Modeling Pharmacokinetics and Pharmacodynamics of Topical Anti-HIV Products and Translation of this Framework into Rational Product Design

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Background

Epidemiologically successful HIV prevention necessitates an armamentarium of approaches, that span diverse user behaviors and biologies. Immunological approaches (vaccines) are in development but not imminent. Oral pre-exposure prophylaxis (PrEP) is proving to have some success and occupies an important epidemiological niche. However, additional prevention methods are needed, especially that are in women’s control. Methods in development include: long acting PrEP (injections and implants – in trials, but irreversible); sustained release, reversible PrEP (e.g. intravaginal rings; in development, one is close to regulatory approval); and rapidly acting on-demand PrEP (e.g. fast dissolving inserts, suppositories and films, in development).

At the core of rational design of new HIV prevention strategies is the understanding of how product characteristics (delivery vehicle and molecular payload) govern its pharmacokinetics (PK) and pharmacodynamics (PD). These are under the control of the designers and developers. Those PK and PD also depend upon biological and physiological characteristics of the users of a product, and upon their patterns of product application in relation to sexual activity. Thus, product performance (as embodied in PK, PD and also acceptability) is a multivariate process. The mandate of rational design is to specify product characteristics that are robust to biological and behavioral variability of users in achieving ‘best possible’ PK and PD, and willingness to use. This project undertakes such an optimization, using mathematical modeling of PK and PD specific to particular dosage forms (vehicles) and molecular payloads (drugs, antibodies).

We currently have first and second generation models for topically applied gels (vagina, rectum), films (vagina), suppositories (vagina), fast dissolving inserts (vagina), and intravaginal rings. These deliver active pharmacological ingredients (APIs) that act either intra-mucosally (e.g. Tenofovir, Dapivirine, IQP 0528, EFdA) or within the lumen (e.g. Cyanovirin-N, Griffithsin). Priorities are improvement and translation of modeling for intravaginal rings and fast dissolving inserts. This CFAR Summer Internship project will contribute to creation and application of next generation modeling for one of these two dosage forms.

Outputs and Uses of Our Modeling

1. Detailed PK across lumen, epithelium, stroma (host cells) and blood – deterministic multicompartment diffusion-convection mass transport modeling (API concentrations vs. time and space/compartment; coupled PDEs solved in Matlab, Comsol).

2. PD based upon interpreting detailed PK predictions: (a) reference to prophylactic concentrations, e.g. concentrations vs. EC50 values in target compartments; and (b) inclusion of
viral transport and infection dynamics, and computation of probability of infection (mass transport PDEs for virions, coupled systems of ODEs for viral dynamics; Matlab, Comsol).

3. Relationships of API concentrations in blood (vs. time) to prophylactic values in target compartments (e.g. luminal fluid, host cells in mucosal stroma) (neural nets)

4. Sensitivity analyses of 1. and 2. to account for variations in user characteristics (e.g. vaginal anatomy and histology, fluid production; Sobol indices). Use of these results in identification of salient product characteristics (e.g. API release rates) governing performance, and in deducing their optimal values to maximize measures of performance/PD.

5. Guidelines for experimental PK studies. Use results from 1. – 4. to inform optimum times for PK sampling (e.g. to best capture tmax, Cmax, AUC, etc.), and optimum locations along vaginal and rectal canals at which to take biopsies.

6. Use of 4. to suggest criteria for PK and efficacy study participant screening and stratification (e.g. influence of cycle phase and parity on PK values).

7. Use 1. – 4. to establish rules for allometric scaling between product applications in humans and other animals (non-human primates [NHPs], sheep) in which PK studies are conducted.

Scope of Internship Project

Weeks 1. Select IVR or FDI and API.

Weeks 2 – 4. Learn and run existing codes to compute PK and some measures of PD.

Weeks 5 – 7. Conduct initial parametric variation and compare results with data from PK studies in humans, NHPs and sheep.

Week 8. Identify limitations of model and work on plans for its improvement.

Week 9 – 10. Write up results for presentation at CFAR symposium, possible late breaking abstract for HIV R4P 2020, and publication.

Desirable Skills

Familiarity with ODEs and PDEs.

Experience with Matlab (or Python) and Comsol.