

Model-Based Pediatric Dosing of Ritonavir-Boosted Darunavir: An Alternative to WHO Guidelines

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Background

- **Treatment options are needed for (antiretroviral-experienced) HIV-1 infected pediatric patients**
- **Darunavir (Prezista®) is a protease inhibitor with potent in vitro antiviral activity against wild-type and PI-resistant HIV-1 strains, and a high genetic barrier to the development of resistance.**
 - registered darunavir formulations are 75-, 150-, (300-), (400-), 600- and 800-mg tablets, and an oral 100 mg/mL suspension.
 - darunavir should be used with a booster, such as rtv, which is available as 100 mg capsules/tablets and a 80 ng/mL solution
- **Prezista boosted with rtv, combined with other ARVs, is approved for HIV-infected patients as of 3 years and 10 (US) or 15 kg (EU)**
- **World Health Organization (WHO) uses standardized pediatric dosing weight bands across products, which differ from those used by Janssen in the pediatric development of ritonavir-boosted darunavir (DRV/rtv)**
- **When considering a FDC for pediatrics, generic manufacturers will likely use a DRV:rtv fixed ratio and the WHO pediatric weight bands**

PREZISTA – BID* Dosing Recommendations (USPI)

	DRV dose	rtv dose	DRV : rtv ratio
Adult patients	600 mg	100 mg	6: 1
Pediatric patients			
≥40 kg	600 mg	100 mg	6: 1
30 kg to < 40 kg	450 mg	60 mg	7.5 : 1
15 kg to < 30 kg	375 mg	48 mg	7.5 : 1
14 kg to < 15 kg	280 mg	48 mg	5.8 : 1
13 kg to < 14 kg	260 mg	40 mg	6.5 : 1
12 kg to < 13 kg	240 mg	40 mg	6.0 : 1
11 kg to < 12 kg	220 mg	32 mg	6.9 : 1
10 kg to < 11 kg	200 mg	32 mg	6.3 : 1

* BID dosing also for treatment-experienced pediatric patients with at least one darunavir RAM

WHO Guideline (June 2013)

Standardized weight bands, BID dosing schedule

	formulation ^{\$}	DRV dose	rtv dose	DRV : rtv ratio
Adult patients	1 adult DRV tablet	600 mg	100 mg	6 : 1
Pediatric patients				
≥35 kg	adult dose	600 mg	100 mg	6 : 1
25 kg to < 35 kg	adult dose ^{**}	600 mg	100 mg	6 : 1
20 kg to < 25 kg	1.5 pediatric tablet [*]	360 mg	60 mg	6 : 1
14 kg to < 20 kg	1 pediatric tablet	240 mg	40 mg	6 : 1
10 kg to < 14 kg	1 pediatric tablet	240 mg	40 mg	6 : 1

^{\$} Pediatric patients <25kg: dosing of DRV/rtv 6:1 with 240/40mg FDC tablet

^{*}: 2 tablets AM, 1 tablet PM

^{**}: assumption

Objective

evaluate through modeling and simulation the WHO proposed DRV/rtv dosing regimen for pediatrics and propose as necessary an adjustment that uses the WHO standardized weight bands and maintains a constant DRV:rtv ratio, while reaching DRV exposures comparable to those in adults, thereby allowing extrapolation of safety and efficacy to pediatric patients

Darunavir Population Pharmacokinetic Model for Simulation of DRV Exposures in Pediatric Patients

- A population pharmacokinetic model of DRV/rtv has been previously established based on pooled richly sampled data from adult and pediatric populations:
 - adults: DUET (TMC125-C206/C216)
 - pediatric: DELPHI (TMC114-C212), ARIEL (TMC114-C228), DIONE (TMC114-C230)
- Full model available at *

$$CL/F_i = \frac{CL_{int}/F \cdot \left(\frac{1}{1 + K_{AFF} \cdot AAG_i} \right) \cdot \left(\frac{WT_i}{70} \right)^\theta \cdot e^{\eta_i}}{F_{rel}}$$

With CL/F_i : individual apparent oral clearance; CL_{int}/F : population estimate of apparent intrinsic clearance; K_{AFF} : affinity constant for AAG, θ : exponent varying with bodyweight; η_i : individual random effect; F_{rel} : relative bioavailability correction for commercial tablet and oral suspension

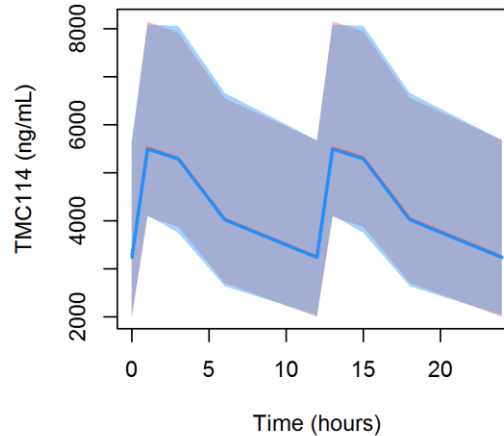
- Dose regimen simulations performed using R software (v12) and NONMEM (v7.1)

