

Activity 1: Dual-Protection Technologies

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David R. Friend, Ph.D.
Director, Product Development



Activity 1

Dual-Protection Technologies

1. **Intravaginal Rings (IVRs) – 90-day sustained release**
 - ▶ Anti-HIV/Contraception
 - ▶ Anti-HIV/Anti-HSV
2. **Barrier Device + Reverse Transcriptase Inhibitor (RTI)**
 - ▶ Modified PATH Woman's Condom
 - ▶ Cervical Cap
 - ▶ SILCs
3. **Dual activity gels**
 - ▶ Anti-HIV/Contraception

The Need for Dual-Protection

A significant number of women, especially in developing countries, need protection against sexually transmitted diseases, in particular HIV/AIDS, and family planning methods to prevent unwanted pregnancies.

◆ People living with HIV/AIDS Global estimates (UNAIDS - 2009)

▶ Total number of people infected.....	33.4 million
▶ New HIV infections in 2008.....	2.7 million
▶ Deaths due to HIV/AIDS in 2008.....	2.0 million
▶ Number of infected people in Sub-Saharan Africa.....	22.4 million
▶ Proportion of infected women	60%
▶ Number of infected people in Latin America.....	1.2 million
▶ Estimated number by 2015*	3.5 million
▶ Sexual transmission accounts for	59-90%

* Science, 2006

The State of the World Population

- ◆ 6.5 billion (2005) → 9.1 billion (2050)
- ◆ Population growing fastest where needs are greatest
- ◆ 76 million unwanted births/yr and 50 million abortions
- ◆ Maternal mortality: 536,000/yr
- ◆ The 49 least-developed countries will triple in size
- ◆ In many of these countries, the HIV/AIDS pandemic is intricately intertwined with overpopulation, poverty, malnutrition, and gender inequality

Challenges and Opportunities

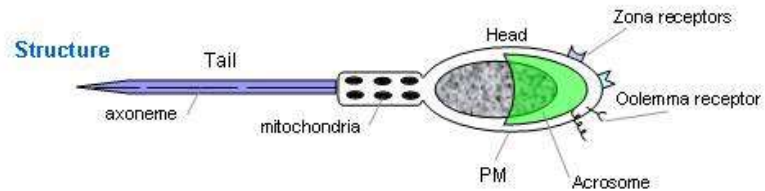
- ◆ Urgent need to develop options that allow women to protect themselves against sexually transmitted diseases, especially HIV
- ◆ Most of these women would also benefit from having a method helping them prevent or delay pregnancy
- ◆ One of these options is **Dual-Protection** (contraceptive and microbicidal) methods
- ◆ Also referred to as Multipurpose Technologies

Main Strategies for Topical Microbicidal Contraceptive Combinations

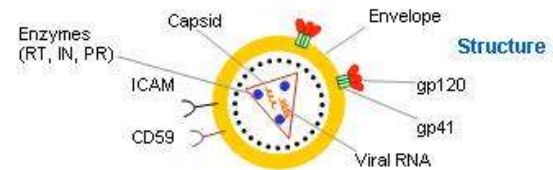
- ◆ Two drugs with different targets and mechanisms of action (MOAs)
- ◆ One drug with contraceptive and microbicidal properties (dual-activity compounds)
- ◆ Drug-device combinations with two or more MOAs
- ◆ Exploit commonalities between HIV infection and fertilization

Commonalities between HIV Infection and Fertilization: Development of Contraceptive Microbicides Dual Protection Products

