



UNIVERSITEIT
STELLENBOSCH
UNIVERSITY

Skaggs School of Pharmacy
and Pharmaceutical Sciences
UNIVERSITY OF COLORADO
ANSCHUTZ MEDICAL CAMPUS

CAN WE IMPROVE STAVUDINE'S SAFETY PROFILE IN CHILDREN?

PHARMACOKINETICS OF INTRACELLULAR STAVUDINE-TRIPHOSPHATE WITH REDUCED DOSING

Steve Innes^{1*}, Louvina van der Laan^{2,3*}, Peter L. Anderson⁴, Mark F. Cotton¹, Paolo Denti³ (*Joint first authors)

¹Family Infectious Diseases Clinical Research Unit, Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town. ²Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa; ³Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, South Africa. ⁴Department of Pharmaceutical Sciences, University of Colorado Denver Anschutz Medical Campus, Aurora, CO, USA

Email: vdlaan@sun.ac.za



Background and Objectives

Stavudine is being phased out as a first-line ART option due to cumulative mitochondrial toxicity, but it **remains a useful replacement option in children**. At the recommended dose, it may cause stigmatizing lipoatrophy in up to a third of children, with mitochondrial toxicity **driven by peak drug concentration (C_{max})**. In 2007, WHO formally reduced **adult dose** from 40 mg to 30 mg twice daily, which maintained efficacy and reduced mitochondrial toxicity.

However, the **paediatric dose** (1 mg/kg twice daily) was not correspondingly lowered due to concerns about efficacy.

We compared intracellular stavudine-triphosphate levels in children receiving 0.5 or 0.75 mg/kg twice daily to adults receiving 20 or 30 mg twice daily, respectively.

Methods

Data

- 23 HIV+ children and 24 HIV+ adults from South Africa received stavudine at 0.5 mg/kg and 20 mg twice daily for 7 days, respectively.
- Stavudine suspension was used for children and capsules for adults.
- Blood samples taken pre-dose and either 1, 2, and 6; or 3, 4, and 8 hrs post-dose.

Assays

- Intracellular stavudine-triphosphate in peripheral blood mononuclear cells was assayed using Liquid Chromatography Tandem Mass Spectrometry.

Model

- Monolix and SAEM (LLOQ data were handled with the M3 method).
- Allometric scaling was applied to apparent clearance(CL) and volume(V).
- A population pharmacokinetic model was developed to explore the effect of dose reduction in HIV+ children. Simulations were employed to optimise the paediatric dosing regimen to target the exposure in adults receiving the current WHO recommended dose of 30 mg twice daily.

Results

Model

- A bi-phasic disposition model with first-order appearance and disappearance described the pharmacokinetics of stavudine-triphosphate.
- Accounting for the effect of body size using allometric scaling based on fat-free body mass improved the model fit. No significant differences - other than those accounted for with allometric scaling - were detected in any pharmacokinetic parameter between adults and children.

Table 1: Patient characteristics.

Characteristics	Adults (n=24)	Children (n=23)
Age (years)	36 (30-40)	8 (7-9)
Males	1 (4%)	9 (39%)
Weight (kg)	83 (70-98, *62-158)	23 (20-26, *18-31)
Fat-free mass (kg)	47 (44-51)	19 (16-20)

