

# Impact of Sex & Semen on TFV-Based PrEP

## MTN 011

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# Making ¢ of TFV Gel Trial Results

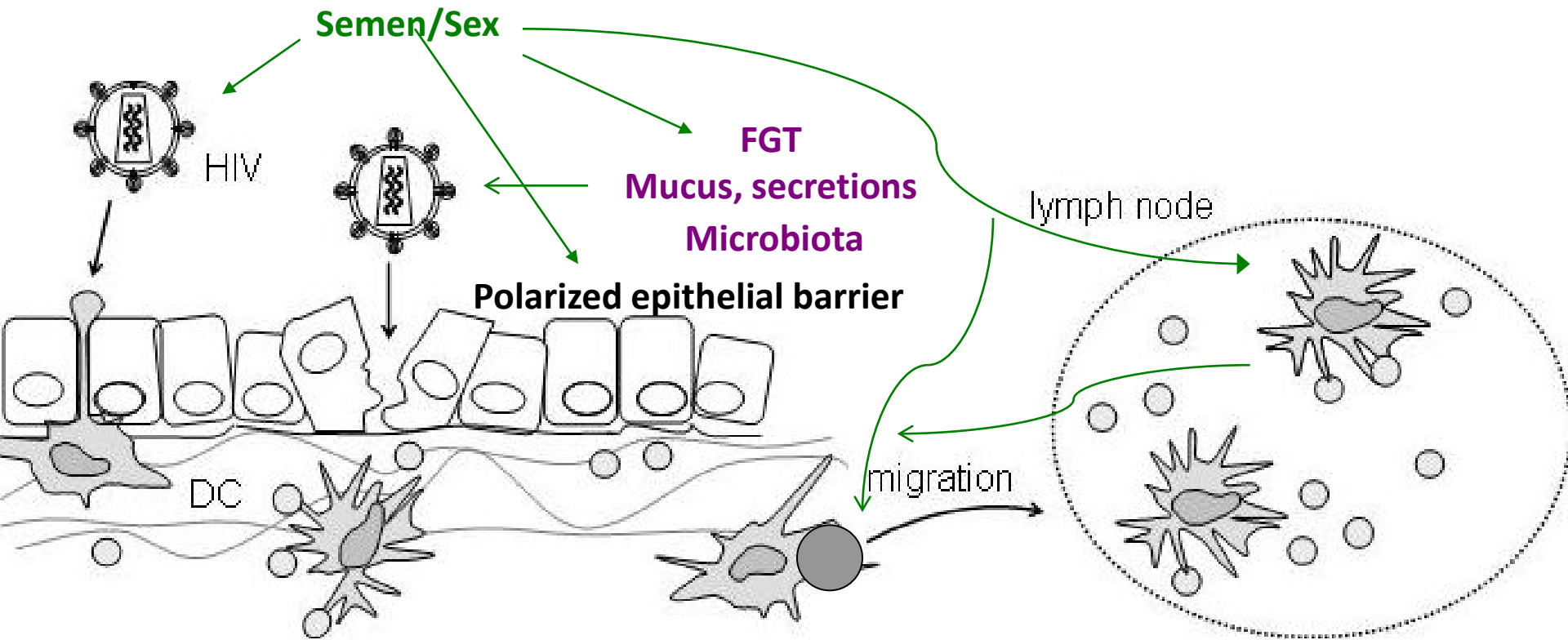
- Discrepancy preclinical & clinical trial outcomes
  - Robust activity in vitro
  - Full protection in NHP models
- Discrepancy in topical clinical trial outcomes:
  - Modest protection CAPRISA 004 vs. none in VOICE
    - Dosing schedule: BAT 24 vs. daily
    - Adherence
    - Sexual practices
    - Hormonal contraception: Required in VOICE
    - Altered mucosal environment in different populations

