Microbicides Research and Development: State of the Art

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Post-Graduate Course, Training in Research in Sexual Health, 9 March 05

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Overview of Presentation

- The need for women-controlled methods
- What are microbicides?
- Mechanisms of action
- Microbicide pipeline
- Public health benefits
- Products in effectiveness trials
- Trial design issues
- Scientific challenges
- WHO Microbicide Project

Overview

- HIV/AIDS pandemic
  - Accounts for more deaths than other infectious disease
  - 40 million people currently infected world wide
  - about 6 out of every 10 new infections are in women
  - nearly 5,000 women are infected with HIV daily
  - 90% of them in developing countries
- HIV preventive strategies
  - Abstinence, monogamy, condom use, reduction in number of sexual partners
  - diagnosis and treatment of sexually transmitted diseases

Women and HIV

- Increasingly Female
  - 67% of African cases in 15-24 year olds
  - In sub-Saharan Africa, 13 women for every 10 infected men
  - In South Africa - 1 in 4 women infected by 22
  - In India - in 2004, 22% of cases in housewives with single partner
- Married, monogamous
- Mother

HIV interventions are often not feasible for many women

- Women with single partners can be exposed to HIV via their partners' other sexual relationships
- reduction of sex partners is not an option for commercial sex workers
- many women do not have the power to insist on condom use
- multiple sexual partners may be the only source of economic and social security
- diagnosis and treatment of sexually transmitted infections are either unavailable or inadequate in may parts of the world, besides many infections in women are asymptomatic

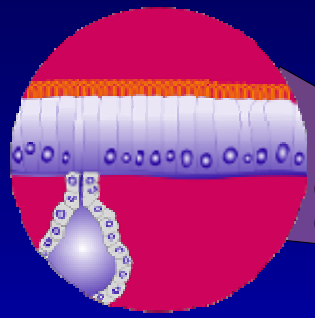
What is a microbicide?

- Any compound that can be applied into the vagina or rectum before sex to kill, neutralize, or block HIV and other sexually transmitted infections
- Todate, no microbicide is available
  - they are under development and/or investigation

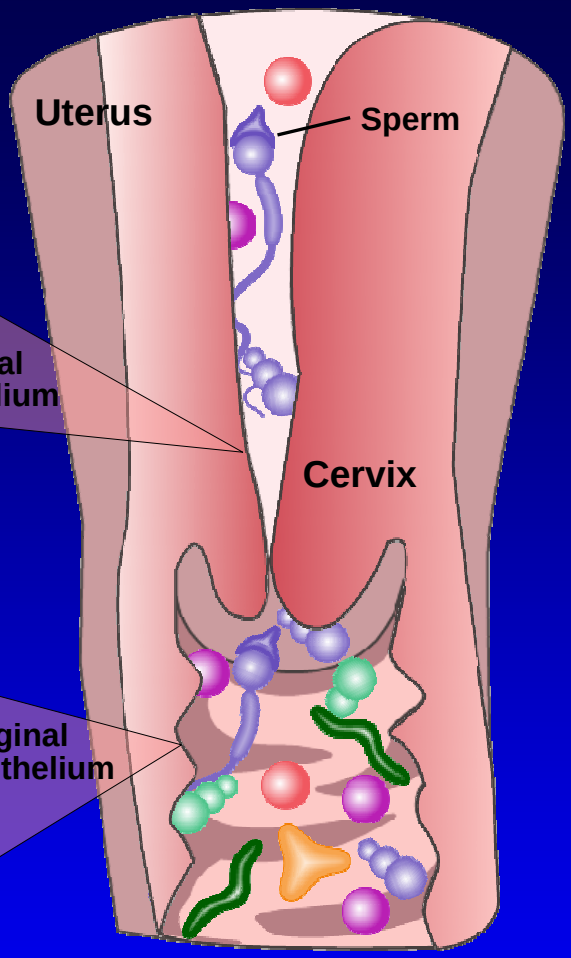
Other Microbicide Features

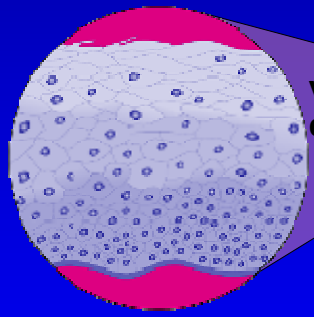
- Microbicides are inserted by women and may not require active negotiation with male partner
- Some are contraceptive, others are not contraceptive
- Potential protection against a range of STIs
- Could be used alone or together with a physical barrier (condoms, cervical barriers) as adjunct or fall-back
- Effective immediately after insertion and remains effective for several hours
- Potential effectiveness for post-coital and rectal use
- Could be made available over-the-counter at low cost

