

Population Pharmacokinetics of Zidovudine and its metabolite in HIV-1 infected children: Evaluation of Doses Recommended

Floris Fauchet^{1,2}, Jean-Marc Treluyer^{1,2,3,4}, Saïk Urien^{1,2,4}, Déborah Hirt^{1,2,3,4}



¹ EA 3620 Université Paris Descartes, Sorbonne Paris Cité, France; ² Unité de Recherche Clinique, AP-HP, Hôpital Tarnier, Paris, France; ³ Service de Pharmacologie Clinique, AP-HP, Groupe Hospitalier Paris Centre, France; ⁴ CIC-901 Inserm, Cochin-Necker, Paris, France

INTRODUCTION

Zidovudine (ZDV) was the first antiretroviral drug approved for the treatment of children with HIV infection. ZDV is mainly metabolized (~70 %) to an inactive metabolite G-ZDV. Maturation of this biotransformation seems to reach adult value during the first month of life¹.

Currently, ZDV-containing regimen are still recommended, twice daily (BID), as a first line combinations regimen for infants and children by the World Health Organization (WHO) and the Food and Drug Administration (FDA).

Bodyweight (kg)	WHO recommendations						FDA recommendations		
	[3-6[	[6-10[	[10-14[	[14-20[	[20-25[	≥25	[4-9[	[9-30[	≥30
Dosage form	Syrup	Syrup	Syrup	Tablet	Tablet	Tablet	Syrup	Syrup	Tablet
Dose and Dosage Regimen	60mg BID	90mg BID	120mg BID	150mg BID	225mg BID*	300mg BID	12mg/kg BID	9mg/kg BID	300mg BID

But, a lot of ZDV adverse events, concentrations related¹, have been observed in an important number of infants that were exposed to ZDV. However, few studies have investigated ZDV pharmacokinetics (PK) in children to evaluate doses administered.

Objectives

Modeling ZDV pharmacokinetics and its biotransformation to G-ZDV allowed: (i) to describe the PK of ZDV in HIV infected children, (ii) to estimate the formation rate of the metabolite then (iii) to identify covariates that can influence this parameter.

Thanks to the final population model, it was possible to compare and evaluate doses recommended by FDA and WHO, then to refine the dose regimens in children.

