



A Semi-mechanistic population pharmacokinetic model quantifying hair concentrations of ritonavir-boosted atazanavir. A study of HIV infected Zimbabweans adolescents.

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Introduction

- Adolescence experience higher levels of non-adherence to treatment of HIV[1].
- Measuring drug concentration in hair promises to be reliable method for assessing exposure to antiretroviral drugs due to accumulation from plasma[2].
- Modelling and simulation approach are necessary to explore the usefulness of quantifying drug concentrations in hair for the benefit of measuring long term adherence.
- Drug plasma measurements cannot reliably be used for adherence monitoring especially in settings where patients took the drugs only towards clinic visits.

Objectives

- To develop a pharmacokinetic model based on drug concentrations determined in the hair
- To identify population characteristics associated with variability in ritonavir-boosted concentrations in hair

Methods and Materials

- Data used in model development and validation was obtained from a study conducted in Zimbabwean adolescents on HIV treatment for at least one month[1].
- Participants were randomized to the intervention or control study arms. Hair samples and other data variables were collected at enrolment and at three-month follow-up.
- Model development was done using NONMEM 7.3[3]. Previously published models describing population pharmacokinetics of as atazanavir or ritonavir in plasma were utilized, and parameter estimates were fixed to literature values[4],[5].
- The fraction of the drug that accumulated in hair was estimated while the hair volume of distribution was fixed to unit for both drugs.
- Stepwise covariate modelling strategy was used for covariate selection[6].
- Model assessment included use of goodness of fit plots in Xpose4[6].

Table 2. Ritonavir final pharmacokinetic model parameter estimates

Parameter	Population mean (SE as %)	Variability (SE as %)
K_a (litres hour ⁻¹)	2.31 fixed	0.45 fixed
CL (litres hour ⁻¹)	12.8 fixed	0.28 (318)
V_2 (litres)	105 fixed	0.50 fixed
FRAC	0.18 (16)	
V_3 (Litres)	1 fixed	
Occasion (Enrolment): FRAC	-0.42 (22)	
Adherence by VAS: FRAC	0.02 (47)	
Disease stage (Early): V_3	-0.37 (43)	
ϵ_{ADD}	0.34 (95)	
ϵ_{PROP}	0.26 (26)	
Ω	1	

