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Microbicides in Human Trials: Making Successful Advances

2007

“If I had a magic bullet to accelerate something, it would be the microbicide.”

Bill Gates, August 2006

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Outline of Presentation

- What is a microbicide?
- How does HIV infect the vagina, etc?
- How does the vagina defend itself?
- How could a microbicide work? – Mechanisms
- Who is involved?
- What is the microbicide development process?
- ...



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Outline of Presentation, cont

- What is USAID's microbicide program?
- Where are we, and what are the prospects?
- What's in the microbicide pipeline?
- What are the key issues?
- Discussion



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What is a Microbicide?

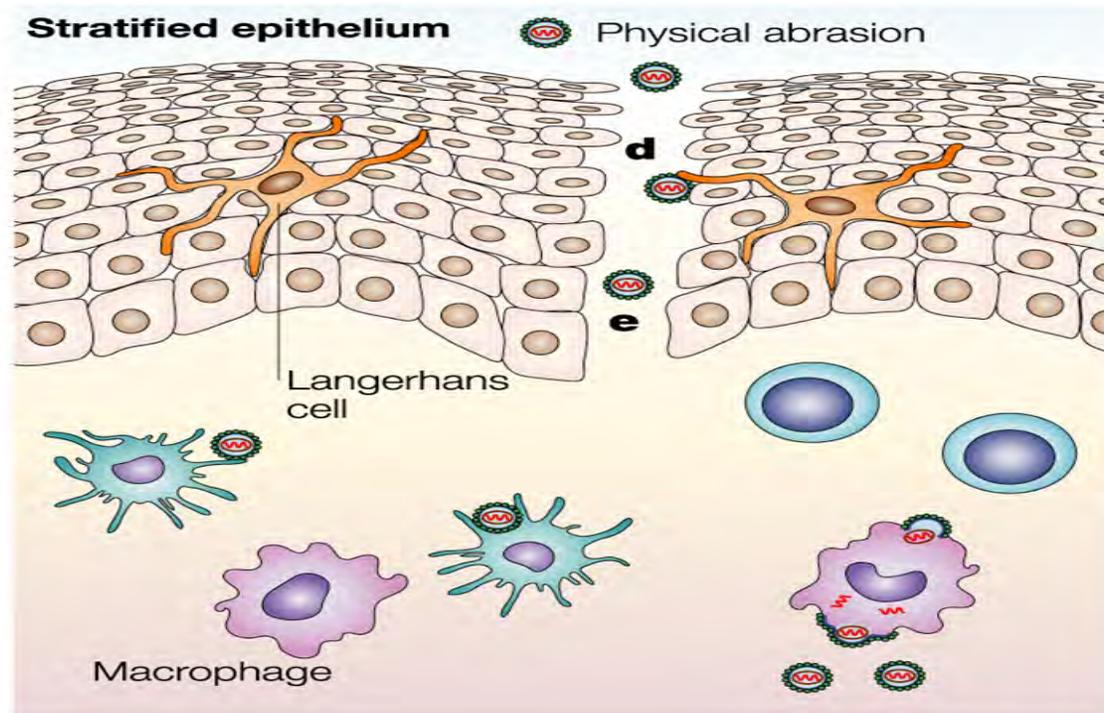
A “microbicide” is a product that will prevent sexual transmission of HIV and potentially other STIs, and is likely to be applied topically to the vagina as a gel, cream, film, suppository, or vaginal ring

Why a Microbicide?



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How does HIV infect the vagina, etc?



