International Partnership for Microbicides

Female-Initiated Prevention: State of the Art

Dr. Zeda F. Rosenberg

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Women's Vulnerability to HIV

- Biological: male-to-female transmission is easier than female-to-male
- Economic: financial dependence on male partners
- Cultural: early marriage, intergenerational sex and marital infidelity
- Sexual exploitation and violence

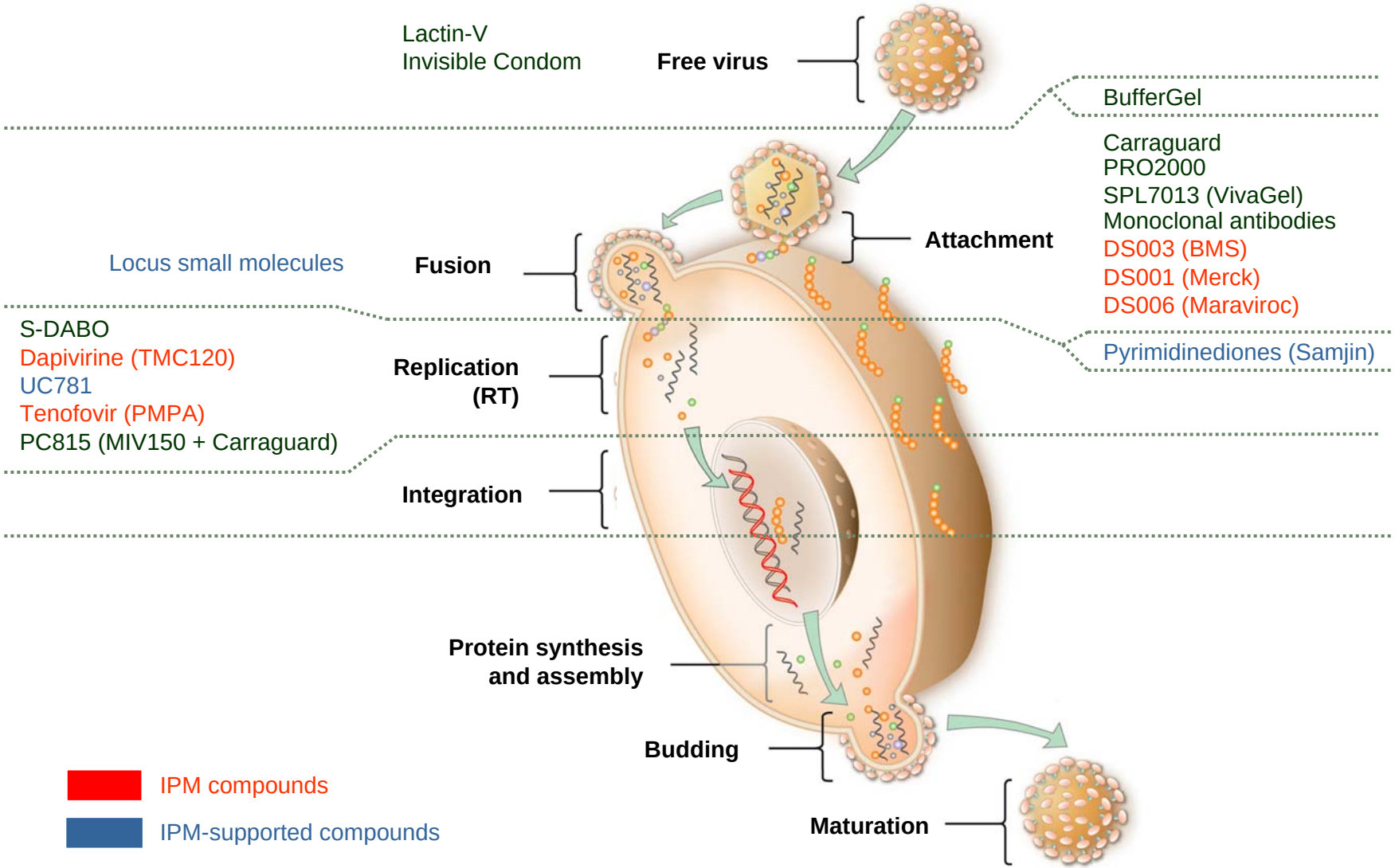
Female Barrier Methods

- Female condoms
  - Contraception and STI prevention
  - High initial acceptability
  - Large programs in Brazil, Ghana, Namibia, South Africa, Zambia
  - Slow uptake
- Diaphragms
  - Contraceptive; STI prevention under study
  - Use currently low—0.3% of reproductive-age women in the US

