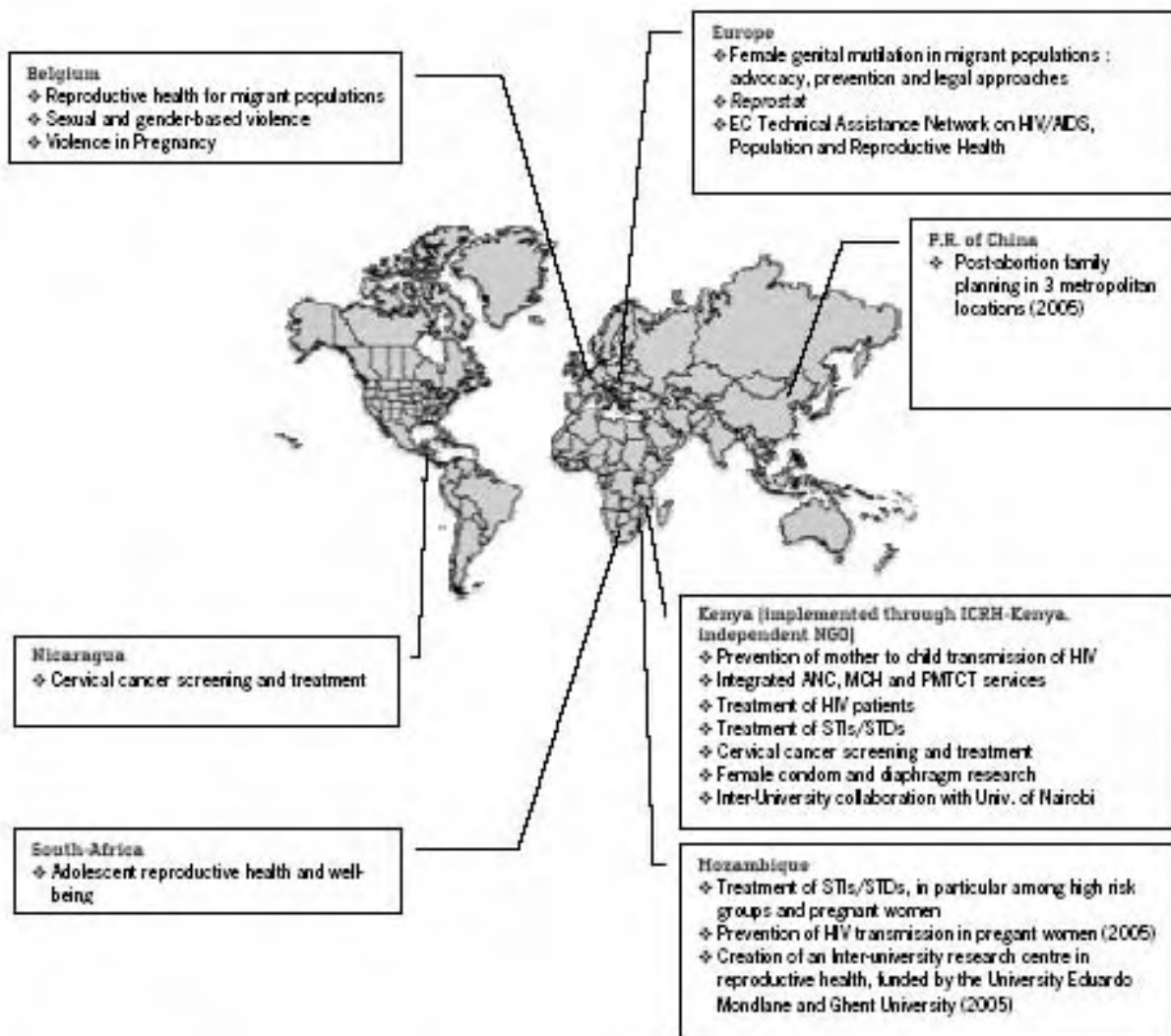


Objectives and strategies

- 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

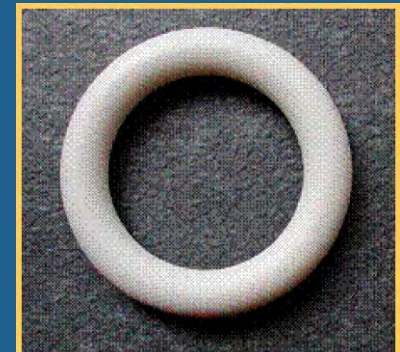


What is a Microbicide?