Presented as median (interquartile range). *Range

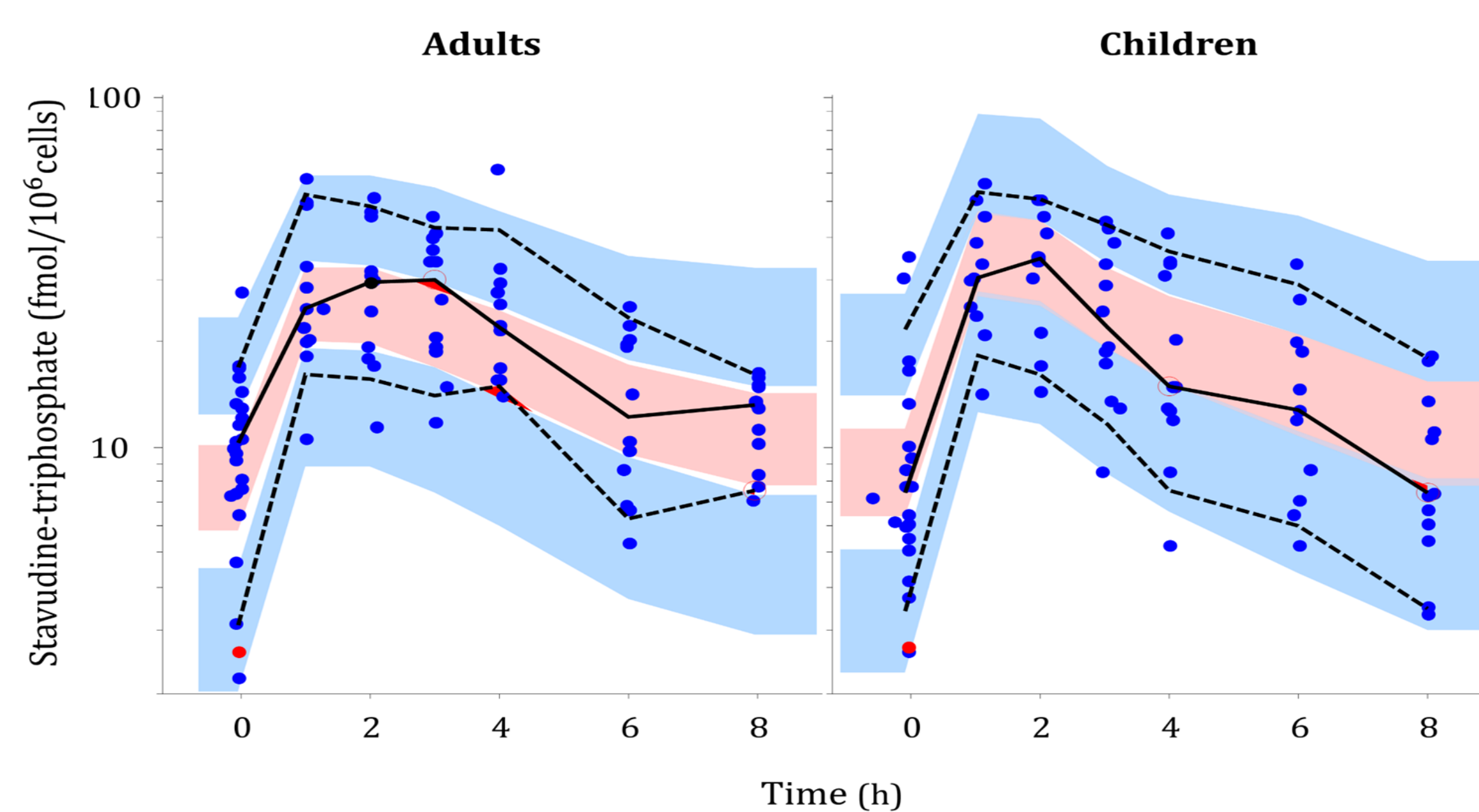


Figure 1. Visual predictive check. Lines represent the 10th, 50th, and 90th percentiles of observed data (20mg vs 0.5mg/kg twice daily), shaded areas are the model-predicted 90% confidence intervals for the same percentiles. Observed data are displayed as dots, including censored data points (LLOQ) in red

