

Title: Population Pharmacokinetic Models and Individualized Bayesian Dose Optimization in HIV Patients

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Objectives: To describe the usefulness of simulated population pharmacokinetic models in the optimization of antiretroviral doses, safety and efficacy in individual patients.

Methods: Antiretroviral population pharmacokinetic models, each with oral absorption into a single compartment, were constructed using the MM-USC*PACK software collection [1] (available at www.lapk.org). PK parameter estimates obtained or derived from over 30 published studies were used to generate, by Monte Carlo simulation with noise, populations of n=50 for each drug. Simulated populations were then analyzed using the Non-Parametric Adaptive Grid (NPAG) program in MM-USC*PACK [2] to generate a population PK model for each antiretroviral drug. The models were applied as part of comprehensive clinical care to outpatients in our HIV clinic using MM-USC*PACK's multiple-model, Bayesian adaptive control to individualize therapy.

Drug	Population	k_a	V_d	CL
Nelfinavir	Children	0.2 h ⁻¹	2.1 L/kg	1.0 L/h·kg
Efavirenz	Children	0.3 h ⁻¹	4.2 L/kg	0.1 L/h·kg
fos-Amprenavir	Adults	3.0 h ⁻¹	5.7 L/kg	0.7 L/h·kg
Atazanavir	Adults	1.0 h ⁻¹	86.2 L	8.1 L/h

Table – Mean model parameter values. Models based on pediatric studies were used for patients with a Tanner Sexual Maturity Rating stage ≤ 3 .

Results: In 3 years, approximately 20 patients in our clinic have had some form of dose optimization; 4 of them will be presented with individual MM-USC*PACK output for each shown in the figure below. **Patient 1** was a 13-year old antiretroviral-naïve African boy (Tanner stage 2), started on an efavirenz-based regimen at the recommended dose for his age. After 2 weeks, his mother reported that he was too drowsy to attend school, more severe than the typical transient drowsiness after starting efavirenz. Suspecting that he was a genetic slow metabolizer, we empirically reduced his dose by half, and a week later measured a serum concentration of 1.37 mg/L 22 hours after his previous dose. His 24-h trough concentration was predicted to remain above a target of 1 mg/L [3]; therefore, he continued on this dose. A follow-up sample confirmed his therapeutic concentrations on 50% dose, and has maintained an undetectable HIV viral load with no further somnolence for the past 2 years. **Patient 2** was a 10 year-old girl (Tanner stage 2) who weighed 30.7 kg. Based on the standard pediatric dose of 55 mg/kg, given formulation limitations, she was prescribed 1875 mg. Since the recommended “maximum” is the adult dose of 1250 mg, we measured a random serum concentration of 4.9 mg/L 4 hours after her previous dose to ensure that she was not in a toxic range. Her predicted peak concentration was 5.9 mg/L and her 12-h trough was 1.6 mg/L, both within a suggested therapeutic range of 1 - 6 mg/L [3], and she never demonstrated toxicity despite the continued “supra-maximal” dose. **Patient 3** was a 45 year-old woman (Tanner stage 5) with a long history of medication intolerance. She was started on a fos-amprenavir containing regimen (without ritonavir), 2 x 700 mg tablets twice daily. After starting the new regimen, she complained of daytime fatigue, which she attributed to the morning dose. She enquired about taking the entire dose at night. Prior to making changes, we measured a serum amprenavir concentration of 1.4 mg/L 4.5 hours after her previous dose. Modeling suggested that although 2800 mg once daily would not maintain her trough concentration above the minimum target of 0.23 mg/L [3], a regimen of 1 tablet at 8am followed by 3 tablets at 6pm (a 10-14 hour schedule) would achieve this goal. She was changed to the latter regimen, and has achieved an undetectable viral load without any further complaints of fatigue. A follow-up level of 0.9 mg/L 4 hours after the morning dose on the new regimen confirmed that her predicted troughs were likely to be therapeutic. **Patient 4** was a 14-year old male (Tanner stage 4) with poor adherence. To encourage better adherence, he was changed to a once-daily regimen that included atazanavir given in combination with low-dose ritonavir. The usual adult dose of atazanavir is 300 mg when given with ritonavir, so he was started on 200 mg based on his small size. Since there were no published pediatric PK data at the time, we obtained a random atazanavir concentration of 0.782 mg/L 18 hours after his previous dose. His predicted trough concentration was 0.380 mg/L, above the minimum target of 0.150 mg/L [4],

so the dose was continued. He initially achieved an undetectable viral load but persistently poor adherence allowed his viral load to rebound partially to about 2000 copies/mL, despite a second confirmed therapeutic concentration of atazanavir, suggesting probable emergence of viral atazanavir resistance.

