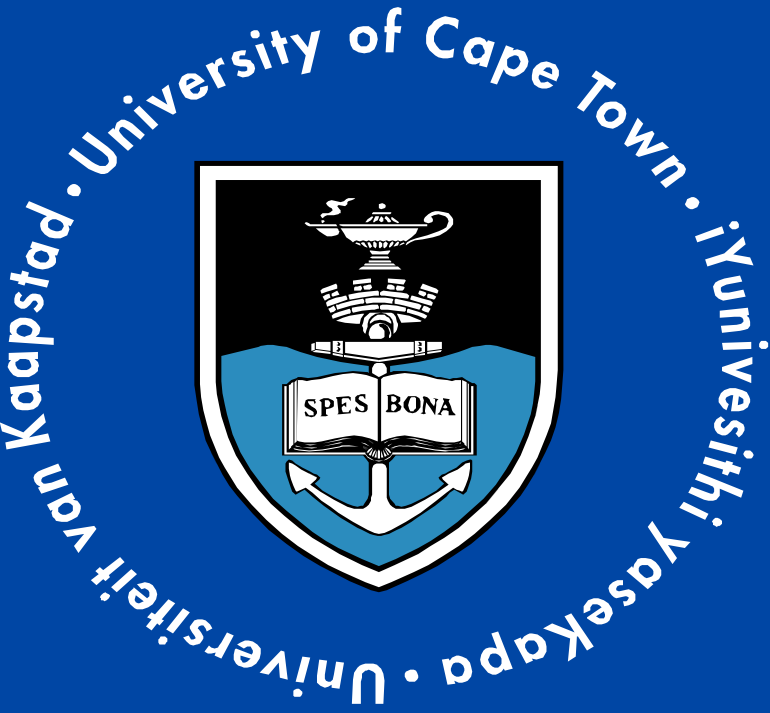


Pharmacokinetics of ritonavir-boosted atazanavir in children and adolescents with HIV: Analysis of CHAPAS-4 and VirTUAL trials



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Background

Children living with HIV are disproportionately affected by tuberculosis (TB). **Rifampicin**, a key component of TB treatment, reduces exposure to many antiretrovirals, complicating co-treatment.

The **CHAPAS-4** trial demonstrated the superiority of dolutegravir (DTG) for **second-line HIV treatment** in children, but it is not always accessible or suitable.

Boosted protease-inhibitors remain important alternatives but options with rifampicin are limited:

- Doubling darunavir/ritonavir (DRV/r) leads to toxicity
- Super-boosted lopinavir/ritonavir (LPV/r) is effective but has high pill burden and is difficult to implement

Atazanavir/ritonavir (ATV/r) is a promising alternative:

- CHAPAS-4** found that ATV/r was effective and safe as second-line therapy
- Once-daily dosing and low toxicity make ATV/r attractive
- However, its use is currently contraindicated in children receiving rifampicin [1]
- In adults** from the **DERIVE** trial (NCT04121195), **doubling ATV/r dosing frequency** (from once- to twice-daily) overcame rifampicin's inductive effects and restored atazanavir exposure [2].

Objectives

- Develop a population pharmacokinetic (PK) model of ATV/r in children and adolescents with HIV receiving **novel and standard-of-care ATV/r formulations and dosing regimens**
- Predict **the impact of rifampicin coadministration** using adult-derived induction effects and **devise pediatric dosing strategies**

Methods

Data in **children with HIV receiving ATV/r** obtained from the **CHAPAS-4** (ISRCTN22964075) and **VirTUAL** (NCT03923231) trials.

CHAPAS-4

A 4x2 open-label factorial randomised trial assessing second-line antiretrovirals and formulations, **including ATV/r** (Table 1), in children aged 3 to 15 years with first-line antiretroviral therapy failure.