Table 2: Final parameter estimates

Parameters	Typical value (%Relative standard error)
CL (10 ¹² cells/h) ^a	454 (9%) [230]
V _c (10 ¹² cells) ^a	2569 (18%) [1037]
Q (10 ¹² cells/h) ^a	469 (30%) [238]
V _p (10 ¹² cells) ^a	7500 (58%) [3027]
k _a (1/h)	1.17 ^b (46%)
F (unitless)	1 (fixed)
Additive error (fmol/10 ⁶ cells)	0.6 (fixed) ^c
Proportional error (%)	27.4 (8%)
IIV CL (%CV)	30.4 (21%)
IOV F (%CV)	36.2 (20%)
IOV k _a (%CV)	30.6 (61%)

^aReported for an adult with the median fat-free mass of 47.2 kg. Values in square brackets [] are for a child with the median fat-free mass of 19.1 kg. ^bBayesian prior (Horton et al 1995) ^cFixed to improve model stability.

Simulations

- Current **WHO-recommended weight-band** dosing for children results in **dramatically higher intracellular drug exposure** (up to **double the C_{max}**) compared to the corresponding adult dose (Figure 2).
- Simulations were used to devise a **reduced dose weight-band** approach using 0.5-0.75mg/kg twice daily (Figure 3).

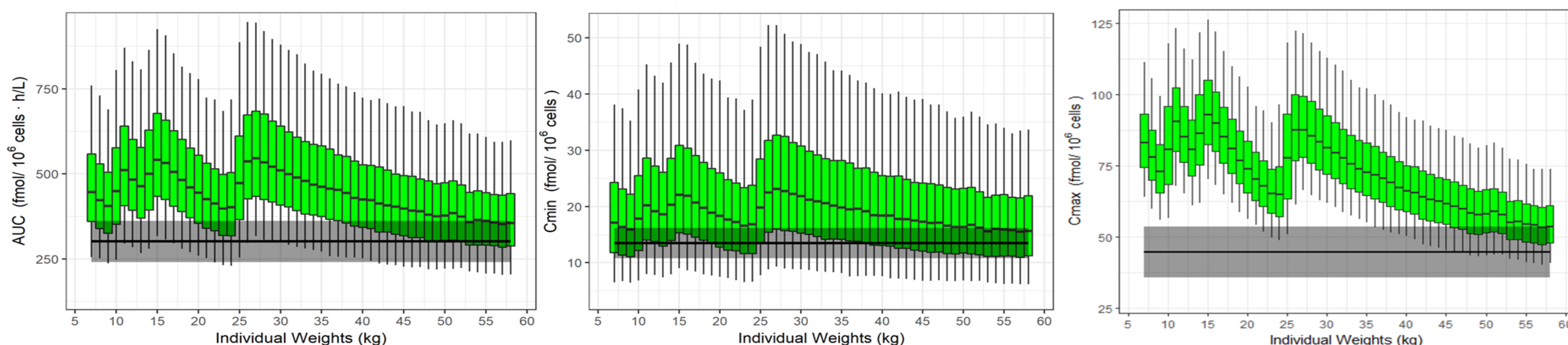


Figure 2. Simulated stavudine-triphosphate exposure vs weight resulting from the WHO-recommended weight-band dosing. The grey band represents the median simulated adult value ±20% for a stavudine dose of 30 mg twice daily.

Table 3. Stavudine dosing guidelines for children

Body weight (kg)	WHO guideline Target 1 mg/kg/dose twice daily	New proposed dosing Target 0.5-0.75 mg/kg/dose twice daily
7-9.9	9 mL (9mg)*	7.5 mL (7.5 mg)*
10-13.9	1 capsule (15 mg)	10 mL (10 mg)*
14-16.9	1 capsule (20 mg)	10 mL (10 mg)*
17-19.9	1 capsule (20 mg)	15 mL (15 mg)*
20-24.9	1 capsule (20 mg)	1 capsule (15 mg)
25-29.9	1 capsule (30 mg)	1 capsule (15 mg)
30-59.9	1 capsule (30 mg)	1 capsule (20 mg)
>60	1 capsule (30 mg)	1 capsule (30 mg)

