Pragmatic Approach for Interpreting Antiretroviral Drug Concentrations Based on a Systematic Review of Population Pharmacokinetic Studies

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OBJECTIVE

To summarize published population pharmacokinetic (Pop-PK) estimates of antiretroviral drugs (ART) in order to derive reference pharmacokinetic curves that can be used for therapeutic drug monitoring (TDM) guided dosage adjustment.

METHODS

A systematic search of Pop-PK studies of 6 ART (efavirenz, nevirapine, etravirine, darunavir, atazanavir, lopinavir) in adult patients was performed in PubMed.

In each study, pharmacokinetic parameters were derived for a typical "baseline" patient (Caucasian male 70 kg, no influencing genetic variants, concomitant medications, nor pathophysiological conditions modulating drug kinetics).

A 1-compartment model was mostly used and retrieved parameters were: clearance (CL), terminal volume of distribution (Vz) and absorption rate constant (ka) with standard errors and interpatient variability. For bi-compartment models, V_z was derived from CL/λ_z. Various absorption models (first order, zero order, mixed absorption, with or without lag time) were reported, which were standardized for a first-order absorption process using the mean absorption time MAT=1/ka:

$$MAT=\frac{1}{k_{a_{original}}}+Lagtime \qquad MAT=\frac{D_1}{2} \qquad MAT=\frac{1}{k_{a_{original}}}+\frac{D_1}{2}+Lagtime$$

Standard errors on estimated and derived parameters for the baseline typical patient were computed by applying the error propagation method. Standard errors on inter-patient variability were directly retrieved from the published papers.

Pharmacokinetic parameters were summarized across studies for each drug using a random-effect meta-analysis approach, using the metafor package in *R (*R-project.org*)*. The weighted mean parameter (θ) with its standard error (SE) and the variance of the inter-individual variability component (ω) were computed as:

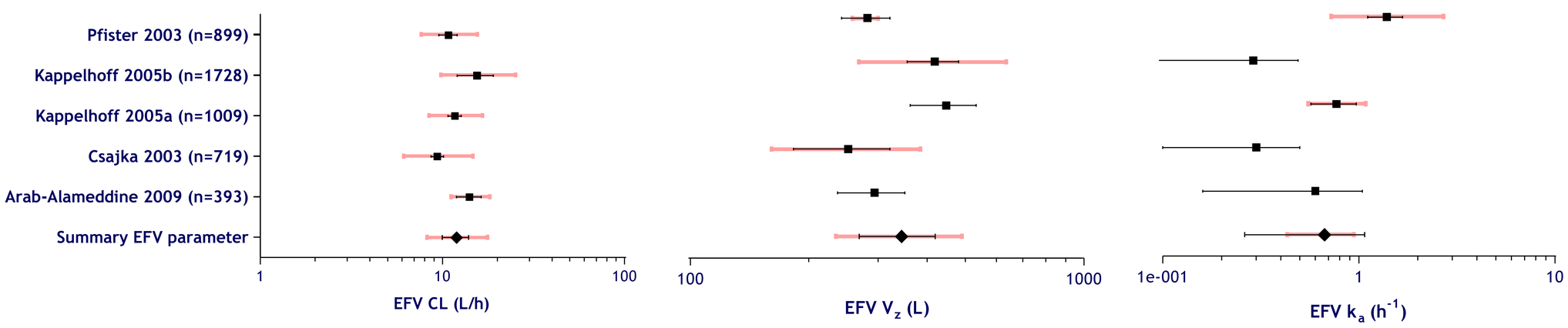
$$M^*=\frac{\sum_{i=1}^{k} W_i^* Y_i}{\sum_{i=1}^{k} W_i^*} \qquad V_{M^*}=\frac{1}{\sum_{i=1}^{k} W_i^*}$$

where M* is the summary parameter (θ or ω) and V_{M^*} the variance of the summary parameter (SE^2); Yi is the parameter estimate of the i^{th} study and Wi* is the weight associated to the i^{th} study, defined as the inverse of the sum of the within- and between-study variances.

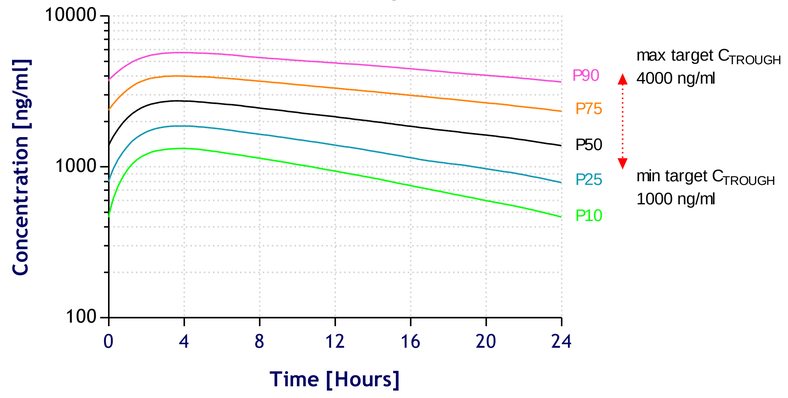
Concordance between individual and summary parameters was assessed using Forest-plots. To test robustness, difference in simulated curves based on published and summary parameters was performed using efavirenz (EFV) as a probe drug.

References concentration vs. time curves over a dosing interval were simulated in 1000 patients using NONMEM® based on the summary population PK estimates of CL, V_z and ka with inter-patient variability, as appropriate.

RESULTS: The example of Efavirenz



Forest plots representing mean parameter estimate with 95% CI (black dots and lines) and inter-individual variability (red lines) for the individual study and the summary parameter (n= number of concentrations)



Simulations of EFV 600 mg QD based on the summary parameters and interpatient variability

- CL was in good agreement throughout all 5 Pop-PK models, suggesting that target concentrations can be derived with good precision. Absorption was however very heterogeneously described.
- Comparison of the percentiles curves after simulation based on the summary model or the published study parameters did not reveal any major bias in EFV concentrations over the dosing interval, except in the few hours after drug intake (maximal bias of 20%)

CONCLUSION

- Many Pop-Pk studies are available for ART drugs that provide useful information regarding their kinetics, but standardization across studies is seldom performed.
- Such a meta-analysis approach incorporating the results of several populations might thus provide a better description of drug pharmacokinetic profile. This approach will be further refined and implemented in the Bayesian TDM of ART with the integration of relevant influencing covariates.