Table S1. Summary of Covariates for Pediatric Data

	N	Minimum	Maximum	Median	Mean	SD
Weight (kg)	39	25	99.4	47	45.9	16.5
Age (yr)	39	6	17	12	11.6	3

Table S2. Fixed Effect Parameter Log for Pediatric Data Only Population Pharmacokinetic Models (*Using 70 kg as Reference Weight)

Model	Study	CL/F (L/hr)	Vc/F (L)	Q/F (L/hr)	Vp/F (L)	Ka (hr^{-1})	Fixed/Simplified Parameters
50	1172	830	51.6	105	$2.62e+10$	0.109	N
54	1172	375	22.6	312	$1.50e+03$	0.193	Vp/F, Ka
200	1172	864	1770.0	692	$6.19e+03$	0.289	Ka
44	1172	770	10400.0			6.910	Q/F, Vp/F dropped (1 compt model)

* = All models allometrically scaled using 70 kg reference weight, CL/F = ATV clearance, Vc/F = ATV volume of distribution, Q/F = ATV intercompartmental clearance, Vp/F = ATV peripheral volume of distribution, Ka = first-order absorption rate constant, N = none, 1172 = A2581172

Table S3. Fixed Effect Parameter Log for Pooled Population Pharmacokinetic Models (*Using 70 kg as Reference Weight)

Model	MIN	OFV	Study	CL/F (L/hr)	Vc/F (L)	Q/F (L/hr)	Vp/F (L)	Ka (hr^{-1})
26	Y	7073.853	1169-1174-1175	529.1	119.10	180.40	15340	0.181
27	Y	1001.126	1169	417.6	239.50	87.36	1886	0.303
28	Y	-1127.208	1174	447.2	38.16	1052.00	5166	0.462
37	Y	5925.601	1175	453.2	128.00	192.30	16070	0.190
Historical	NA	NA	1012	284.0	270.00	73.00	1500	0.264

* = All models allometrically scaled using 70 kg reference weight except Historical model that utilized a fixed Vp/F, CL/F = ATV clearance, Vc/F = ATV volume of distribution, Q/F = ATV intercompartmental clearance, Vp/F = ATV peripheral volume of distribution, Ka = first-order absorption rate constant, MIN = minimization status, Y = successful, N = not successful, OFV = objective function value, NA = not applicable, 1169 = A2581169, 1174 = A2581174, 1175 = A2581175, 1012 = A3841012

Table S4. Pharmacokinetic Parameter Estimates from Previous Population PK Analysis (Using 70 kg as Reference Weight)

	Point Estimate	%SE
CL/F (θ_2)	$283(L/h)$	0.593
$\text{CL/F} \sim (\text{WT}/70)^{0.75}$		
Vc/F (θ_3)	$272(L)$	2.23
$\text{Vc/F} \sim (\text{WT}/70)^{1}$		
Q/F (θ_4)	$82(L/h)$	6.34
Vp/F (θ_6)	$1500(L)$	NA
Ka (θ_1)	$0.0798(h^{-1})$	15.3
Ka-Dose (θ_5)	0.0433	17.4
F1-Age (θ_7)	0.834	15.2
$\Omega^{1.1}CL/F$	0.1 ($CV = 31.7\%$)	21.4
$\Omega^{1.2}COV_{CL/F-Vc/F}$	0.0603 ($r = 0.21$)	69.5
$\Omega^{2.2}Vc/F$	0.848 ($CV = 92.1\%$)	21.7
$\Omega^{1.3}COV_{CL/F-Ka}$	-0.0606 ($r = -0.97$)	41.4
$\Omega^{2.3}COV_{Vc/F-Ka}$	0.00965 ($r = 0.05$)	1040
$\Omega^{3.3}Ka$	0.0393 ($CV = 19.8\%$)	185
$\Omega^{4.4}Ka_{IOV}$	0.165 ($CV = 40.6\%$)	11.6
$\sigma^{1.1}pro$	0.196	6.39
Residual Variability as CV		
ATV CV	44.3 (CV%)	

Q/F and Vp/F not allometrically scaled in previous PK analysis, Vp/F fixed to 1500 L in previous PK analysis, ATV = atorvastatin, CL/F = ATV clearance, Vc/F = ATV volume of distribution, Q/F = ATV intercompartmental clearance, Vp/F = ATV peripheral volume of distribution, Ka = first-order absorption rate constant, F1 = relative bioavailability, Ka-Dose = dose effect on Ka, F1-Age = age effect on F1, IOV = interoccasion variability, Ω = inter-individual variance or covariance (COV), σ = residual variance, r = correlation, CV = coefficient of variation, %SE = percent standard error, NA = not applicable

Table S5. Standard Deviation and Shrinkage Estimates for ATV Base Model with BQL and Full Model with BQL