Conclusions: Our method for converting reported PK data into population PK models can be used locally to optimize safety and efficacy in individual patients. Successful therapeutic drug *management* (as opposed to passive monitoring) tailored to patients representing 4 scenarios was presented: 1) altered metabolism; 2) supra-“maximal” doses; 3) dosing schedules not FDA approved; and 4) dosing with limited relevant published PK data. As individual dose optimization requires expertise and *by definition* is difficult to standardize, we submit that clinical trials are unlikely to show the true benefit of such a process, and that additional case reports would encourage application of population PK/PD models supplemented by individualized Bayesian adaptive control to the care of patients, beyond models’ current primary domain of drug development.

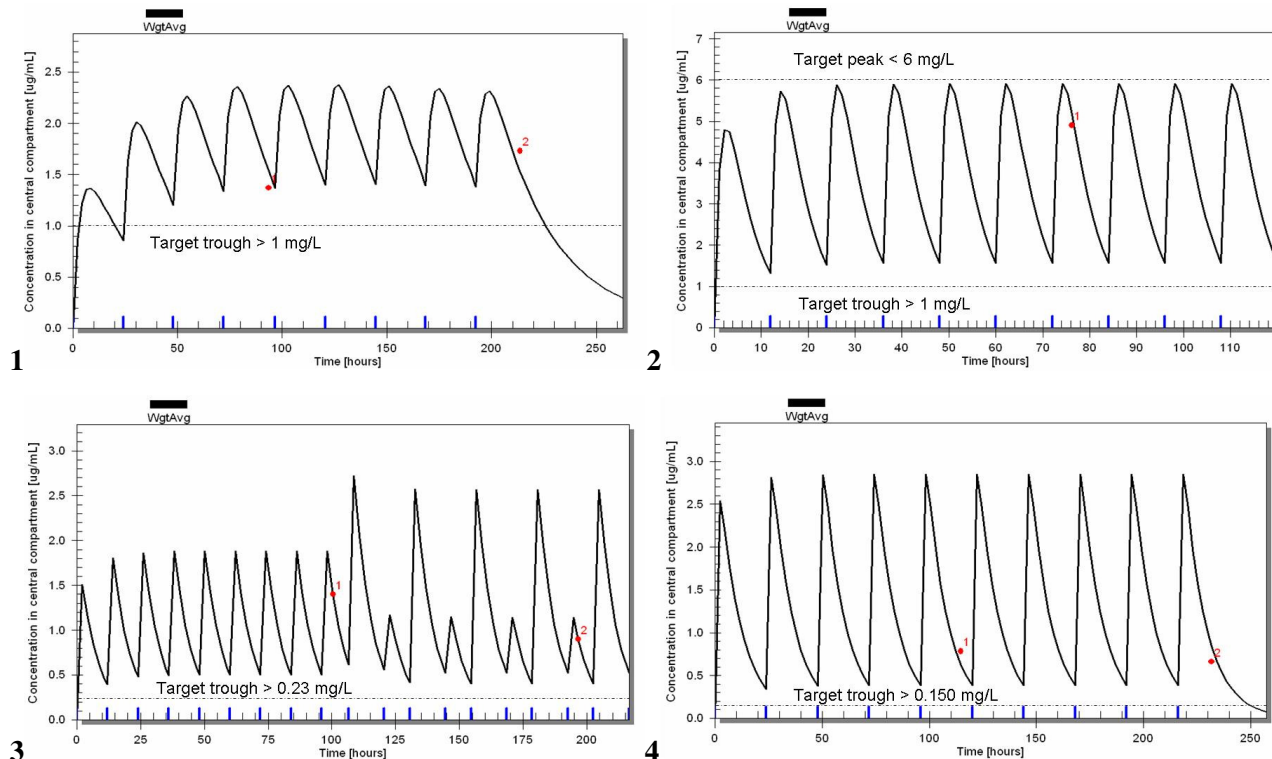


Figure – MM-USC*PACK output for each patient. Black lines are weighted average Bayesian-posterior predicted concentrations, red dots are measured serum concentrations, and blue lines are dose events. Intervals between measured serum concentrations have been compressed for clarity.

References:

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