



A Computer Artificial Intelligence System to Aid in the Interpretation of Plasma Lopinavir and Efavirenz Drug Concentrations

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Introduction

- Therapeutic drug monitoring (TDM) allows for individual pharmacologic evaluation, but is limited by the interpretation of the individual concentrations.
- If TDM is practical in a real-world clinical setting, a strategy must be developed to interpret patient plasma concentrations in the context of expected or population ideal concentrations.
- In addition to pharmacokinetic (PK) modeling the artificial intelligence (AI) system will need to incorporate patient characteristics (i.e. therapy naïve versus experienced, CD4 count, drug toxicity) and HIV factors (i.e. baseline HIV viral load, HIV RNA response to therapy, HIV drug resistance) in determining an individual's optimal therapeutic concentration.
- The objective of this study was to develop a computer-based expert system for modeling and interpreting pharmacokinetic data for lopinavir (LPV) and efavirenz (EFV).

Methods

Knowledge Base System: This is an expert system designed to emulate clinical decision making. There are three primary components to the system: (1) Knowledge Base, (2) Inference Engine and (3) User Interface.

1. AI Knowledge Base: Data were extracted from CCTG 578, a prospective study of therapeutic drug monitoring in 199 antiretroviral-naïve and -experienced patients. An expert committee of HIV clinicians and pharmacologists evaluated real-time pharmacokinetic data and recommended therapy to study investigators. From these recommendations, decision algorithms were generated to interpret plasma concentrations. These algorithms formed the knowledge base of the expert artificial intelligence system (Figure 1).

Concentration Modeler: The expert committee modeled LPV and EFV concentrations using a Bayesian nonlinear curve fitting approach to estimate 4-hour post dose concentration (C_{1-h}) and trough concentration (C_{trough}). The AI system modeler utilized Monte Carlo simulations to compute estimated trough and 4-hour post-dose PK metrics. Monte Carlo simulation is a method for calculating probability distributions in which a process is simulated a large number of times and its results are used to infer a solution. Simulations were based on published intensive PK models and parameters which generated the equations for the LPV and EFV. The individual patient concentrations and the population distribution percentiles are graphed (Figure 2).

2. Inference Engine: The AI system uses multiple logic techniques to integrate PK modeling with clinical data, including: prior ARV history, HIV RNA treatment response, and HIV phenotypic drug susceptibility to generate a therapeutic drug monitoring recommendation (Figure 3).

3. User Interface: The physician-user enters patient data into a web-based interface (Figure 1).

Statistics: Paired t-tests were used to compare numerical means of estimated trough and 4-hr post dose concentrations between those generated by the expert committee and the artificial intelligence system. κ statistic was used to measure the inter-rater agreement between the expert committee recommendations to make dose adjustments or not with the artificial intelligence recommendations.

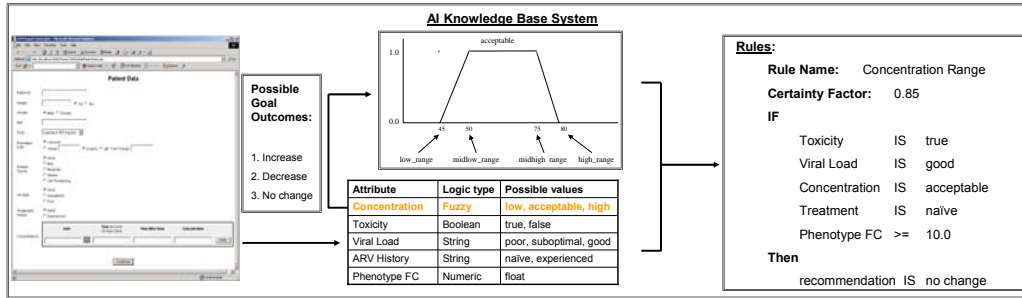


Figure 1. Simplified schematic of AI Knowledge Base decision algorithm. The physician-user first enters patient data. The knowledge base contains: 1. Goals, Attributes and Rules. Possible decision goals are to recommend: increase, decrease or no change in ARV exposure. Data from the physician-user input are organized into attributes and assigned a particular logic type which interprets the data. For example, concentration data is interpreted using fuzzy logic which can adjust for systems with imprecise limits and rates the degree of certainty for a given conclusion. Next, the system looks for rules that can be fired with the current working memory (forward chaining) to construct a recommendation output (i.e. increase, decrease, no change).

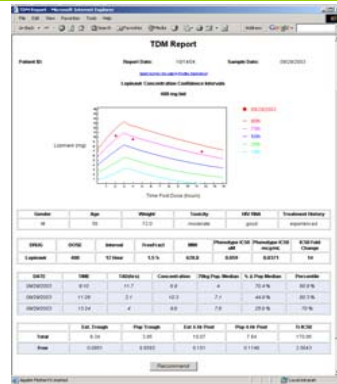


Figure 2. Sample TDM Report. The graph contains the patient's individual concentrations and five population distribution percentile curves plotted versus hours post dose. The displayed curves are for the 10th, 25th, 50th, 75th, and 95th percentiles.



Figure 3. Sample TDM Recommendation. A confidence factor that reflects the overall confidence in a recommendation is calculated using an ad hoc method combining fuzzy logic's degree of truth and other certainty factors. When multiple rules suggest the same conclusion, the confidence in one parameter is reinforced by the other.

Results

- Sixty-six patients on LPV, 47 on EFV and 3 on both were analyzed.
- Correlations were high for both LPV and EFV in 4-hour and 12-hour predicted concentration between the expert committee and artificial intelligence systems ($r > 0.89$ for all comparisons, $p < 0.0001$).
- There was no statistical difference between artificial intelligence and expert committee therapeutic drug monitoring modeled values for trough concentrations of either drug, but differences were seen for predicted 4-hour concentrations (Table 1):
 - Agreement between expert committee and artificial intelligence therapeutic drug monitoring recommendations were seen in 53 of 69 LPV cases ($\kappa = 0.53$, $p < 0.001$) and 47 of 49 EFV cases ($\kappa = 0.91$, $p < 0.001$).
 - For LPV, there were 16 discordant recommendations, three of which the committee recommended an improvement in adherence (not an option in the AI system) while the AI system did not recommend a change.

Table 1. Comparison of Pharmacologist Modeled Concentration and AI Modeler. Paired student t-tests were used to compare numerical means of estimated trough and 4-hour post dose concentrations.

Parameter	Mean	Std. Dev.	P value
LPV (C_{trough}) Pharmacologist modeler	6.45	2.9	0.62
LPV (C_{trough}) AI modeler	6.15	3.2	
LPV (C_{4-h}) Pharmacologist modeler	8.79	3.4	<0.001
LPV (C_{4-h}) AI modeler	7.99	3.3	
EFV (C_{trough}) Pharmacologist modeler	2.01	1.1	0.39
EFV (C_{trough}) AI modeler	2.01	1.1	
EFV (C_{4-h}) Pharmacologist modeler	3.89	1.4	0.02
EFV (C_{4-h}) AI modeler	4.16	1.9	

Conclusions

Good agreement was seen between the expert committee and artificial intelligence modeled values for trough concentrations. The artificial intelligence system successfully predicted committee recommendations for EFV better than LPV, though both had good κ statistics.

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