- 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



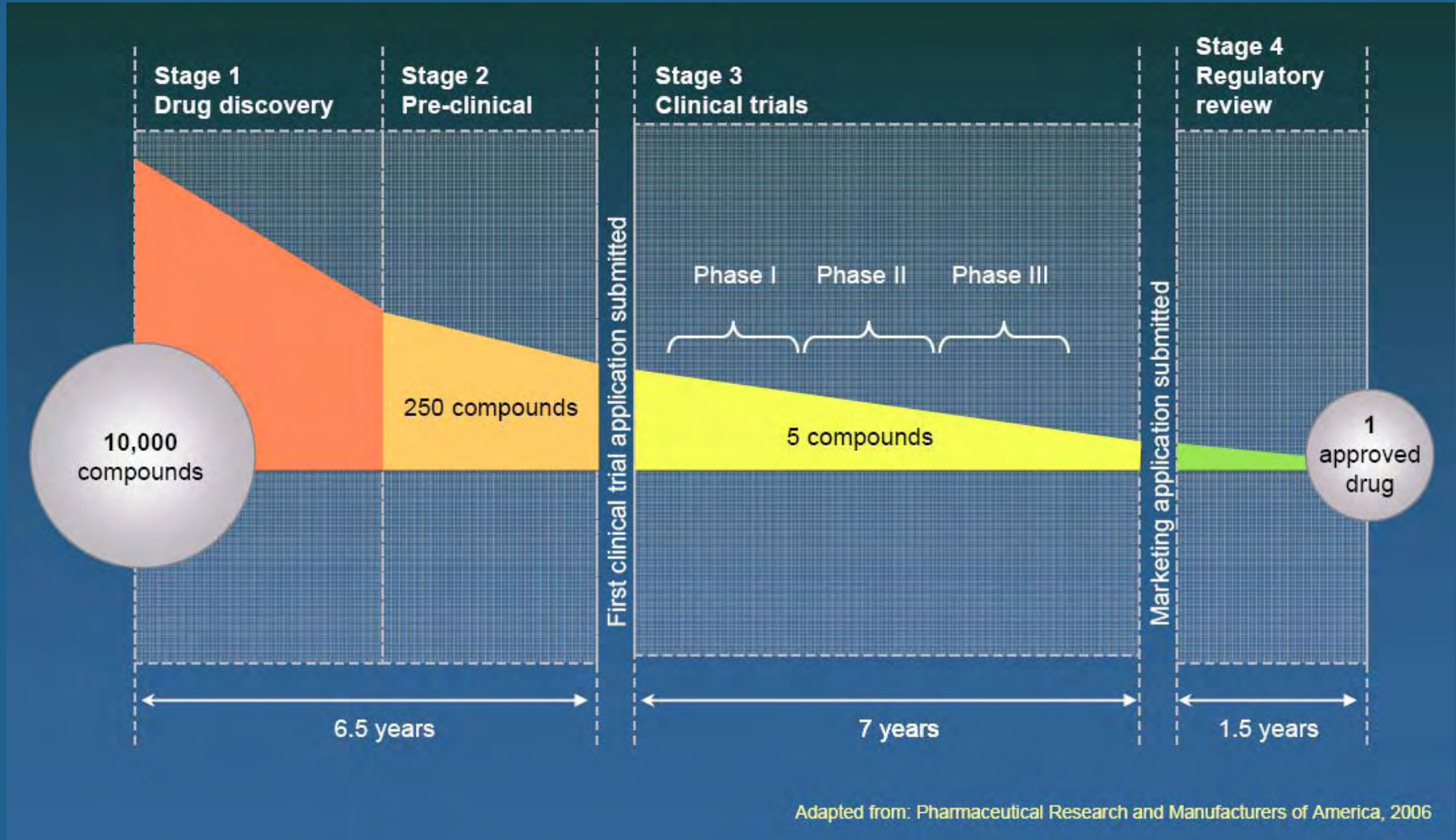
Comprehensive Approaches to HIV/AIDS

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

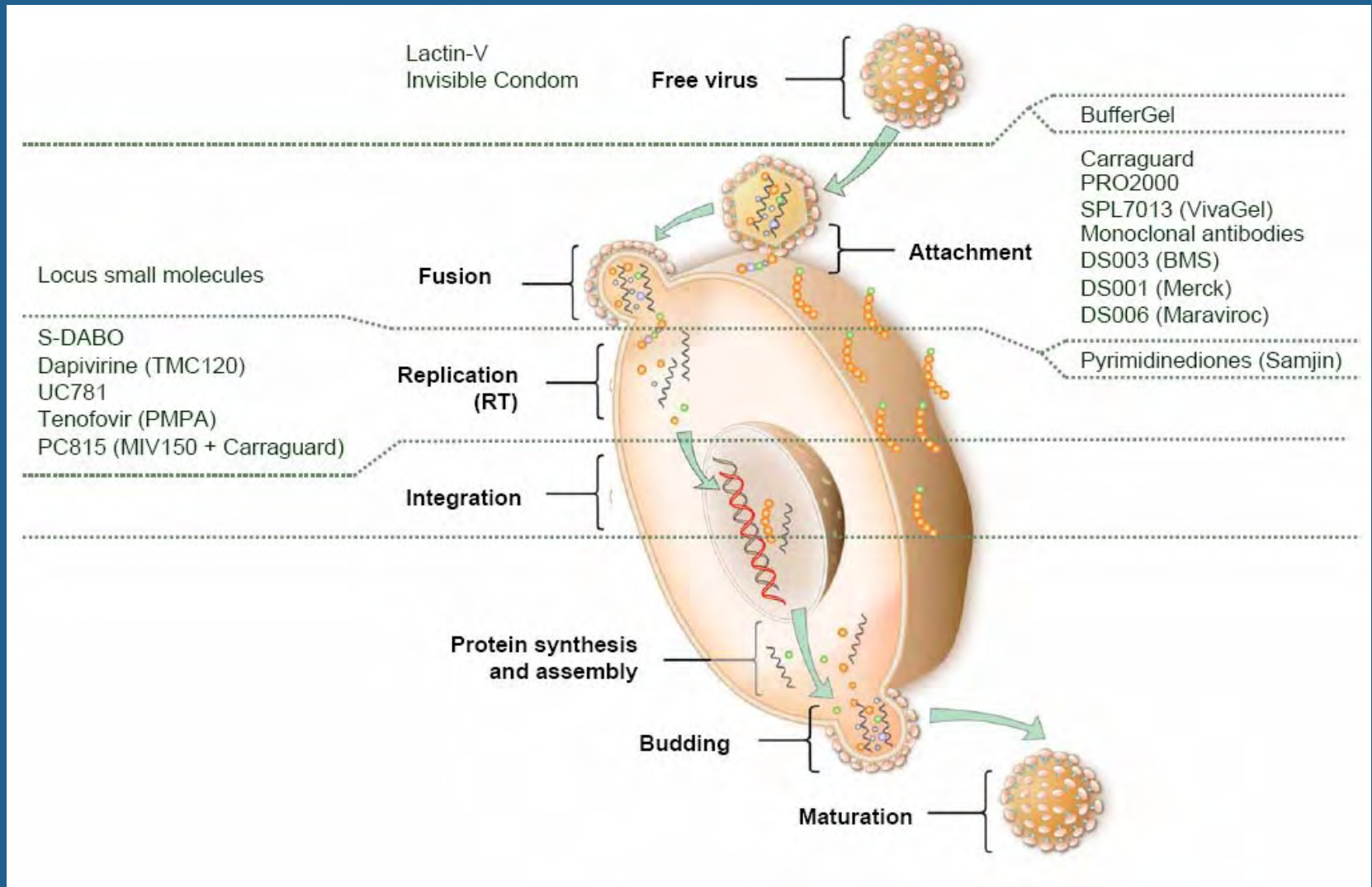
Microbicides would offer a woman-initiated method to reduce HIV transmission



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>
3	Carraguard® gel†	Entry/fusion inhibitor	South Africa
	0.5% and 2% PRO 2000/5 gels	Entry/fusion inhibitor	South Africa, Tanzania, Uganda, Zambia
2B	1% Tenofovir gel ("CAPRISA 004")	Replication inhibitor	South Africa
2/2B	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
2	1% Tenofovir/PMPA gel	Replication inhibitor	India, United States
1/2	Dapivirine (TMC120) vaginal ring†	Replication inhibitor	Belgium
	Dapivirine (TMC120) gel†	Replication inhibitor	Rwanda, South Africa, Tanzania
	Invisible Condom™ gel	Entry/fusion inhibitor	Cameroon
1	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
N/A	Vaginal ring safety and acceptability study	Placebo ring‡	Kenya, South Africa, Tanzania

Source: Alliance for Microbicide Development (www.microbicide.org).