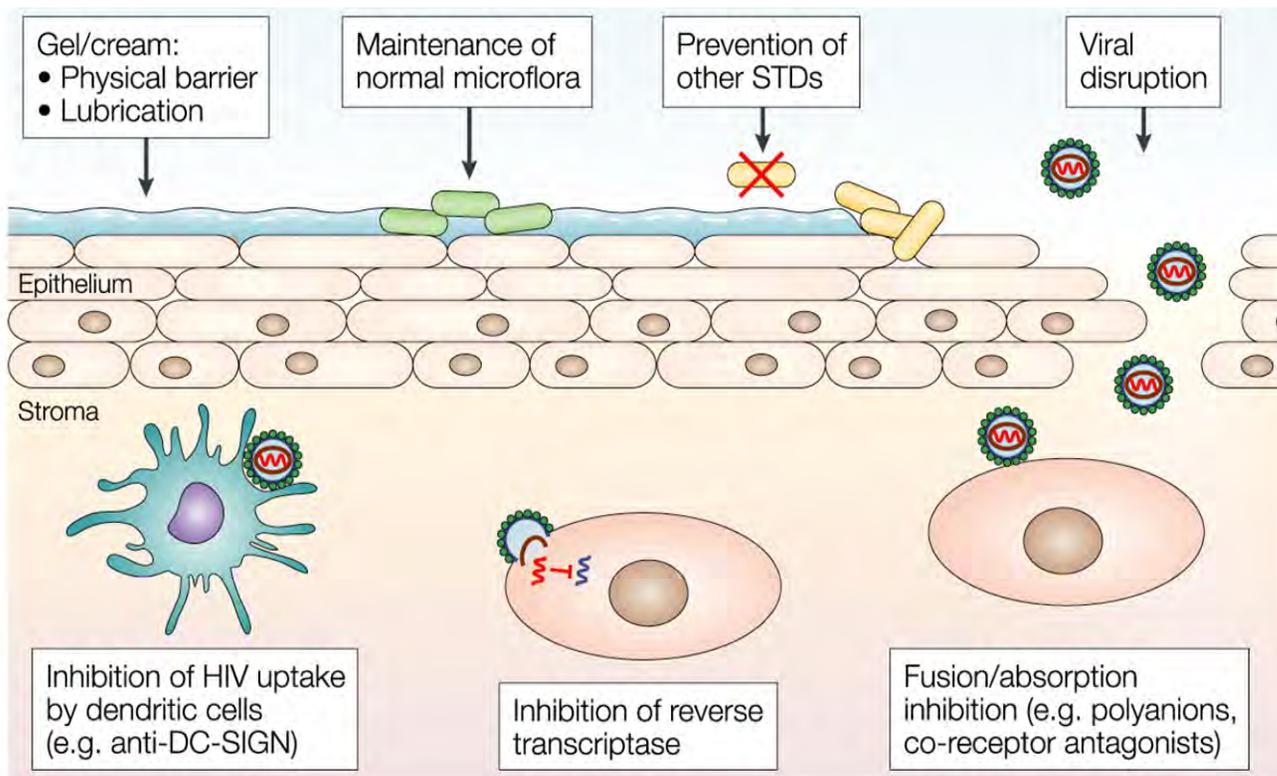
Nature Reviews | Microbiology

Source: R. Shattock, St. George's Hospital Medical School



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How could a microbicide work?



Nature Reviews | **Microbiology**

Source: R. Shattock, St. George's Hospital Medical School



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Characteristics of an Ideal Microbicide

- Multiple mechanisms of inhibiting HIV infection
- Effective against multiple STIs and HIV
- Maintains the integrity of vaginal epithelium and normal microflora
- Non-inflammatory
- Ease of use and acceptability
- Affordable



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Microbicide Funding and Partners

<u>USAID Obligation</u>	FY01	FY02	FY03	FY04	FY05	FY06	FY07
TOTAL (in thousands)	12000	15000	17891	21870	29760	39600	39600

- **USAID Primary Partners**

- CONRAD
- Family Health International
- PATH
- WHO
- Various sub-recipients...
- Global Campaign for Microbicides
- Population Council
- International Partnership for Microbicides
- Centers for Disease Control

