

Influence of drug-drug interactions on the pharmacokinetics of atorvastatin and its active metabolite *ortho*-OH-atorvastatin in people living with HIV



Perrine Courlet¹, Monia Guidi^{1,2}, Matthias Cavassini³, Deolinda Alves³, Thierry Buclin¹, Catia Marzolini⁴, Laurent A. Decosterd¹, Chantal Csajka^{1,2}.

¹Service of Clinical Pharmacology, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland

²School of Pharmaceutical Sciences, University of Geneva, University of Lausanne, Geneva, Switzerland

³Division of Infectious Diseases, Lausanne University hospital and University of Lausanne, Lausanne, Switzerland

⁴Departments of Medicine and Clinical Research, University Hospital of Basel and University of Basel, Switzerland



Introduction and objectives

- People living with HIV (PLWH) are ageing and experience age-related comorbidities, such as cardiovascular diseases.
- Atorvastatin is a widely prescribed lipid lowering agent, subject to extensive first-pass and pre-systemic metabolism.
- Atorvastatin is metabolized by CYP3A4 into 2 active metabolites: the major *ortho*-hydroxy (*o*-OH-atorvastatin) and the minor *para*-hydroxy atorvastatin (*p*-OH-atorvastatin)¹. The organic anion transporting polypeptide (OATP1B1/1B3) facilitates the entry of atorvastatin in the liver².
- Protease inhibitors substantially increase atorvastatin exposure due to inhibition of OATPs thus interfering with the entry of atorvastatin in the liver and its subsequent biotransformation thereby potentially leading to serious side effects such as rhabdomyolysis.
- Aims of the work:**
 - To describe the pharmacokinetic (PK) profile of atorvastatin and *o*-OH-atorvastatin
 - To identify influencing factors
 - To evaluate drug-drug interactions (DDIs) with antiretroviral drugs (ARVs).

Methods

- Full PK profiles (87 samples) collected in 8 PLWH and 78 sparse samples obtained from 55 PLWH.
 - Below the limit of quantification (BQL) data : 34% of *o*-OH-atorvastatin concentrations treated using the M6 approach and 44% of *p*-OH-atorvastatin concentrations excluded from the analysis.
 - Atorvastatin plasma concentrations ranged from 0.3 to 106 ng/mL (0.6 to 190 nmol/L), while *o*-OH-atorvastatin concentrations varied from 0.5 to 24 ng/mL (0.9 to 42 nmol/L).
 - Atorvastatin and *o*-OH-atorvastatin were analyzed simultaneously using NONMEM® 7.4.3
- FR fraction of the dose converted into metabolite during first-pass metabolism
 CL_{ator} apparent atorvastatin clearance
 $CL_{o-OH-ator}$ apparent *o*-OH-atorvastatin clearance
 V apparent volume of distribution
 k_a total absorption rate constant
 k_{12} absorption rate constant from depot to atorvastatin compartment
 k_{13} absorption rate constant from depot to *o*-OH-atorvastatin compartment
 k_{23} metabolic rate constant
 k_{20} atorvastatin elimination rate constant
 k_{30} *o*-OH-atorvastatin elimination rate constant
- Linear or allometric models for continuous (age, body weight) and discrete (sex and comedication) covariates
 - Comparison of AUC_{0-24} of drug, metabolite and active moiety ($AUC_{0-24,AM} = AUC_{0-24,ator} + AUC_{0-24,o-OH-ator}$) between 1000 simulated PLWH receiving boosted vs non-boosted ARV drugs.