Microbicides

- Vaginal product to prevent or reduce HIV transmission
- Could potentially be delivered in many forms
- A woman could initiate use independently to protect her health
- Ideally safe, effective, low-cost and user-friendly

Microbicides in Product Development



Early-Generation Microbicides

- Non-specifically block HIV from interacting with target cells
- In most advanced stage of clinical trials (Carraguard, PRO2000, BufferGel)
- Partial, low or no effectiveness
- Short-acting (used near time of sex)

Next-Generation Microbicides

- Based on antiretroviral drugs (ARVs) with known efficacy in humans
- Long half-life or can be formulated for sustained release
- Products may contain a combination of drugs that act at different stages of HIV replication

Delivery: Offering Choices

- Semisolids/Solids
  - Gels
  - Vaginal Tablets
  - Films
  - Emulsions
- Devices
  - Vaginal Ring
  - Sponge
  - Diaphragm

Product Acceptability Studies

- Semisolid formulations
  - Market research study in Kenya, South Africa and Zambia
  - Helped define what women want in a gel
  - Supports acceptability of a daily product
- Vaginal ring (placebo)
  - Study launched in February 2007
  - 4 sites in South Africa, Tanzania and Kenya
  - Do women find the ring acceptable?
  - Collect early safety data

Microbicide Development

- Formulation
- Pre-clinical testing
- Safety studies (Phase I)
- Expanded safety studies (Phase II)
- Efficacy studies (Phase III)
- Post-licensure studies

Safety Studies (Phases I/II)

- Focus on safety
  - Damage to vaginal epithelium
  - Colposcopy
  - Systemic toxicity
- Also address acceptability
- Healthy female volunteers
  - Small sample size (10s-100s participants)
  - Sexually abstinent
  - Sexually active

Lessons from Safety Studies

- Little epithelial damage
- More use of a product $\Rightarrow$ more irritation, ulceration (especially for detergent-like agents)
- Trials are not large enough to measure ultimate safety concern – potential enhancement of HIV infection

Efficacy Studies (Phase III)

- Randomized and placebo-controlled
- Study population
  - Thousands of volunteers
  - High background HIV incidence
  - Low use of condoms
  - Good adherence to product use
  - Low loss to follow-up
  - Low level of rectal sex and IV drug use

Estimating HIV Incidence

Building Site Capacity

- Community education and engagement
- Infrastructure:
  - Physical facilities plus medical, telecom, transport, administrative equipment
- Referral networks for medical care/support
- Staff & training:
  - 15-20 staff per site: doctors, nurses, counselors, community workers, data entry, management, admin
  - GCP, lab and study-specific training

Efficacy Study Challenges

- Limited clinical trial capacity
- HIV incidence lowered in trial settings ⇒ relatively rare endpoints
- Requires high level of adherence
- Unclear regulatory pathways

Ethics of HIV-Prevention Trials

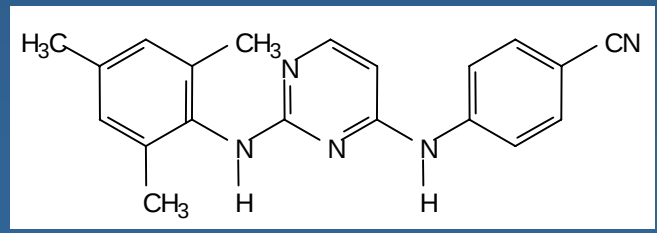
- Informed consent
- Family planning counseling
- Pre/Post HIV-testing counseling
- Referrals for women becoming pregnant
- Referrals for those screening HIV positive
- Treatment of STIs
- Treatment of those who become HIV-infected during the trial
- Treatment of adverse reactions
- Resistance

