

Population Pharmacokinetics of Twice Daily Zidovudine (ZDV) in HIV-Infected Children and an Assessment of ZDV Exposure Following WHO Dosing Guidelines

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INTRODUCTION

- Zidovudine (ZDV) is a common component of antiretroviral therapy for treatment of HIV infection in children.
- The WHO devised a simplified dosing system for children based on weight bands; which was updated in 2010 from those outlined in 2006. Some weight bands introduced higher doses despite previously being adequate.
- Pharmacokinetic (PK) data of ZDV administered twice daily following WHO dosing guidelines are limited.

OBJECTIVES

- Develop a population PK model to describe twice daily ZDV plasma concentrations in HIV-infected children.
- Estimate exposures of plasma ZDV likely to be obtained with WHO dosing guidelines.

METHODS

- Patients:** Data were pooled from 6 paediatric PK studies¹⁻⁵. In total, 100 HIV-infected children (n=63 girls; n=58 African; n=38 Thai) stable on ZDV tablets (n=54 profiles) or syrup (n=73 profiles) were included (Figure 1A).
- Median (range) age, weight, serum creatinine (SCr) and haemoglobin (Hb) were: 5 yr (1-18), 18 kg (6-59), 0.3 mg/dL (0.2-0.8) and 11.6 g/dL (6.3-14.5), respectively.
- Children were dosed according to National or WHO guidelines [median (range) 150 mg (60-300); 9 mg/kg (5.1-24.0); 214 mg/m² (144-559)].
- PK model:** Non-linear mixed effects modelling was applied to ZDV concentration-time data (NONMEM v. 7.2). The influence of covariates age, weight, sex, ethnicity/site, SCr and Hb on ZDV PK parameters were investigated.
- Model fit was assessed by statistical and graphical methods. A decrease in the minimal objective function value (OFV) of at least 3.84 points was required to accept a model with one extra parameter, as well as showing good graphical diagnostics.
- Simulation & visual predictive check (VPC):** A 90% prediction interval (P5-P95) was generated from 1000 simulations using the final model estimates and observed data superimposed. At least 90% of data points within the prediction interval was indicative of an adequate model.
- Using the final model ZDV plasma exposures based on WHO 2006 and 2010 dosing guidelines were simulated and compared.

RESULTS

- PK model:** A 2 compartment model with first-order and zero-order absorption assigned to tablets and syrup, respectively best described the data.
- Inclusion of weight on clearance (CL/F, Q/F) and volume of distribution (Vc/F, Vp/F) parameters using allometric scaling significantly improved the fit.
- A positive linear association between CL/F and age was also observed.
- Diagnostic plots obtained from the final model are shown (Figure 1B, 1C) and final parameter estimates summarised (Table 1).

Figure 1. Graph of (A) ZDV plasma concentrations over time included in the model and goodness-of-fit plots for the final model of (B) population predictions vs. observed, (C) individual predictions vs. observed.