Results

Table 1: Population Description

¹strong CYP3A4 and OATP1B1 inhibitors / ²strong CYP3A4 inducers

Patients' characteristics (N=59)	median [IQR] or n (%)
Age (years)	64 [58-71]
Body weight (kg)	73 [65-84]
Men	46 (78)
Comedications in samples ³ (N=165)	n (%)
Ritonavir-boosted darunavir ¹	39 (24)
Cobicistat-boosted darunavir ¹	24 (15)
Ritonavir-boosted atazanavir ¹	2 (1)
Cobicistat-boosted elvitegravir ¹	2 (1)
Efavirenz ²	12 (7)
Etravirine ²	18 (11)
Nevirapine	4 (2)
Rilpivirine	2 (1)
Dolutegravir	80 (49)
Raltegravir	15 (9)

Table 2: PK parameters of the final model with bootstrap results.

¹based on preliminary analysis of atorvastatin rich pharmacokinetic data

Final population pharmacokinetic model	Estimate (RSE %)	Median	Bootstrap results (n=2000) CI 95%
k_a (h^{-1}) FIX ¹	3.06	3.06	
BSV _{k_a} (CV%)	308 (10)	185	62-43651
Logit(FR)	-1.51 (0.3)	-1.44	-2.39 to -0.92
BSV _{logitFR} (CV%)	66 (2)	68	62-77
$\theta_{boosted\ ARVs/logit(FR)}$	-2.01 (28)	-1.97	-14.3 to -0.73
CL_{ator} (L/h)	256 (0.08)	250	178-348
BSV _{CL_{ator}} (CV%)	64 (41)	71	64-80
$\theta_{boosted\ ARVs/CL_{ator}}$	-0.61 (7)	-0.61	-0.74 to -0.46
V (L)	3090 (0.07)	2845	1119-6683
BSV _{V} (CV%)	137 (10)	102	80-140
Q (L/h)	111 (0.1)	104	38-626
V_p (L)	624 (64)	697	298-10804
k_{23} (h^{-1})	0.006 (0.02)	0.006	0.001-0.01
$CL_{o-OH-ator}$ (L/h)	115 (0.05)	113	50-172
$\sigma_{ator, prop}$ (CV%)	40 (7.10 ⁻⁵)	38	30-47
$\sigma_{o-OH-ator, prop}$ (CV%)	29 (0.002)	28	22-34
$\sigma_{o-OH-ator, add}$ (nmol/L)	43 (26)	42	4-59
Correlation ator/ <i>o</i> -OH-ator	0.66 (2.10 ⁻⁵)	70	34-80

- TVLogit(FR) = -1.51-2.01 x boosted ARVs and TV CL_{ator} = 256 x (1-0.611 x boosted ARVs)
- FR = 18% and 3%, without and with boosted ARVs, respectively
- CL_{ator} = 256 L/h and 100 L/h, without and with boosted ARVs, respectively

Figure 1: Prediction- and variability corrected visual predictive check of the final model of (a) atorvastatin and (b) *o*-OH-atorvastatin. Open circles: observed plasma concentration; solid and dashed lines: median and P_{95%} of the observed data; shaded surfaces: corresponding 90% confidence interval (shaded yellow and grey surfaces for the median and low/high percentiles, respectively). Horizontal black lines: lower limit of quantification (LLOQ) of atorvastatin (0.54 nmol/L) *o*-OH-atorvastatin (0.87 nmol/L). In the lower panel, shaded areas: P_{95%} of the simulated BQL data; close circles: fraction of observed BQL data.

