# From the Bench to the Bedside & Back Again…

## Lessons from HPTN035

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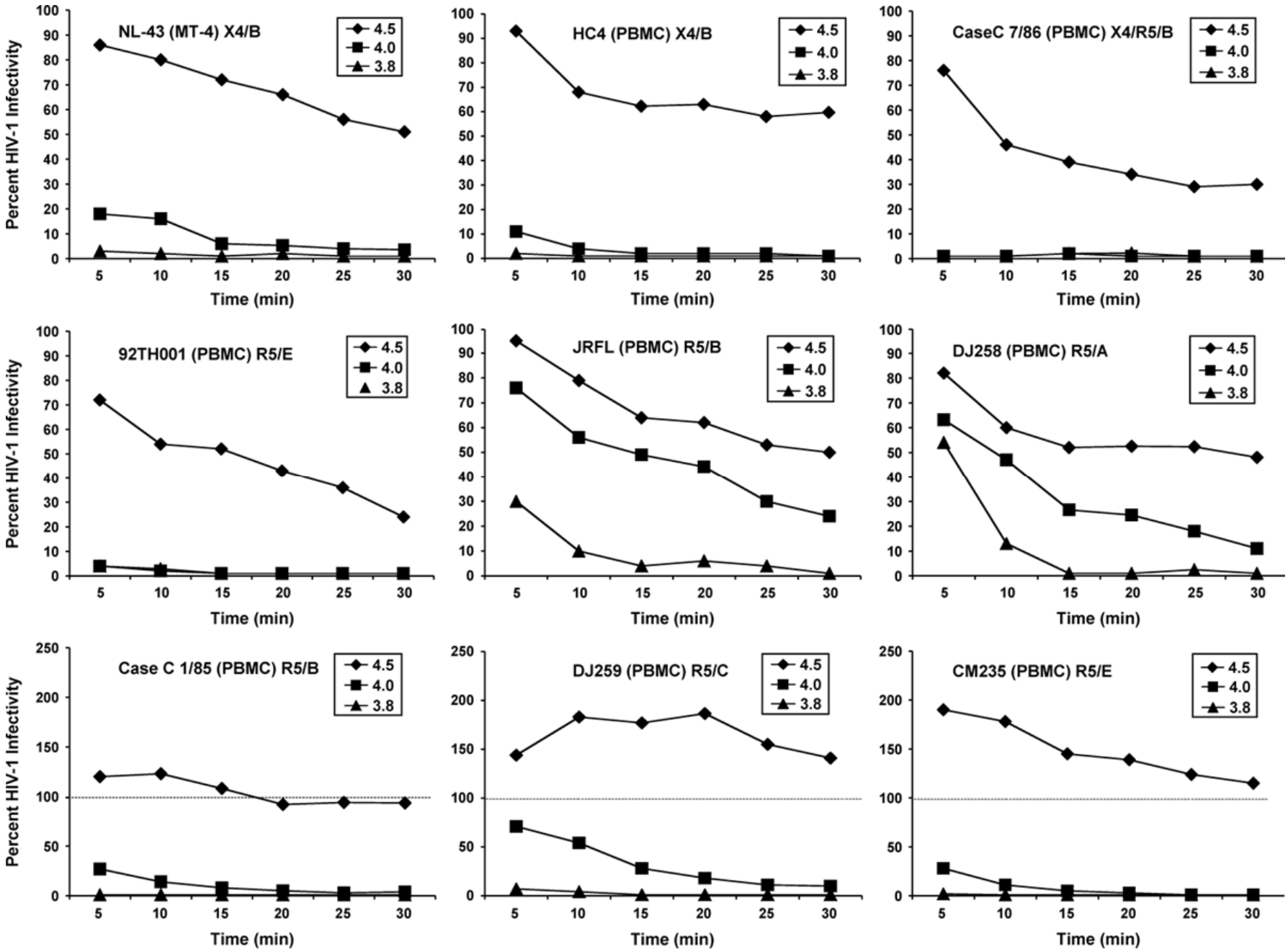
- How well did preclinical **efficacy** models predict outcomes?
- How well did preclinical **safety** models predict outcomes?
- How should we modify the models to provide more predictive biomarkers of efficacy & safety?

