Microbicides II
Clinical Science

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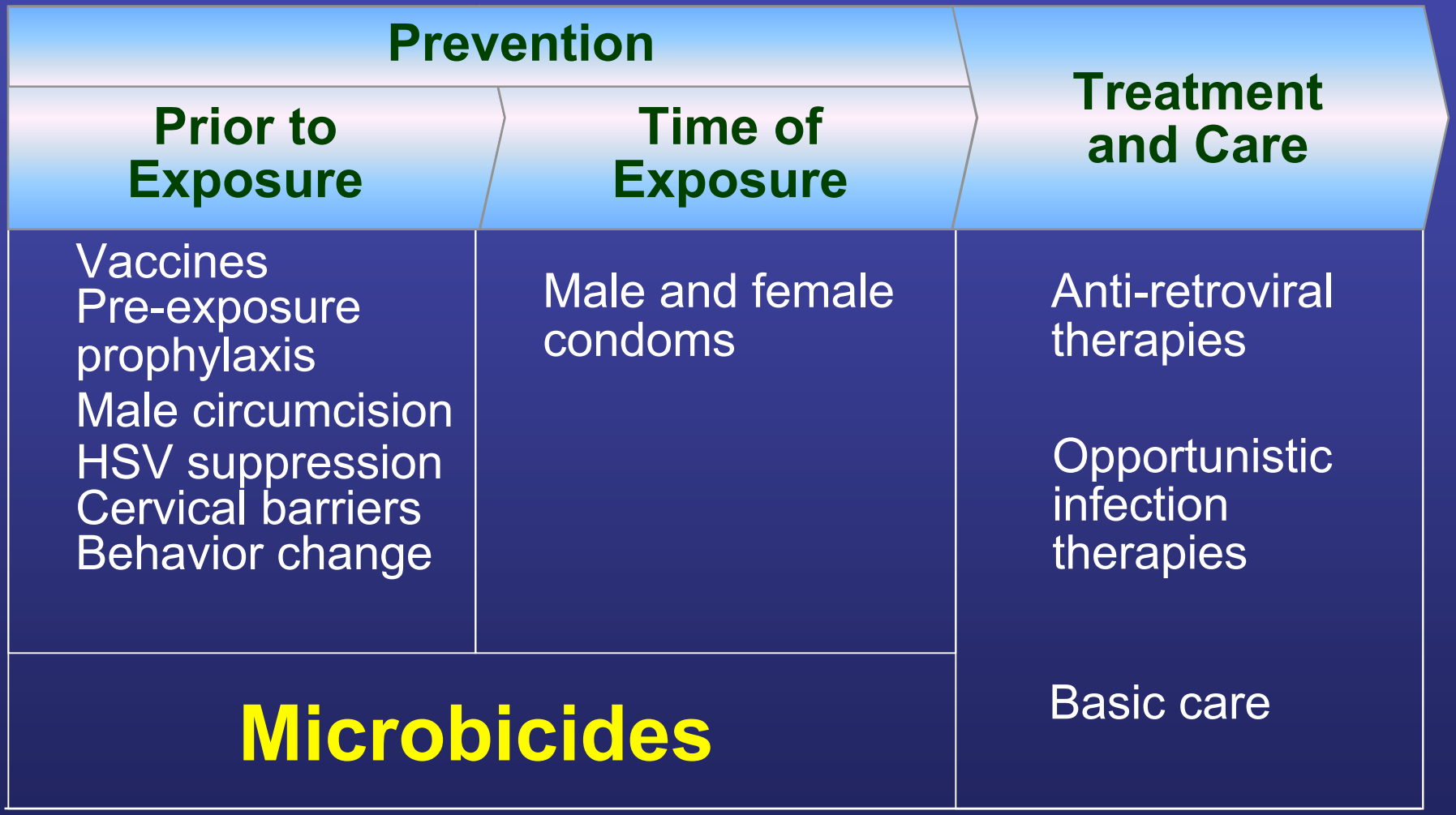
Comprehensive Approaches to HIV/AIDS



What about Microbicides?

- Substances that can substantially prevent or reduce transmission of HIV when applied to the vagina, rectum, or penis
- Could potentially be made in many forms:
  - gel or cream
  - sponge
  - film
  - lubricant
  - suppository
  - ring or diaphragm

Any microbicide must be "safe, effective, cheap, user-friendly"

- **Safe** - must have no localized toxicity, including no damage to the vaginal epithelium during sustained, repetitive use, with no localized inflammatory responses.
- **Effective** - must have a significant degree of efficacy in routine use.
- **Cheap** - pricing strategy must optimize distribution and availability.
- **User-friendly** - must be compatible with use during sex and must be used both consistently and reliably in a real life setting.

Some Microbicides in the Pipeline

	PreClinical	Safety	Efficacy
Entry/fusion inhibitors	Cyanovirin Plant lectins BMS 806 Coreceptor antagonists gp41 inhibitors New polyanions (K5-N OS)	SPL7013 (dendrimer) CAP Polystyrene sulfonate	PRO2000 Carraguard Cellulose sulfate Buffer gel
NRTI		PMPA	
NNRTI	DABO	UC781 TMC 120 MIV 150	
Membrane-disruptive agents			C31G
Unclassified	Drug- expressing lactobacilli SiRNA		
Combinations	NRTI/NNRTI NRTI/Polyanion NNRTI/Polyanion NRTI/NNRTI/Polyanion CCR5-inhibitors/BMS806/C52L		

What would it take to demonstrate efficacy?