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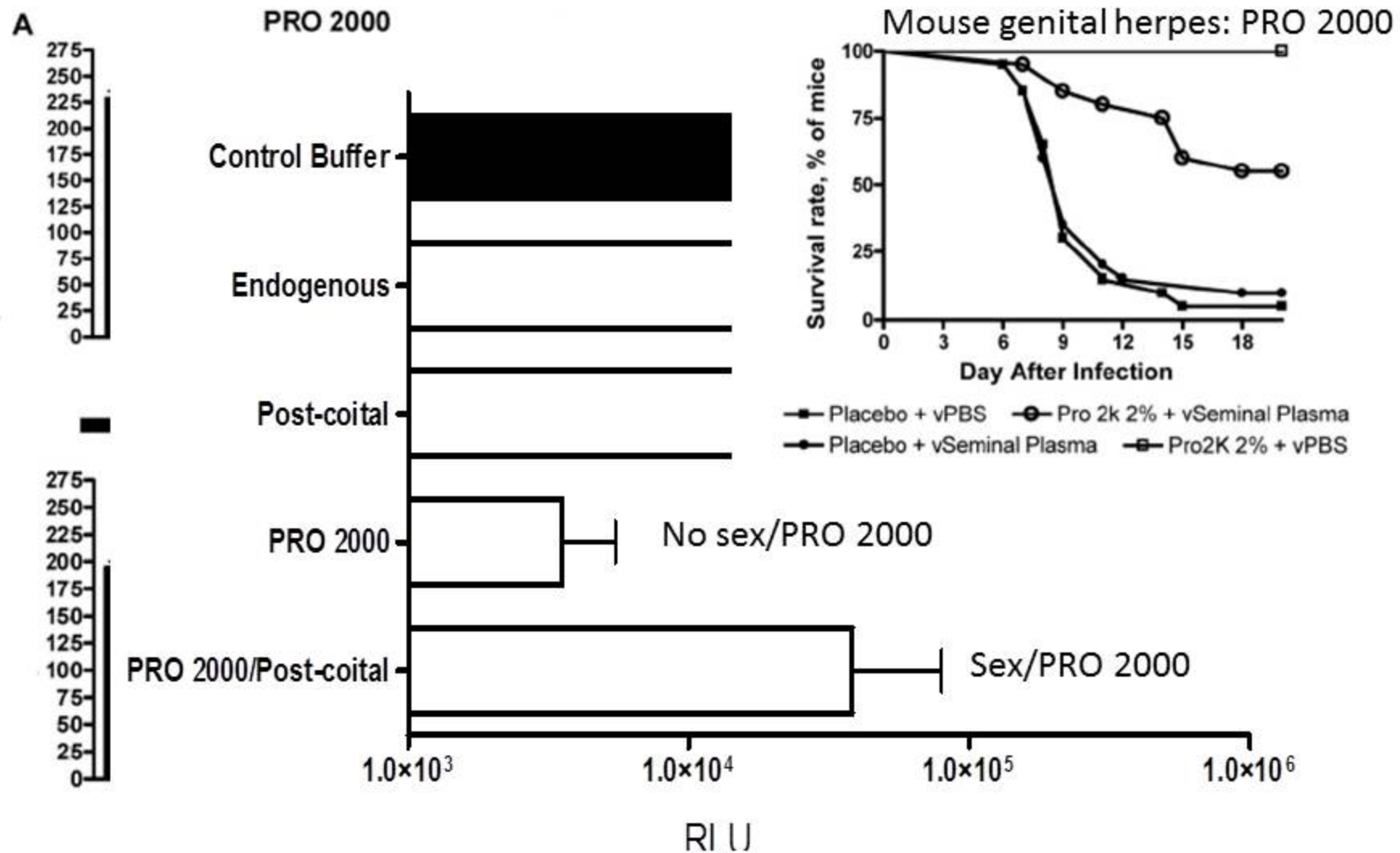
★ Sex & semen modulate PK/PD & HIV risk

# Sex and Semen Fuel the HIV Epidemic



Does sex/semen also modulate PK/PD?