Simulated DRV PK profiles as per WHO recommendations (June 2013)

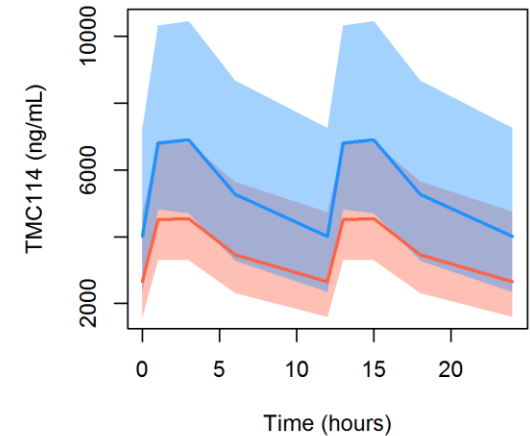
Light-blue: DRV/rtv regimen USPI
10 to <15 kg DRV 20 mg/kg bid,
15 to <30 kg DRV 375 mg bid
30 to <40 kg DRV 450 mg bid,
≥40 kg DRV 600mg bid
Profiles simulation, shaded areas represent
90% prediction interval, lines represent
median profiles

Red: WHO guideline (June 2013)
10 to <14 kg: DRV 240 mg bid;
14 to <20 kg: DRV 240 mg bid;
20 to <25 kg: DRV 480 mg AM 240mg PM,
≥25 kg DRV 600 mg bid
Profiles simulation, shaded areas represent
90% prediction interval, lines represent
median profiles

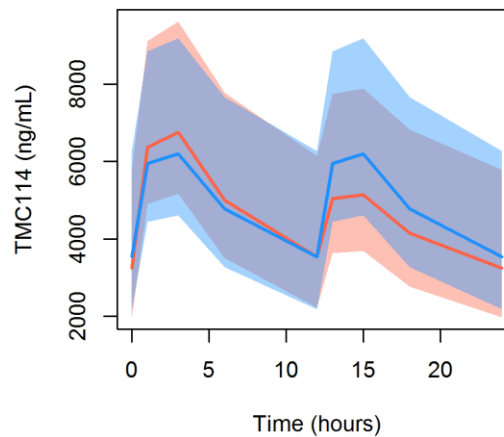
10 to <14 kg



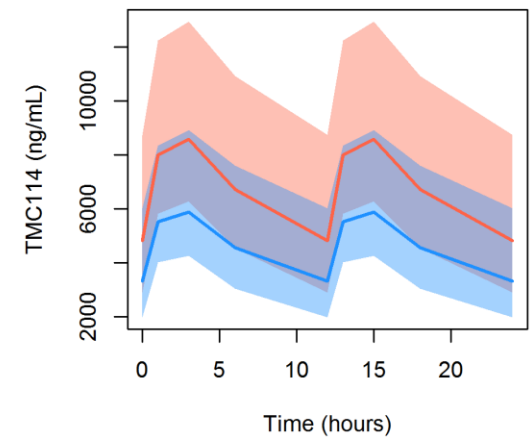
14 to <20 kg



20 to <25 kg



25 to 35 kg



WHO suggested regimen for children of 14 to 20 kg leads to low DRV exposure
WHO suggested regimen for children of 25 to 35 kg leads to high DRV exposure

Simulated DRV PK profiles with adjusted dosing regimen still using DRV/rtv 240/40 mg and per WHO weight bands

Blue: DRV/rtv regimen USPI
10 to <15 kg DRV 20 mg/kg bid,
15 to <30 kg DRV 375 mg bid
30 to <40 kg DRV 450 mg bid,
≥40 kg DRV 600mg bid

Profiles simulation, shaded areas represent
90% prediction interval, lines represent
median profiles

Red: adjusted regimen

10 to <14 kg: DRV 240 mg bid;

14 to <20 kg: DRV 480 mg AM 240mg PM*;

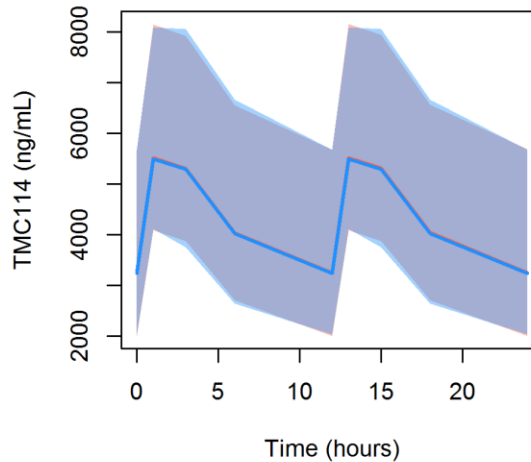
20 to <25 kg: DRV 480 mg AM 240mg PM*;