Courtesy: Janneke van de Wijgert



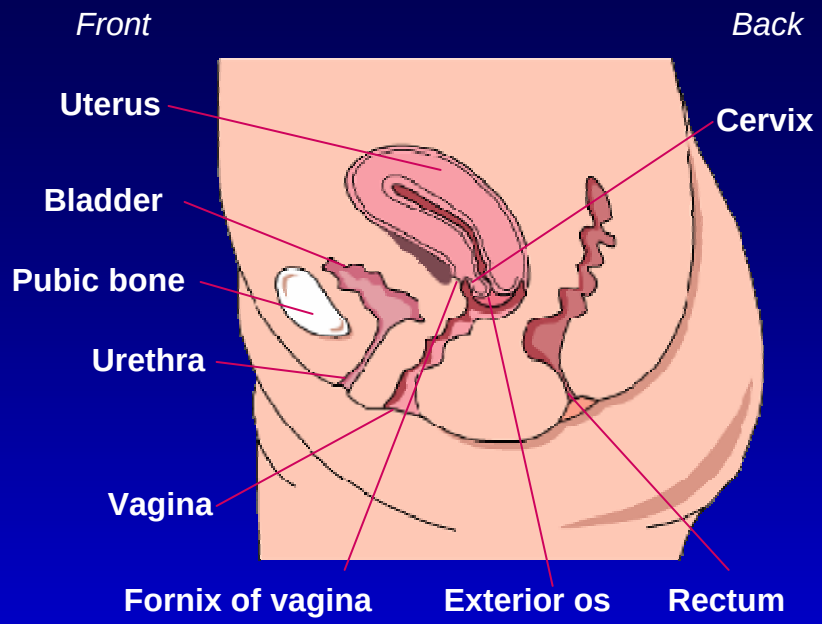
Cervical epithelium





Vaginal epithelium

Female Anatomy



Fungi

Candidiasis

Protozoa

Trichomonas

Viruses

HIV

Human papilloma
Cytomegalovirus
Hepatitis

Bacteria

Neisseria gonorrhoeae
Chiamydia trachomonas
Treponema pallidum
Haemophilus

Lactobacillus

Courtesy: Zeda Rosenberg, PhD

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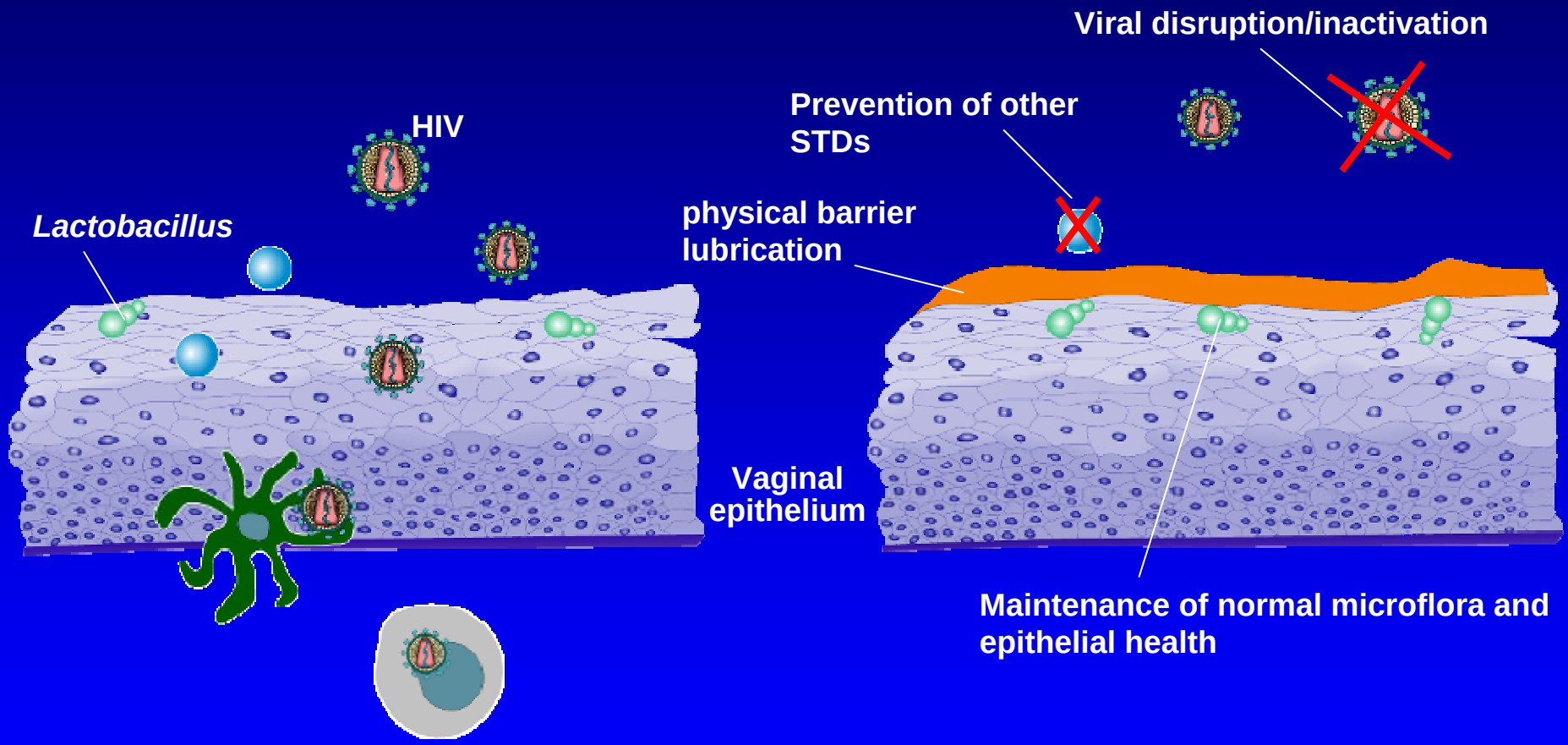
How Microbicides Work (1)