# Semen Interferes with Polyanionic Drugs: Bench to Bedside



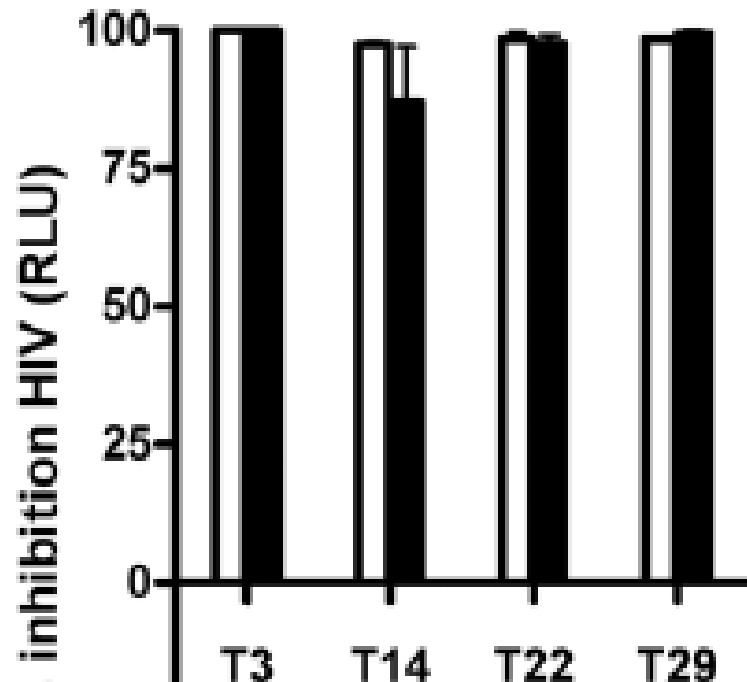
# No Adverse Effect of Semen on Tenofovir Activity Ex Vivo

Women applied TFV gel x 14 days (no sex!)

Cells exposed to Day 7 secretions (cervicovaginal lavage)

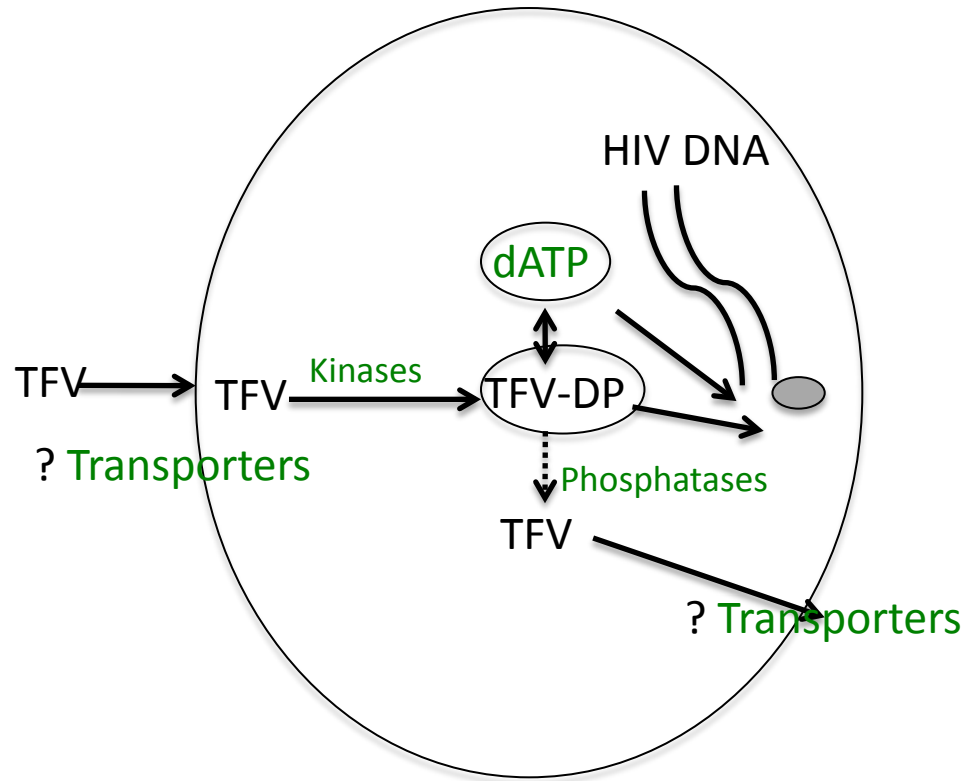
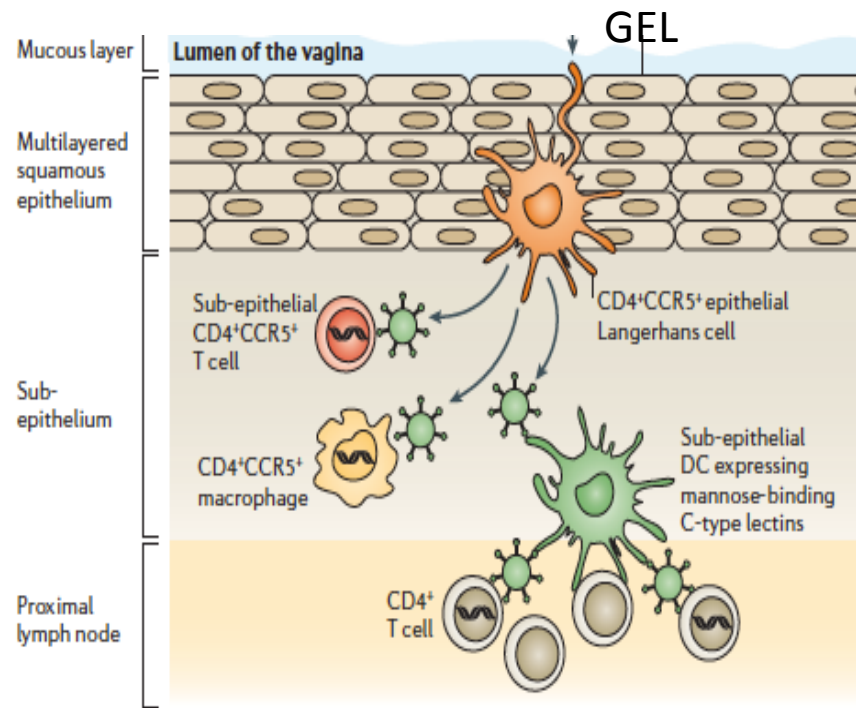
Challenged with HIV in buffer (white) or in 25% semen (black)