- Verified use of product during every act of unprotected intercourse.
- High incidence of HIV-1 infection in control arms to provide sufficient statistical power.

Human behavior and clinical trial ethics mean that efficacy may only ever be evaluated in animal models

So what would it take to demonstrate effectiveness

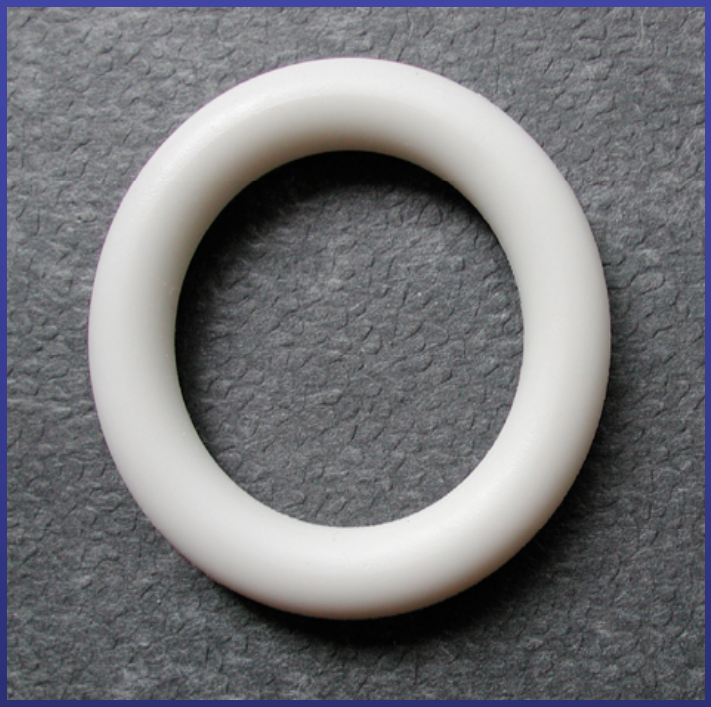
- **Large Phase III trials (7-12K women)**
- **Prevention of an infection with relatively low incidence after counseling about safe sex practices**
- **A high level of compliance by those not, or infrequently, using condoms**
- **Commitment of a vast majority of resources in late stage development without any prior proof of concept**

Therefore only limited candidates can be taken into trials

Reducing existing trial burdens

- **Increase clinical trial capacity**
- **Establishing better methods for incidence prediction**
- **Develop novel trial designs that reduces compliance burden**
  - **Better compliance indicators**
  - **Once a day gels**
  - **Sustained release technology**
- **Early analysis for futility (lack of incidence, lack of efficacy)**

How will they be used



	Coitally dependent gel	Once-a-day gel	30 day ring	90 day ring
Units/year	100	365	12	4
$ cost/unit	0.6	0.6	5-10	5-10
$ cost/year	60	219	60-120	20-40

(based on phase 3 unit costs - source: IPM)

Why aren't more products moving into clinical trails?

- **Relatively few viable concepts**
  - **Polyanions, acid buffers and surfactants (coitally dependent)**
  - **Anti-retroviral drugs**
  - **Entry inhibitors**
- **No major queue for for phase III trials**
- **Current trials due to finish in 2007-9**
- **Product Feasibility studies may question plausibility of different approach**
  - Production costs (cost and ease of synthesis/scale up)
  - Formulation (stability, compatibility, delivery technology)
- **Phase I/II trials may raise issues of safety and or acceptability**

Further Challenges

- ***Strategies to deal with partially effective products*** *(increased trial complexity)*
- ***Strategies to deal with multiple failures/adverse events*** *(fatigue/hostility - participants, investigators, activists, funders, politicians)*
- ***Integrating with other prevention strategies*** *(Cervical barriers, circumcision, PreP, HSV Suppression, vaccines)*

Key principles for Clinical Trials:

- Community engagement & communications
- Informed consent
- HIV risk-reduction
- STI diagnosis and treatment
- Referral for individuals who test HIV-positive at screening
- Provision of treatment for trial participants (standards of care)
- Services for study staff
- Treatment and compensation for physical harm
- Post-trial access

The tipping point: What would it take to make a difference

- What level of uptake and compliance would be required to have an impact on incidence rates?
- What level of effectiveness would encourage use? How would perceived risk influence uptake?
- How important is bidirectional protection or rectal protection?
- How attractive is an HIV only product (other STIs, contraception, genital hygiene, sexual pleasure)
- What makes for effective product promotion: fear or desirability?
- What makes a prevention product desirable?
- What target groups would have a major impact on transmission networks
- How to introduce into 15-24 age group

Potential distortions from increased funding

- ***Increasing the width but not the quality of pipeline development***
- ***Increasing donor competition rather than cooperation (products, sites, investigators)***
- ***Over development of trial capacity***
- ***Pressure to perform clinical trials with products that may lack scientific credibility or duplicate effort ("me to products")***

Rational and effective drug development continues to be dependent upon effective triage of multiple compounds and concepts

Potential advantages from increased funding

- ***Rational product development and selection***
- ***Pipeline acceleration (different concepts and strategies)***
- ***Filling of priority gaps in Microbicide development (MDS)***

Promotion of critical pathways to proof of concept