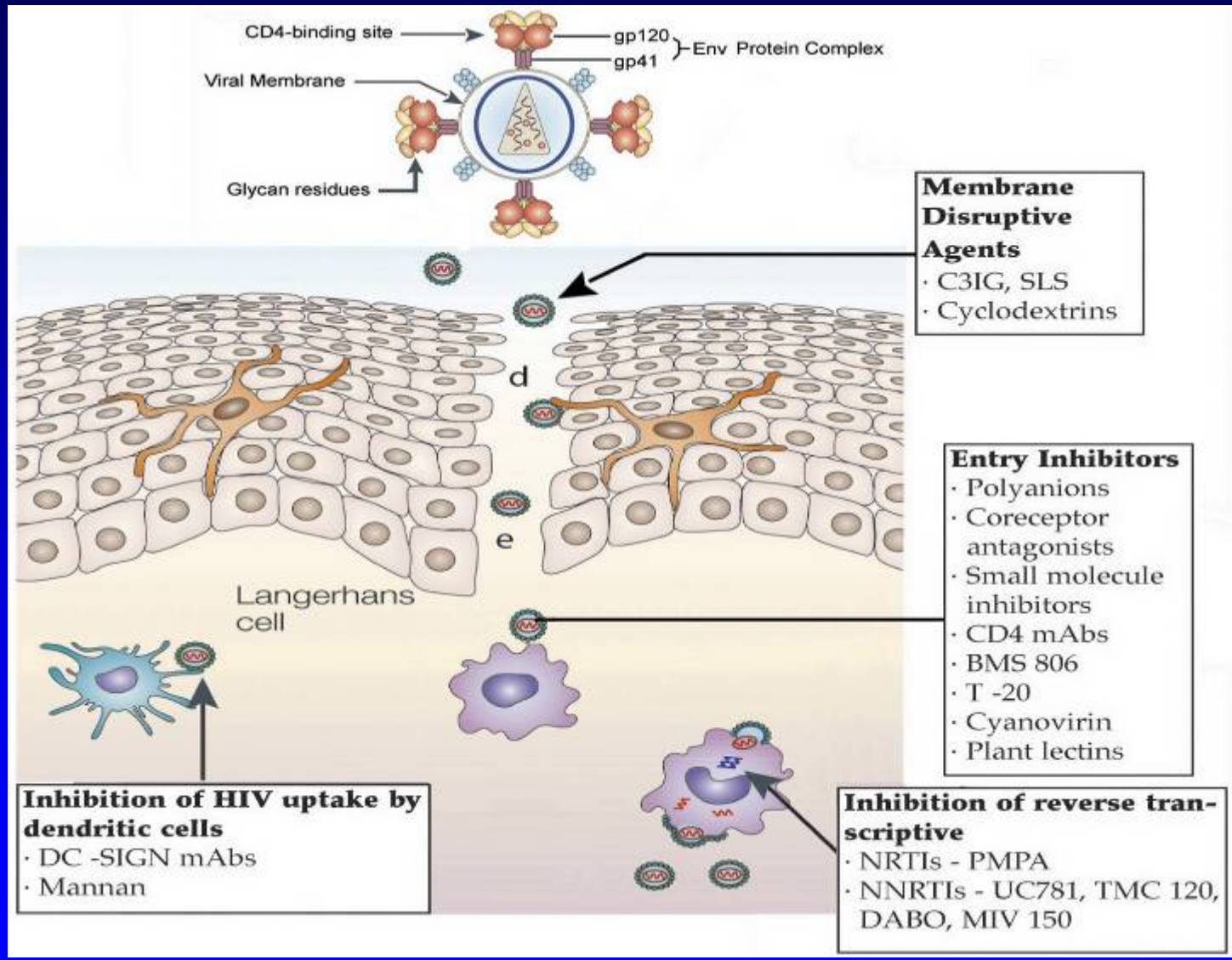
Courtesy: Zeda Rosenberg, PhD

How Microbicides Work (2)