METHODS

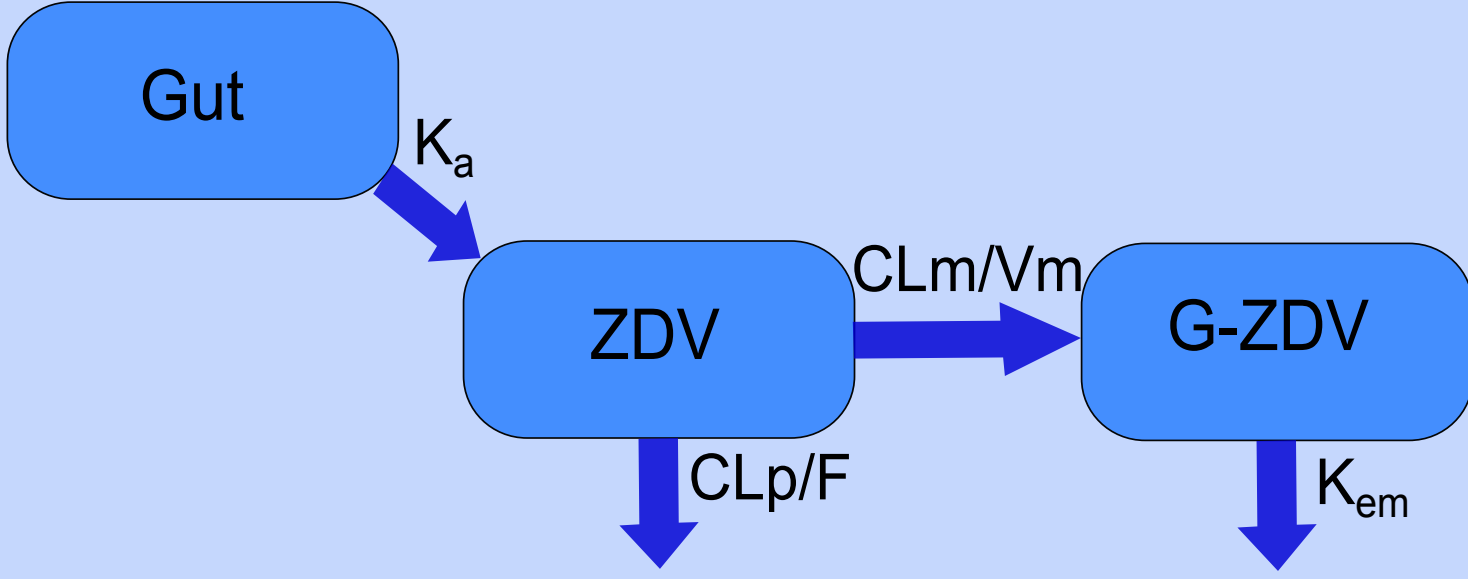
Characteristics of Patients

ZDV and G-ZDV concentrations were collected in 247 children. ZDV was administered twice daily or three times daily (TID).

Item	Median	Range
Gender (M/F)	39/61	-
Age (years)	10.8	0.5-18
Weight (kg)	32.2	6-85
Number of samples	3.6	1-19
Dose per day (mg)	600	36-600

Modeling

A population pharmacokinetic model was developed with Nonmem 6.2. FOCE Interaction method was used.



The parameters estimated with the model are: K_a , absorption rate; CLp/F , apparent elimination clearance for ZDV; V/F , apparent central volume of distribution for ZDV; CLm/Vm , hybrid parameter; K_{em} , elimination rate constant for G-ZDV.

Doses Simulations

In order to compare WHO and FDA recommendations, patients were divided in several classes and 400 simulations were performed using those recommendations. The exposures of ZDV (AUC_{ZDV}) values were derived from the estimated individual PK parameters.