*The proprietary liquid formulation (1mg/mL) requires refrigeration. For patients who do not have access to a refrigerator, an adult capsule may be opened and dispersed in water. Available capsules include 15, 20 and 30 mg

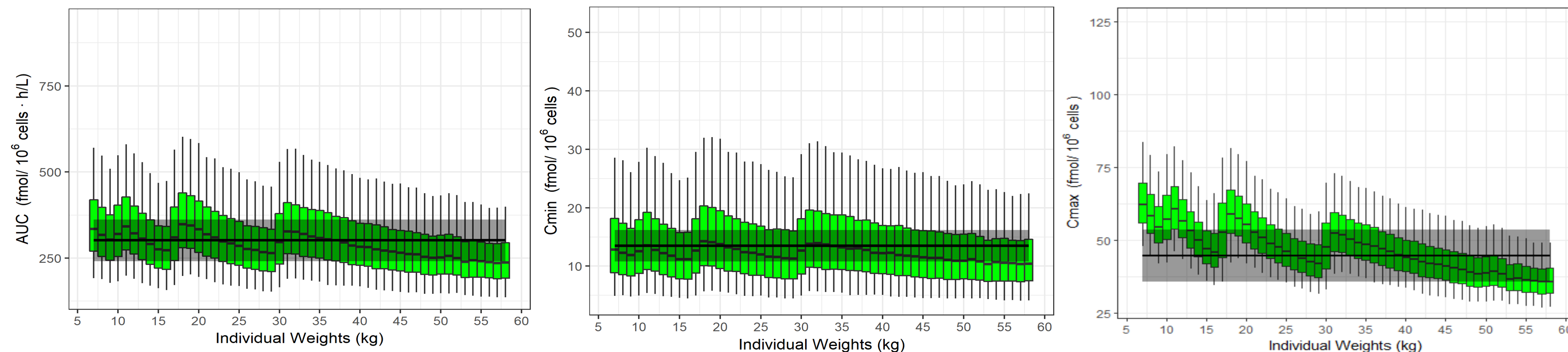


Figure 3. Simulated stavudine-triphosphate exposure vs weight using the new proposed dosing guideline. The grey band represents the median simulated adult value ±20% for a stavudine dose of 30 mg twice daily.

Conclusions

- A decreased stavudine dose in children >7kg would have a reduced toxic effect while maintaining viral suppression**
- Pharmacokinetics of stavudine-triphosphate in children receiving the reduced dose of 0.5 mg/kg twice daily was similar to adults receiving 20 mg twice daily, with allometric scaling for body size being the only significant effect detected.

- Weight-band dosing using a stavudine dose up to 0.75mg/kg shows comparable exposures to adults receiving 30 mg twice daily.
- Similar studies for other ARVs might support reduced dosage or frequency.



BILL & MELINDA
GATES foundation

Acknowledgements: The authors thank the adults, children, and parents for participating in this study. The authors are indebted to Mr. Lane Bushman and personnel at the Colorado Antiviral Pharmacology Laboratory, Department of Pharmaceutical Sciences, University of Colorado Denver Anschutz Medical Campus, for performing the stavudine triphosphate assays; and to Ms Andrea Gutschmidt at the Division of Molecular Biology and Human Genetics, Stellenbosch University, for performing and curating the PBMC extractions. We also thank Maxwell Chirehwa, Dr Elin Svensson, and Mine de Kock for their help with the simulations of exposure performed in R. A special recognition to the University of Cape Town ICTS High Performance Computing team (<http://hpc.uct.ac.za>) for the use of their facilities and to Novartis for sponsoring the Monolix workshop Dr. van der Laan attended.

Funding: This trial was supported by a grant from the Bill & Melinda Gates Foundation (#OPP1065257). Paolo Denti was partly supported by the National Research Foundation of South Africa (Grant number 109056). The content is solely the responsibility of the authors and does not necessarily represent the official views of the funders