

November 3-4, 2011 – Washington, DC

## Microbicide pharmacokinetics – dependence on dosage form and regimen as predicted by compartmental models

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### OBJECTIVES

Experimental *in vivo* data for microbicide pharmacokinetics are invaluable but limited in humans. *In silico* compartmental drug delivery models can play a valuable role, but there has been relatively little such modeling to date. We created mechanistic compartmental models for vaginal gels and rings

### METHODS

Compartments are: vehicle, vaginal fluid, semen (if present), epithelium, stroma (with clearance to bloodstream). Drug (API) transport is by diffusion and convection mechanisms. A system of coupled transport equations is created. Details depend on vehicle properties, and API mechanism. The equations predict the time and space-dependent concentrations of APIs (and their derivatives from host cell interactions, if relevant) within each compartment. Repeated dosage at specific intervals is included. Equations are solved using MatLab (gel) and Comsol (ring) software.

### RESULTS

Model results for the 1% tenofovir gel were compared with PK data from CONRAD and MTN-001 studies. Measurements in punch biopsies were simulated by summing model predictions of total tenofovir in epithelial + stromal compartments. The model accurately predicted data on: (1) 2 log drop in concentration from vaginal fluids to biopsy; (2) 1 log and 5X concentration drops in vaginal fluids and biopsy over 24h interval post gel application. Delivery from a ring was strongly influenced by the amount of vaginal fluid, reaching ~steady state in 24h.

### CONCLUSION

These models are an analytical tool, which can simulate variations in key factors governing microbicide drug delivery, to help design and interpret experimental PK. Initial applications are promising. We are rescaling the models for macaques and other species. (U19 AI077289)