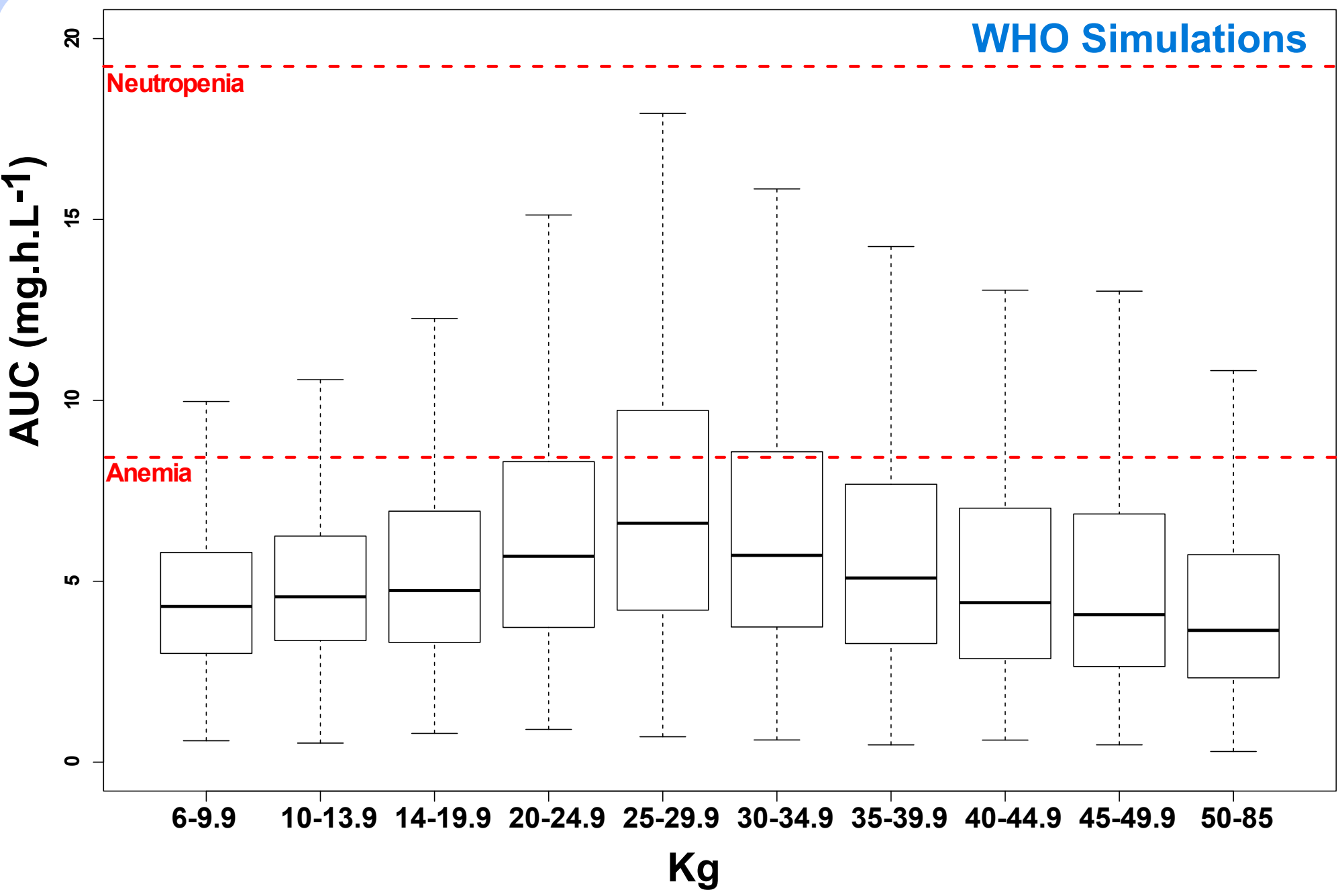
RESULTS

Model Parameters

Strucural model				Statistical model			
Parameters	Estimate	RSE%	95%CI	Parameters	Estimate	RSE%	95%CI
K_a (h^{-1})	2.86 ^b	-	-	$\omega_{CLp/F}$	0.701	17.9	0.572-0.820
CLp/F ($L \cdot h^{-1}$)	89.7	7.1	77-102	$\omega_{V/F}$	0.807	22.9	0.597-0.693
β_{CLp}^{WT}	0.858	11.1	0.67-1.1	$\omega_{CLm/Vm}$	0.352	20.7	0.213-0.473
V/F (L)	229	12.4	181-291	$Corr(CLp/V)$	0.733	-	0.501-0.850
β_V^{WT}	0.54	24.5	0.22-0.81	a (mmol/L)	0.1 ^b	-	-
CLm/Vm ($h^{-1} \cdot L^{-1}$)	12.6	20.7	8.2-18	σ_{ZDV}	0.56	8.5	0.514-0.614
K_{em}	2.27	16.2	1.6-3.1	σ_{G-ZDV}	0.69	7.0	0.643-0.742

Key: RSE% relative standard error (standard error of estimate/ estimate *100); b, fixed values; ω and σ between-subject and residual variabilities; Corr, correlation between two parameters; a, additive part of the combined error model; β , significant effect of a covariable (superscript) on a parameter (subscript)

