Population pharmacokinetic meta-analysis of 7 antiretroviral drugs

Implementation in the TDM software EzeCHiel

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S. Petitprez[(1)], Y. Thoma[(2)], Y. Sutter [(2)], R. Hooper [(2)], A. Chaouch [(1,3)], M. Arab-Alameddine [(4)], T. Buclin [(1)], C.Csajka [(1,5)], M.Guidi [(1,5)]

(1) Division of Clinical Pharmacology and Toxicology, University Hospital, Lausanne, Switzerland
(2) School of Engineering and Business of the Canton of Vaud, Yverdon, Switzerland
(3) Division of Biostatistics, Institute for Social and Preventive Medicine, University Hospital, Lausanne, Switzerland
(4) Merck Biopharma, Quantitative pharmacology-global early development, Switzerland
(5) School of Pharmaceutical Sciences, Universities of Geneva and Lausanne, Switzerland

Objectives

To perform a systematic review of population pharmacokinetic (Pop-PK) studies in order to generate meta-models of seven different antiretroviral (ART) drugs. These models are implemented into a Bayesian TDM software (EzeCHieL) currently under development and used in the context of therapeutic drug monitoring (TDM) for the optimization of dosage regimens.

Methods

- Systematic litterature search on Pubmed of Pop-PK studies of:
  - Non-nucleoside reverse transcriptase inhibitors (NNRTI): Efavirenz (EFV), Nevirapine (NVP), Etravirine (ETV)
  - Protease inhibitors (PI): Unboosted Atazanavir (ATV), and Lopinavir (LPV/r), Atazanavir (ATV/r) and Darunavir (DRV/r) boosted with Ritonavir
  - Integrase inhibitor (II): Raltegravir (RAL)
- Pop-PK parameters normalized for a typical individual (70 kg, male, Caucasian, carrying reference allele for all influencing genetic covariates).
- Meta-analysis with R using fixed effect models, on 1 or 2 compartment models with simplified absorption phase (*i.e.* 1st order)
- PK percentiles (5, 50, 95%) for standard dosage regimens generated with EzeCHieL

Results

- Reference studies retrieved from Pubmed and combined in the meta-analysis

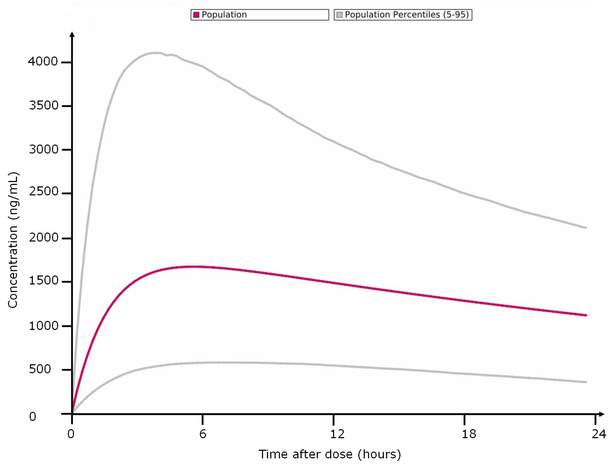
NNRTI					
EFV		**ETV**		**NVP**	
Sanchez et al	2011	Kakuda et al	2016	Guidi et al	2012
Arab Alameddine et al	2009	Lubomirov et al	2011	Foissac et al	2012
Kappelhof et al A	2005	Kakuda et al	2010	Lehr et al	2011
Kappelhof et al B	2005			Schipani et al	2011
Pfister et al	2003			Dailly et al	2009
Csajka et al	2003			Elsherbini et al	2009
				Molto et al	2008
II				Kappelhof et al	2005
RAL				de Maat et al	2002
Arab-alameddine	2012			Zhou et al	1999