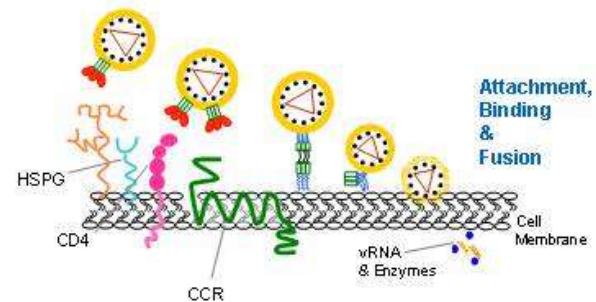
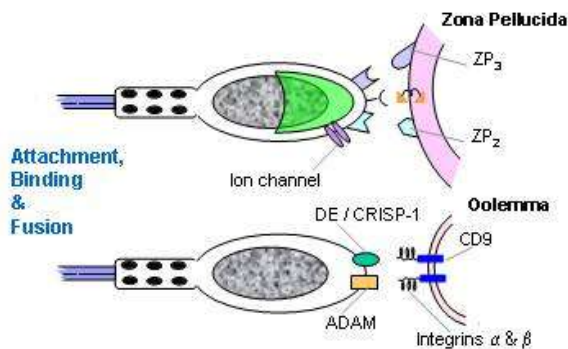
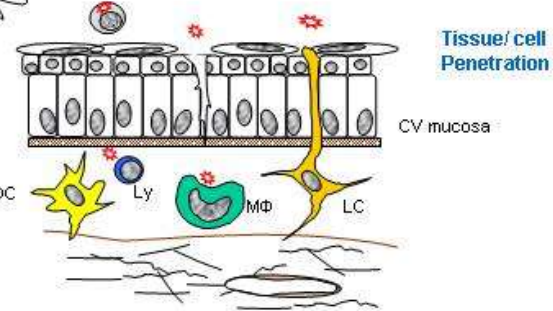
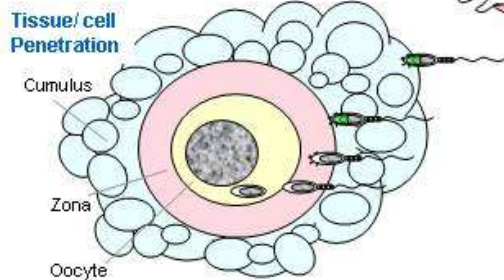
Sperm - Egg Fertilization



HIV Mucosal Infection



Anatomical Context Of Fertilization and HIV infection



Microbicial contraceptive

Semen
CA HIV
CF HIV

Uterus

Vagina



HIV/HSV Rationale

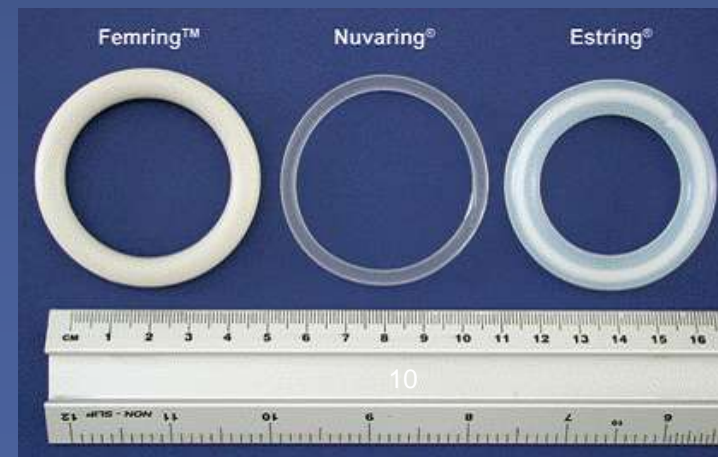
- ◆ Common in women in Africa
- ◆ HSV infection may enhance HIV transmission
- ◆ Goal is to reduce recurrences through intravaginal administration of ACV

Dual-Protection Activities

- ◆ Contraceptive/microbicide combination
 - ▶ IVR: Progestin (levonorgestrel, LNG) + reverse transcriptase inhibitor (RTI, UC781)
 - Polyurethanes (Utah), ethylene-vinyl acetate copolymers (EVAc) (Polymer Sciences), Pod-based IVR (Oak Crest)
 - ▶ Gel: Sperm function inhibitor (e.g., Carbopol) + RTI (UC781)
 - ▶ Barrier + RTI
 - Modified PATH Woman's Condom
 - Cervical cap
- ◆ Combination (HIV/HSV) microbicides
 - ▶ IVR: RTI (tenofovir, TFV) + Acyclovir (ACV)
 - Polyurethanes (Controlled Therapeutics)
 - Pod-based IVR (Oak Crest)