Lumen

Epithelium

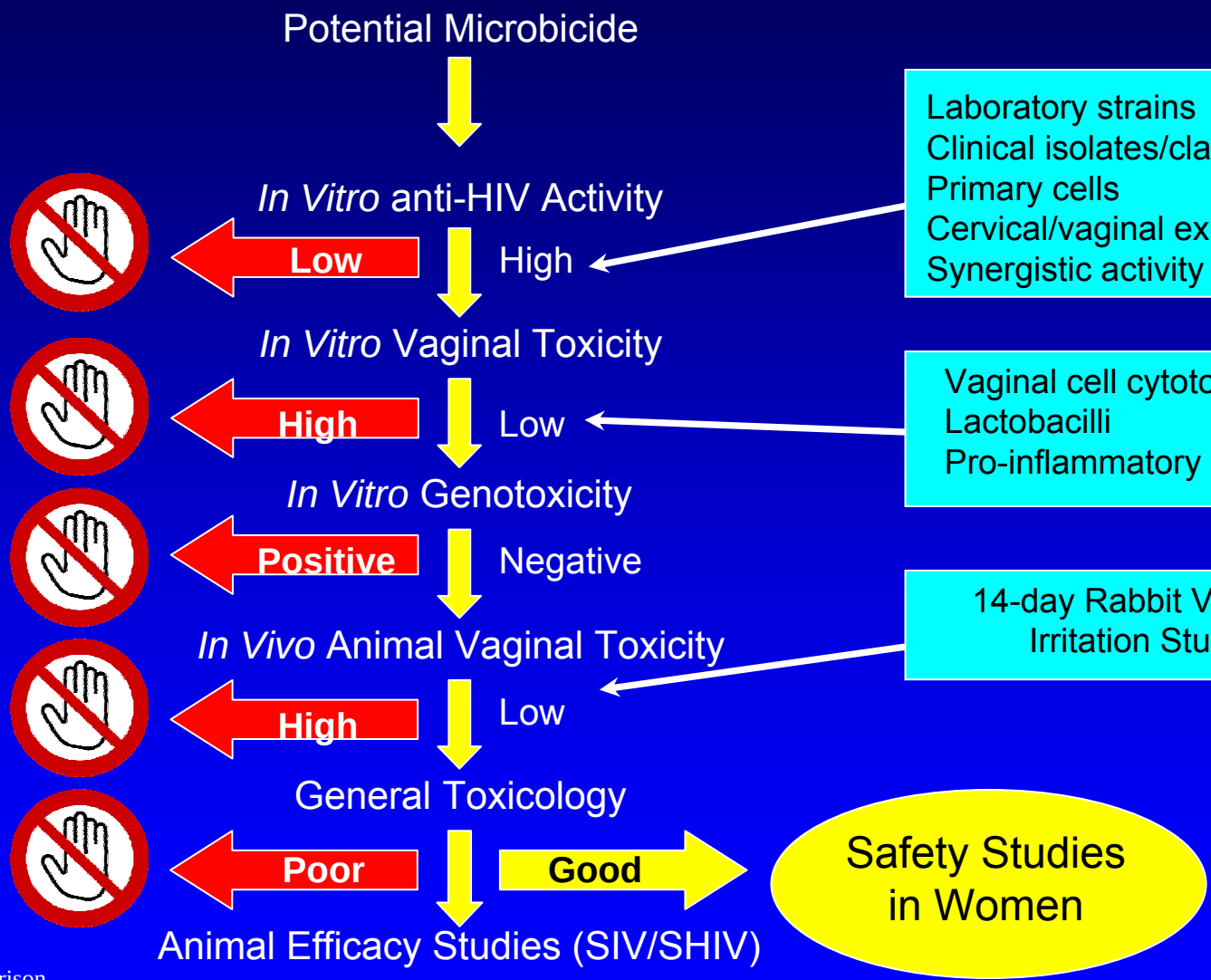
Stroma



Public Health Impact

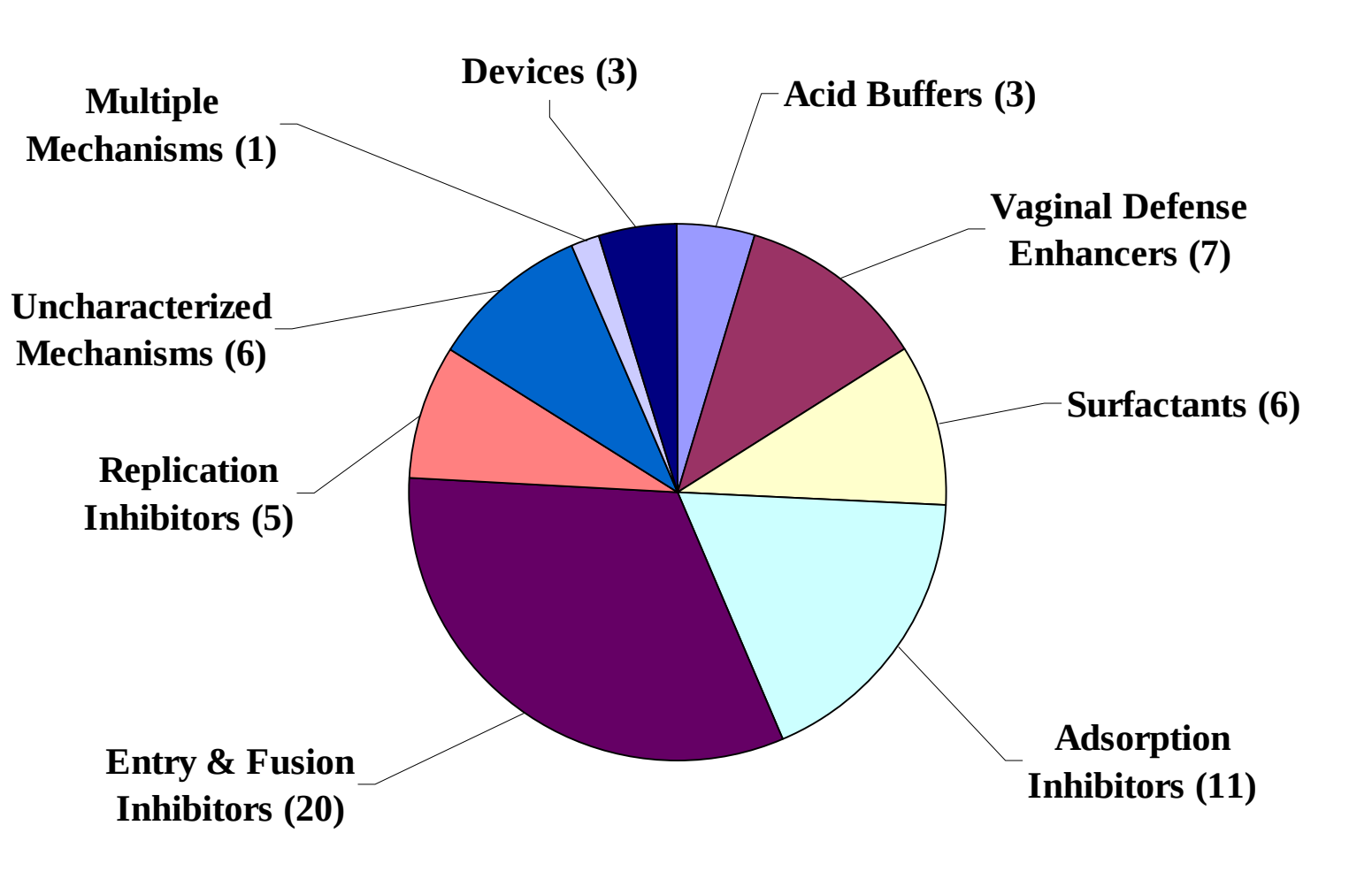
- Research showed that offering more prevention choices results in more sex acts being protected and higher levels of condom use
- Scientists at LSHTM calculated that **2.5 million infections** could be averted over 3 years if a microbicide that is 60% effective were used by 20% of women in half of all sex acts that do not involve a condom. This would save society **$2.7 billion** in health care costs and **$1 billion** in productivity gains.

Product Selection Algorithm



Courtesy: Polly Harrison

The Pipeline by Mechanism of Action



Courtesy: Polly Harrison

Scientific challenges
Basic science research (1)

- Cellular and molecular process at mucosal level not well understood → microenvironment
- Products with one mode of action → may have limited efficacy and potential for resistance
- products with uncharacterised mechanisms of action → cannot advance through the pipeline
- non-specific inhibition or blocking of receptor sites → potential toxicity
- combination products → which products?
- difficulties in formulation

Scientific challenges
Basic science research (2)

- Pre-clinical assessment was initially based on assays for contraceptive and therapeutic products
- need to develop in vivo testing assays, ex vivo and animal models relevant to microbicides
- different labs use different assay systems, thus difficulties in comparing results
- animal models do not capture relevant features of sexual transmission in humans
  - interpretation of animal data is complicated
  - viral stocks lose mucosal infectivity over time

Scientific challenges
Ideal formulation

- Maintenance of vaginal PH
- Chemical and physical stability
- Activity throughout shelf life
- odorless
- Non-irritating to genital epithelium
- Non-disruptive to innate vaginal microflora
- rapid and sustained release of active ingredient
- retention of active ingredients over time