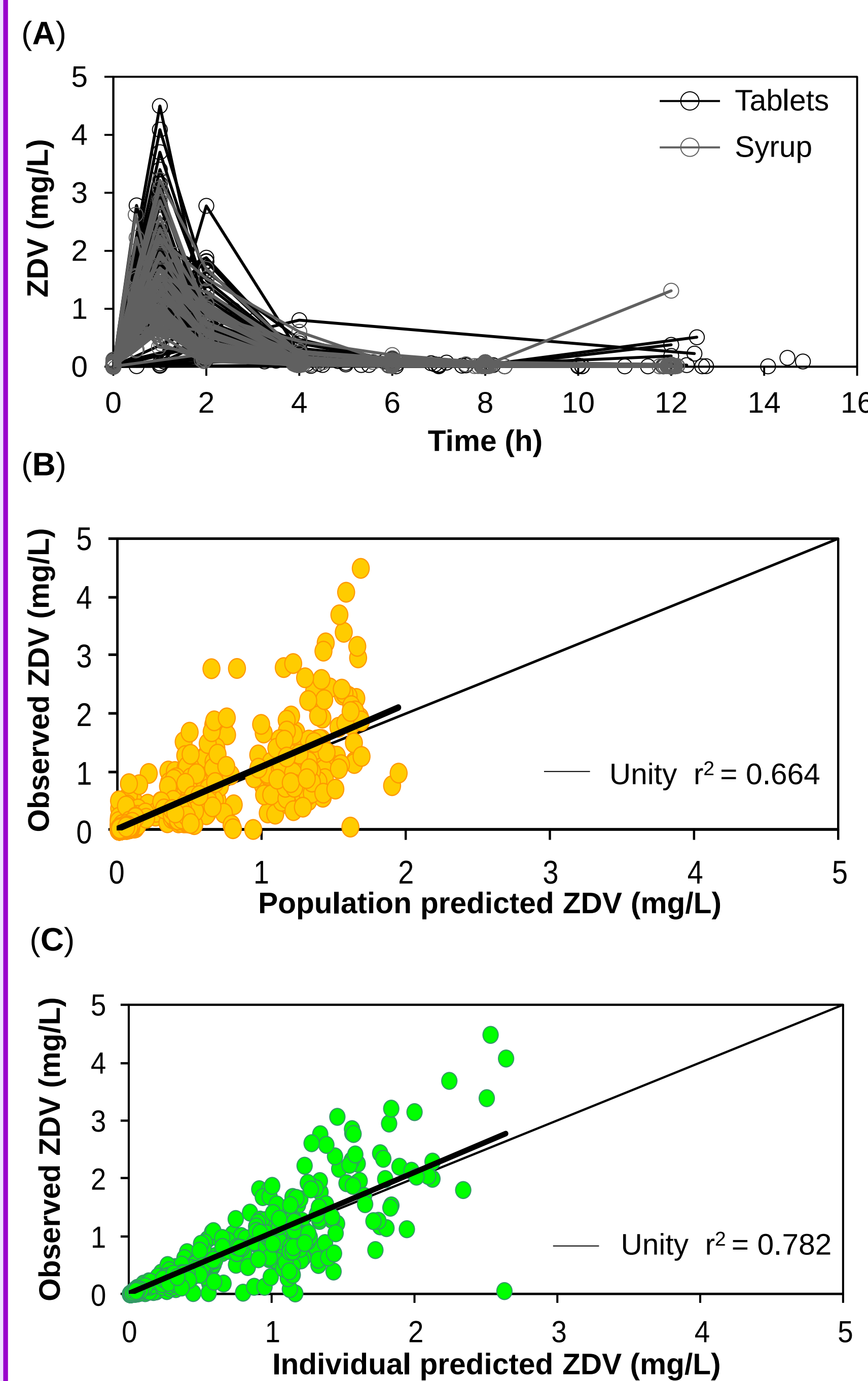


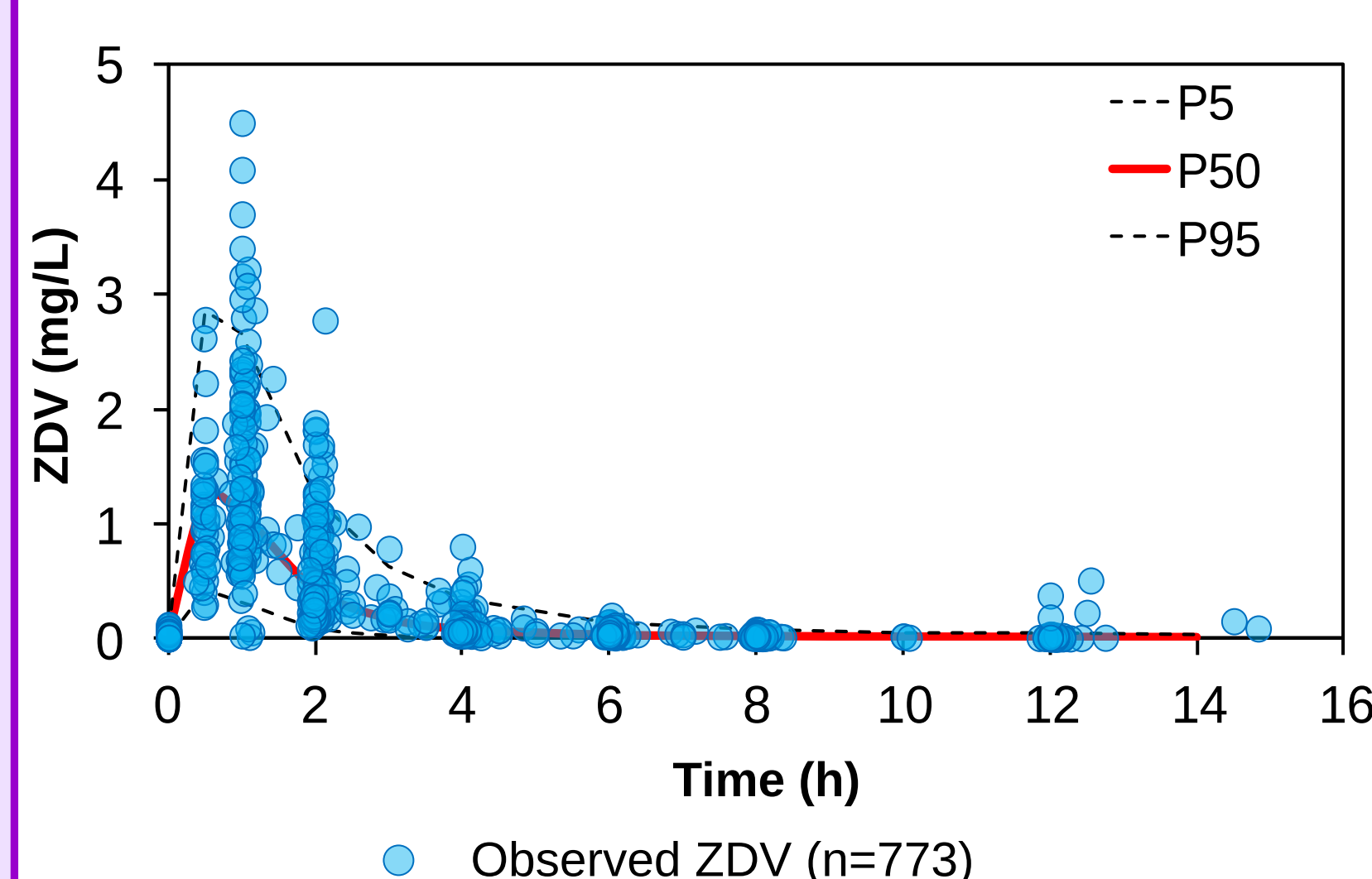
Table 1. ZDV parameter estimates and relative standard errors (RSE) obtained from the final model.