- **Other Funding Organizations**



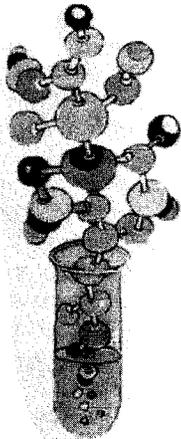
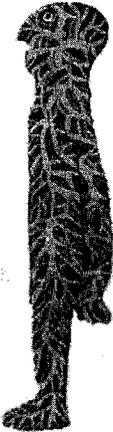
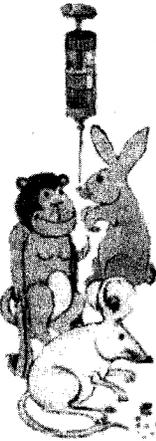
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Microbicide Development Process

Pre-Clinical

Phase I

Phase II

10 years	1-2 years	1-2 years	2 years	1-2 years
				
Years of laboratory testing and screening of many compounds may result in a promising contraceptive drug.	Any possible toxicity of the compound is thoroughly checked and its pharmacology is assessed in animals.	Lack of toxicity and minimum effective dose are assessed in groups of 10 to 20 volunteers in different countries.	Long-term toxicity studies begin in animals as well as studies on reproduction, mutagenicity and carcinogenicity.	The first check of efficacy in humans involves up to a few hundred volunteers; acceptability studies begin.

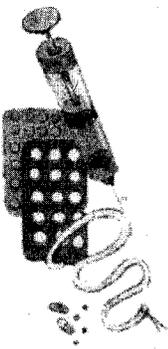
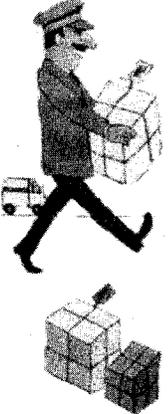


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Microbicide Development Process, cont

Phase III

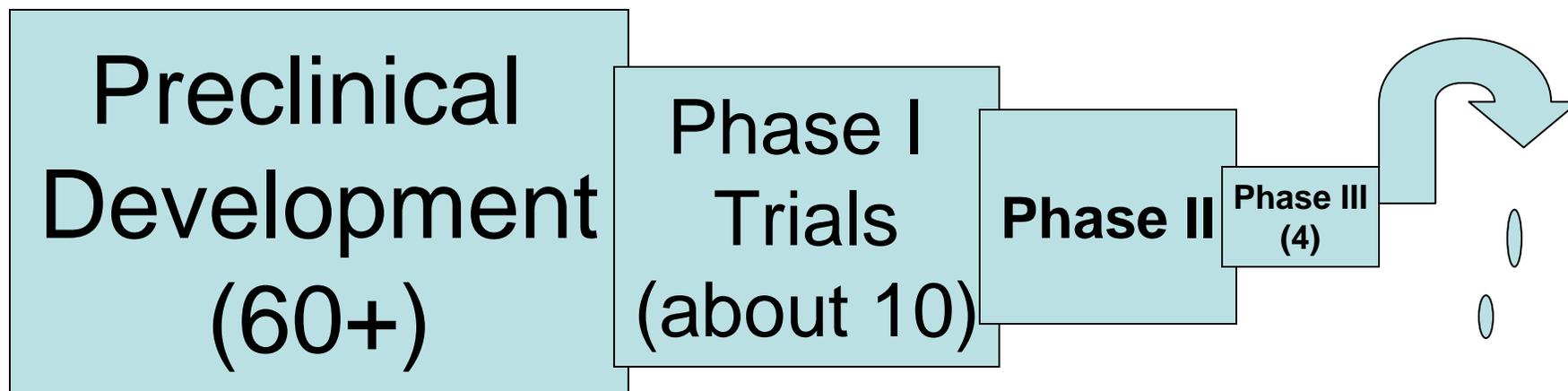
Phase IV

2-3 years	1 years	1-3 years	Indefinitely	Indefinitely
				
<p>Large-scale studies (1,000 subjects) start, lasting up to one year in various countries; acceptability studies continue.</p>	<p>Final arrangements are made for manufacture of the new contraceptive, and for its appropriate packaging.</p>	<p>All clinical and animal data are transmitted to national drug regulatory agencies, whose approval will be essential.</p>	<p>The finished product is supplied to family planning clinics, whose staff are trained in its delivery.</p>	<p>The drug becomes freely available: long-term surveillance guards against any rare adverse risks to health.</p>