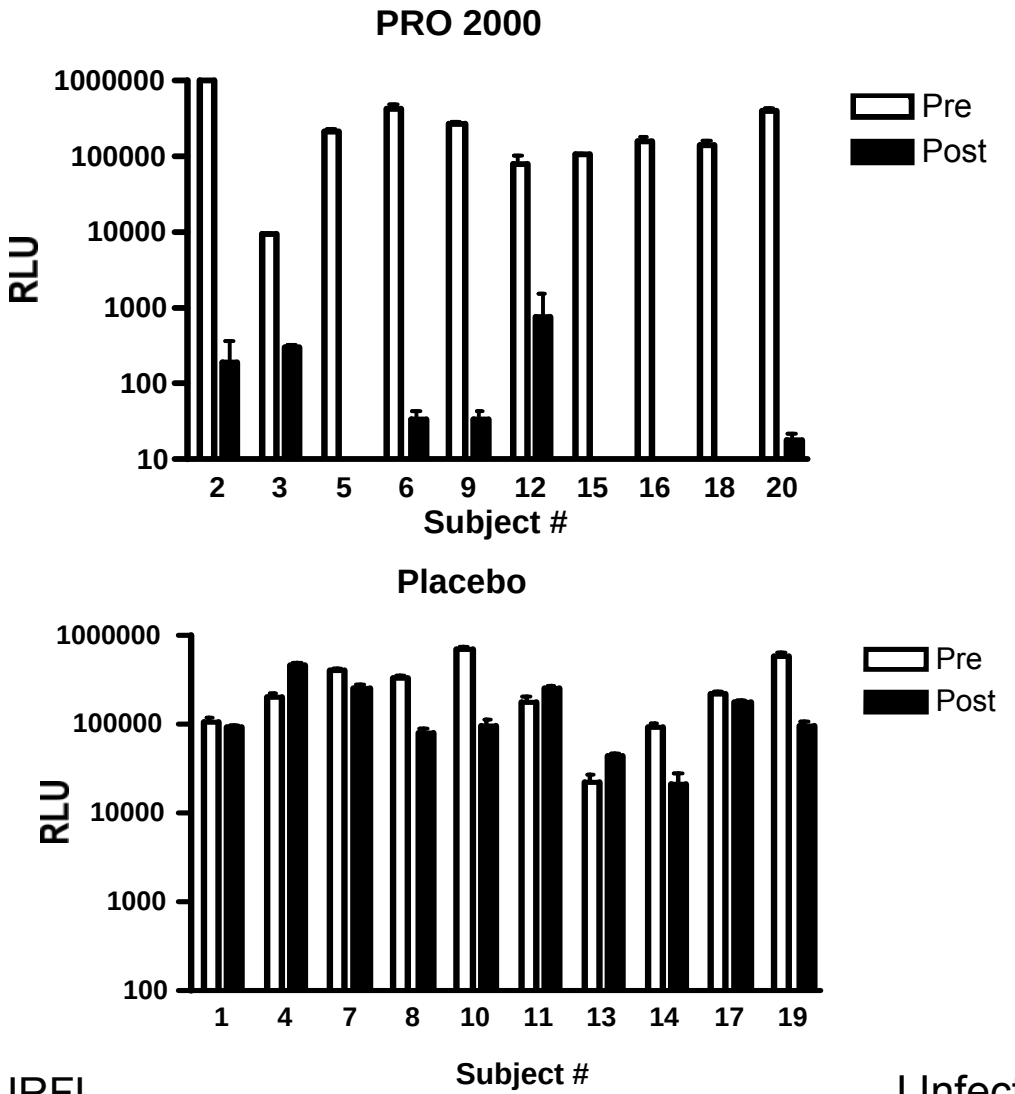
# Pre-Clinical Evaluation Score Card: HIV

| | PRO 2000 | BufferGel | Cellulose sulfate |
|---|---|---|---|
| Multiple clades | Yes | Variable; some enhancement[4] | Yes |
| Cell-associated vector transmission | Yes | Yes; ↓ motility & viability of immune cells pH 5.0[2] | Yes |
| Activity in seminal plasma | ↓4-fold(R5)[1] | Semen:Gel 1:1→pH **4.5-5.0**[2]<br>Semen:Gel:3:1→pH 5.3-5.7 | ↓↓57-fold (R5)[1] |
| Half-life | ? Hours | Short acting | ?? |
| Inflammation | Mild/↓SLPI | Tested with diaphragm/↓SLPI[3] | moderate |
| Epithelial barrier | Minimal | Not done | moderate |