PI					
ATV		**ATV/r**		**LPV/r**	
Goutelle et al	2013	Schipani et al.	2013	Wang et al	2014
Kile et al	2012	Foissac et al.	2011	Lopez Aspiroz	2011
Foissac et al.	2011	Barrail-Tran et al	2009	Urien et al	2011
Schipani et al.	2010	Dickinson et al	2009	Lubomirov et al	2010
Colombo et al.	2006	Solas et al	2008	Bouillon-Pichault et al	2009
DRV/r		Colombo et al	2006	Molto et al	2008
Dickinson et al	2016			Jullien et al	2006
Molto et al	2013			Crommentuyn et al	2006

- Percentiles obtained with the meta-models generated by Ezechiel

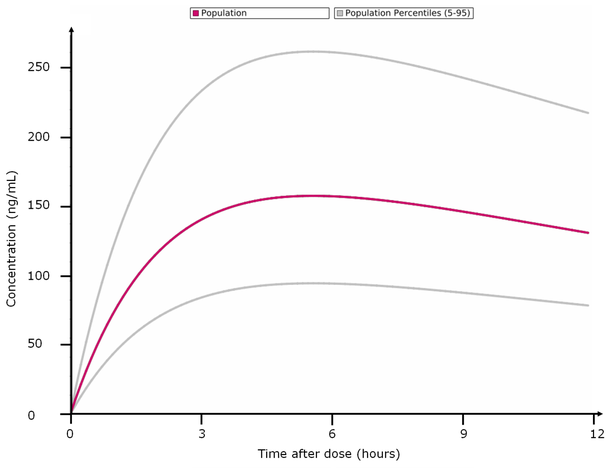
EFV	Estimate	*RSE %*
CL (L/h)	11	*2*
Vc (L)	314	*4*
k_a (h^{-1})	0.59	*9*
IIV CL (CV%)	0.54	*8*
IIV V (CV%)	0.63	*14*
IIV Ka (CV%)	0.42	*24*
Prop. residual error (%)	0.20	*5*

Fig. 1. Percentile curves derived from EFV pop-PK simplified model (600mg QD)



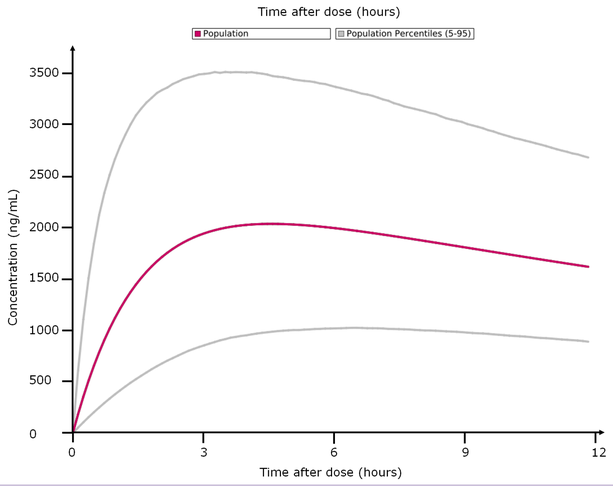
ETV	Estimate	*RSE %*
CL (L/h)	43	*3*
Vc (L)	986	*2*
k_a (h^{-1})	0.47	*18*
IIV CL (CV%)	0.63	*8*
Prop. residual error (%)	0.31	*2*

Fig. 2. Percentile curves derived from ETV pop-PK simplified model (200mg BID)