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Microbicide Development Pipeline



(Same as for other drugs)



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USAID Microbicide Program, 2007: Moving Forward

- **Preclinical Testing** – screening and characterizing in vitro and in animals
- **Clinical Studies** – safety, coverage, contraceptive effects, effectiveness against HIV (*about 75% of FY05 and FY06 funds have supported phase III clinical trials*)
- **Capacity Building** – identifying, equipping, training new clinical sites
- **Ethics** - informed consent, community preparedness, *involvement*, and benefit
- **Access** - policy development, licensing, manufacturing, product introduction, delivery, and provision



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Where are we? What are the prospects?

Phase III clinical studies with USAID support

- *Carraguard* – finished, results imminent
- *Savvy* - closed
- *Cellulose sulfate* - closed
- *Buffergel* - ongoing
- *Tenofovir* - ongoing
- (*others* ongoing, partially supported)

Progress

Next generation leads



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What happened?

- **SAVVY** (surfactant) – Trial was closed due to futility at both sites. No harm was observed.
- **Cellulose Sulfate** (entry inhibitor) – Trial was closed due to potential harm in the product arm. Reasons are currently unknown, but further testing and analysis are ongoing.



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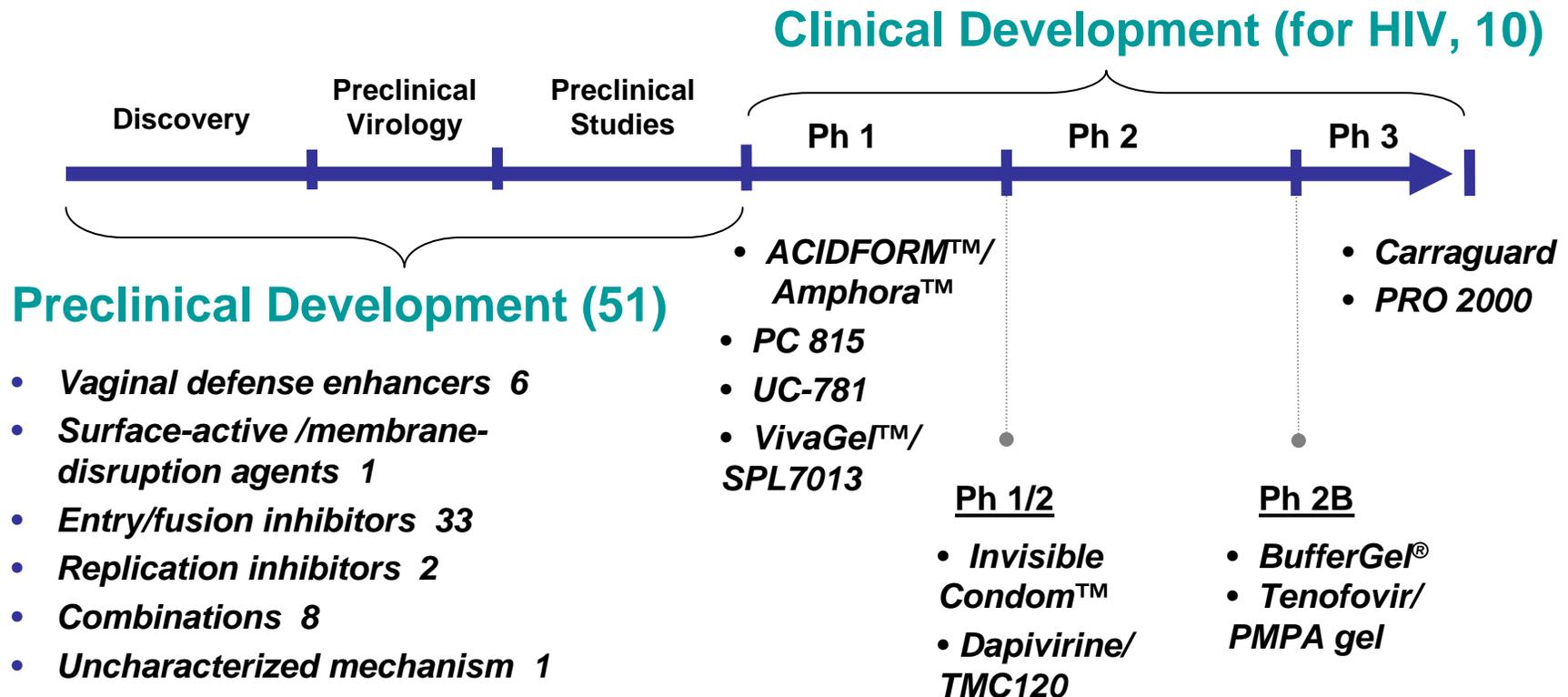
Points about Trial Closures