[1]*BMC Infect Dis.* 2006; 6: 150
[2]BMC Infect Dis. 2005 30;5:79
[3]Am J Reprod Immunol. 2009 61(2):121
[4]J Acquir Immune Defic Syndr. 2006;43(4):499


NL-43 (MT-4) X4/B
HC4 (PBMC) X4/B
CaseC 7/86 (PBMC) X4/R5/B
92TH001 (PBMC) R5/E
JRFL (PBMC) R5/B
DJ258 (PBMC) R5/A
Case C 1/85 (PBMC) R5/B
DJ259 (PBMC) R5/C
CM235 (PBMC) R5/E
4.5
4.0
3.8
Percent HIV-1 Infectivity
Time (min)

# Anti-HIV Activity in CVL Pre & Post Gel: Spiking Strategy

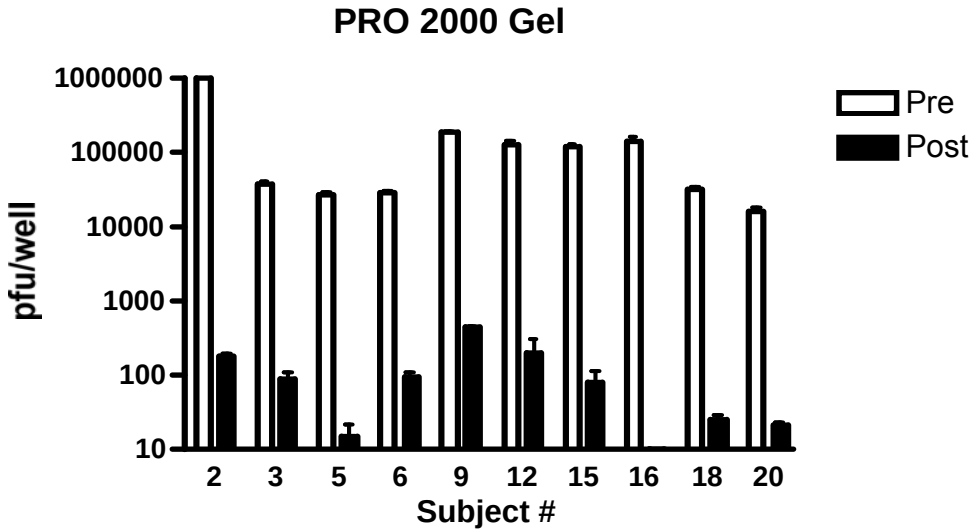


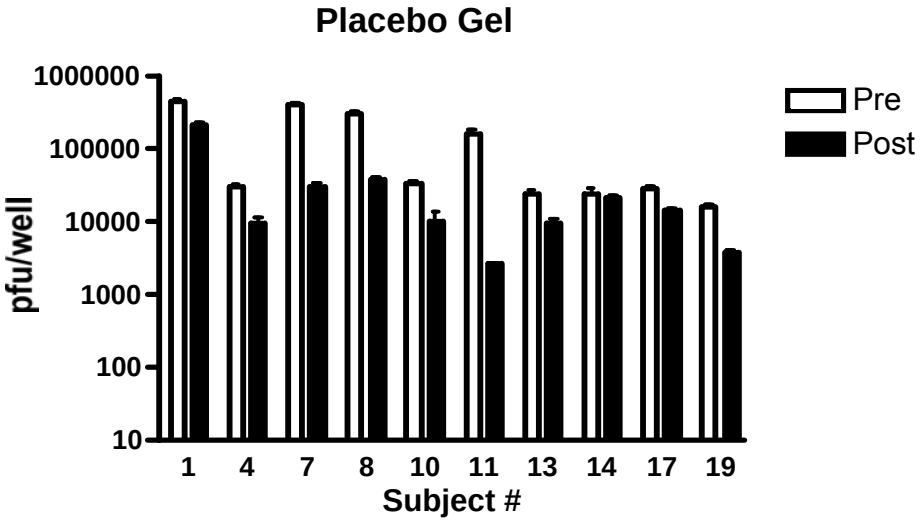

$p < 0.001$