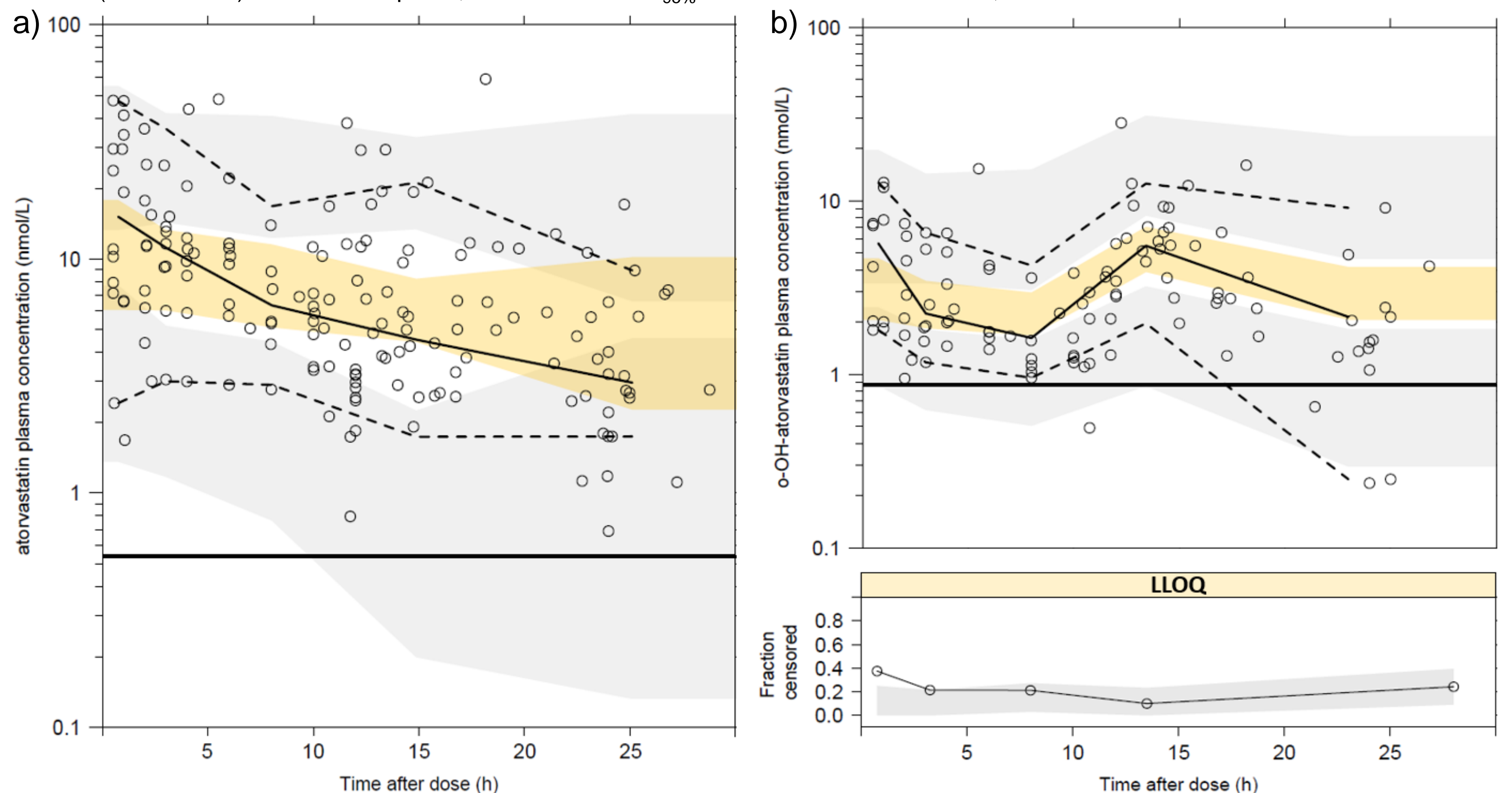
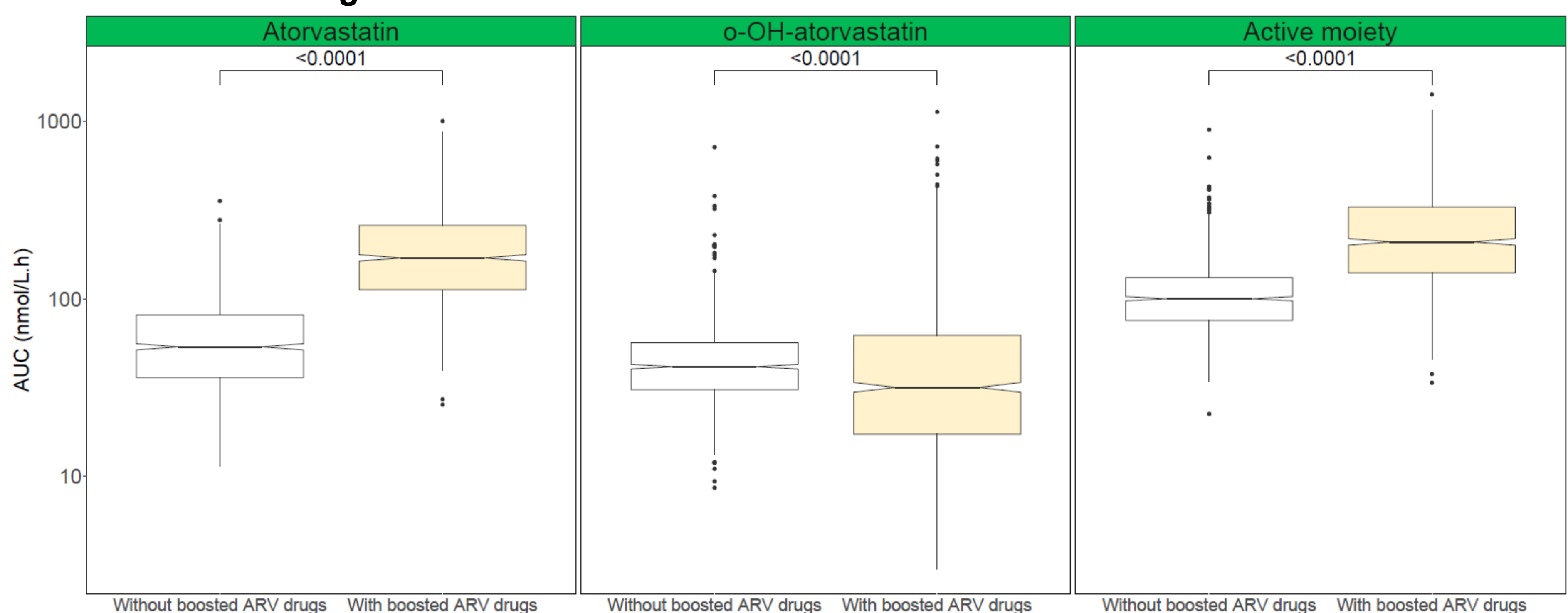