TFV retained antiviral activity



# But What About the Clinical Setting?

## Drug Needs to be at the Right Place and at the Right Time

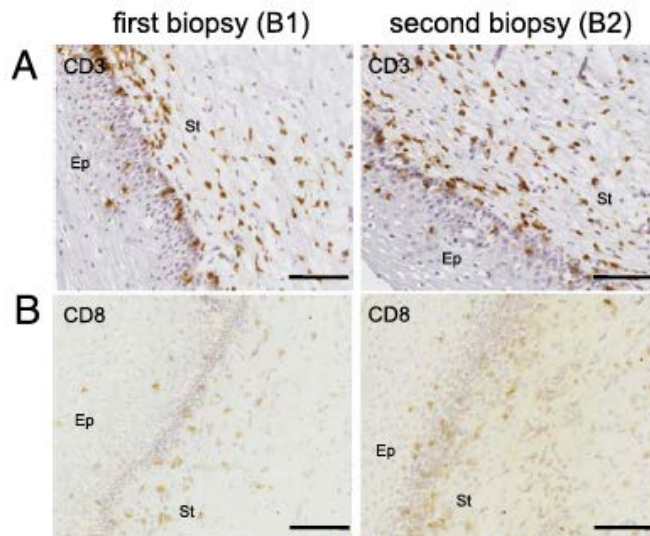
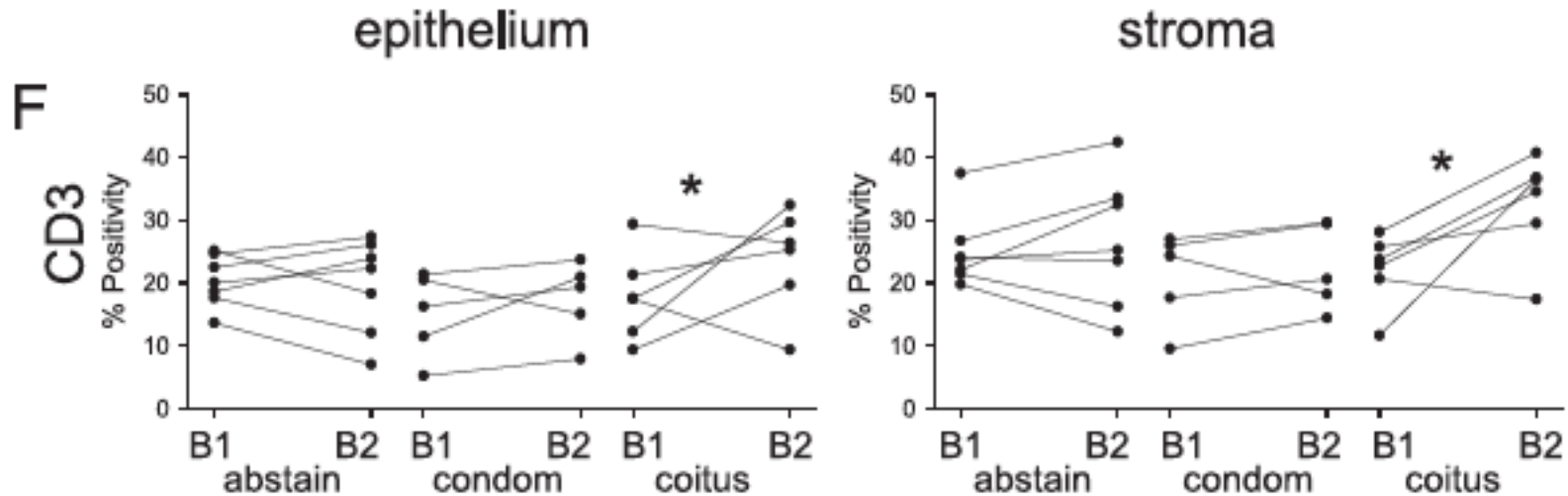