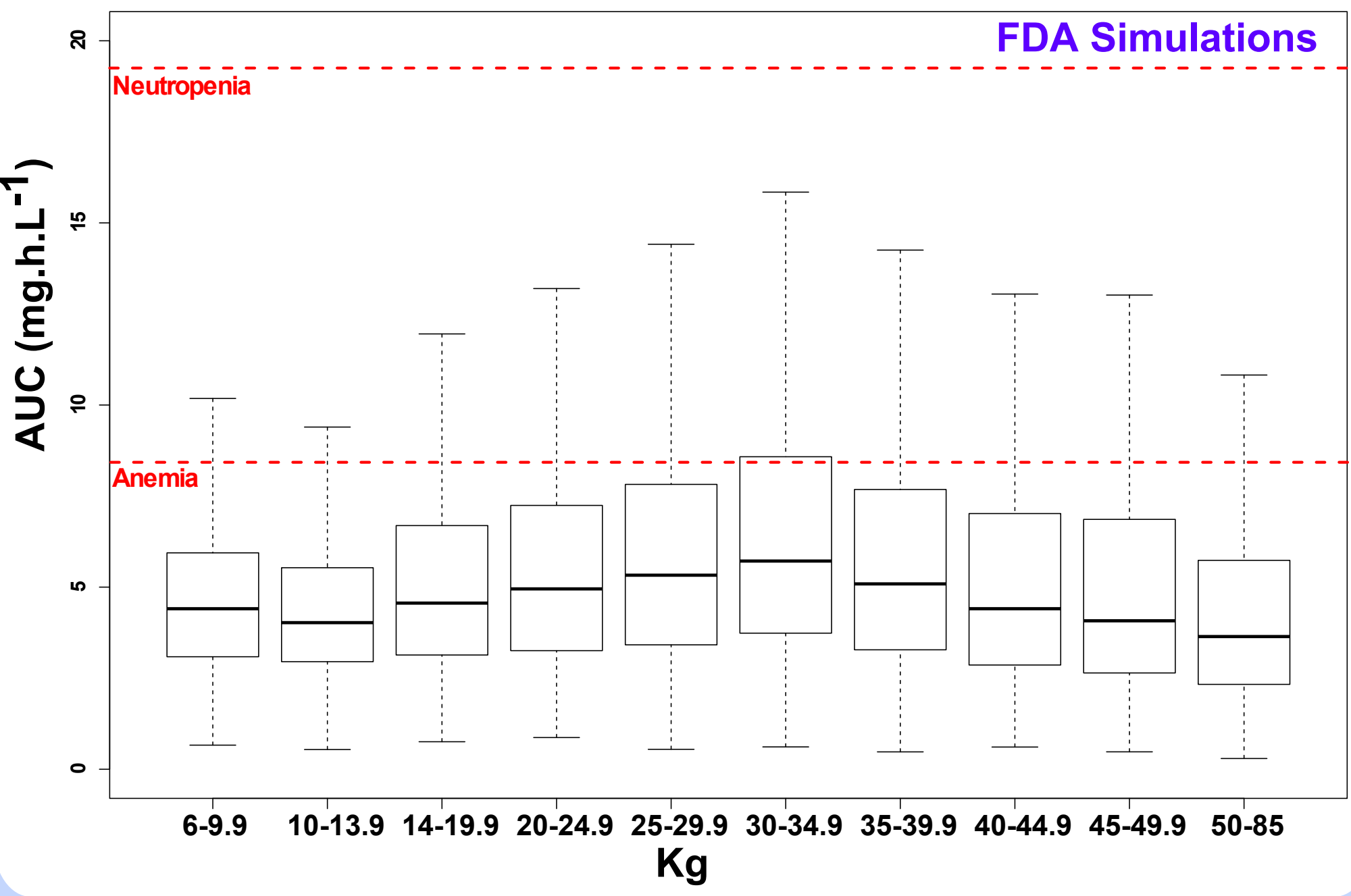
Doses Simulations



A mean AUC_{ZDV} of 8.4 $mg \cdot h \cdot L^{-1}$ increases the risk of anemia by 32 %² while a mean AUC_{ZDV} greater than 19.2 $mg \cdot h \cdot L^{-1}$ increases significantly the risk of neutropenia ($p=0.01$)³.

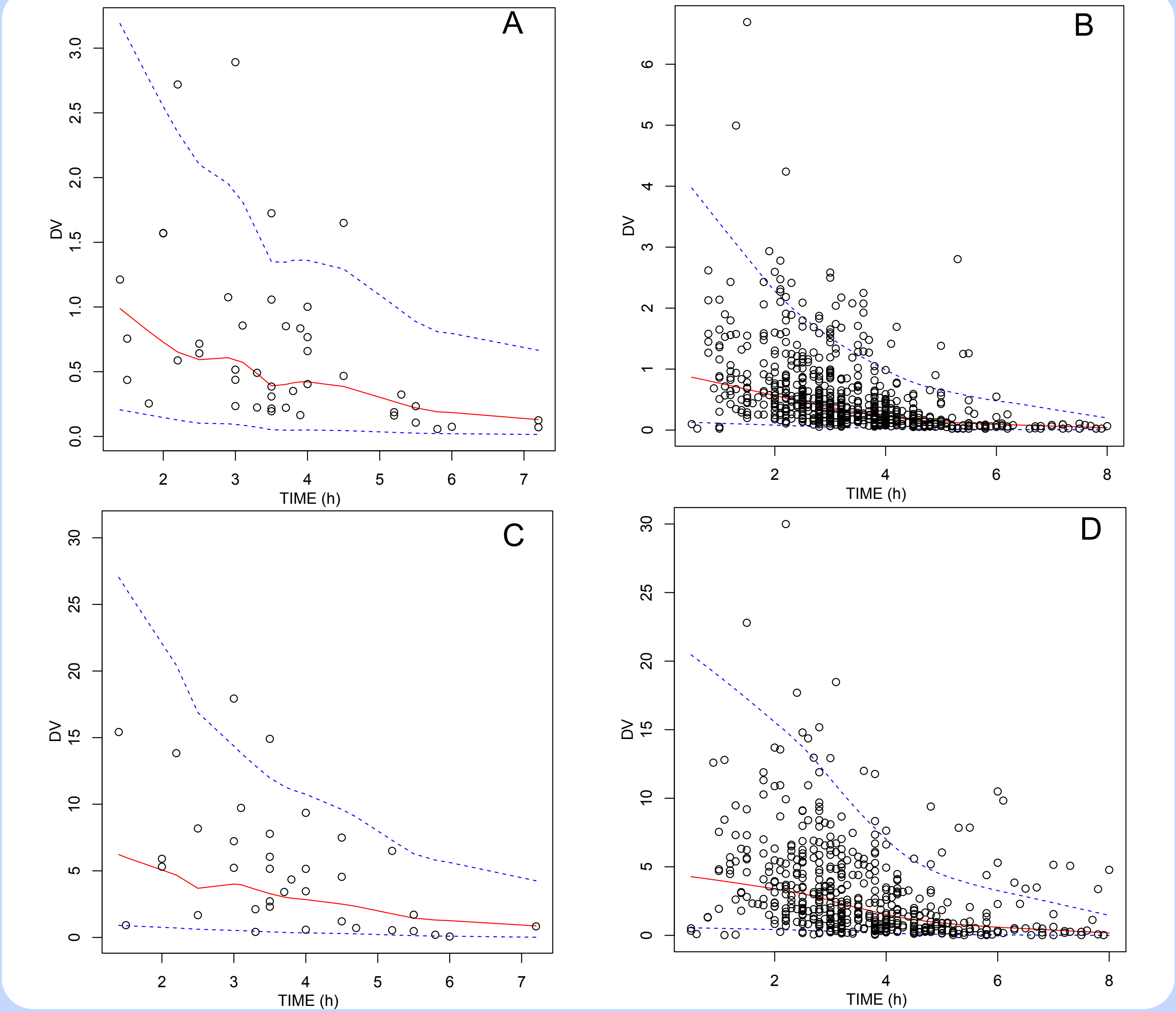
The probabilities of observing efficient exposures (between 3 to 5 $mg \cdot h \cdot L^{-1}$) with less adverse events is higher following the FDA recommendations than the WHO recommendations.

