

Population pharmacokinetic analysis of dolutegravir in HIV-1 infected individuals



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Objectives

- The aims of this observational study were
 - to characterize dolutegravir (DTG) pharmacokinetic (PK) profile
 - to quantify interpatient variability
 - to identify potential factors that could influence drug exposure

Methods

- All DTG plasma concentrations data were collected as part of routine therapeutic drug monitoring performed in our centre, between June 2014 and December 2015 from HIV antiretroviral treatment-naive and experienced patients.
- A population PK analysis was performed by comparing various structural models using NONMEM®.
- The effect of relevant demographic factors (gender, body weight, age, race) aspartate aminotransferase (AST), alanine aminotransferase (ALT) and antiretroviral co-medications on DTG disposition was explored.

Results

DATA

- A total of 594 plasma levels were measured in 514 HIV-positive patients under steady state regimen conditions.
- Plasma concentrations ranged between 31 and 7971 ng/mL drawn between 1 and 52 hours after drug intake.

Population description

Characteristics	n (%) or median (range)
Male	395 (77%)
Age (years)	47 (17-79)
Body weight (Kg)	73 (37-131)
Smoking (yes)	189 (36%)
Naive patients	75 (15%)
ALT (U/I)	29 (6-792)
AST (U/I)	28 (5-343)
Atazanavir (ATV)	14 (3%)
Darunavir (DRV)	98 (19%)
Etravirine (ETV)	15 (3%)

Structural and error model

- A one compartment model best characterized DTG pharmacokinetic. Average clearance (CL) was 0.99 L/h (CV 3%), volume of distribution (V_d) 18.9 L (CV 8%) and constant absorption (k_a) 1.37 h⁻¹ (CV 35%).
- A mixed model error was used to describe intra-patient variability, where additive residual error and proportional residual error were 230 ng/mL and 33.1% respectively.

Covariate model

- Body weight and age increased DTG CL/F by 29% and 24% respectively as well as smoking status (17%).
- Co-administration of atazanavir decreased DTG clearance by 38% and the association of darunavir increased its CL/F by 14%.

Pharmacokinetic parameters in the final model with bootstrap results

Parameters	Final Population PK parameters		Bootstrap (n=1000 samples)	
	Estimate	RSE (%)	Median	CI 95%
CL/F (L/h)	0.93	3	0.93	0.87-1.00
V_d/F (L)	18.9	8	18.53	15.6-22.0
k_a (h ⁻¹)	1.27	59	1.25	0.34-3.41
IIV _{CL/F} (%)	27.5	10	27.1	0.4-0.1
Θ_{ATV}	-0.38	25	-0.37	-0.67
Θ_{DRV}	0.14	36	0.13	0.04-0.25
$\Theta_{Smoking}$	0.16	26	0.16	0.8-0.25
Θ_{Age}	0.24	28	0.24	0.1-0.37
Θ_{BW}	0.29	35	0.28	0.08-0.47
Proportional residual error (%)	33.6	8	33.6	28-39
Additive residual error (ng/mL)	230	15	223.6	112.1 -296.4

CL/F: apparent clearance, **V_d/F** apparent volume of distribution, **Θ_{ATV}** : relative decrease of clearance in the presence of atazanavir, **Θ_{DRV}** : relative increase of clearance in the presence of darunavir, **$\Theta_{Smoking}$** : effect of smoking status on DTG CL/F, **Θ_{age} , Θ_{BW}** : effect of age and body weight on DTG CL/F

