Pharmacokinetics and Pharmacodynamics: Implications for PEP Recommendations and Regulatory Approvals

Charles Flexner, MD
Johns Hopkins University

Disclosures

- **Research grants and contracts:** NIH
- **Consulting:** Gilead, GlaxoSmithKline, Merck, Navigen, Theratechnologies, ViiV Healthcare
- **Honoraria:** IAS-USA, Virology Education, McGraw Hill
- **Stockholder and equity:** Navigen
- **Patents and intellectual property:** Six issued patents related to the development of long-acting formulations for delivery of antiretroviral drugs.

PK/PD: Outline

I. What are the PK targets?

II. Value of Bridging and Modeling

III. Regulatory and Scientific Challenges: Pharmacology Perspectives

IV. Limitations of Existing Data

V. Questions and Conundrums

What are the PK targets for HIV PEP?

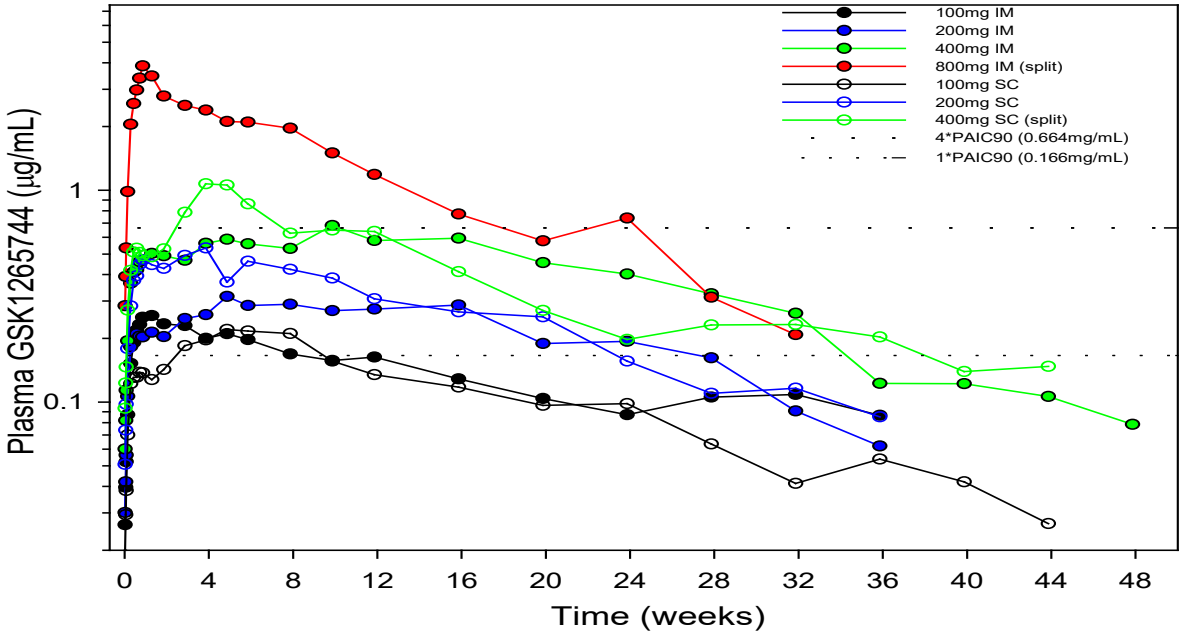
PK targets for HIV PEP?

- It is biologically plausible that drug concentrations capable of preventing HIV in a PrEP setting should also be effective for PEP.
- The generally accepted target for ARV's in the prevention setting is the IQ4 (4X the protein adjusted IC_{90}).
  - Difficult to validate in prospective clinical trials
- There are established *post hoc* correlations between ARV concentrations (especially intracellular TFV-DP) and likelihood of PrEP failure in clinical trials.
- These correlations are biased by lack of randomization, lack of adjustment for level of risk, and "adherence pollution."

LA/ER Cabotegravir Single Injection Provides Detectable Drug in Plasma for >48 Weeks

JOHNS HOPKINS MEDICINE

Mean Plasma CBT Concentration-Time Profiles following Single Dose IM or SC Injections in Healthy Subjects



