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Original article

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Naïm Bouazza[1,2,3†], Frantz Foissac[1,2,3†], Floris Fauchet[1,2,3], David Burger[4], Jean-René Kiechel[5], Jean-Marc Treluyer [1,2,3‡], Edmund V Capparelli[6‡], Marc Lallemant[5‡], Saïk Urien[1, 2, 3‡]*

[1]EA 7323, Université Paris Descartes, Sorbonne Paris Cité, Paris, France

[2]Unité de Recherche Clinique, Assistance Publique – Hôpitaux de Paris (AP-HP), Hôpital Tarnier, Paris, France

[3]CIC-0901 Inserm, Cochin-Necker, Paris, France

[4]Department of Pharmacy, Radboud University Medical Center, Nijmegen, the Netherlands

[5]Drugs for Neglected Diseases initiative (DNDi), Geneva, Switzerland

[6]University of California San Diego, La Jolla, CA, USA

*Corresponding author e-mail: saik.urien@cch.aphp.fr

[†]Contributed equally as first authors

[‡]Contributed equally as last authors

Abstract

Background: Lopinavir/ritonavir (LPV/r) is available in a liquid formulation far from ideal for treatment of children in resource poor settings. Flexible, low-cost, solid, fixed-dose oral combinations (FDC) of LPV/r with nucleoside reverse transcriptase inhibitors (NRTI) (LPV/ABC/3TC and LPV/ZDV/3TC) is needed to improve both management and adherence of children. This work was aimed to develop appropriate drug ratios and dosing for each FDCs.

Methods: Data from 25 combined datasets included therapeutic drug monitoring and clinical studies from IMPAACT and PENTA. Population pharmacokinetic analyses were performed using Monolix. Monte-Carlo simulations of WHO and FDA dosing recommendations were performed to assess their ability to provide optimal exposure in children weighing 4 to 25 kg based on consensus plasma targets. The LPV:3TC:ZDV(ABC) dose ratios were 2.67: 1: 2(2) respectively.

Results: Using WHO dosage, LPV efficacy target was reached in all weight-bands. Given the recommended drug ratios, the dosage for the 4-6 kg weight band (LPV/ZDV: 120/90 mg BID) showed more than 20% of subjects had ZDV levels at high risk of neutropenia. Reducing the LPV/ZDV dose to 80/60 mg BID decreased frequency of high ZDV concentrations but retained the LPV efficacy criteria.

Conclusions: This defined a flexible and simple FDC containing 40 mg LPV, 10 mg RTV, 15 mg 3TC and 30 mg ABC or ZDV. According to the weight-bands defined by WHO, 4-6 kg, 6-10 kg, 10-14 kg, 14-20 kg, 20-25 kg, therapeutic

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doses would be 2, 3, 4, 5, or 6 individual units administered by oral route twice-daily.

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Short title: Fixed-dose combinations of LPV/r plus 3TC and ABC or ZDV

Introduction

Despite the spectacular progress made over the past two decades in the prevention of mother to child transmission, pediatric HIV remains a major public health problem. An estimated 3.4 million children aged less than 15 years were living with HIV worldwide in 2013, with the number of newly infected children estimated at 260,000. Sub-Saharan Africa has the largest burden of disease, accounting for over 90% of the global pediatric HIV population. In 2010, 250,000 children suffered AIDS-related deaths [1]. In the absence of antiretroviral therapy (ART), up to 35% of HIV-positive children in sub-Saharan Africa will die in their first year of life, and 80% will die from AIDS-related causes before their fifth birthday [2].

The introduction of ART for children has considerably reduced the risk of mortality and hospitalization and has transformed the prognosis of HIV-infection from a deadly disease into a manageable chronic illness in high income and some middle income countries [3]. However, in low to middle income countries only 28% of HIV-positive children are estimated to be on ART, with coverage far lower in young children (less than five years of age) due to limited access to the early HIV diagnosis required for infants [4].