Figure 3. Goodness of fit plots for the ritonavir final pharmacokinetic model

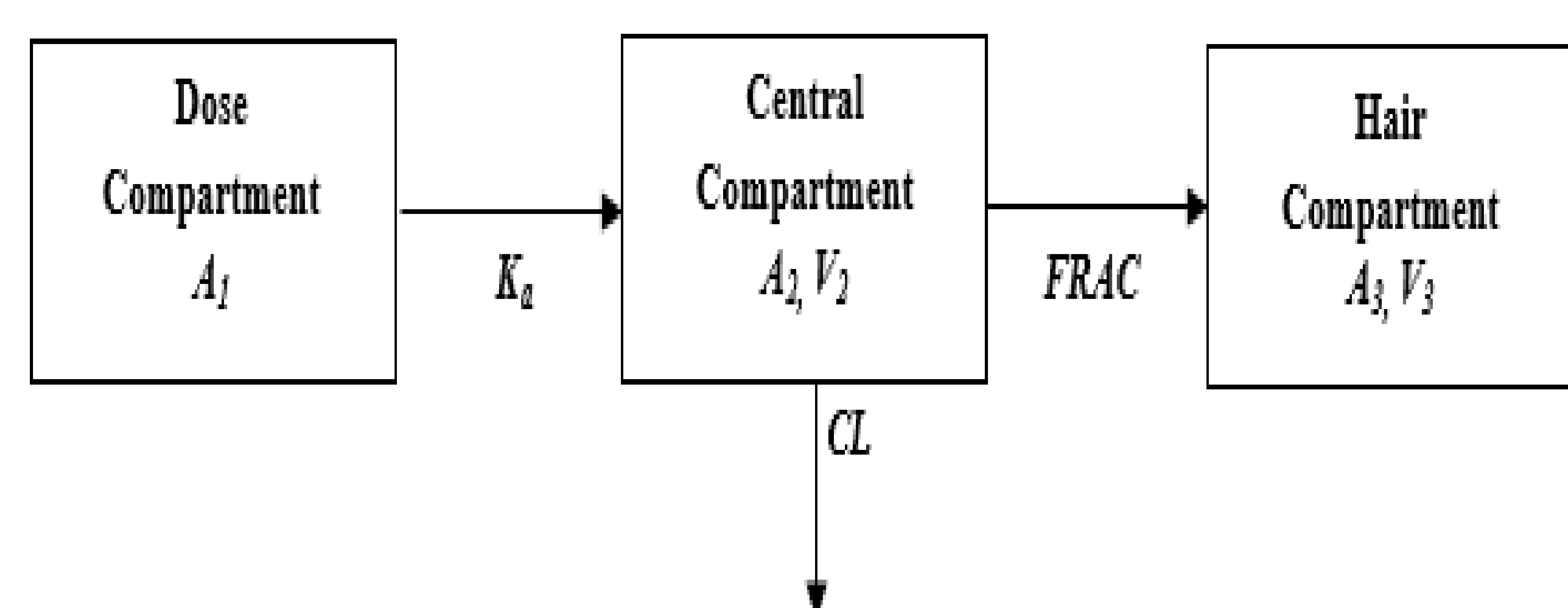
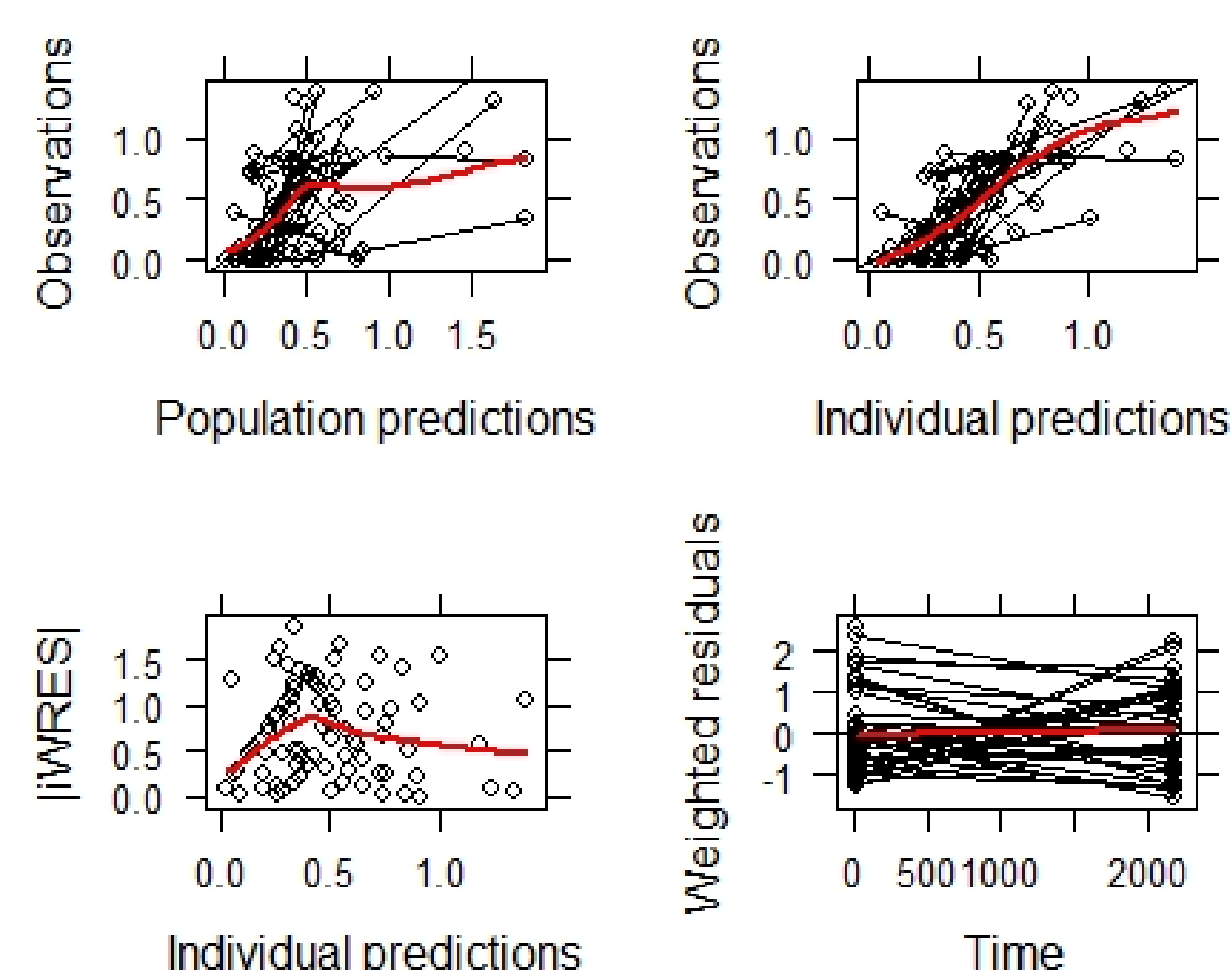