### Sex/semen might:

- Reduce effective dose due to leakage/dilution if applied shortly prior to sex
- Alter drug permeability & transport
- Impact metabolism
- Recruit new immune targets
- Activate immune cells
- Alter TFV:dATP stoichiometry

# Sex Associated with ↑ Immune Cells

- Collected 2 biopsies each from women at baseline and then 48 h later, 12 h following coitus with (n=5) or without condom (n=6) or no coitus (n=7)





# Sex/Semen Trigger Inflammatory Responses

Inflammatory mediators in semen and/or female response to semen/sex:

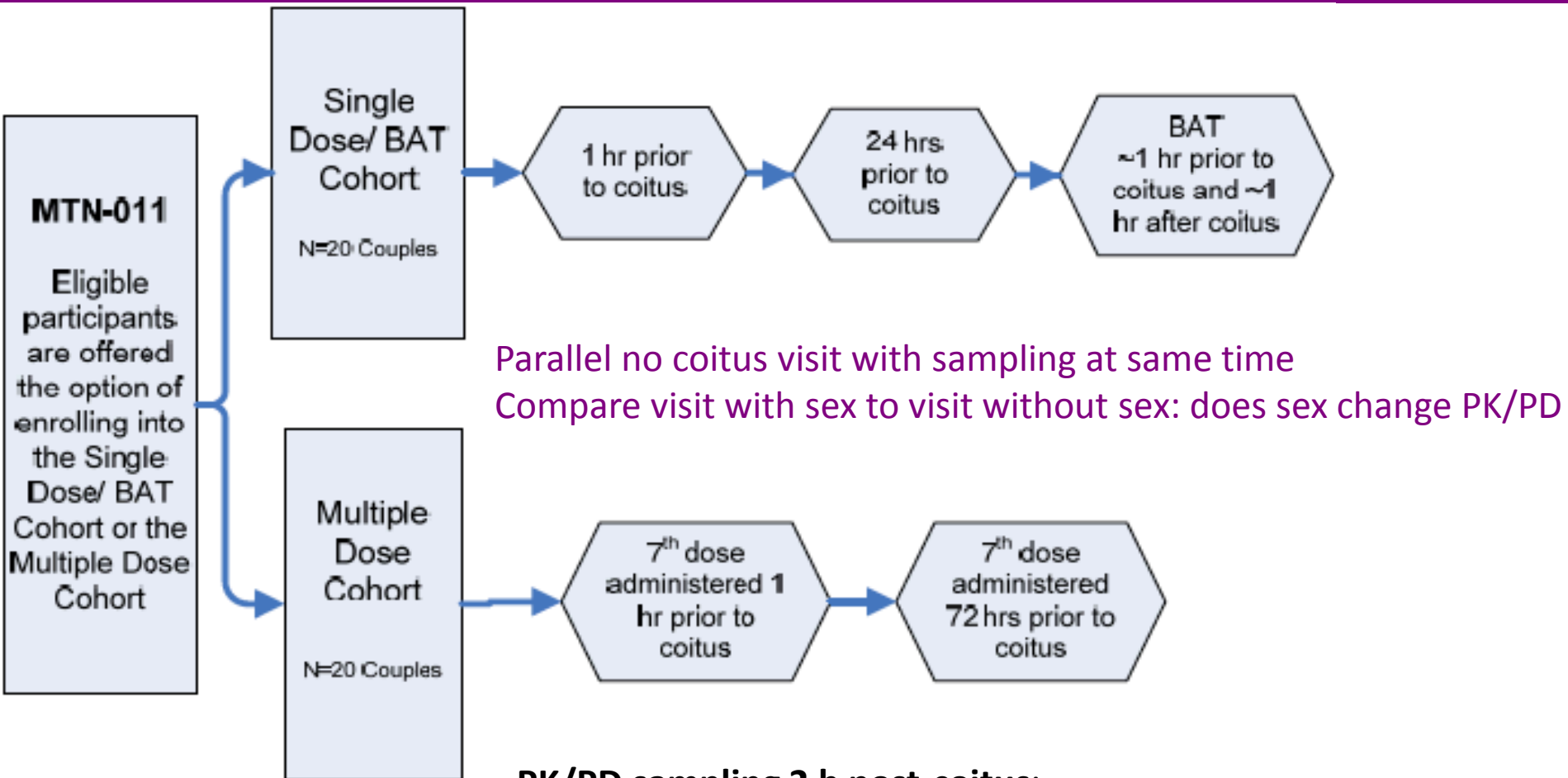
- Disrupt epithelial barrier
- Recruit Immune cells from lymph node or circulation
- Activate resident immune cells
- Increase dATP stores (shifting dATP: TFV-DP balance)
- Alter TFV uptake/metabolism