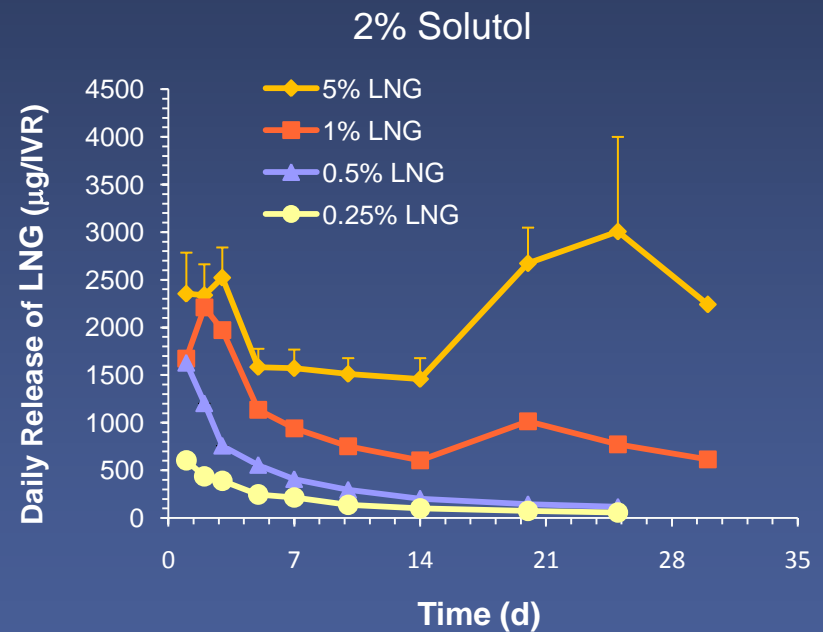
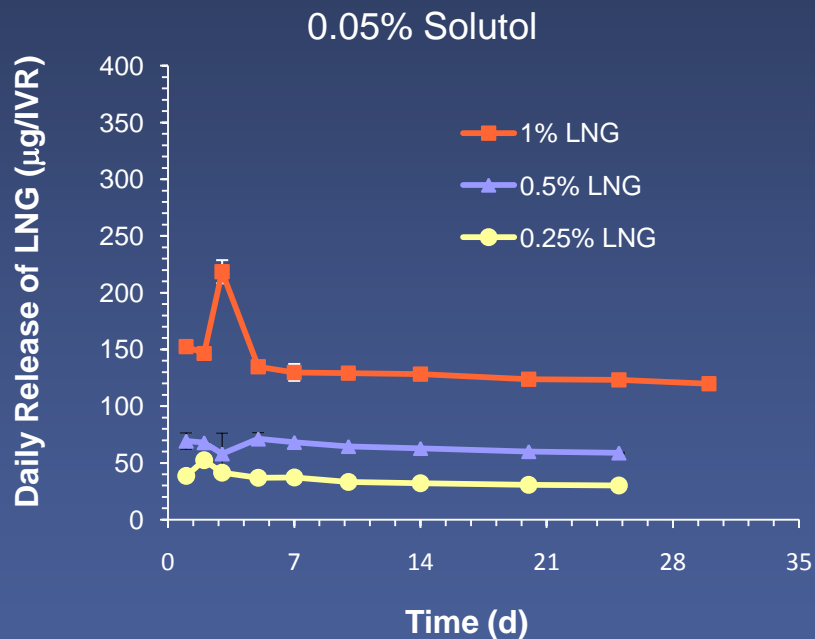
Contraceptive Microbicides: RTI/Progestin IVRs

- ◆ Long-term controlled release LNG and UC781
- ◆ Progestin-only contraceptives are well accepted
 - Long track-record of safety and efficacy
 - LNG-releasing IUS (market); effective for 5 y
- ◆ Non-contraceptive benefits: reduction of menorrhagia, anemia, and endometrial atypia
- ◆ UC781 in vitro release from IVRs for several months
- ◆ UC781-releasing IVR tested in monkeys for safety and PK