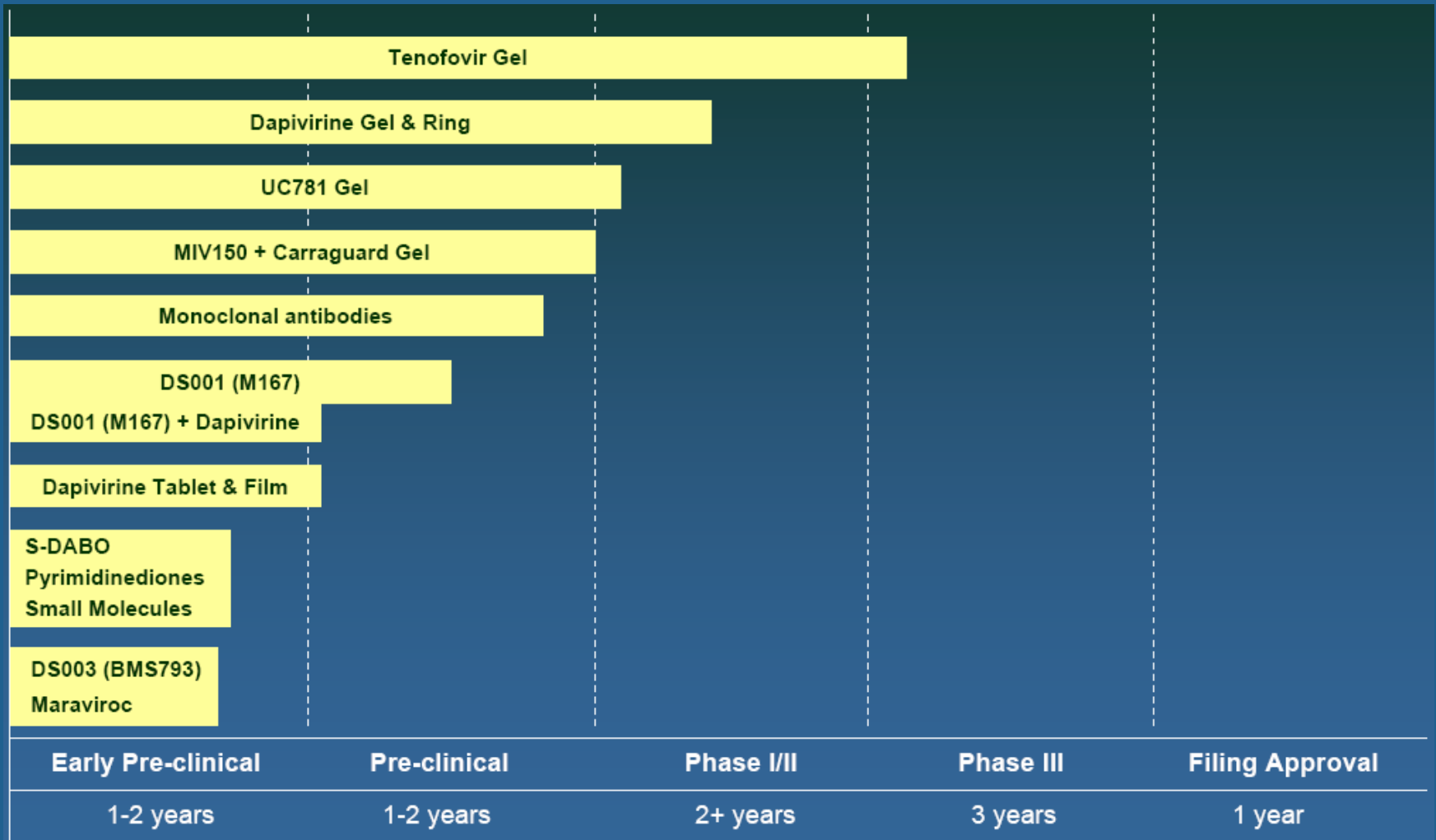


Next Generation Microbicides

- 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

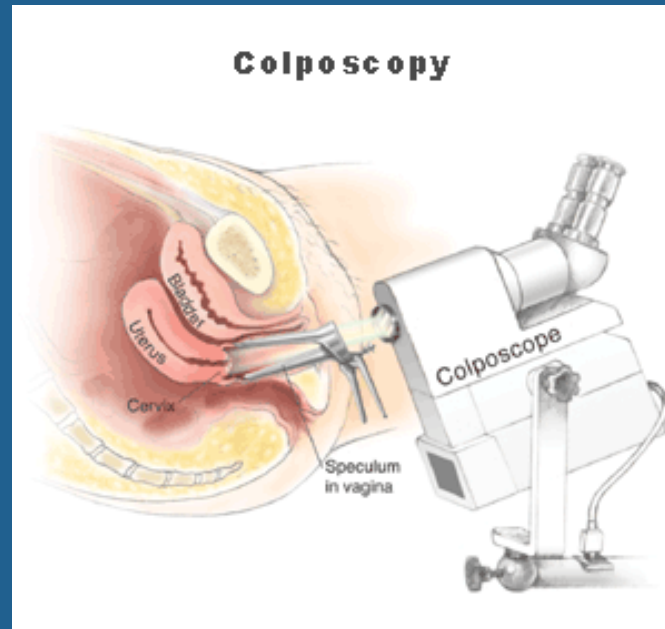


Next generation product development



Assessment of microbicide safety

Colposcopy

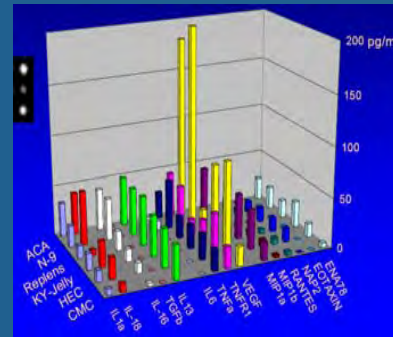
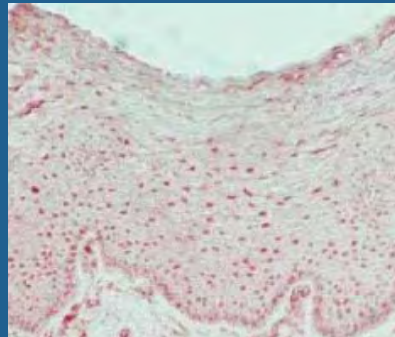


Constraints include:

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

Assessment of microbicide safety

Biomarkers of microbicide safety