- **All candidate products must pass a host of preclinical studies and smaller Phase 1 safety studies in humans before they are tested in larger Phase 3 clinical trials involving thousands of participants. This rigorous scientific process is mandated by the FDA for product approval.**
- **The failure of some clinical trials is part of the R&D process; for every successful trial, there are many that fail for one reason or another.**
- **Until we have “proof of concept” for an effective microbicide in humans, we will have no idea which of the many preclinical tests in cells, tissues and animals are most reliable as predictors of effectiveness. Finding predictive tests will save precious resources, time, and lives.**
- **Most importantly, although we critically need a product that women can use to protect themselves against HIV, we must err on the side of safety in the pursuit of an effective microbicide.**



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Microbicide Pipeline – mid 2007, entire field



Source: Alliance for Microbicide Development



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Key Issues in Microbicide Development: Principal obstacles, strategic gaps, emerging issues

- 1. No proof of concept** - microbicidal prevention of HIV not shown yet
- 2. Preclinical testing** – determining “best in class” product to move into clinical trials is not definitive
- 3. Difficulty of phase III testing** – high cost, delays, number of feasible clinical sites with technical capacity and high incidence, difficult production scale-up, pregnancy rates, protocol compliance – These are all severely limiting
- 4. Ethical concerns** - achieving informed consent, community involvement and benefit, adequate care and treatment during and after trials, future access to products – are great challenges



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Key Issues, cont.

5. **Coordination of efforts** - multiple agencies and funding flows need to be optimized – in US and internationally
6. **Product introduction** – issues / barriers in policy, manufacturing, distribution, public health messages, cost, service delivery
7. **Regulatory requirements** – need clarification and standardization nationally and internationally
8. **Next generation products** – safe, effective, and affordable new agents and combinations still needed, with optimal formulations for coverage, duration, stability, and acceptability, including alternative use regimens
9. **Resistance** – concern regarding continuous use of ARVs and development of resistance



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Looking Ahead:

Continuing advances across R&D spectrum

- **Scale-up Strategy** – Once a particular microbicide is shown to be effective, a new phase begins.
 - Manufacturing, distribution, and delivery logistics
 - Getting product to those with greatest need - ensuring access
 - How to ultimately market? Is there a niche in Developed Countries?
- **Appropriate place in a HIV prevention hierarchy?**
- **Development of more effective microbicides**
 - Enhanced formulations and delivery mechanisms
 - Effective against multiple STDs
 - Novel/multiple mechanisms of action



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Additional Information

- **Reports to Congress** - Health-Related R & D Activities at USAID, June 2006 *
 - **OHA Brief** – Microbicides, 2006 *
 - **Info Reports** – Microbicides: New potential for protection, January 2005 *
 - **Microbicide Quarterly** – Alliance for Microbicide Development *
 - **Mini-U Presentation** – Handout, 2007
 - **The Future of HIV Prevention: Prospects for an Effective Anti-HIV Microbicide** – Handout, 2007
 - **Reference List** - Handout
- * See Reference List for URL



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Discussion

- Questions
- Suggestions
- Comments
- Requests
- Further information
- Pearls