Products in Clinical Research

Phase 1	Phase 1/2	Phase 2	Phase 2/2B	Phase 3
Acidform™/ Amphora™ + Diaphragm	Invisible Condom™	Human monoclonal antibodies (C2F5, C2G12, C4E10)	BufferGel™ PRO 2000 (0.5%)	Carraguard®
Carraguard®	Praneem Polyherbal	PRO 2000 (0.5%) Tenofovir/ PMPA		Cellulose sulfate
Cellulose acetate phthalate		Protected lactobacillus in combination w/ BZK		PRO 2000 (0.5%, 2%)
Cellulose acetate phthalate 13%		Tenofovir/ PMPA		Savvy™/C-31G
Cellulose sulfate + Diaphragm				
Lactin-V capsule				
Lime Juice				
Polystyrene sulfonate (PSS)				
TMC-120 Gel				
TMC-120 + Ring				
UC-781				
SPL7013				

Courtesy: Polly Harrison

Phase III Clinical trials Endpoints

- **primary endpoint for all is *HIV***
- **secondary endpoints:**
  - **BV *(BufferGel™, PRO 2000)***
  - **chlamydia *(BufferGel™, Cellulose sulfate, PRO 2000, Savvy™)***
  - **genital ulcer disease (*BufferGel™, PRO 2000)***
  - **gonorrhea *(BufferGel™, Cellulose sulfate, PRO 2000, Savvy™)***
  - **HSV-2 *(BufferGel™, PRO 2000)***
  - **syphilis *(BufferGel™, PRO 2000)***
  - **trichomoniasis *(BufferGel™, PRO 2000)***
- **3 are contraceptive:**
  - **BufferGel™, Cellulose sulfate, Savvy™**

Courtesy: Polly Harrison

Clinical Trial Phases

- Phase I
  - Initial trials in human, involving a few subjects
  - To evaluate the safety/acceptability of the product
- Phase II
  - Expanded safety/acceptability
  - To determine appropriate dosage
  - Proof-of-concept
  - IIa: efficacy and short term safety
  - IIb: efficacy, side effects and clinical toxicity
- Phase III
  - To determine efficacy
  - Large trial involving hundreds or thousands of people

Phase IIB/III TRIALS

- CONRAD Trial
  (Cellulose sulfate)
- HPTN 035 Trial
  (BufferGel & PRO 2000)
- MDP 301 Trial
  (0.5% & 2% PRO 2000)
- Carraguard Trial
  (Carrageenum)
- SAVVY Trial
  (C31G)

CONRAD TRIAL

- Phase III trial, to start in late 2004
- Randomized, triple-blind, placebo-controlled
- Two arms (6% cellulose sulfate and placebo)
- Sample size-2,574 HIV-negative women
- Sites
  - Chennai, India (one more site)
  - Cotonou, Benin
  - Bobo Dioulasso, Burkina Faso
  - Durban, South Africa
  - Kampala, Uganda

HPTN 035 TRIAL

- Phase II and IIb safety and effectiveness study
- Randomized, four-arm (2 active products, 2 control arms)
- Active arms-BufferGel and PRO 2000
- Control arms (placebo and No-gel arm)
- Sample size 3100 HIV-negative women
  - 800 women in the phase II portion
- Sites
  - Pune (India), Blantyare and Lilogwe (Malawi), Chitungwiza and Harare (Zimbabwe), Durban (South Africa), Lusaka (Zambia), Moshi (Tanzania)

MDP 301 TRIAL

- To start in 2005
- Phase III trial
- Sponsorship: UK MRC, DfID, Indevus
- Active products: 0.5% and 2% PRO 2000/5 gel
- Sample size-11,920 HIV-negative women
- Current Sites
  - Primary health care facilities in Durban, Johannesburg and Mtubatuba (South Africa)
  - Primary health care facilities in Mazabuka (Zambia)
  - Nakambala sugar estate (Mazabuka, Zambia)
  - HIV sero-discordant couples (Masaka, Uganda)
- Future sites?
  - Sex workers in Yaounde, Cameroon
  - Big Bend sugar estate, Swaziland

CARRAGUARD TRIAL

- Previously known as PC-515
- Phase III safety and effectiveness study
- Randomized, two-arms
- Products: Carraguard versus Methyl cellulose placebo
- Sample size 6,270 HIV-negative women
- Sites (all in South Africa)
  - Gugulethu (Cape Town)
  - Soshanguve (Pretoria)
  - Isipingo (Durban)
- Recruitment started in March 2004

SAVVY TRIAL

- Known as C31G
- Sponsorship: FHI, Biosyn/Cellegy & USAID
- Two Phase III trials in West Africa (Ghana and Nigeria)
- Products (C31G versus placebo)
- Sample size 4,400 HIV-negative women
- Sites
  - Kumasi and Accra (Ghana)
  - Lagos and Ibadan (Nigeria)
- Completion expected in mid-2006

