

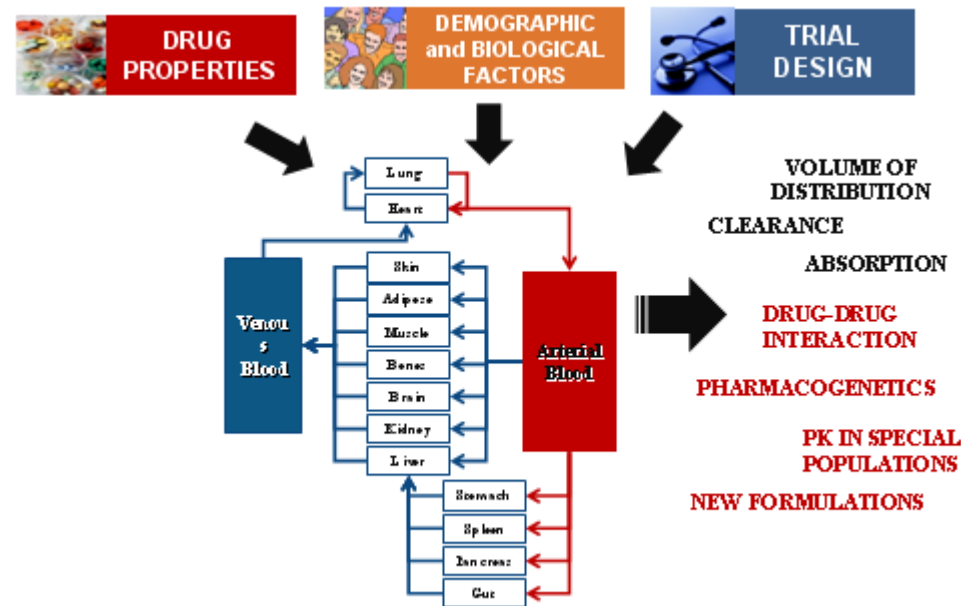
using a Physiologically Based Pharmacokinetic Model

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Background: Erlotinib (ERL) is used to treat patients with non-small lung or pancreatic cancer. ERL is mainly metabolized by CYP3A4, providing a rationale for drug interactions with antiretroviral drugs.

Physiologically based pharmacokinetic (PBPK) modelling is the mathematical description of anatomical, physiological and molecular processes defining drug distribution, through the integration of drug characteristics and patient-specific factors.

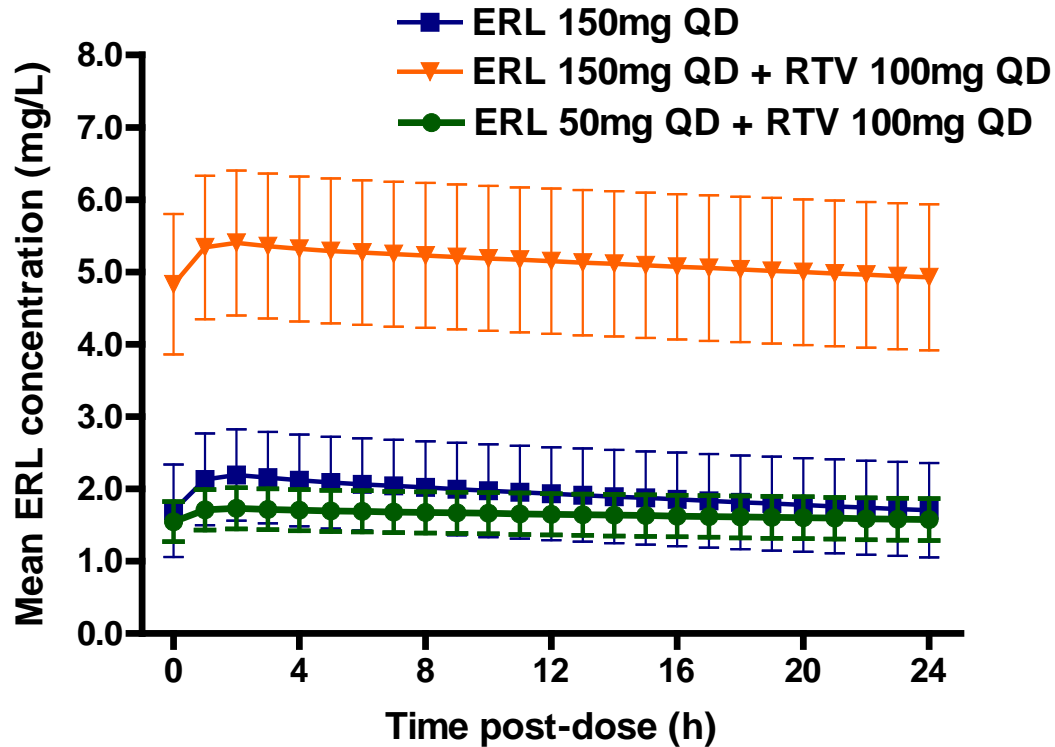


Aims: To simulate the interaction between ERL and ritonavir (RTV) using a PBPK model, and to hypothesize potential dose adjustments to overcome this interaction.

Methods

- A virtual population of 50 individuals was generated using a population physiology model.
- Validated equations were used for the calculation processes regulating ADME.
- *In vitro* data on chemical properties and ADME of ERL, RTV and MDZ, as well as the inhibition/induction potential of CYP3A4 by RTV were obtained from the literature.
- **Simulation of drug concentration-time profiles**
(Simbiology; MATLAB, v. 2013b).
 - **Scenario 1:** ERL 150mg QD for 21 days.
 - **Scenario 2:** RTV 100mg QD for 21 days.
 - **Scenario 3:** Single dose MDZ 2mg with/without RTV 400 mg BID.
 - **Scenario 4:** ERL 150mg QD plus RTV 100mg QD for 21 days.
 - **Scenario 5:** ERL 50mg QD plus RTV 100mg QD for 21 days

Results



GMR (90% CI) for PK of ERL + RTV vs. ERL 150mg QD

	ERL150mg QD + RTV 100mg QD	ERL 50mg QD + RTV 100mg QD
C_{trough}	3.01 (2.74-3.31)	0.97 (0.88-1.06)
C_{max}	2.51 (2.33-2.71)	0.81 (0.75-0.87)
AUC_{0-24}	2.74 (2.52-2.98)	0.88 (0.81-0.96)

Conclusions

- The developed PBPK model predicted the *in vivo* pharmacokinetics of ERL and RTV and their interaction.
- The increase in ERL exposure driven by RTV 100mg QD may be mitigated by reducing the ERL dose to 50mg QD.
 - However, these results should be validated in clinical practice.
- PBPK modeling may be a useful tool for both prediction of drug-drug-interactions and selection of doses to be explored in prospective clinical trials.