- Cytotoxicity
- Cytokines/Chemokines
- Soluble mediators of inflammation
- Leukocyte number and phenotype
- Epithelial disruption
- Lactobacilli inhibition
- HIV/HSV infection
- ...



Assessment of microbicide safety

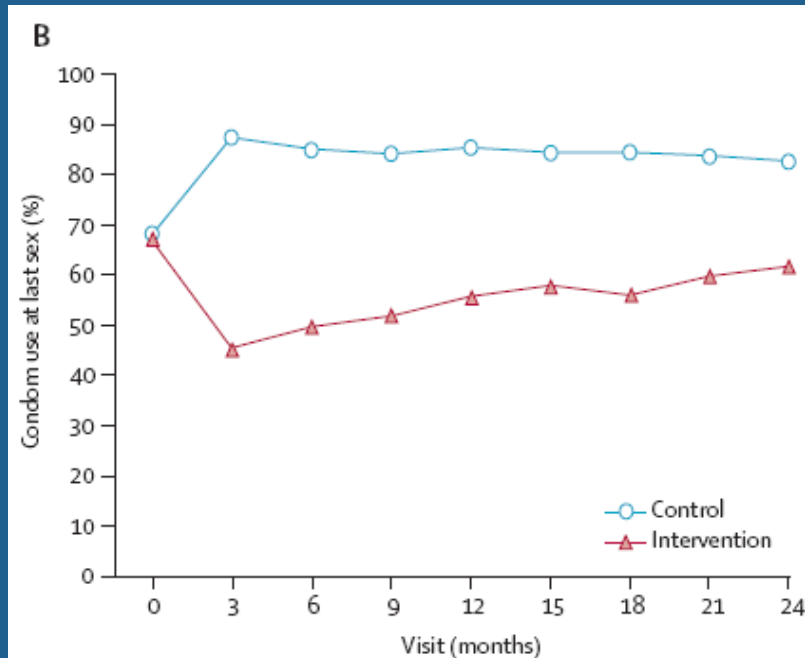
Constraints include:

- 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.





ICRH



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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