Phase III Trials and US FDA

- Two years ago, US FDA was consulted by the HPTN
- Initial advice: 2 phase III trials at 2-sided 0.05 significance
- Disadvantages:
  - Large sample sizes of 16,000 people
  - Very expensive (20m-80m US dollars)
  - if initial study is significant, unethical to conduct the other
- Revised FDA position:
  - Equivalent of one and half trials (12,000 people)
  - Choice of control arms

Potential Mechanisms of effect of Microbicides and placebos

~ Antimicrobial effects

~ Physical Barrier effects

~ Lubrication effects

~ Other

Design to Address Multiple Mechanisms

Courtesy: Thomas Fleming, PhD

Choice of Control Arm

- Randomization
  - Ensures balance of factors related to individual risk and to patterns of condom and product use
  - Cannot balance changes of behaviour once study group has been revealed
- Require good masking (or blinding)
- Placebo-controlled double-blind trial
  - Preferred whenever feasible
  - Gives unbiased estimate of product effectiveness

Rationale for a No-Product Arm

- "Placebo" may have some activity
  - potential for activity due to low pH; preservatives; dilution; physical barrier
- Provides a comparator that reflects the "real world" effectiveness of the products (i.e., versus no gel at all).
  - takes into account potential changes in behavior associated with use or non-use of a microbicide product.
  - Incidence among women in no-product arm
- Allows for possibility or performing analyses of the potential effects of the placebo gel on HIV transmission.

No-product Arm?

- Essential when no placebo product available
  - Cannot rely on randomization and blinding to balance behaviours and condom use
  - Must collect high-quality, extensive and reliable data on product and condom use
- Analysis adjusted for reported behaviours
  - Expected misclassification dilutes estimated effect
- Two control groups?
  - Costly, potentially confusing,

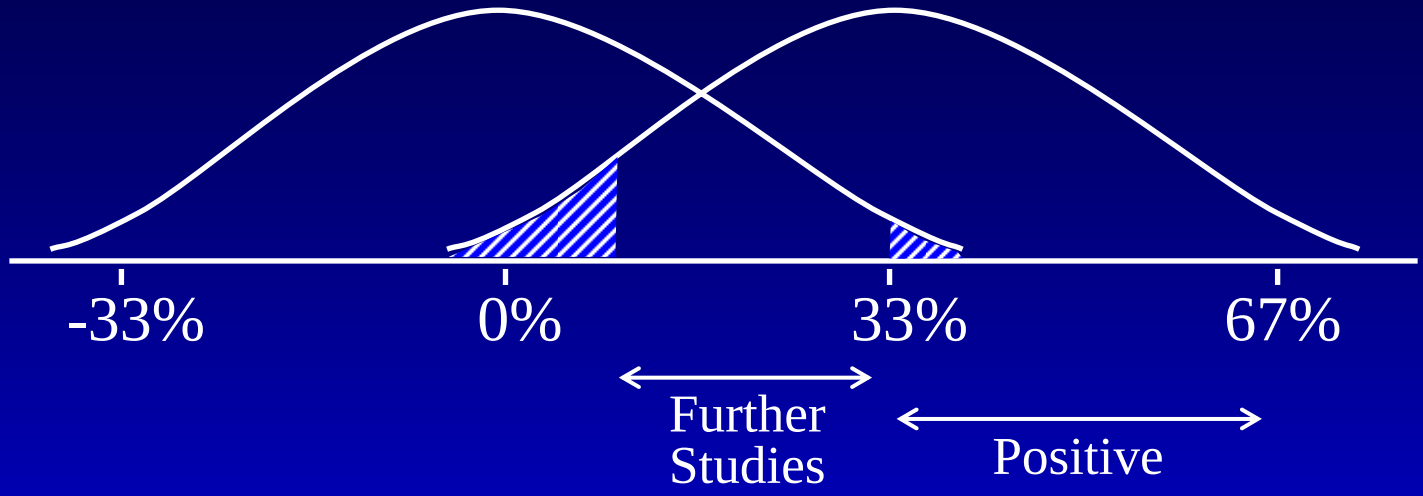
HIV incidence in Active gel vs placebo vs no-product arm

Placebo = active = No-product (2%, 2%, 2%)	-Active not effective -Placebo has no effect
Placebo > active No-product = active (3%, 2%, 2%)	-Active is effective? -Placebo could be harmful
Placebo = active No-product > active (2%, 2%, 3%)	-Active is effective -placebo appears protective -ingredient in active is inactive
Placebo > active No-product > active (3%, 2%, 3%)	-Active is effective -Placebo has no effect

