Pharmacodynamics:
Genital Tract Pharmacodynamics

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Use of Mucosal Assays in Microbicide Trials
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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

• 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

- 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

- 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

- 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 $ED_{50}$ 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

- 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
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