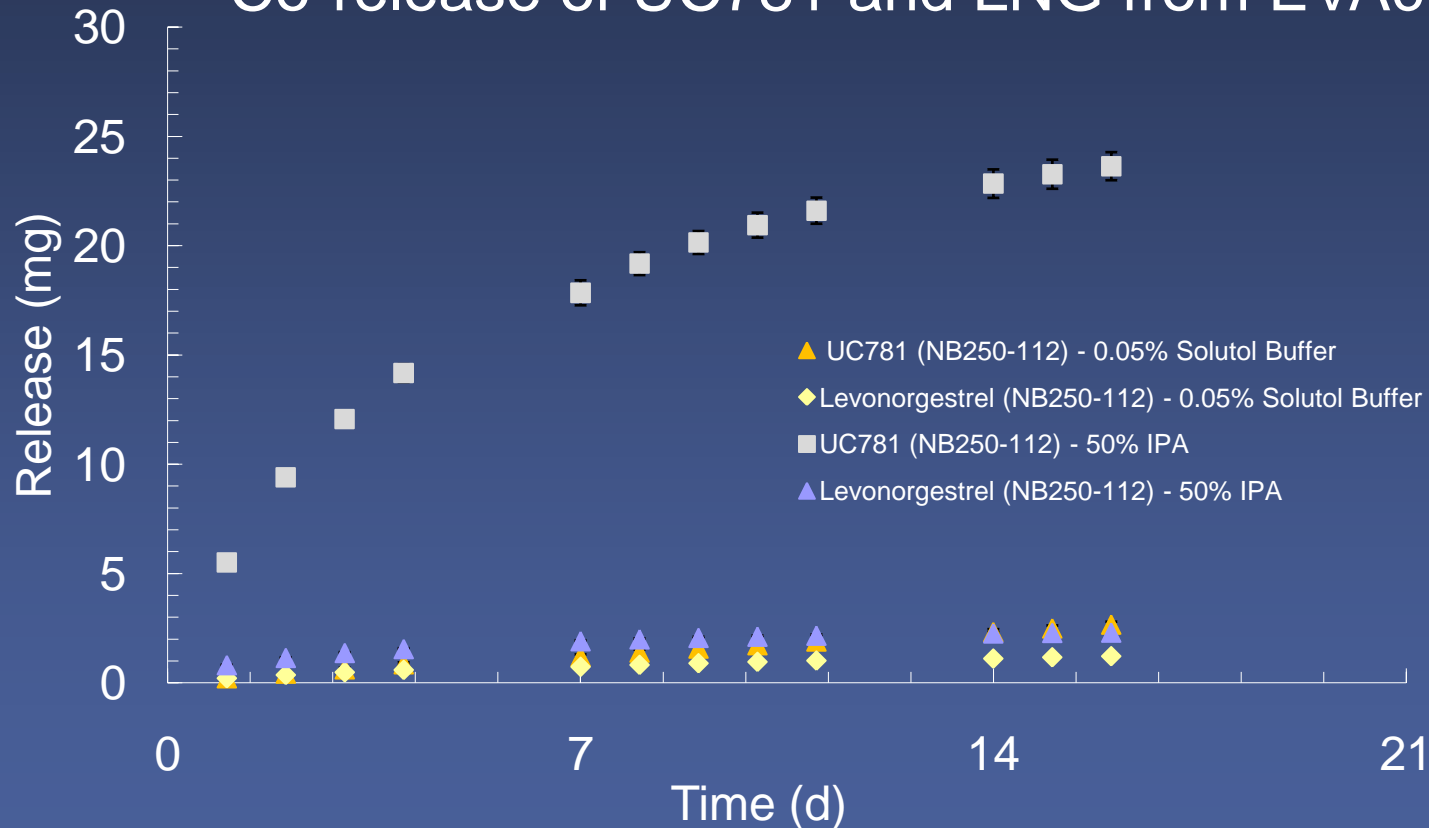
UC781/LNG IVRs: Polyurethane Matrix

In Vitro Release of LNG from Polyurethane IVRs under
Non-sink and Sink Conditions^a



UC781/LNG IVRs: EVAc

Co-release of UC781 and LNG from EVAc IVR

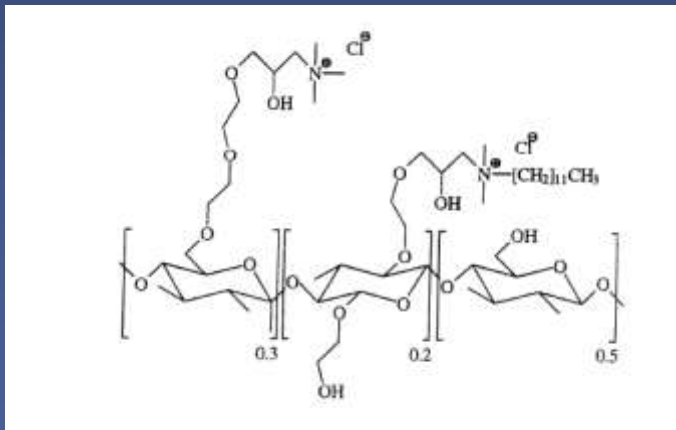


IVR Loading: 25 mg UC781 + 2.7 mg LNG;

In vitro release media: 50/50 Isopropanol (IPA)/water (H₂O) or 0.05% Solutol (pH 4.2)