Parameter	Estimate (RSE%)	IIV (%) (RSE%)	IOV (%) (RSE%)
CL/F (L/h/18.3 kg)	61.7 (6)	32(37)	17 (52)
Vc/F (L/18.3 kg)	65.7 (6)		
Q/F (L/h/18.3 kg)	6.7 (9)		
Vp/F (L/18.3 kg)	52.9 (14)	68 (32)	
k _a (h ⁻¹) ^a	3.0 (15)	60 (40)	
D2 (h) ^b	0.74 (6)		
F1 ^c	1 (fix)		
Covariates			
θ _{AGE} CL/F	0.022 (46)	33 (39)	
Residual error			
Proportional (%)	42 (7)		

RSE = (SE_{estimate}/estimate) * 100
IIV: interindividual variability
IOV: interoccasion variability
^a first-order absorption, tablets
^b zero-order input, syrup
^c relative bioavailability set to 1

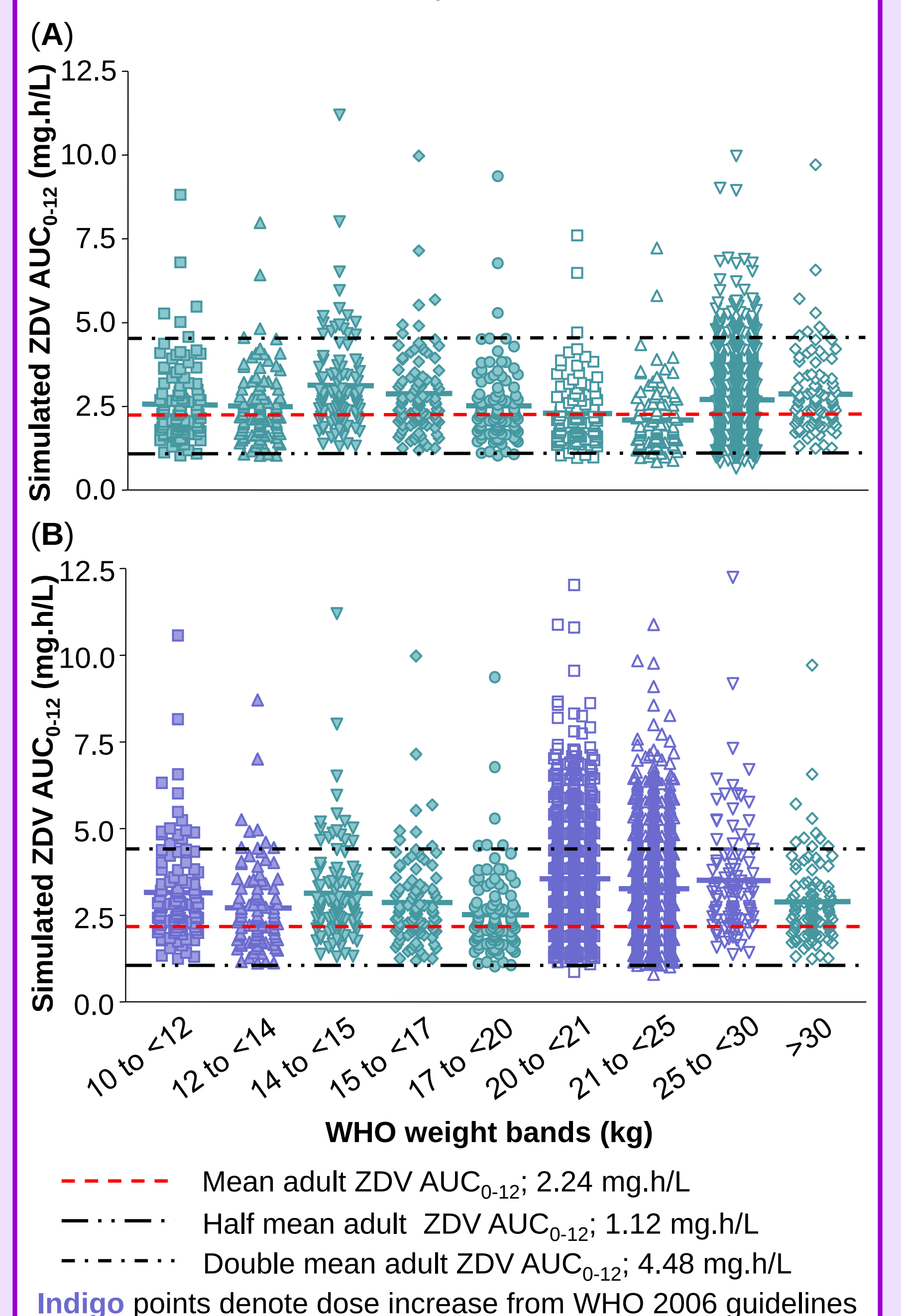
CL/F_{ij} = θ₁ * (WT_{ij}/18.3)^{0.75} * (1 + θ_{AGE} * (AGE_{ij}-5.0)) * exp(η_i + κ_{ij})

Figure 2. Ninety percent prediction interval of ZDV obtained from 1000 simulated patients using the final model and the same ages, weights and distribution of occasions as the original data set. Observed ZDV were superimposed.



- Simulation & VPC:** 91% of observed ZDV plasma concentrations were within the 90% prediction interval (P5-P95), suggesting an adequate model (Figure 2).
- Mean ZDV AUC₀₋₁₂ in this cohort of children was 25% higher compared to published adult data⁶ (2.81 vs. 2.24 mg.h/L).
- Based on 100 simulations at each weight band following WHO 2006 and 2010 guidelines, resulting mean ZDV exposures were higher for 2010 compared to 2006 guidelines due to dose increases (2.52-3.55 mg.h/L vs. 2.10-3.13 mg.h/L; Figure 3)
- Percentage of simulated AUC₀₋₁₂ below the average adult value was 19-50% vs. 25-68% for 2010 and 2006 guidelines, respectively.
- Using arbitrary cut-offs of half and double mean adult exposure, 0-7% and 0-3% of simulated ZDV AUC₀₋₁₂ were below 1.12 mg.h/L and 3-16% and 6-25% were above 4.48 mg.h/L for 2006 and 2010 guidelines, respectively (Figure 3).

Figure 3. Scatter plots of simulated ZDV AUC₀₋₁₂ in children following (A) WHO 2006 guidelines and (B) 2010 guidelines. Each point is an AUC₀₋₁₂ value; solid lines represent mean AUC₀₋₁₂ values.



CONCLUSIONS

- A model to describe twice daily plasma ZDV PK in children has been developed and used to simulate exposure following WHO dosing guidelines.
- Mean plasma ZDV exposure was higher in children than previously reported in adults.
- Safety and tolerability data are needed following higher WHO 2010 doses to help inform a toxicity threshold for ZDV. Potentially the higher 2010 doses could increase incidences of adverse events.
- Impact of higher doses on active intracellular ZDV triphosphate requires evaluation along with the resultant effect on viral load.

REFERENCES

1. Fillekes Q et al. *Pediatr Infect Dis J* 2013 (submitted); 2. van der Lee M et al. *Antivir Ther* 2006; 11 (4): 439-45; 3. Burger D et al. Unpublished data 2000; 4. Burger D et al. Unpublished data 2003; 5. Chokeyhaibulkit K et al. *Antivir Ther* 2011; 16 (8): 1287-95; 6. Aurobindo Pharma Ltd. Zidovudine 100 mg Capsules Summary of Product Characteristics 2011