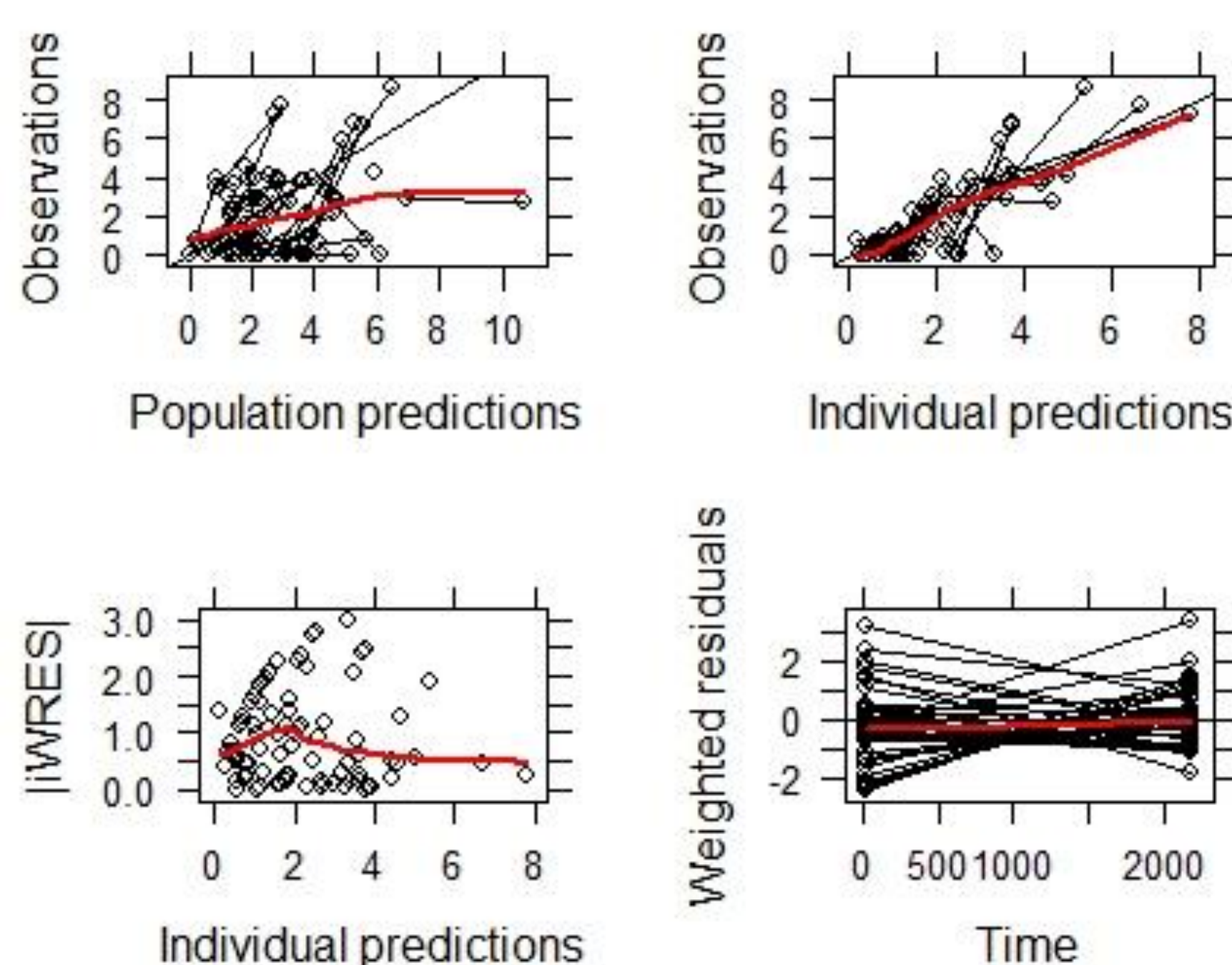
Figure 1. Schematic representation of a semi-mechanistic pharmacokinetic model to predict drug concentrations measured in hair. A_1 , A_2 & A_3 - amount of drug in the dose, central and hair compartments respectively; K_a - absorption rate constant; CL - renal clearance; V_2 & V_3 - volume of distribution in compartment 2 and 3 respectively; $FRAC$ - fraction of the drug which accumulates into hair.

