

# Pharmacodynamics: Genital Tract Pharmacodynamics

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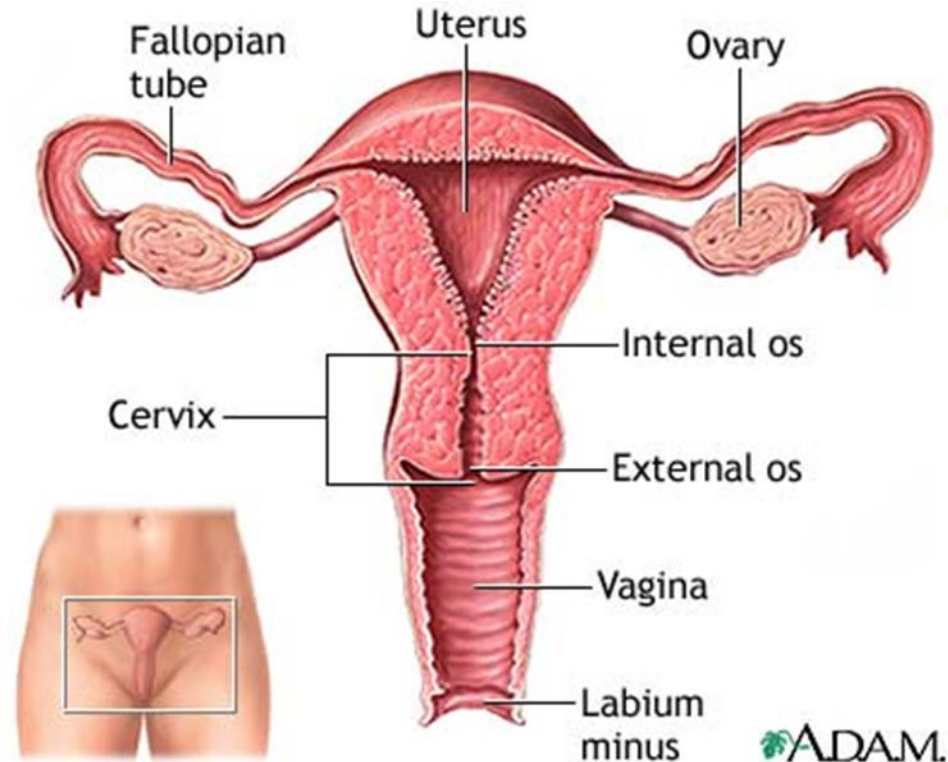
*Use of Mucosal Assays in Microbicide Trials*

August 26, 2015



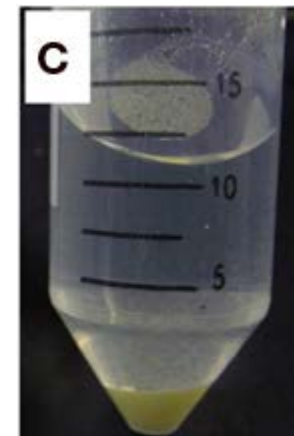
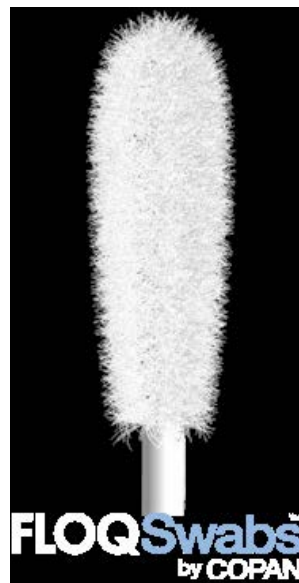
# Today's discussion

- Genital tract secretions
  - Easily obtained
  - Swabs have minimal dilution and volume
  - Cervicovaginal lavage (CVL) is dilute, but larger volume
- Genital tract tissue
  - More invasive
  - Variability in immune cells
  - Reproducibility/sample bias
  - Vaginal vs cervical tissue