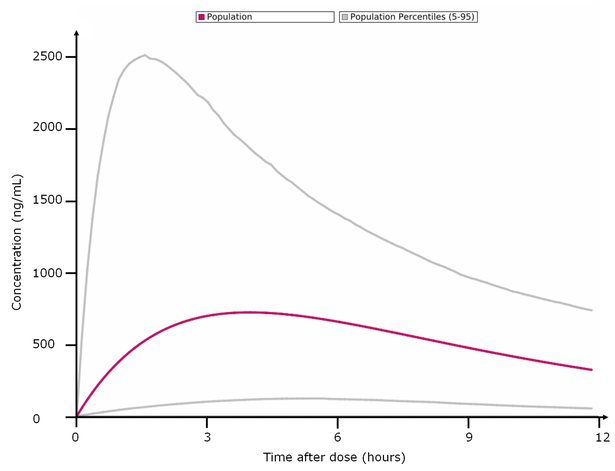
NVP	Estimate	*RSE %*
CL (L/h)	3.3	*4*
Vc (L)	82	*2*
k_a (h^{-1})	0.65	*7*
IIV CL (CV%)	0.31	*4*
IIV V (CV%)	0.31	*3*
IIV Ka (CV%)	0.66	*17*
Prop. residual error (%)	0.24	*2*

Fig. 3. Percentile curves derived from NVP pop-PK simplified model (200mg BID)



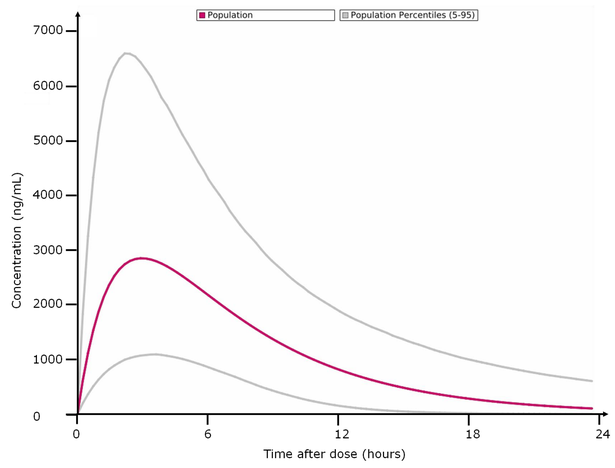
RAL	Estimate	*RSE %*
CL (L/h)	45	*44*
Q (L/h)	6.4	*54*
Vc (L)	167	*53*
Vp (L)	85	*41*
k_a (h^{-1})	0.21	*16*
IIV V (CV%)	0.87	*93*
IIV Ka (CV%)	0.94	*53*
Prop. residual error (%)	0.60	*36*

Fig. 4. Percentile curves derived from RAL pop-PK simplified model (400mg BID)



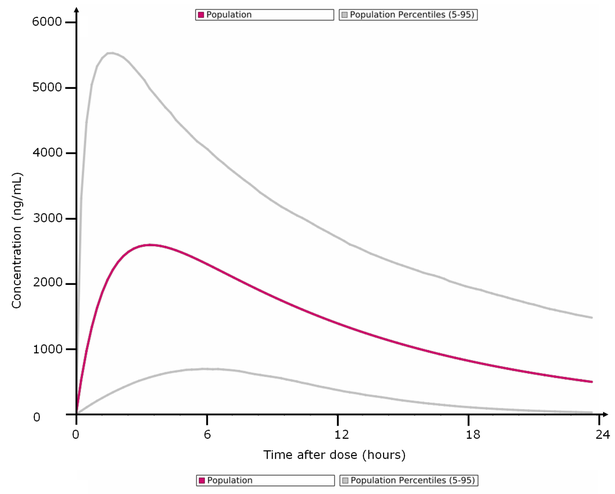
ATV	Estimate	*RSE %*
CL (L/h)	15	*11*
Vc (L)	83	*13*
k_a (h^{-1})	0.57	*13*
IIV CL (CV%)	0.23	*18*
IIV V (CV%)	0.50	*6*
IIV Ka (CV%)	0.25	*45*
Prop. residual error (%)	0.41	*16*

Fig. 5. Percentile curves derived from ATV pop-PK simplified model (400mg QD)