# MTN 011: PK/PD Study of TFV Gel

## Dosing with Coitus

- Purpose: Obtain PK/PD data on timing of dosing relative to sex
- Primary objective:
  - PK: TFV & TFV-DP levels in CVL, cytobrush, biopsies, rectal sponge, blood
  - PD: Anti-HIV activity of CVL
- Secondary/Exploratory
  - Acceptability of postcoital/biopsy study
  - Impact of coitus & drug on mucosal immunity (soluble/cellular)
- Study Design: Phase I multi-sequence open label
- Study Population: 40 monogamous couples; 21-46 yrs
- Sites: Pittsburgh and Cleveland

# MTN 011: Postcoital PK/PD Study

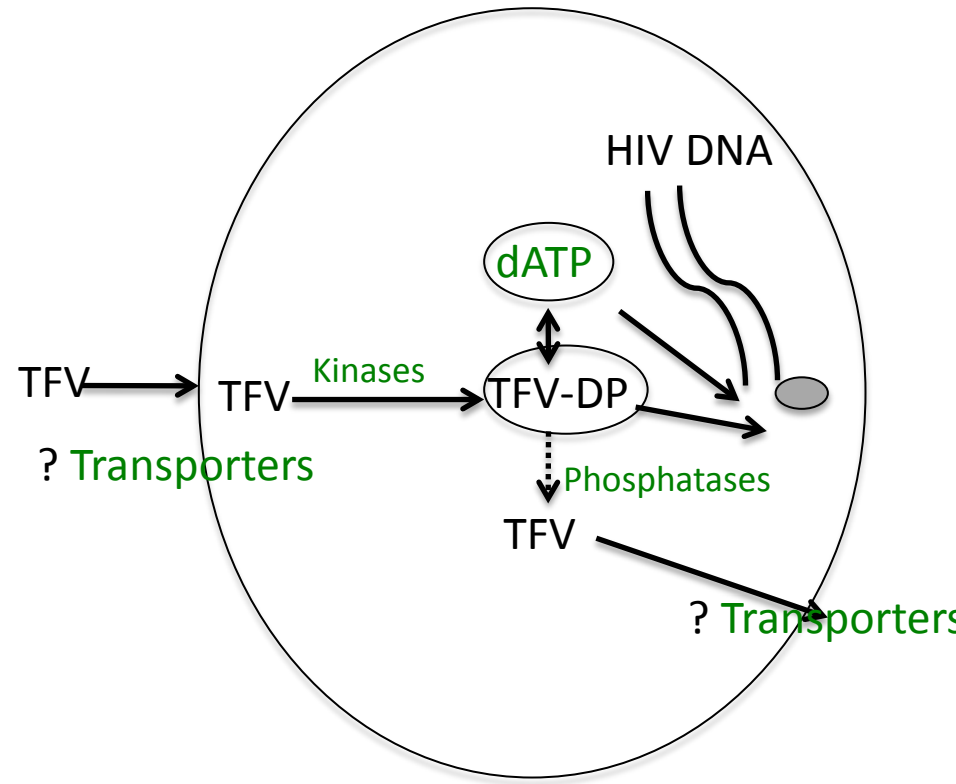
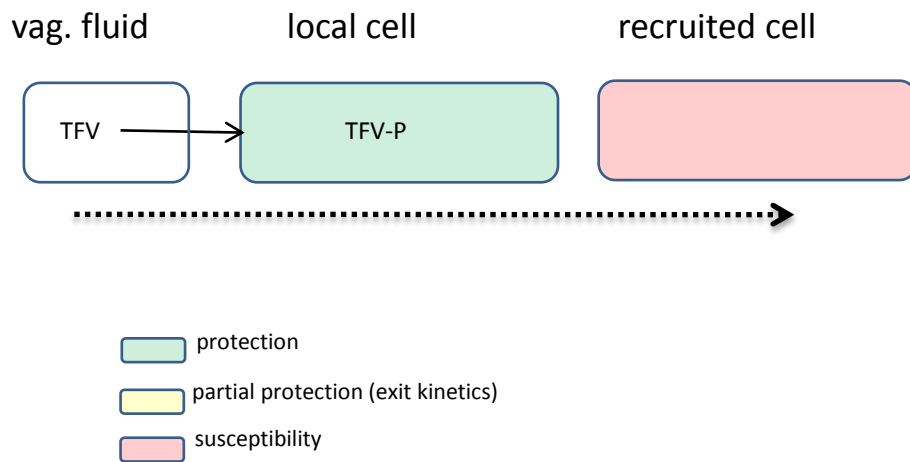


**PK/PD sampling 2 h post-coitus:**

- CVL
- Cytobrush
- Rectal sponge
- Vaginal & cervical biopsies
- Blood

# Putting it all together.. Predicting PK/PD

	CVL	Cytobrush	Biopsies
1 h prior to coitus			
24 h prior			
BAT (-1/+1)			
7 <sup>th</sup> daily dose -1h			
7 <sup>th</sup> daily dose-72			



# CONRAD 113: PK/PD TFV Gel Study

- **Primary Objective:** To assess TFV and TFV-DP in genital samples and blood plasma/PBMCs after a **single sex act** and **after two weeks of twice weekly sex**