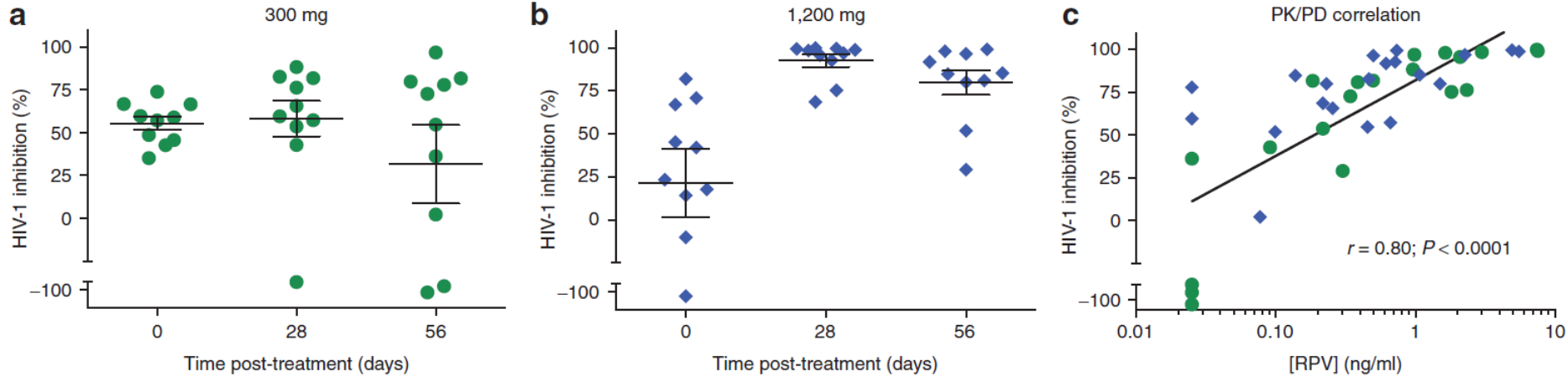


# Secretions collected

- Mucosal (cervical, vaginal) swabs / sponges, tearflo strips, and cytobrushes
- Cervicovaginal lavage (typically 5 or 10 ml)