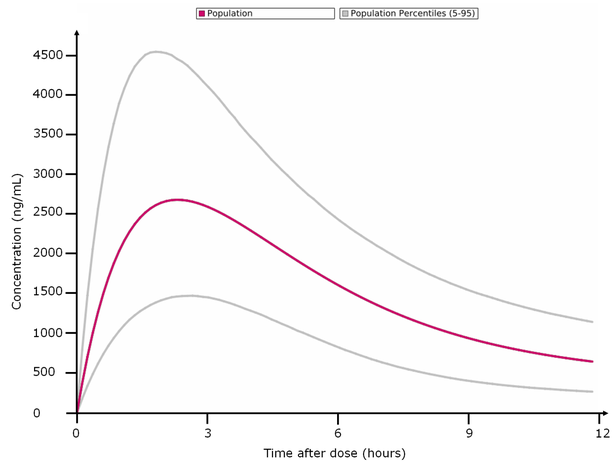
ATV/r	Estimate	*RSE %*
CL (L/h)	8	*3*
Vc (L)	86	*4*
k_a (h^{-1})	0.69	*6*
IIV CL (CV%)	0.43	*9*
IIV V (CV%)	0.50	*9*
IIV Ka (CV%)	1.28	*10*
Prop. residual error (%)	0.28	*8*

Fig. 6. Percentile curves derived from ATV/r pop-PK simplified model (300mg QD)



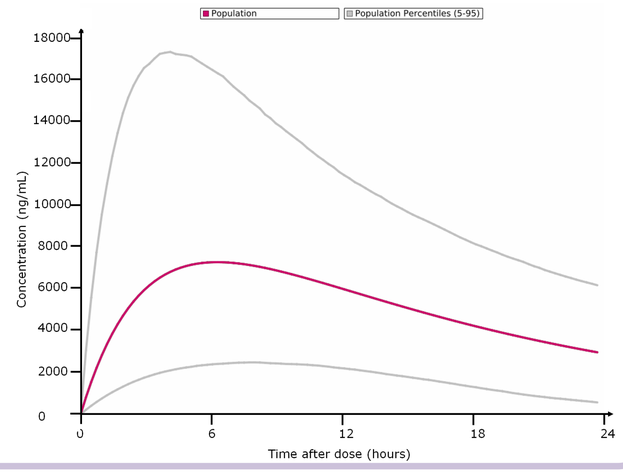
DRV/r	Estimate	*RSE %*
CL (L/h)	12	*5*
Q (L/h)	21.8	
Vc (L)	113	*7*
Vp (L)	454	
k_a (h^{-1})	0.63	*5*
IIV CL (CV%)	0.31	*14*
IIV V (CV%)	0.45	*14*
IIV Ka (CV%)	0.37	*13*
Prop. residual error (%)	0.25	*16*

Fig. 7. Percentile curves derived from DRV/r pop-PK simplified model (600mg BID)



LPV/r	Estimate	*RSE %*
CL (L/h)	3.3	*3.8*
Vc (L)	82	*1.9*
k_a (h^{-1})	0.65	*7.4*
IIV CL (CV%)	0.31	*0.5*
IIV V (CV%)	0.31	*0.9*
IIV Ka (CV%)	0.66	*41*
Prop. residual error (%)	0.24	*0.5*

Fig. 8. Percentile curves derived from LPV/r pop-PK simplified model (800mg QD)



Conclusions

- CL, V, Ka values as well as their IIVs could be extracted from all the studies (except for ETV were only IIV CL was available in publications)
  - Simplified 1 compartment meta-models with 1st order absorption were generated for EFV, ETV, NVP, ATV, ATV/r and LPV/r
  - Only one group studied RAL Pop-PK. The corresponding 2 compartments model (simplified to 1st order absorption) was directly implemented in EzeCHieL
  - 3 studies describe DRV/r Pop-PK , but the meta-analysis was performed only with the 2 publications describing 2 compartments models.
- The current limitations of the fixed-effect meta-analysis method use in this study as well as the percentile curves generation are currently addressed through the development of new methods.
- Combined with the use of EzeCHieL, an user-friendly and state-of-the-art Bayesian TDM software, these results will provide a valuable tool for optimizing antiretroviral therapy based on best available evidence.