Intensive sampling over 24 hours was conducted 6 weeks after initiating second-line treatment

WHO weight bands	Number of tablets				Daily dose
	100 mg ATV	25 mg RTV	300/100 mg ATV/r		
14-19.9 kg	2	3	-		200/75 mg*
20-24.9 kg	2	3	-		200/100 mg
25-34.9 kg	-	-	1		300/100 mg
35- kg (adult)	-	-	1		

*If required 100 mg RTV may be used to boost ATV
ATV, atazanavir; RTV, ritonavir; ATV/r, fixed-dose combination ritonavir-boosted atazanavir

VirTUAL

A separate observational study in children and adolescents receiving **ATV/r as part of clinical care** (Table 2).

Opportunistic sampling was conducted across three clinic visits.

Weight bands	Number of tablets				Daily dose
	150 mg ATV	200 mg ATV	100 mg RTV	300/100mg ATV/r	
14-19.9 kg	1	-	1	-	150/100 mg
20-24.9 kg	-	1	1	-	200/100 mg
25- kg (adult)	-	-	-	1	300/100 mg*

*Alternatively, 2x150 mg ATV and 1x100 mg RTV
ATV, atazanavir; RTV, ritonavir; ATV/r, fixed-dose combination ritonavir-boosted atazanavir

Atazanavir quantified using LC-MS/MS (LLOQ: 0.105 mg/L [CHAPAS-4], 0.0300 mg/L [VirTUAL])

- Data below the LLOQ were imputed to 0 (M7+ method) with extra additive error component of 100% LLOQ for the imputed data [3]. Modelling performed in NONMEM (v.7.5.1) with FOCE-I.

Model development used CHAPAS-4 data, and predictive performance was assessed with VirTUAL data using a VPC prior to joint parameter estimation with both datasets.

Simulations of rifampicin coadministration extrapolated adult pharmacokinetic changes [2] – observed with **standard first-line rifampicin** – to children receiving ATV/r. The observed changes included a 3.12-fold increase in clearance and a 53% reduction in bioavailability with once-daily dosing, and a 2.04-fold increase in clearance for twice-daily dosing (Table 3).

Results

Table 3: Participant characteristics

Characteristic	CHAPAS-4 N = 60 ¹	VirTUAL N = 11 ¹	Overall N = 71 ¹
Age (years)	10 (3, 16)	16 (12, 18)	11 (3, 18)
Weight (kg)	26 (15, 64)	47 (33, 85)	30 (15, 85)
Sex (males)	32 (53)	7 (64)	39 (55)
Weight band and ATV/r dosing regimen			
≥ 25 kg 300/100 mg (FDC)	32 (53)	8 (73)	40 (56)
≥ 25 kg 200/100 mg (non-FDC)	-	1 (9.1)	1 (1.4)
≥ 25 kg 150/100 mg (non-FDC)	-	2 (18)	2 (2.8)
< 25 kg 200/100 mg (non-FDC)	4 (6.7)	-	4 (5.6)
< 25 kg 200/75 mg (non-FDC)	24 (40)	-	24 (34)

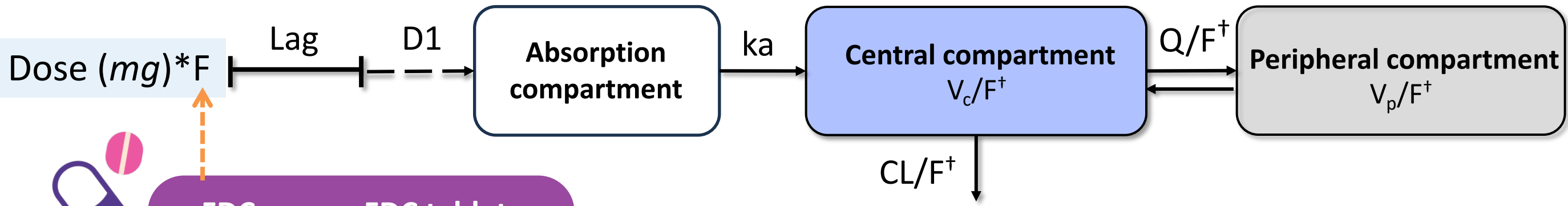
¹Median (Min, Max); n (%)
ATV/r, ritonavir-boosted atazanavir. FDC, fixed-dose combination