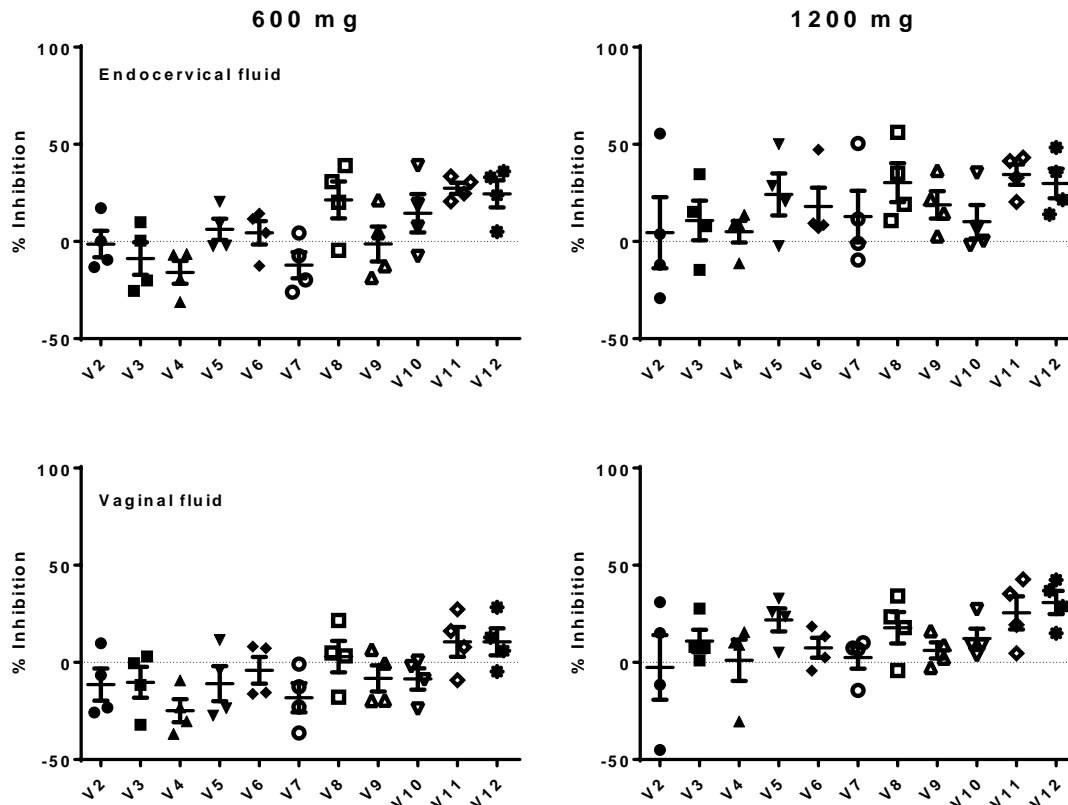


# PD activity – CVL



- RPV-LA PK dose ranging study; single dose
- CVL collected at baseline, one month and two months post injection
- PD dose-response defined and established PK/PD correlates

# PD activity – swab elutes



- RPV-LA PK dose ranging study; single dose
- Swabs collected at baseline, 1 day, 7 days and monthly thereafter post-injection
- No PD dose-response noted; drug did not elute from swab

# PD activity - tissue



# Ex vivo challenge assay

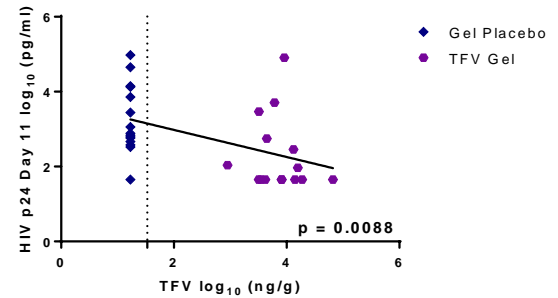
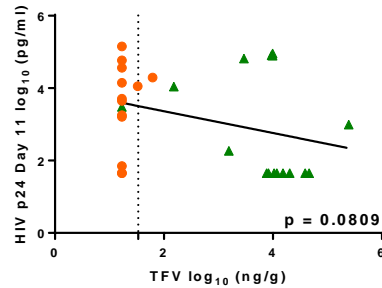
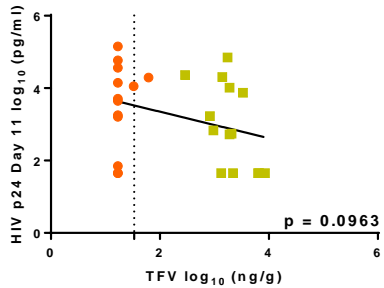
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- Participants use a product for a specified period of time
- Tissue biopsies (cervical and/or vaginal) are taken and transported to the laboratory as soon as possible
- The tissues are exposed to HIV-1
- After 2 hours, the tissues are washed, weighed, and HIV-1 infection is followed for 11 days

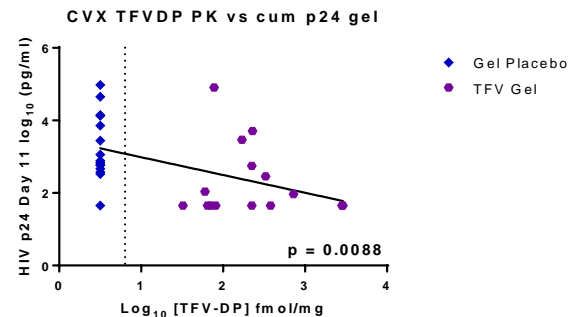
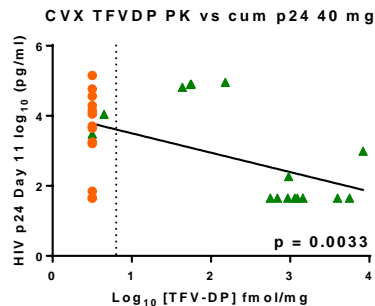
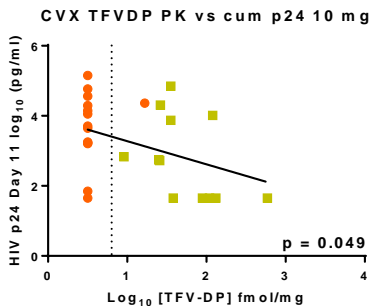