HeLaCD4-CCR5 cells & JRFL

J Infect Dis. 2006193(1):27

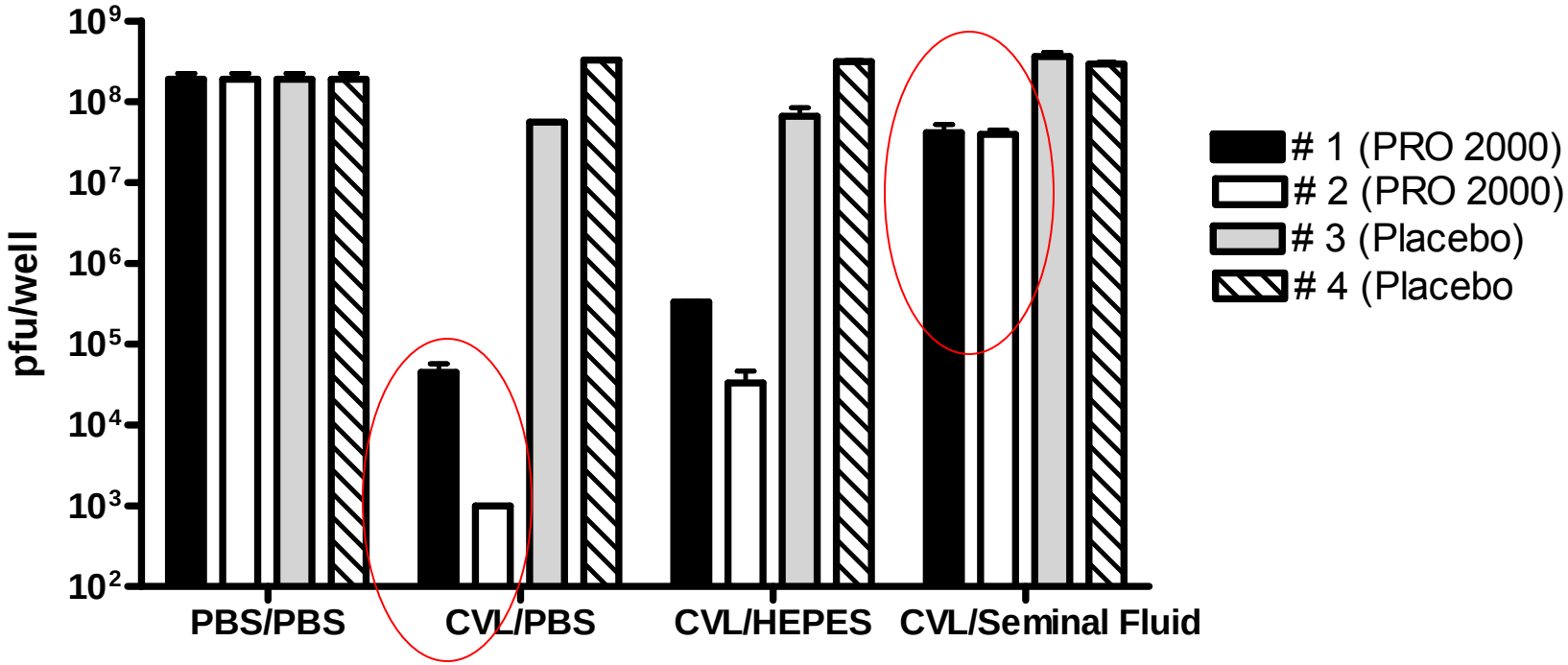
# CVL Post-Application Inhibits HSV




$p < 0.001$

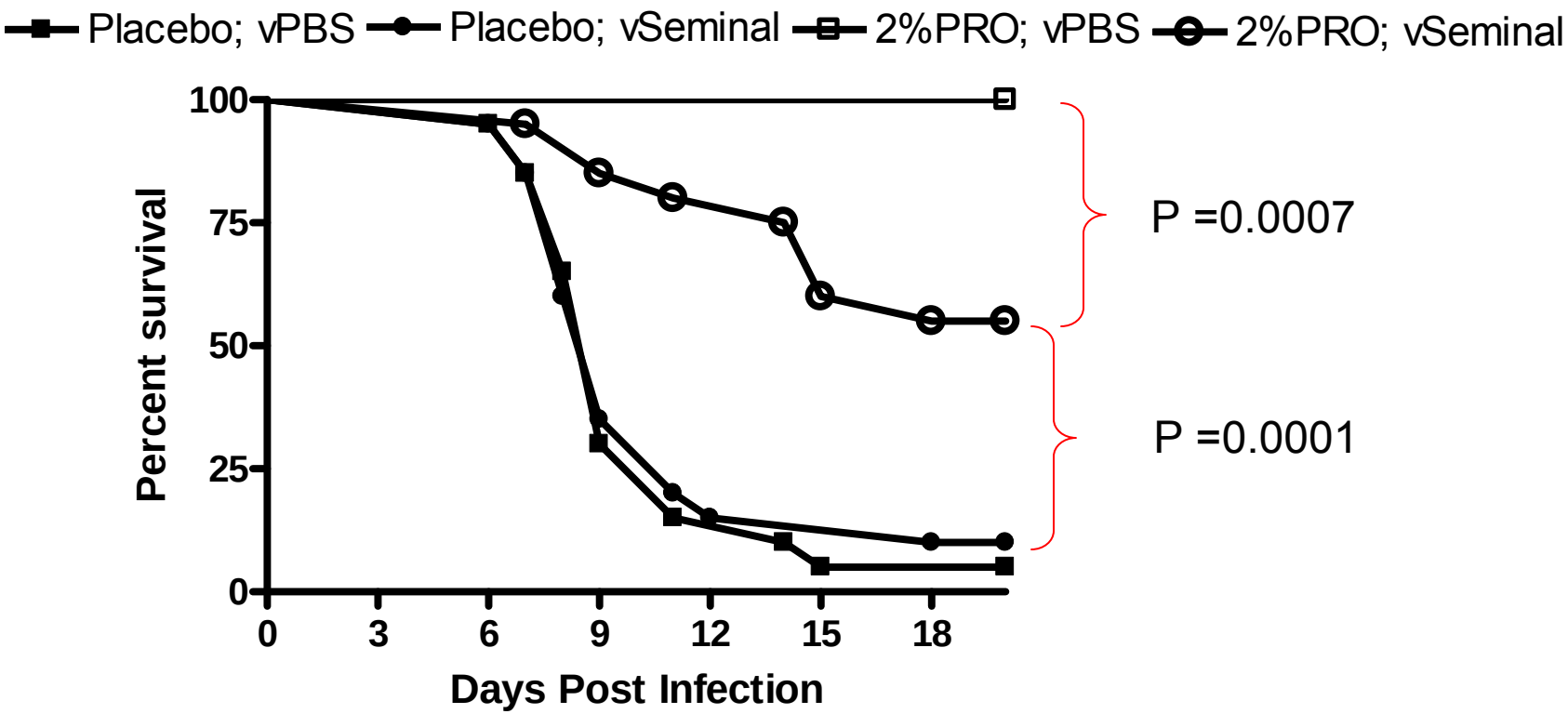
# Anti-HSV Activity Reduced if Virus Introduced Diluted in Seminal Plasma




The PRO 2000 in CVL samples were 97 and 166 μg/ml.

J Infect Dis. 2007;196(9):1394

# Interference Translates to Murine HSV Model




N = 20

# Post-Coital PRO 2000 Gel Study

| Visit 1 | Visit 2 | **Visit 3** | **Visit 4** |
|---|---|---|---|
| No drug<br>No coitus | No drug<br>Coitus | Drug<br>Coitus | Drug<br>No coitus |
| Intrinsic anti-viral activity in CVL | Impact of semen on intrinsic anti-viral activity | Impact of semen on drug & anti-viral activity following spiking | Anti-viral activity following spiking |

# Why no efficacy against HSV ?

- Greater interference by semen
- **Anatomy**
  - Drug needs to be at the introitus & labia to prevent HSV; applicators designed to deliver drug to the posterior vagina/cervix
  - MRI studies demonstrate ↑ bare spots in the lower vagina (3 cm above the introitus)*
- Higher attack rate