Base Model with BQL

parameter	sd($\hat{\eta}$)	ω	η_{shrink} (%)
ETA1	0.524	0.499	−5.0
ETA2	0.798	0.893	10.6

Full Model with BQL

parameter	sd($\hat{\eta}$)	ω	η_{shrink} (%)
ETA1	0.587	0.559	−4.8
ETA2	0.732	0.833	12.1

Inter-individual random effects associated with CL/F (ETA1) and Vc/F (ETA2); standard deviation of individual estimates ($sd(\hat{\eta})$); standard deviation of variance estimate (ω); $\eta_{shrink}(\%) = 100 \cdot \left(1 - \frac{sd(\eta)}{\omega}\right)$

Table S6. Fixed Effect Parameter Log for Combined Parent-Metabolite Population Pharmacokinetic Models (Using 70 kg as Reference Weight)

Model	MIN	CL/F	Vc/F	Q/F	Vp/F	Ka	Vcm/fm	Qm/fm	Vpm/fm	fm	CLm/fm	F1Tan1	Fixed
355	*Y*	668	1880	315	1990	0.265	3.54	420	2210	1	625	0.7613	fm, No priors
331	*N*	753	432	215	2010	0.183	1140	327	1920	0.982	592	0.7870	Vcm/fm, Vcpm/fm
356	*Y*	701	992	223	1950	0.198	407	371	2030	0.993	612	0.7518	none, priors
340	*Y*	699	1020	227	1960	0.2	401	368	2040	1	616	0.7521	fm, priors
334	*N*	753	432	215	2010	0.183	1140	327	1920	0.982	592	0.7870	Vcm/fm, Qm/fm, Vpm/fm
357	*Y*	618	2340	550	2250	0.272	168	*NA*	*NA*	1	616	0.7340	fm, 1 compt metab.

ATV = atorvastatin, CL/F = ATV clearance, Vc/F = ATV volume of distribution, Q/F = ATV intercompartmental clearance, Vp/F = ATV peripheral volume of distribution, Ka = first-order absorption rate constant, fm = fraction of bioavailable dose converted to metabolite, CLm/fm = o-ATV CL, Vcm/fm = o-ATV volume of distribution, Qm/fm = o-ATV intercompartmental clearance, Vpm/fm= o-ATV peripheral volume of distributio, F1Tan1 = relative bioavailability Tanner Stage 1, MIN = minimization status, Y = successful, N = not successful, NA = not applicable, priors = model used informative priors

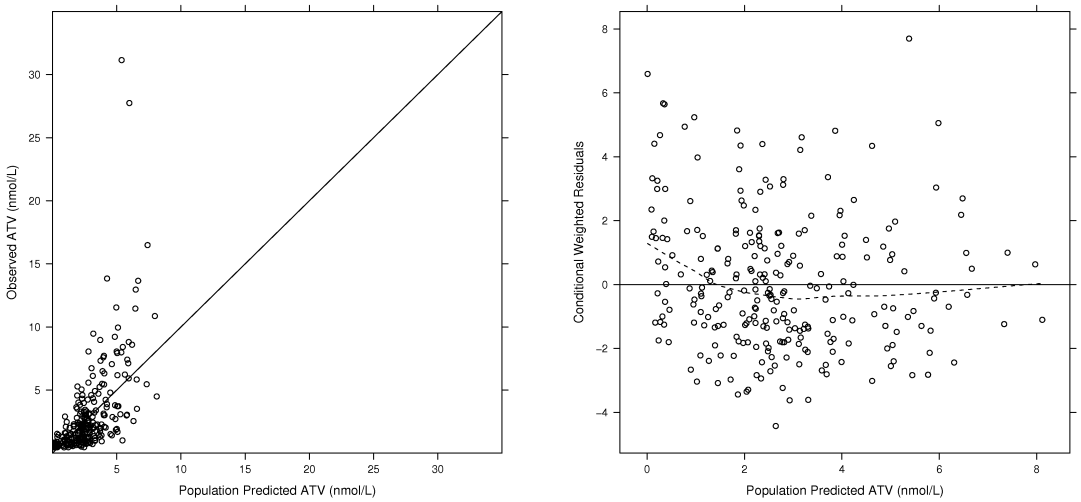
Table S7. Standard Deviations and Shrinkage Estimates of Inter-Individual Random

Effects for Final Parent-Metabolite Model

parameter	sd($\hat{\eta}$)	ω	η_{shrink} (%)
ETA1	0.468	0.463	−1.1
ETA2	0.988	1.058	6.6
ETA3	0.423	0.434	2.4

Inter-individual random effects associated with CL/F (ETA1), Vc/F (ETA2), and CLm/fm (ETA3); standard deviation of individual estimates (sd($\hat{\eta}$)); standard deviation of variance estimate (ω); η_{shrink} (%) = $100 \cdot (1 - \frac{sd(\hat{\eta})}{\omega})$

Figure S1. Diagnostic Plots for ATV Base Model. Observed ATV concentrations are plotted versus population predictions (left) and CWRES are plotted versus population predictions (right). Values are indicated by open circles. The line of identity (solid black) is included as a reference (left) or a dotted black lowess trend line is included (right).