Figure 2: Comparison of simulated estimates of AUC_{0-24} after a dose of 10 mg once daily for atorvastatin, *o*-OH-atorvastatin and the active moiety between PLWH receiving or not boosted ARV drugs.



- Simulated average $AUC_{0-24,ator}$ indicates a 3.2 increase in atorvastatin exposure and a 23% decrease in $AUC_{0-24,o-OH-ator}$ in PLWH receiving boosted-ARV drugs compared to those who received unboosted regimens. In total, $AUC_{0-24,AM}$ was increased by two-fold in PLWH treated with boosted-ARVs compared to PLWH treated with unboosted regimens.

Conclusions

- Important inter-individual variability in atorvastatin pharmacokinetics that remained largely unexplained after inclusion of covariates.
- Drug exposure is doubled when coadministered with boosted ARV drugs. In principle, a half dosage is recommended in PLWH receiving boosted regimens, to provide the most efficient and safest patient's care.

1. Lennernas H. Clinical pharmacokinetics of atorvastatin. *Clinical pharmacokinetics*. 2003;42(13):1141-60.

2. Wu X, Whitfield LR, Stewart BH. Atorvastatin transport in the Caco-2 cell model: contributions of P-glycoprotein and the proton-monocarboxylic acid co-transporter. *Pharm Res*. 2000;17(2):209-15.

3. Food and drug administration. Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. [Available from: <https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm>.