25 to <35 kg: DRV 480 mg bid;

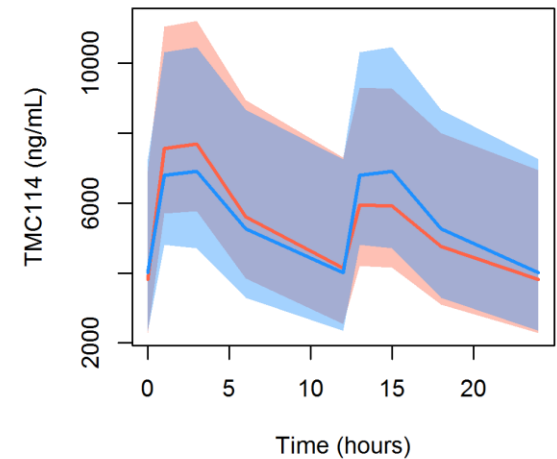
≥35 kg: DRV 600mg adult tablet

Profiles simulation, shaded areas represent
90% prediction interval, lines represent
median profiles

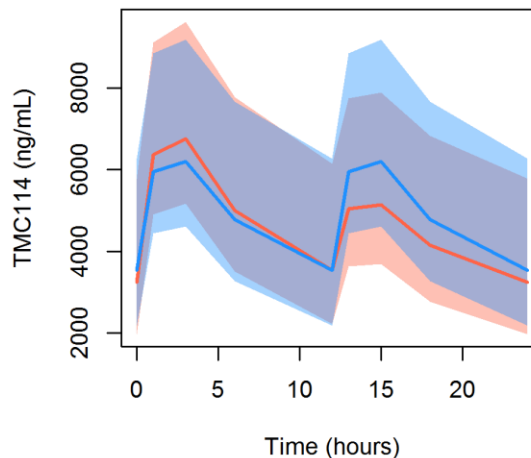
10 to <14 kg



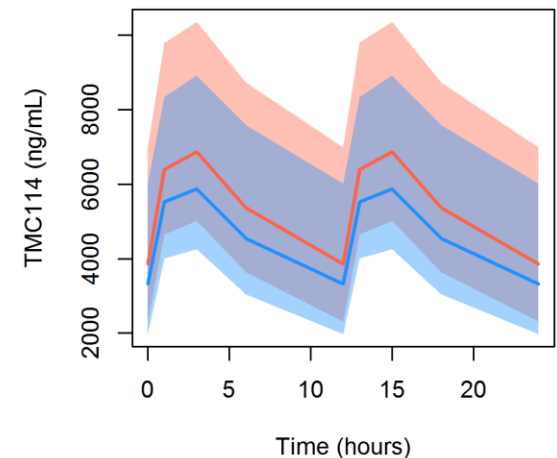
14 to <20 kg



20 to <25 kg



25 to 35 kg



Adjusted proposal for DRV/rtv pediatric dosing regimen with fixed DRV:rtv ratio and per WHO weight bands

	Formulation ^{\$}	DRV dose	rtv dose	DRV : rtv ratio
Adult patients	1 adult tablet	600 mg	100 mg	6 : 1
Pediatric patients				
≥35 kg	adult dose	600 mg	100 mg	6 : 1
25 kg to < 35 kg	2 pediatric tablets	480 mg	80 mg	6 : 1
20 kg to < 25 kg	1.5 pediatric tablet*	360 mg	60 mg	6 : 1
14 kg to < 20 kg	1.5 pediatric tablet*	360 mg	60 mg	6 : 1
10 kg to < 14 kg	1 pediatric tablet	240 mg	40 mg	6 : 1

^{\$} Pediatric patients <35kg: dosing of DRV/rtv 6:1 with 240/40mg FDC tablet

*: 2 tablets AM, 1 tablet PM

Bold represents differences compared to WHO guideline (June 2013)

Summary and Conclusion

- Population PK modelling can help guide recommendations for effective and practical pediatric ARV regimens
- Simulations suggest that pediatric DRV dosing according to WHO guidelines (June 2013) might lead to either low DRV exposures in a lower weight band and/or high DRV exposures in a higher weight band
- Changes to the current WHO recommended dosing schedule could improve the anticipated DRV exposure in pediatric patients while still maintaining a fixed DRV:rtv dosing ratio and per standardized weight bands.
- This could allow simplification of treatment options by developing DRV/rtv FDCs which would allow dosing aligned with recommendations across the unified WHO weight bands.

Acknowledgments

- HIV infected pediatric patients in DRV clinical trials, and their families and caregivers
- Prezista team members
- Janssen Global Public Health
- Pediatric Antiretroviral Working Group (convened by WHO)