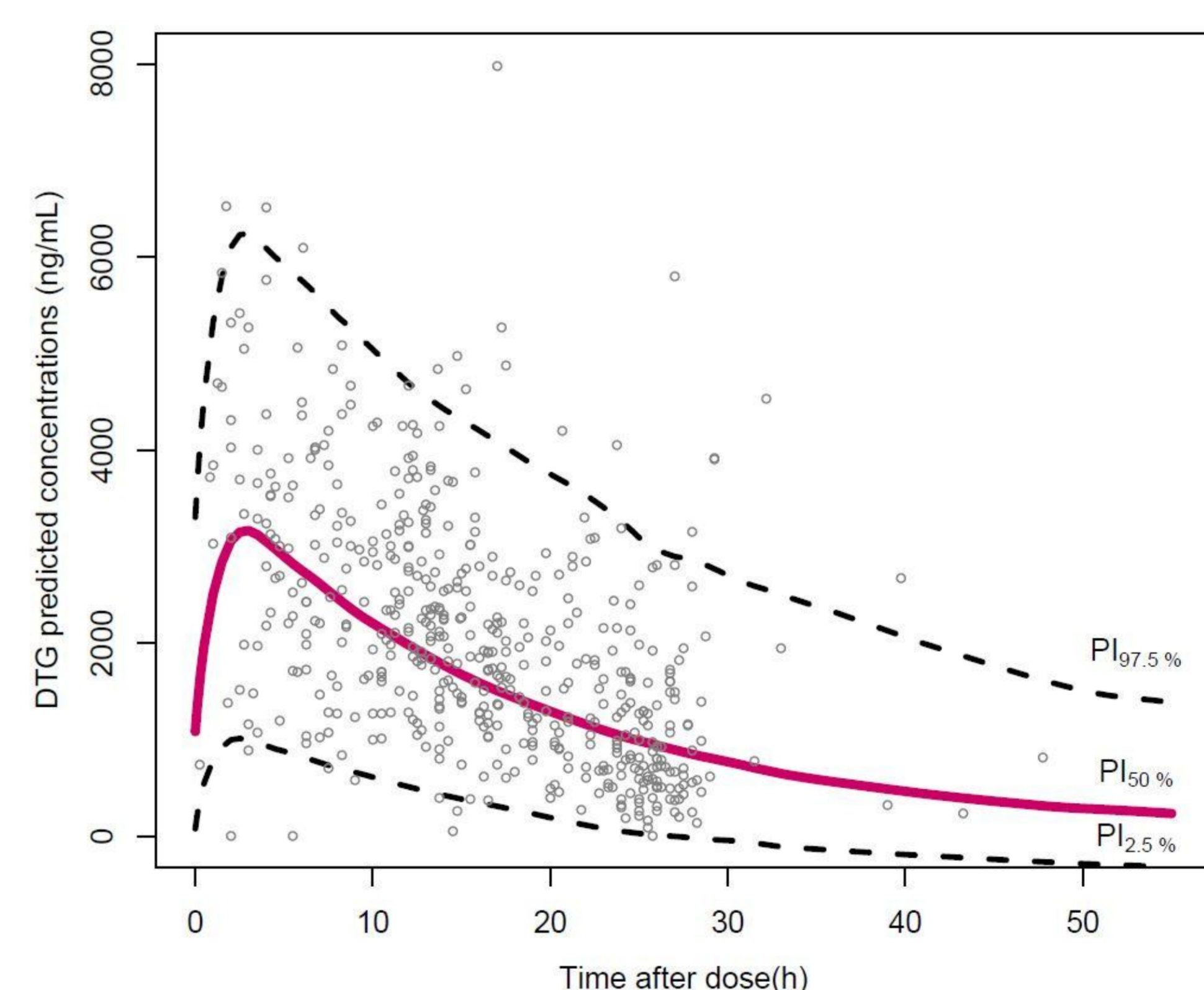


Figure: Dolutegravir observed plasma concentrations (open circles) with median population prediction (continuous line) and 95% prediction intervals (PI) (dashed lines).

Final DTG model:

$TVCL = 0.93 \times (1 - 0.38 \text{ ATV}) \times (1 + 0.14 \text{ DRV}) \times (1 + 0.16 \text{ Smoking}) \times (1 + 0.29 \text{ (BW-73/73)}) \times (\Theta_{Age} \text{ (Age/47)})$
ATV: atazanavir; DRV: darunavir,

Conclusions

- The variability in DTG pharmacokinetics appears to be lower than in other antiretroviral drugs.
- Several covariates influencing DTG exposure were identified. However, their effect appears to be relatively modest and seems not to be clinically significant except for ATV co-administration.
- This model will serve to elaborate a Bayesian tool for DTG dosage individualization in specific situations. (<http://www.ezechiel.ch/>).

References

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