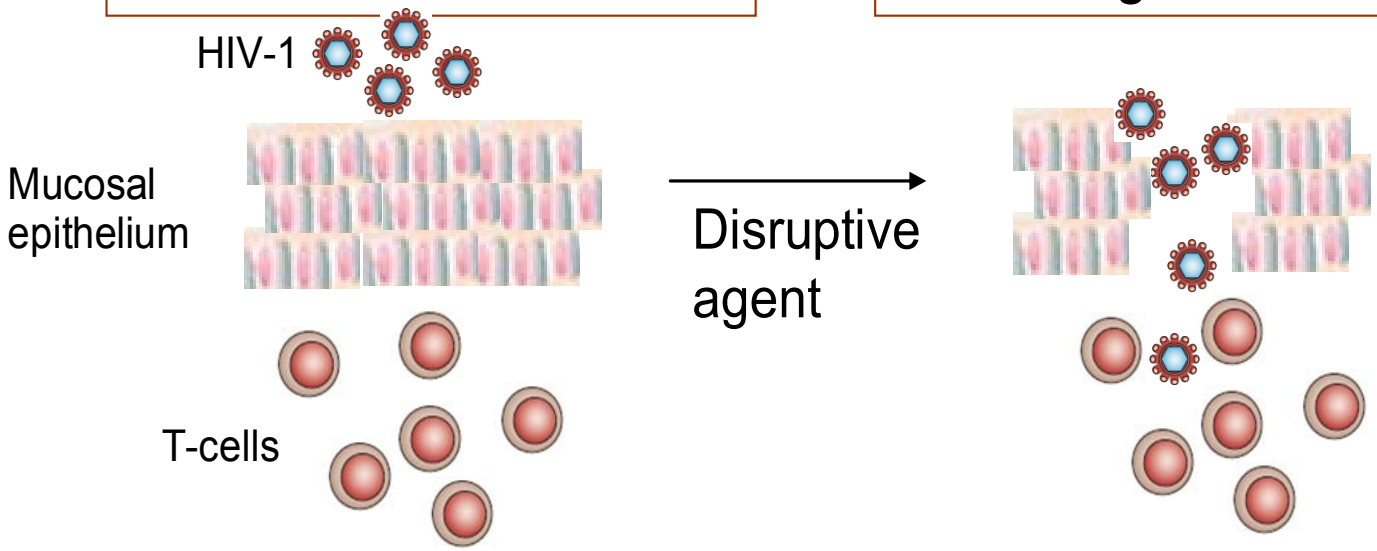
*Contraception. 2009 Apr;79(4):297-303

# Safety models

- Dual chamber model
- Murine model
- Expanded Phase I safety model

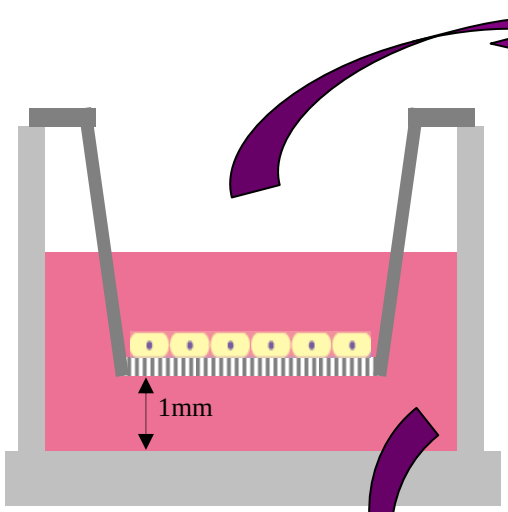
**Intact mucosal epithelium is impervious to HIV-1**

**Disrupted epithelium allows HIV-1 across to infect target cells**

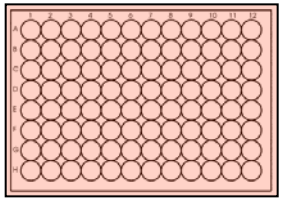


# Dual Chamber Model

- Impact on epithelial integrity
  - Cell architecture (confocal)
  - Transepithelial Electric Resistance (TER







- Inflammatory response
- Impact on HIV-1 translocation
  - p24 detection
  - Confocal microscopy

# Summary of Findings

- N-9 and cellulose sulfate, but not PRO 2000 or tenofovir, triggered drop in TER
- Drop in TER associated with increased migration of HIV across epithelial barrier & infection of immune cells in basal compartment
- Cellulose sulfate, but not PRO 2000 or tenofovir, activated NF-kB pathways and enhanced HIV replication in U1 cells.

Mesquita et al JID, 2009 in press.

# Moving forward…

- Clades important
- Cell-free vs. cell-associated
  - Data inconclusive… ? both transmit
  - How do IC50's translate; which assays?
- Rapid onset of action &sustained effect critical
- Postcoital studies
- Modify HSV models
  - HSV & HIV infect different sites?
  - Male-female transmission models (? cotton rat)
- Modify Phase I studies