Table 4: Model parameters

Parameter	Atazanavir			
	Typical value	95%CI	Variability (%CV)	95%CI
Clearance, CL/F (L/h) ^a	4.69	4.22 – 5.09	BSV: 18.1	15.9 – 23.4
Change in CL due to rifampicin (OD ATV/r dose) (-fold) ^c	3.12 FIX			
Change in CL due to rifampicin (BD ATV/r dose) (-fold) ^c	2.04 FIX			
Central volume, Vc/F (L) ^a	40.6	37.2 – 45.1		
Lag time, lag (h)	1.01	0.970 – 1.15	BOV: 65.2	55.9 – 77.2
Zero-order input, D1 (h)	0.925	0.745 – 1.11		
First-order input, ka (h ⁻¹)	2.91	2.09 – 3.08	BOV: 149	123 – 191
Bioavailability, F (.)	1 FIX		BOV: 33	27.6 – 38.8
Change in F for cohorts receiving non-FDC (%) ^b	-22.2	-16.0 – -33.7		
Change in F due to rifampicin (OD ATV/r dose) (%) ^c	-53.0 FIX			
Scaling factor on BOV for unobserved dose (-fold change)	1.43 FIX			
Peripheral volume, Vp/F (L) ^a	130	69.4 – 201		
Intercompartmental clearance, Q/F (L/h) ^a	0.641	0.522 – 0.817		
Proportional error (%)	13	10 – 15		
Additive error (mg/L)	20% LLOQ FIX			

^aAllometrically scaled for a 26 kg individual
^bnon-FDC, non-fixed dose combination atazanavir/ritonavir tablets. Includes children <25 kg receiving 2x100 mg atazanavir and 4x25 mg or 100 mg ritonavir tablets, and ≥25 kg participants receiving 200 or 100 mg atazanavir with 100 mg ritonavir tablets.
^cRifampicin assumptions extracted from Kengo *et al.* model [5]. Included for simulations of ATV/r dosing scenarios in children receiving rifampicin

Figure 1: Structural diagram



^a Allometrically scaled for a 26 kg individual. FDC, fixed-dose combination

Participants weighing ≥25 kg and receiving the 300/100 mg FDC had 22.2% higher atazanavir exposure compared to participants receiving a non-FDC formulation. The cohort receiving non-FDC also included smaller children and those receiving lower ritonavir doses.

Conclusion

A **population PK model** developed using CHAPAS-4 trial data adequately characterized atazanavir pharmacokinetics in children and adolescents **and was externally validated** using VirTUAL trial data.

- Observed atazanavir exposures were in line with previous pediatric and adult studies [4, 6].
- Formulation type (**FDC vs non-FDC tablets**) was the strongest predictor of exposure differences. This effect is confounded by **lower ritonavir doses and smaller body size** in some participants of the non-FDC cohort, and requires confirmation whether formulation alone is responsible.