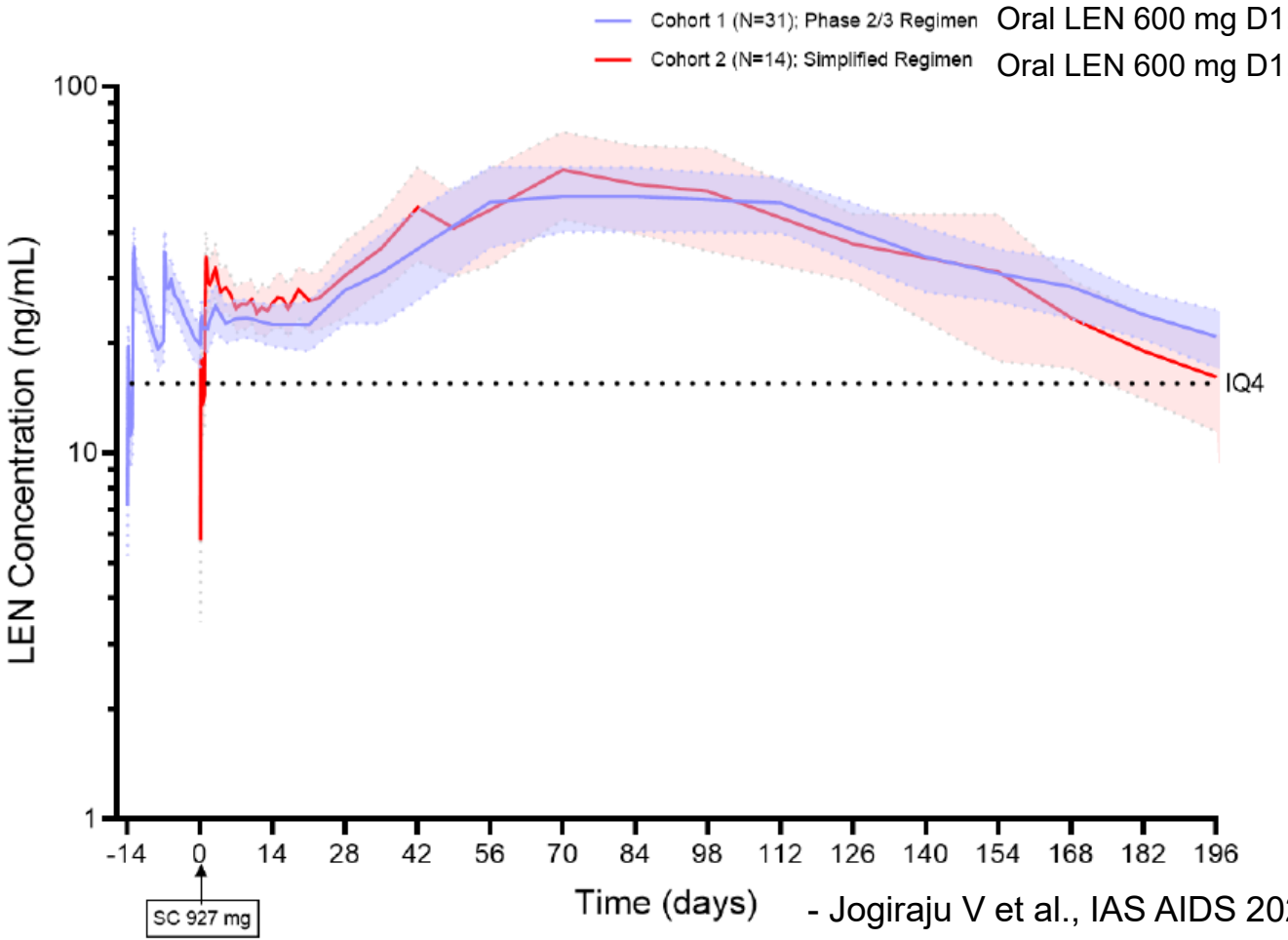
- WR Spreen et al., Current Opinion HIV AIDS 2013

Bridging and Modeling

Bridging and Modeling

- Bridging PK and efficacy data from PrEP studies to PEP is limited by the different relationship between timing of virus exposure, and time to achieve target drug concentrations in the effect compartment.
- Bridging data from treatment and PrEP trials could be used to eliminate the requirement for extensive safety data in PEP.
- Modeling can be used to determine how quickly different regimens achieve required target concentrations.
  - Importance of loading doses?
  - Dose requirements for immediate effect?
- Modeling can predict the impact of circulating drug resistance.
- Modeling could be used to “pick the winners!”
  - For example, the NNRTI MK-8527 can achieve effective plasma concentrations within one hour of oral administration.
  - May be faster than some current oral drugs or injectables, even with loading.

