PLENARY 3

Charles Flexner Johns Hopkins University

"How long does a BE study need to be for a LAI ARV?"

"We need to flip flop how we think about BE for LA formulations as compared to oral drugs"

What is "steady state" (SS) for LAIs?

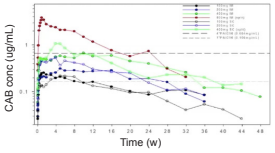
Achieving SS within BE studies may not even be relevant.

- It takes a very long time for most LAI formulations to reach SS.
- FDA did not require CAB-LA or LEN to reach SS in P1 or P3 studies.
- LAIs have different PK principles than oral formulations.
  - ◊ LAIs exhibit absorption-dependent (flip flop) kinetics: Rate of absorption (Ka) is much slower than the rate of elimination (Kel).

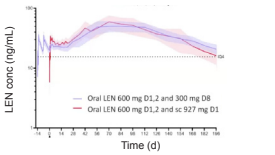
	Oral	LAI
Systemic exposure	• Depends on the rate of absorption (From GI tract) and clearance (Hepatic).	• Depends more on the release rate (From IM/SC depot) and absorption than clearance (Hepatic or renal).
Important PK parameters for BE	• Cmax and AUC.	• **Absorption rate.**

Why are we thinking about BE in the same way for LAI and oral formulations?

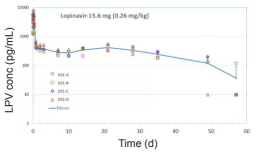
- Shouldn't BE be focused on absorption for LAIs?
  - ◊ Particularly if Ka does not change significantly over time.
  - ◊ As long as the drugs are safe, Cmax and AUC are not the important PK parameters.
- Absorption curves for LAI ARVs.
  - ◊ SD CAB-LA (100-800mg) IM.
    WR Spreen et al, Curr Op HIV AIDS 2013
    * A complex formulation with remarkably **constant drug absorption for nearly 1y**.



  - ◊ SD LEN (927mg) SC.
    Jogiraju V et al, IAS AIDS 2022
    * Substantially more complex formulation in terms of distribution and absorption.
    * Once the distribution phase is complete (~ 8w), **constant drug absorption for 4m.**



  - ◊ SD TLC-ART 101 SC.
    Bender Ignacio R et al, Int AIDS Congress 2024
    * Intermediate complexity between CAB-LA and LEN.
    * Rapid LPV release during the distribution phase (First 4-5d), then **constant LPV release and absorption for nearly 2m**.



Does BE for LAIs require PK sampling over the entire period of detectability?

Why not accept Ka as evidence of equivalence if it remains unchanged for a "reasonable" amount of time?

- CAB-LA (See absorption curve above).
  - ◊ Modeling the absorption rate for any of the CAB-LA curves would yield a similar Ka, and that Ka does not change for almost 1y.
- LEN (See absorption curve above).
  - ◊ Measuring Ka at any time point during the 4-month interval after the distribution phase would yield a similar result.

BE (As defined by RAs) is a probability statement.

- The degree of confidence one needs determines how much data must be collected.
  - ◊ Measuring PK properties of one formulation vs another using standard statistics within a predetermined confidence bound assures us that two formulations are similar enough to warrant using one in place of the other in a clinical setting.
- **At what point can we be confident that a new formulation has reproduced the absorption curve of the originator? (e.g. CAB-LA).**

BE as a Bayesian probability statement

Bayesian vs traditional frequentist statistics.

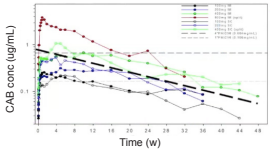
- Bayes' postulate: A probability statement is likely to be more accurate if it takes into account that which has already occurred (Bayesian prior).
- Bayesian probability thought experiment.
  - ◊ Fill a box with 50 black and 50 white balls, then remove balls one at a time in a blinded fashion.
  - ◊ What is the probability at any moment in time that you will remove a black or white ball?

Frequentist Thinking	Bayesian Thinking
• **The probability is always 50:50.**	• It is highly unlikely that one would pull out 50 black balls then 50 white balls. • **The make up of the first 50 balls drawn changes the probability of any ball picked later.**

- **We are all Bayesian thinkers. Why aren't we all Bayesian statisticians?**
  - ◊ Complexity. Incorporating prior data into a probability statement is much more complicated than traditional frequentist probability analysis.
  - ◊ Limited exposure. Bayesian statistics are not typically taught in medical or graduate schools.
  - ◊ Controversy regarding what constitutes a Bayesian prior.

Applying Bayesian probability analysis to BE studies.

- Pre-existing PK data are Bayesian priors that all can agree on.
- Partial AUCs (pAUC) are a good idea.
  - ◊ How much of a pAUC is needed to reach a reasonable consensus on BE?
  - ◊ CAB-LA example (i.e., A "well-behaved" formulation).
    * Would you agree to receive a new formulation with a 2-month prior? 3 months? 6 weeks?
    * Given the Ka stability, the probability that Ka 0.02 at 2m would be 0.05 or 0.01 at 6m is vanishingly small.



- Possibility of Bayesian drug regulation.
  - ◊ Collect partial data.
  - ◊ Inform recipients about the level of confidence for the probability of equivalence rather than accumulating all data and conducting a huge frequentist BE analysis.
  - ◊ Obtain informed consent early in drug development. Individuals agree to receive the low-cost formulation knowing that absolute BE determinants have not yet been met from a regulatory point of view but that data collection will continue with updates on BE status.

Our statistical philosophy impacts our clinical philosophy

A cautionary tale: Frequentist data analysis has sometimes led us astray.

- *Neural-tube defects and ARV treatment regimens in Botswana*.
- Frequentist analysis (Zash R et al, NEJM 2019) led to a regulatory decision that DTG should not be given to women of reproductive potential (i.e., They received less effective ARVs).
  - ◊ Counted the number of infants with neural-tube defects (NTDs) per number of exposures.
    * **Statistically significant increase in NTDs after DTG exposure at conception.**
- Bayesian analysis of same data (JHU).
  - ◊ Incorporated all known pregnancies with DTG exposure from prior clinical trials and published studies (Bayesian priors).
    * **The difference in neural-tube defects does not meet statistically significant bounds.**