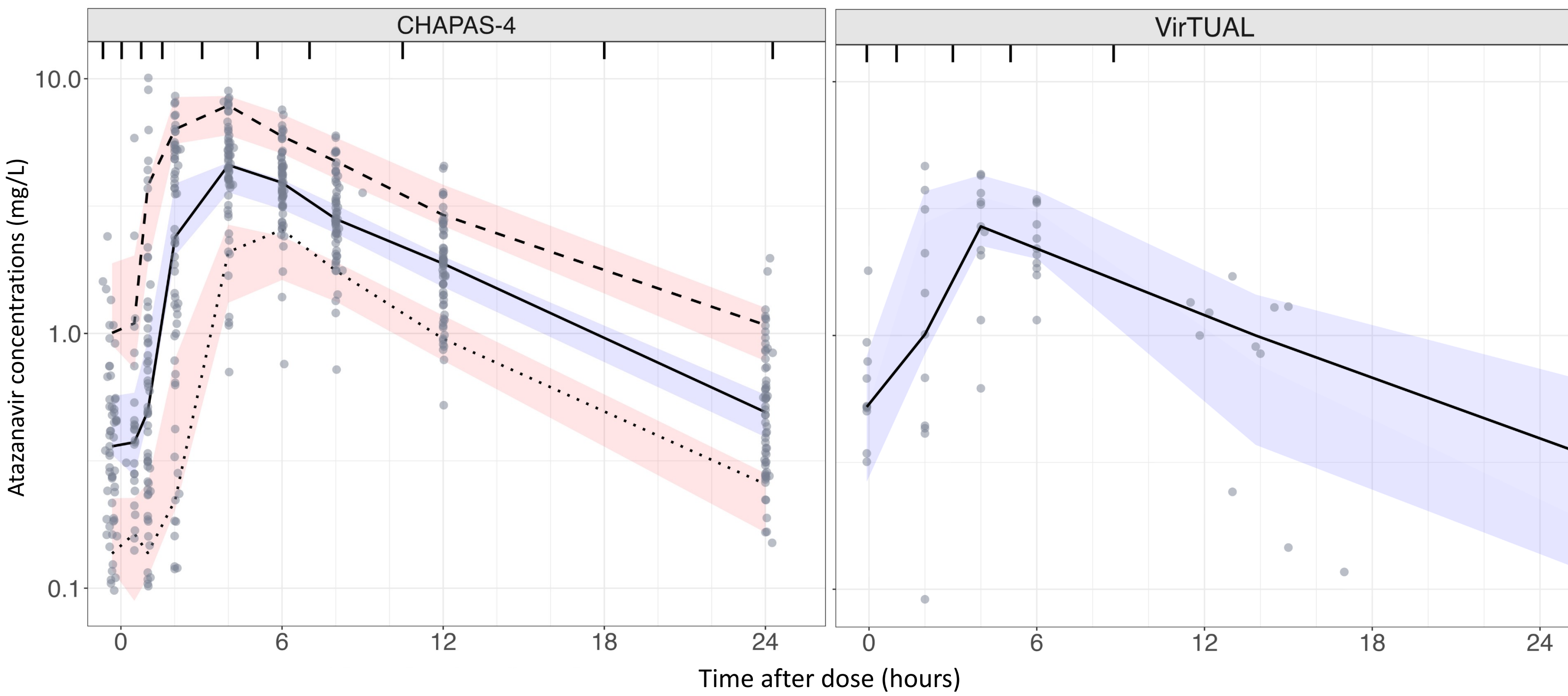
Doubling the ATV/r dosing frequency could mitigate rifampicin-induced reductions in atazanavir exposure in children ≥15 kg (Figure 3), consistent with adult data from the DERIVE trial [2].

- Our findings support recent PBPK modeling [7] which predicts that twice-daily dosing of 300/100 mg ATV/r could achieve adequate trough concentrations in children ≥25 kg co-treated with rifampicin.

- Our simulations assume** that the rifampicin-induced effects on clearance and bioavailability are similar in children and adults, and that 200/75 mg ATV/r dosed twice daily produce similar compensatory effects.