- **Study Design:** Randomized to dosing regimen and to time of sample collection after a single sex act and after two weeks of twice weekly sex; n=90 couples; 5 sites

Genital sampling 4, 12 or 72 hours post-single sex act	
BAT 24	gel → <sup>1h</sup> sex → <sup>1h</sup> gel
PRECOITAL	gel → <sup>1h</sup> sex
POSTCOITAL	sex → <sup>1h</sup> gel

For each of 9 groups (Regimen x Time-point)  
N=10

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## Two weeks of twice-weekly sex

	Genital Sampling Time-points					
	4 hours post-sex	12 hours post-sex	72 hours post-sex	5 days post-sex	10 days post-sex	14 days post-sex
<b>BAT 24</b>						
gel → <sup>1h</sup> sex → <sup>1h</sup> gel	N=10	N=10	N=10	N<30		
<b>PRECOITAL and POSTCOITAL</b>						
gel → <sup>1h</sup> sex	N=5	N=5	N=5	N<30		
sex → <sup>1h</sup> gel	N=5	N=5	N=5			
<b>DAILY</b>						
last gel → <sup>12h</sup> sex	N=10	N=10	N=10	N<30		

# Implications of 2 Studies

- Inform population as to how to best use products
- Advance new products/formulations
- Understand interplay between sex and TFV PK/PD
- Lay groundwork for more intensive future PK/PD studies that ideally will precede Phase III trials
- Gain insight into VOICE & CAPRISA 004 outcomes