Equation S1. ATV Pharmacokinetic model

$$CL/F_i = \theta 1 \cdot \left(\frac{WT_i(\text{kg})}{70(\text{kg})}\right)^{0.75} \cdot \exp\left(\eta_{CL/F_i}\right)$$

$$Vc/F_i = \theta 2 \cdot \left(\frac{WT_i(\text{kg})}{70(\text{kg})}\right)^{1} \cdot \exp\left(\eta_{Vc/F_i}\right)$$

$$Q/F_i = \theta 3 \cdot \left(\frac{WT_i(\text{kg})}{70(\text{kg})}\right)^{0.75}$$

$$Vp/F_i = \theta 5 \cdot \left(\frac{WT_i(\text{kg})}{70(\text{kg})}\right)^{1}$$

$$T1_i = \left(\frac{CL/F_i}{Vc/F_i}\right)$$
$$T23_i = \left(\frac{Q/F_i}{Vc/F_i}\right)$$
$$T32_i = \left(\frac{Q/F_i}{Vp/F_i}\right)$$
$$L2_i = \left((T1_i + T23_i + T32_i) - \frac{\sqrt{(T1_i+T23_i+T32_i)^2 - 4 \cdot T1_i \cdot T32_i}}{2}\right.$$

$$Ka_i = \theta 4 + L2_i$$

$$C_{ij} = \hat{C}_{ij}(1 + \varepsilon_{pij}) + \varepsilon_{aij}$$

Where all parameters are as defined in the text and individual PK parameters are denoted by the subscript i.

Equation S2. Combined ATV/o-ATV Pharmacokinetic model

$$CL/F_i = exp(\theta 1 + \log(\frac{WT_i(\text{kg})}{70(\text{kg})}) * 0.75 + \eta_{CL/F_i})$$

$$Vc/F_i = exp(\theta 2 + \log(\frac{WT_i(\text{kg})}{70(\text{kg})}) + \eta_{Vc/F_i})$$

$$Q/F_i = exp(\theta 3 + \log(\frac{WT_i(\text{kg})}{70(\text{kg})}) * 0.75)$$

$$Vp/F_i = exp(\theta 5 + \log(\frac{WT_i(\text{kg})}{70(\text{kg})}))$$

$$CLm/fm_i = exp(\theta 10 + \log(\frac{WT_i(\text{kg})}{70(\text{kg})}) * 0.75 + \eta_{CLm/fm_i})$$

$$Vcm/fm_i = exp(\theta 6 + \log(\frac{WT_i(\text{kg})}{70(\text{kg})}))$$

$$Qm/fm_i = exp(\theta 7 + \log(\frac{WT_i(\text{kg})}{70(\text{kg})}) * 0.75)$$

$$Vpm/fm_i = exp(\theta 8 + \log(\frac{WT_i(\text{kg})}{70(\text{kg})}))$$

$$f = \theta 9$$

$$fm = 1 - f$$

$$T1_i = (\frac{CL/F_i}{Vc/F_i})$$

$$T23_i = (\frac{Q/F_i}{Vc/F_i})$$

$$T32_i = (\frac{Q/F_i}{Vp/F_i})$$

$$L2_i = ((T1_i + T23_i + T32_i) - \frac{\sqrt{(T1_i+T23_i+T32_i)^2 - 4 \cdot T1_i \cdot T32_i}}{2}$$

$$Ka_i = \exp(\theta 4 + L2_i)$$

$$F1TannerStage2 = \theta 11$$

$$F1TannerStage1 = \theta 12$$

$$K12_i = Ka_i$$

$$K25_i = \frac{Q/F_i}{Vc/F_i}$$

$$K52_i = \frac{Q/F_i}{Vp/F_i}$$

$$K23_i = \frac{(CL/F_i) * fm_{oATV}}{Vc/F_i}$$

$$K34_i = \frac{Qm/fm_i}{Vcm/fm_i}$$

$$K43_i = \frac{Qm/fm_i}{Vpm/fm_i}$$

$$K20_i = \frac{(CL/F_i) * fm_{ATV}}{Vc/F_i}$$

$$K30_i = \frac{(CLm/fm_i) * fm_{ATV}}{Vcm/fm_i}$$

$$C_{ij} = \hat{C}_{ij}(1 + \varepsilon_{pij})$$

Where all parameters are as defined in the text and individual PK parameters are denoted by the subscript i.