Topical Tenofovir

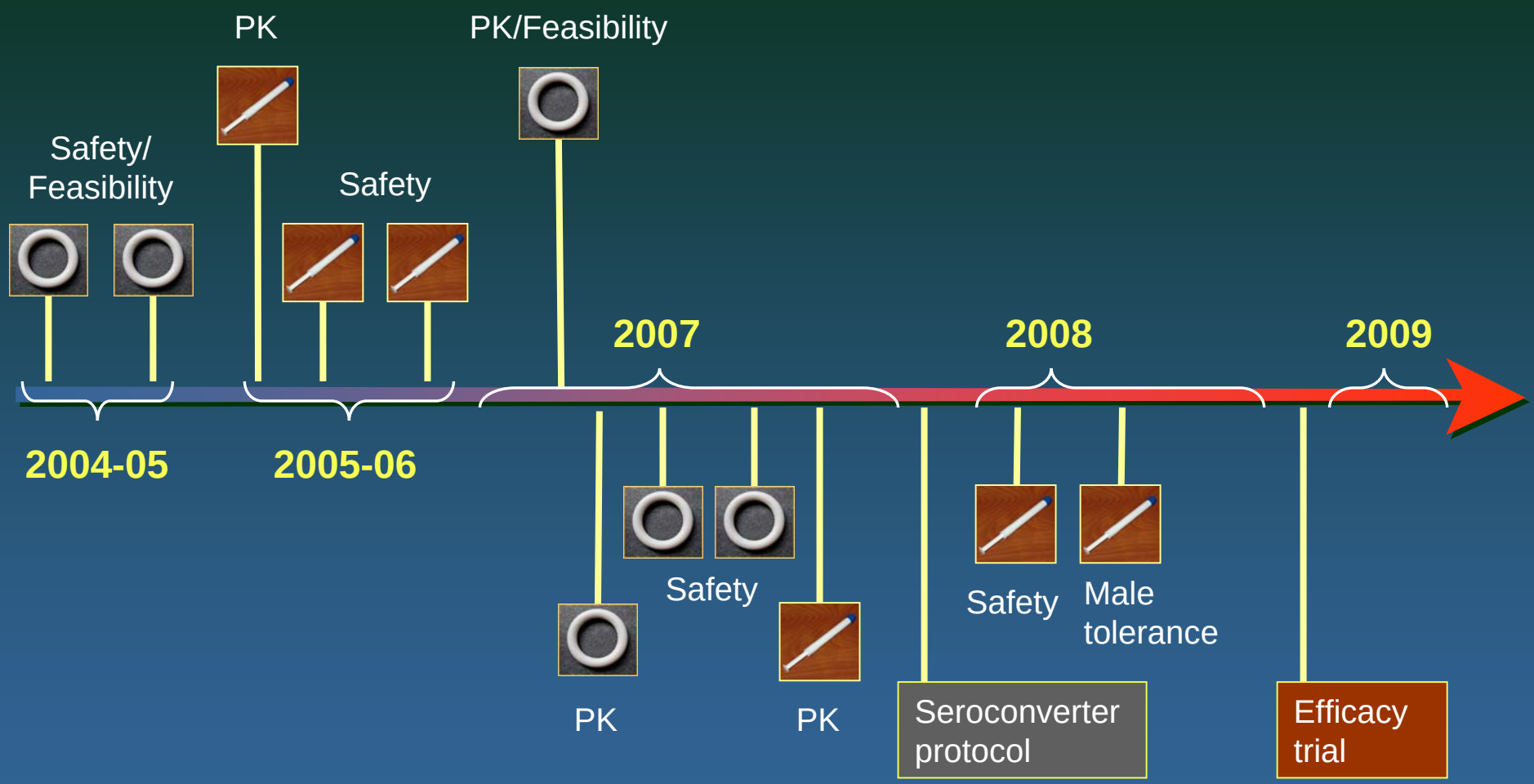
- NRTI developed by Gilead
- HPTN 050 Phase I Safety Study completed
  - Well tolerated
  - Low serum levels in 56% of subjects
- HPTN 059 Phase II Safety Study ongoing in US and India
- PK study of 1% tenofovir gel to determine systemic and local tissue levels
- Caprisa 004 Phase IIB in South Africa

Dapivirine

- NNRTI developed by Tibotec/J&J
- 11 clinical studies conducted as therapeutic
- Highly potent ARV
- Low cytotoxicity, non-mutagenic, non-teratogenic
- Easily manufactured, cheap
- Stable drug substance
- IP clarity
- Multiple dosage forms



IPM Clinical Studies of Dapivirine



Studies in Belgium, Kenya, Rwanda, South Africa, Tanzania