Contraceptive Microbicides: Sperm inhibitor/RTI gel

- ◆ Sperm function inhibitors delivered intravaginally (immediate release)
- ◆ Formulation of UC781 and sperm-immobilizing agents (Q-2/Carbopol) in preclinical phases of development



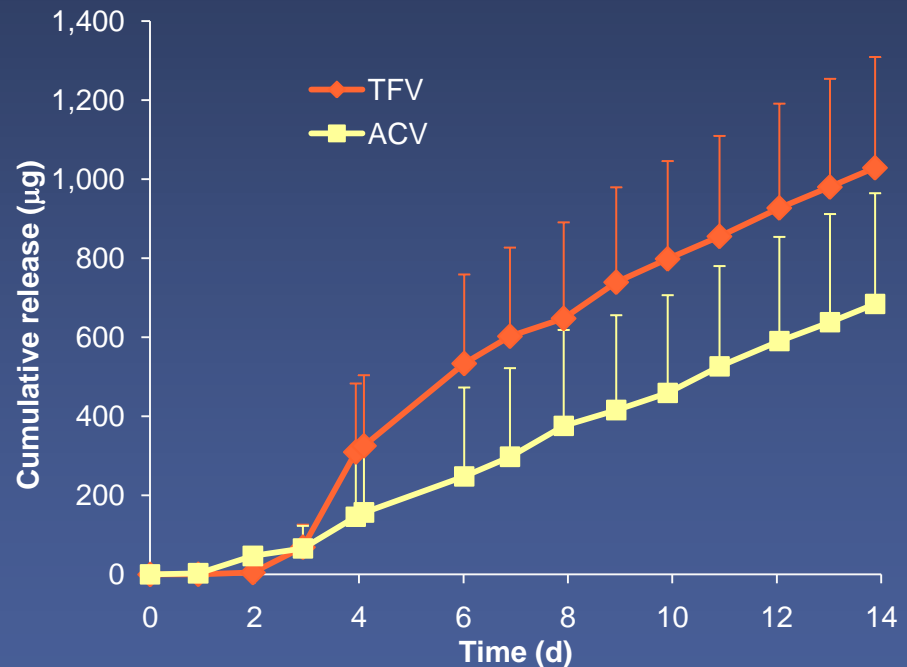
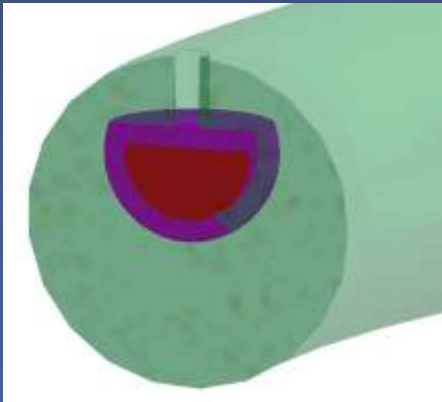
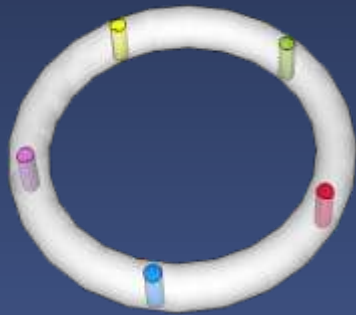
Contraceptive Microbicides: Modified PATH Woman's Condom

- Fast-dissolve polyvinyl alcohol (PVA) film can be used to deliver UC781
- Microbicide-condom work performed at Magee (L. Rohan)



Dual Purpose (HIV/HSV) : TFV/Acyclovir IVRs

Oak Crest Pod-Based IVR System Co-release of TFV and ACV from Ring Segments^a



^a1 TFV pod (15 mg, 1 mm window), 1 ACV pod (15 mg, 1.5 mm window) per ring segment. In vitro release media: pH 4.2 acetate buffer, 10 mL.

Dual-Protection Work Plan for Y2-Y3

- ◆ IVRs – UC781/LNG, TFV/ACV
 - ▶ Coordinated selection of lead IVR formulations:
 - In vitro release and permeability
 - In vivo PK
 - Stability
 - Predicted manufacturability (cost, material supply)
- ◆ RTI+Barrier Devices – Woman's Condom, Cervical Cap
 - ▶ Formulation development
- ◆ Dual activity gels – RTI + Sperm Function Inhibitor
 - ▶ Formulation development

Acknowledgments



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