# PD activity - analyte

## Tenofovir



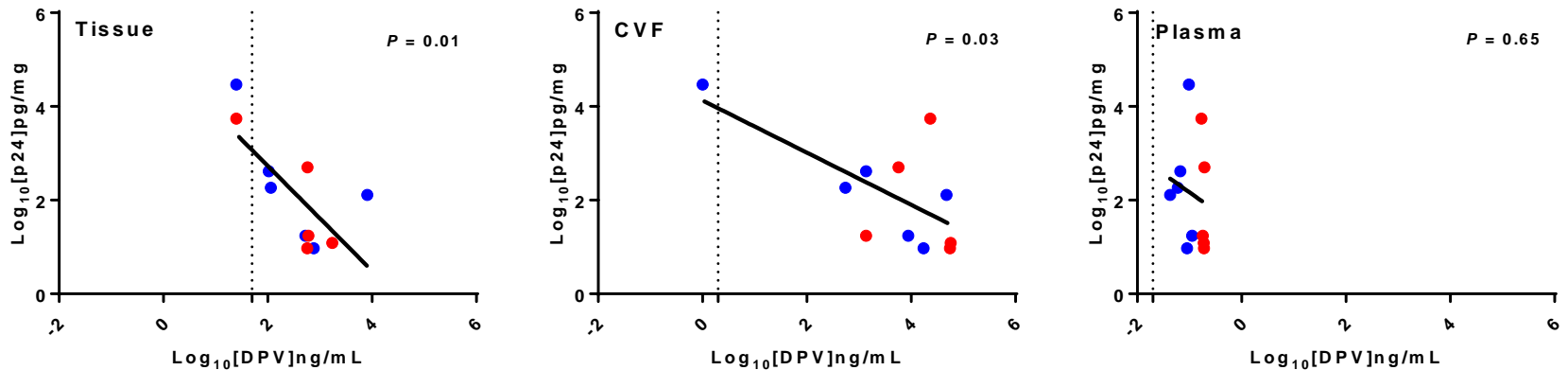
## Tenofovir-diphosphate



- FAME-04 evaluating 10 mg and 40 mg TFV film & TFV gel for PK/PD
- N=15 per arm



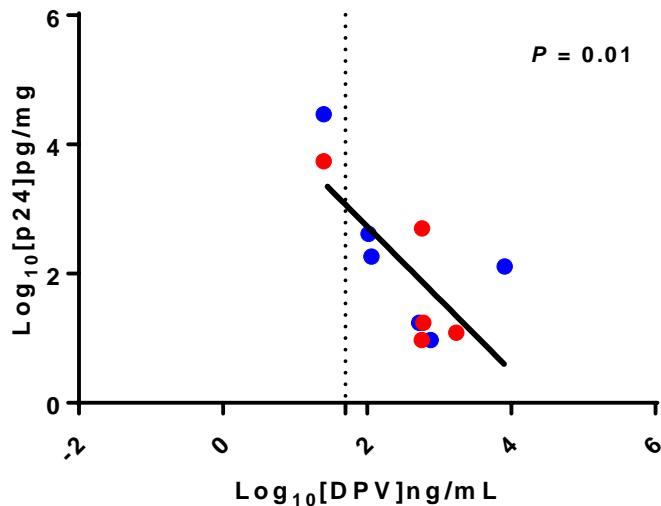
# PD activity – multi-compartment



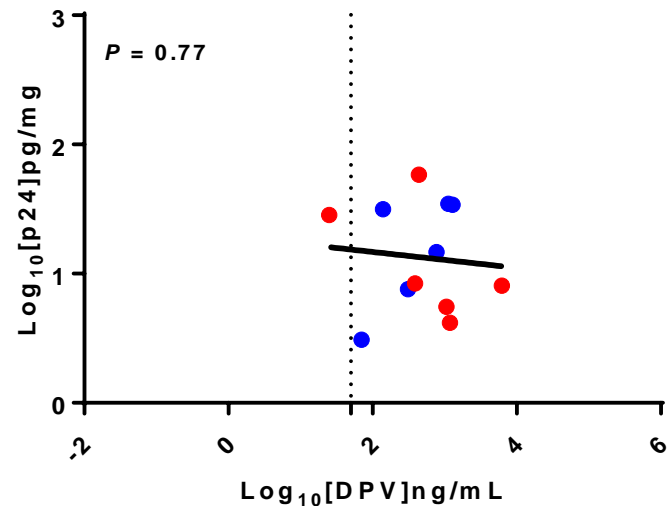
- MTN-013 evaluating IVR containing DPV, MVC, or both
- Best PK / PD correlates found in matrix closest to site for HIV infection
- N = 6 in each group; red DPV IVR & blue DPV/MVC IVR

# PD activity – fresh vs frozen tissue

## Fresh

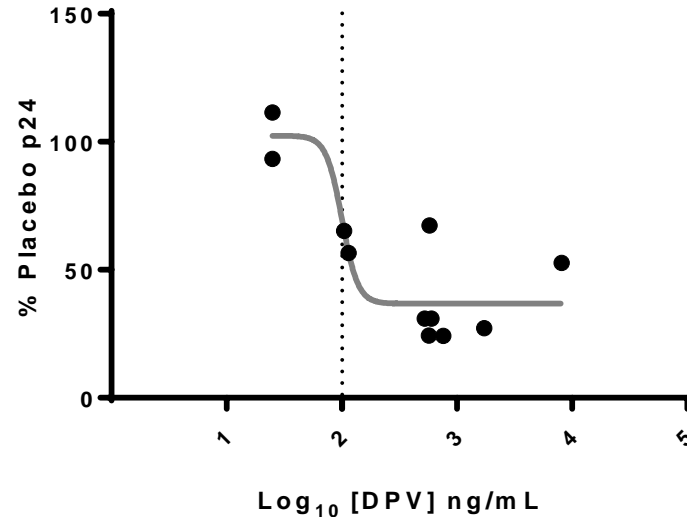


## Frozen



- MTN-013 N = 6 in each group; red DPV IVR & blue DPV/MVC IVR
- Fresh tissue was processed in real time for the ex vivo challenge assay.
- Frozen tissue was cryopreserved at the site and sent to a central lab for the ex vivo challenge assay

# Defining effective drug concentrations



- MTN-013 estimating  $\text{ED}_{50}$  DPV concentration in cervical tissue: 100 ng/mL
- Non-linear  $E_{\text{max}}$  model was fit to the data using the placebo as the virus control

# PD caveats

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- Luminal fluid may not inform tissue activity, but likely represents a biomarker
- Tissue cryopreservation is being evaluated to optimize viral infection/replication; however, drug effects (solubilize and wash away) have not been defined
- Amount of HIV added to the systems ensures adequate baseline signal; likely over-estimate of transmitting inoculum

# Key points

- Tailoring specimen collection based on the molecule being tested
- Understand HIV infection dynamics (variability) in mucosal tissue (imputing p24 or PCR values) to differentiate drug effects from lack of HIV infection to develop PK/PD correlates
- Develop integrated models to define effective drug levels – efficacy biomarker
- Focused working group(s) to provide best practices on data analysis

# Acknowledgements

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- Participants

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GATES *foundation*

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