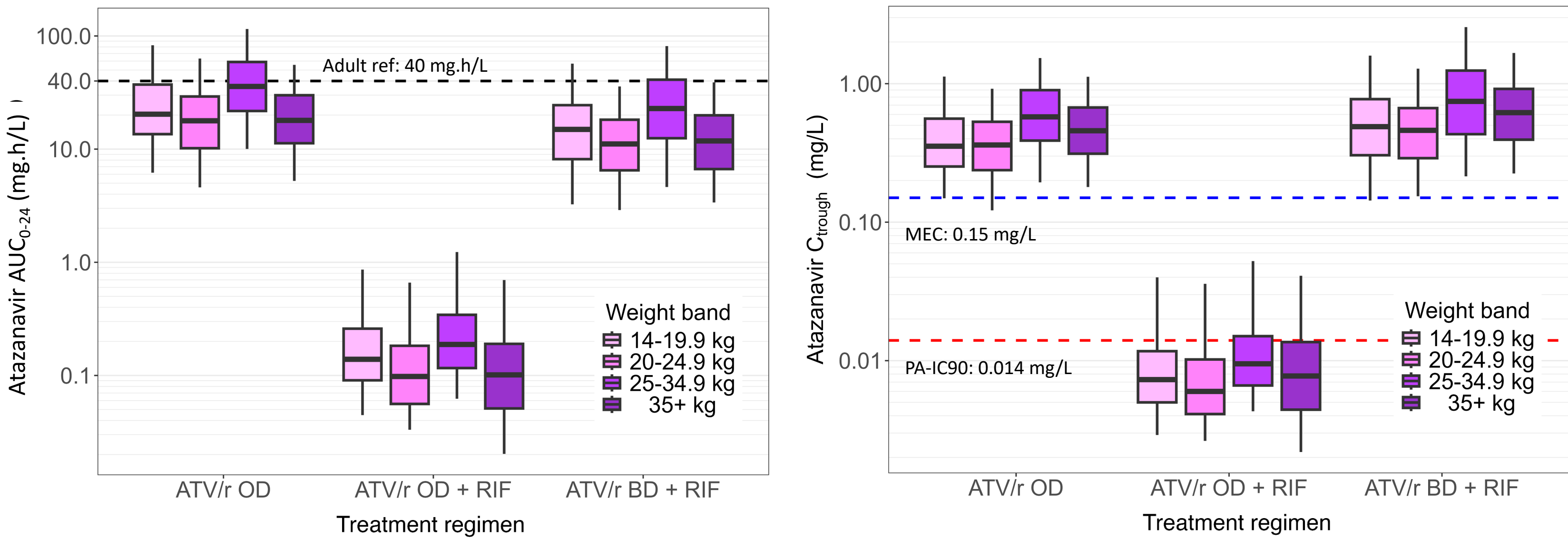
- Clinical studies are warranted to evaluate the safety and efficacy of this approach in children.

Figure 2: Visual predictive check



The visual predictive check for atazanavir in children enrolled in the CHAPAS-4 (left) and VirTUAL (right) trials. Solid circles represent observed data. The solid, dotted, and dashed lines represent the 50th, 5th, and 95th percentiles of observed data. The shaded areas represent the model-predicted 95% confidence intervals for the same percentiles. *Four observations at 40 hours were cropped from the VirTUAL VPC for visualization purposes.*

Figure 3: Atazanavir simulations with rifampicin



Simulated atazanavir AUC₀₋₂₄ (left) and trough concentrations (right) in children receiving CHAPAS-4 ATV/r doses (Table 1) with or without rifampicin. Dashed lines represents geometric mean AUC₀₋₂₄ in adults receiving 300/100 mg ATV/r once daily without rifampicin [4] (black). ATV/r, ritonavir-boosted atazanavir. OD, once-daily. BD, twice-daily. RIF, rifampicin. MEC, minimum effective concentrations [4]. PA-IC90, protein-adjusted 90% inhibitory concentration [5].

Without rifampicin: Dosing in CHAPAS-4 (Table 1) achieved atazanavir exposures comparable to those observed in adults receiving standard ATV/r 300/100 mg once-daily and achieved C_{trough} > MEC and PA-IC90.

With rifampicin: As expected, simulated co-administration of rifampicin reduced atazanavir concentrations. Doubling the dosing frequency of ATV/r is expected to restore atazanavir concentrations to levels without rifampicin.

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