Results

Table 1. Atazanavir final pharmacokinetic model parameter estimates

Parameter	Population mean (SE as %)	Variability (SE as %)
K_a (litres hour ⁻¹)	0.44 fixed	0.45 fixed
CL (liters hour ⁻¹)	10 fixed	1.04 (99)
V_2 (litres)	63.4 fixed	0.50 fixed
FRAC	0.16 (16)	
V_3 (liters)	1 fixed	
Occasion (enrollment): FRAC	-0.30 (23)	
Adherence by VAS: FRAC	0.02 (18)	
Age-adjusted BMI (thin): FRAC	-0.54 (22)	
Age-adjusted BMI (overweight): FRAC	0.21 (121)	
Guardian (parent): FRAC	0.53 (56)	
Guardian (uncle/aunt): FRAC	0.12 (177)	
Guardian (sibling): FRAC	-0.54 (35)	
Study arm (control): V_3	0.53 (56)	
ϵ_{ADD}	0.30 (1)	
ϵ_{PROP}	0.50 (2)	
Ω	1	

Figure 2. Goodness of fit plots for the atazanavir final pharmacokinetic model



Conclusions

- To the best of our knowledge this is the first study to attempt quantifying how much antiretroviral drug is absorbed in hair from plasma using modelling and simulation.
- Most important determinants of increased concentrations in hair were monitoring at follow up event, body weight and care.
- It is important to establish the relationship between hair pharmacokinetic parameters and a measure of treatment response such as viral loads or CD4 count.

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References

- [1] T. D. Chawana*, D. Katzenstein, K. Nathoo, B. Ngara, and C. F. B. Nhachi, "Evaluating an enhanced adherence intervention among HIV positive adolescents failing atazanavir/ritonavir-based second line antiretroviral treatment at a public health clinic," *J. AIDS HIV Res.*, vol. 9, no. 1, pp. 17-30, Jan. 2017.
- [2] T. D. Chawana et al., "Defining a cut-off for atazanavir in hair samples associated with virological failure among adolescents failing second-line antiretroviral treatment," *J. Acquir. Immune Defic. Syndr.* 1999, May 2017.
- [3] Alison J. Boeckmann, Lewis B. Sheiner, and Stuart L. Beal, "NONMEM Users Guide - Part V".
- [4] F. Foissac et al., "Population pharmacokinetics of atazanavir/ritonavir in HIV-1-infected children and adolescents," *Br. J. Clin. Pharmacol.*, vol. 72, no. 6, pp. 940-947, Dec. 2011.
- [5] C. Zhang, P. Denti, E. H. Decloedt, Y. Ren, M. O. Karlsson, and H. McIlleron, "Model-based evaluation of the pharmacokinetic differences between adults and children for lopinavir and ritonavir in combination with rifampicin," *Br. J. Clin. Pharmacol.*, vol. 76, no. 5, pp. 741-751, Nov. 2013.
- [6] R. J. Keizer, M. O. Karlsson, and A. Hooker, "Modeling and Simulation Workbench for NONMEM: Tutorial on Pirana, PsN, and Xpose," *CPT Pharmacomet. Syst. Pharmacol.*, vol. 2, no. 6, p. e50, Jun. 2013.