In order to improve the FDA recommendations, ZDV doses should be reconsidered for the weight band 20-40 kg.



Zidovudine exposures obtained with 400 simulations of the doses recommended by the FDA (A) and the WHO (B). Patients were grouped according to the different weight bands. Dashed lines correspond to exposure of 8.4 and 19.2 $mg \cdot h \cdot L^{-1}$

Validation



Key: Visual Predictive Check, comparison between the 5th (dashed line), 50th (full line) and 95th (dashed line) obtained from 400 simulations and the observed data (points) for: (A) plasma ZDV concentrations for TID administration, (B) plasma ZDV concentrations for BID administration, (C) plasma G-ZDV concentrations for TID administration, (D) plasma G-ZDV concentrations for BID administration

Recommendations

Bodyweight (kg)	WHO recommendations				FDA recommendations				Our recommendations			
	[20-25[	[25-30[	[30-35[	[35-40[	[20-25[	[25-30[	[30-35[	[35-40[	[20-25[	[25-30[	[30-35[	[35-40[
Dose and Dosage Regimen	225mg BID*	300mg BID	300mg BID	300mg BID	9mg/kg BID	9mg/kg BID	300mg BID	300mg BID	8mg/kg BID	8mg/kg BID	250mg BID	250mg BID
Median AUC_{ZDV} $mg \cdot h \cdot L^{-1}$	5.8	6.6	5.8	5.2	5.2	5.4	5.8	5.2	4.5	4.8	4.8	4.4
$AUC > 8.4 mg \cdot h \cdot L^{-1}$ %	25.4	40.0	26.7	21.5	17.9	21.4	26.7	21.5	12.4	15.3	17.0	13.1
$AUC > 19.2 mg \cdot h \cdot L^{-1}$ %	0.90	2.10	1.43	0.94	0.35	0.61	1.43	0.94	0.10	0.28	0.48	0.31

The most appropriate doses should be decreased from 9 to 8 mg/kg BID for the weight band [20-30[, from 300 to 250 mg BID for the weight band [30-40[. The highest dose, 300 mg , should be started from 40 kg .

CONCLUSION

In conclusion, the pharmacokinetic model presented here describes the time course of ZDV in children. Modeling and simulations of ZDV PK suggest that FDA recommendations are more appropriate than WHO recommendations but lower doses should be considered for the weight band 20-40 kg .

¹ Hirt D et al, 2013, J acquir Immun; ² Capparelli EV et al, 2003, J Clin Pharmacol; ³ Balis FM et al, 1989, Ann Int Med;