Figure 1. Mean* LEN Plasma PK Profiles Following Phase 2/3# and Simplified^ Regimens



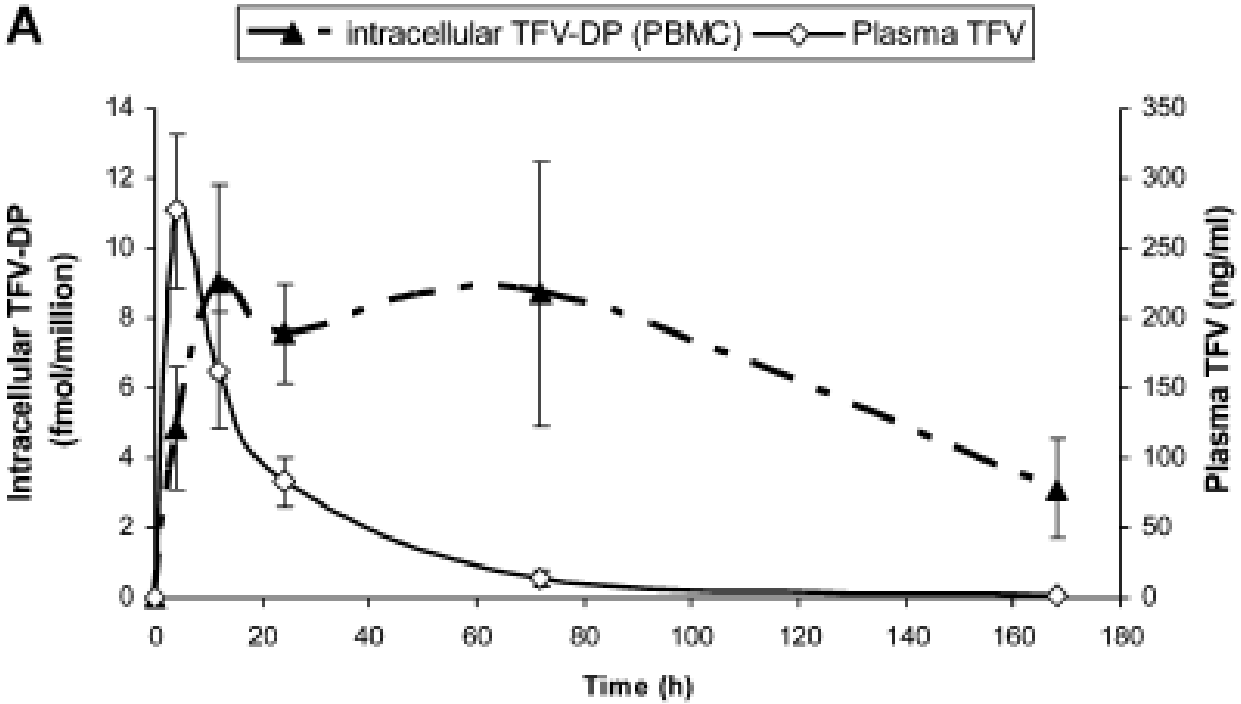
- Jogiraju V et al., IAS AIDS 2022

Regulatory and Scientific Challenges: Pharmacology Perspectives

Regulatory and Scientific Challenges

- We need human data!
  - Regulatory bodies like the FDA are unlikely to approve an indication based solely on animal data or PK bridging.
- A PEP label would likely require a "timestamp" (e.g., "initiate within X hours").
  - Collecting sufficient human data to establish this may not be feasible or ethical.
  - Unclear if substituting in vitro and/or animal data would be acceptable.
- Plasma, tissue, and intracellular concentrations of ARV’s and their metabolites all tell different stories.

Tenofovir PK: Plasma versus intracellular



- Chen J et al., *J Acq Immun Defic Syndr.* 2012; 61: 593-599

Limitations of Existing Data

Limitations of Existing Data

- PK data for daily orals in treatment or prevention is difficult to use for bridging to PEP due to guesswork around adherence.
- Regulatory agencies have not accepted intracellular or tissue concentrations of any ARV as a surrogate for PK exposure.
- While animal models provide important proof of principle, biological differences between species mean results must be validated in humans for a label indication.

Questions and Conundrums

Questions and Conundrums

- Must target concentrations in the PEP setting be reached “immediately,” or would a more gradual increase (e.g., hours or days) be equally effective?
  - The paradox of orals versus injectables in the PEP setting
- How should the window of intervention, and the point of futility, be defined?
- What data would be required to prove that a single (novel) agent is adequate for effective PEP?
- Is there value in developing PEP guidelines that are drug and formulation agnostic, or should recommendations always be tailored to the PK/PD characteristics of each product?
  - Value of Target Product Profiles?
- Will recommendations depend on the route of exposure (i.v. versus sexual versus needle stick)?

Acknowledgements

- Craig Hendrix, JHU
- Kim Struble, FDA
- Logan Donaldson and Veronica Miller, The Forum