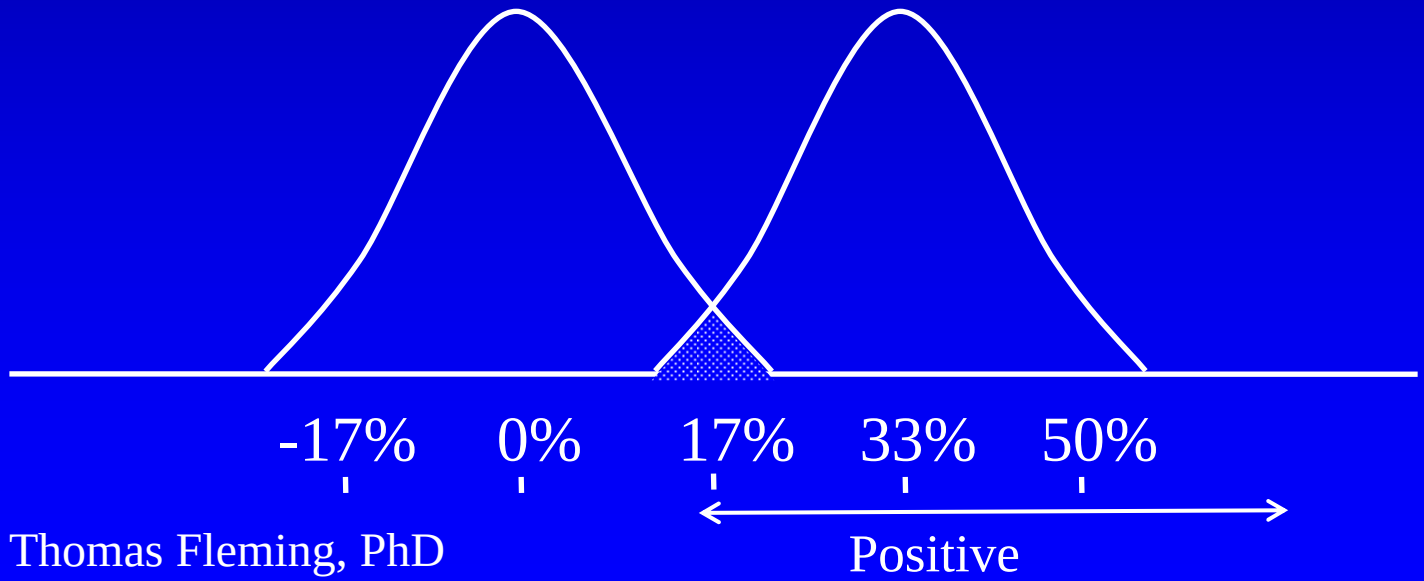
Strength of Evidence

- Two independent studies at $P < 0.05$
  - Desirable
  - Ethical Review Committees unlikely to approve
- Single study at $P < 0.0013$
  - equivalent to two independent $P < 0.05$ studies
- Single $P < 0.05$ study may not convince
- When would a second study be no longer ethical? $P < 0.05, 0.04, 0.03, 0.02, 0.01, \ldots?$

Intermediate Trial Design



Phase 3 Trial Design



Courtesy: Thomas Fleming, PhD

Rationale for Phase II Run-In

- “Traditional” Phase II studies - expanded safety and proof of concept
- No proven surrogates for either one at this time
- Sample sizes as large as for a Phase III
- HPTN 035 – 800 women will be followed under a phase II safety design with a DSMB review at the end of 3 months of follow-up
- Phase II participants contribute to the Phase III effectiveness analyses
- Study operations are maintained at the participating study sites throughout the Phase II/III transition

WHO Microbicide Project

- Main objective
  - –To accelerate the development and deployment of a safe, effective and accessible topical microbicide for use especially in developing countries
- Specific objectives
  - –To conduct clinical trials of promising candidate microbicides in countries with a major or emerging HIV epidemic
  - –To develop and/or strengthen the research capacity of clinical sites in developing countries to participate in microbicide research
  - –To facilitate discussions on ethics and derive an international consensus on the scientific basis for regulatory decisions on microbicides

Research Capacity Strengthening for Microbicide Research

- Rationale:
  - many more microbicide leads going into human trials
  - few centers with experience on clinical trials in developing countries where microbicides are urgently needed
  - ensure the highest standards in the conduct of microbicide trials
- Selection of clinical sites interested in microbicide research
- needs assessment on research capacity
- capacity strengthening-staff training, facility upgrades, equipment, data management,networking

Ethics and Regulatory Issues

- Facilitate discussions on ethics
  - ethical problems and challenges of microbicide research
- derive international consensus on prerequisites for microbicide research and registration
  - different views on competing requirements of urgency and proof of safety and effectiveness of microbicides
  - what safety and effectiveness data will national drug regulatory authorities need prior to registration of a microbicide in their country
  - Several international and regional meetings held in Switzerland, Botswana, India

Acknowledgements

Colleagues in microbicide R&D committed to accelerating access to novel products

United States Agency for International Development for financial support