In June 2013, the World Health Organization (WHO) Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection were updated to recommend early diagnosis (as soon as possible after birth) and treatment for all HIV-positive infants and children under five years [5]. The recommended regimen for children less than three years of age of the combination of a boosted protease inhibitor (PI) with two nucleoside reverse transcriptase inhibitors (NRTIs) offers the most effective first-line therapy. Although these antiretrovirals (ARVs) exist for children, the most commonly used PI in infants is lopinavir/ritonavir (LPV/r). LPV/r exists as solution for use in infants and young children but this is far from an ideal formulation. It contains ethanol and propylene glycol as excipients, its taste is poorly-tolerated, it must be refrigerated for long term storage, has a short shelf-life and a high price. These factors have contributed to the WHO recommendations not being as widely implemented as desired. According to a 2011 WHO survey in 45 countries, only 12.2% of children with HIV were receiving a first-line treatment containing a PI (mostly lopinavir/ritonavir), 97% of whom were in South Africa.

In order to facilitate implementation of the new pediatric recommendations and adherence to therapy, experts have advised the development of flexible solid oral fixed dose combinations of lopinavir/ritonavir with either abacavir/lamivudine or zidovudine/lamivudine as NRTI backbones. In adults, a fixed-dose combination of LPV/r-AZT-3TC is currently in development [6,7], however such combinations remains unavailable for pediatric population.

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The development of such combinations necessitates the determination of a single ratio of these drugs with appropriate dosing across all weight bands allowing, by simple increments, to cover the whole weight range. However, previous dosing recommendations have been established single drug by single drug, by the first regulatory agency to approve the originator product, on a per kilo or square meter basis, with occasional adjustments in the younger age groups. To simplify concurrent dosing of each component of a combination therapy, WHO ARV dosing recommendations for children have been further redefined according to the same broad weight bands, for all drugs. As a consequence, these weight band dosing recommendations do not provide completely consistent drug ratios across all weight bands.

The challenge of a program targeting the definition of dosage strength and regimen for pediatric populations for such a multidrug combination is that the metabolic pathway of each component of a combination and the elimination routes differ, and that the mechanisms involved in absorption, distribution, metabolism and excretion do not mature at the same rate over the period from birth to adolescence. We therefore decided to perform a meta-analysis of the pediatric PK data available for lopinavir, abacavir, zidovudine and lamivudine, to model the pharmacokinetics of each drug and perform simulations using the original FDA dosing recommendations, the 2010 WHO weight band dosing, and its subsequent modifications. In this way we were able to estimate the proportions of children who would reach efficacy targets and those who would risk reaching exposure levels above toxicity targets, for each of the weight bands. We assumed that dosing regimens producing plasma drug concentrations similar to those observed in adults should be effective to control viremia in children.

Methods

Source of the data:

Lopinavir/ritonavir co-formulation:

The data set for this analysis included 5 published data: i) 3 therapeutic drug monitoring studies from France, ii) International Maternal-Adolescent AIDS Clinical Trials (IMPAACT)/Pediatric AIDS Clinical Trials Group (PACTG) protocol P1030 from United States and Brazil and iii) IMPAACT/PACTG protocol P1038 from United States [8–11].

Lamivudine:

These datasets were pooled from 9 published studies: i) therapeutic drug monitoring data from France, ii) the BURKINAME – Agence Française de Recherches sur le VIH/Sida et les Hépatites Virales (ANRS) 12103 from Burkina Faso and iii) PACTG/IMPAACT protocols: 300, 353, 356, 358, 386 from United States and 1056, 1069 from Thailand [12–14].

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Abacavir:

The data consisted of 5 pooled studies, i.e., 4 previously published data i) therapeutic drug monitoring from France, ii) Paediatric European Network for Treatment of AIDS (PENTA) protocol PENTA 13 from United Kingdom, iii,iv) IMPAACT/PACTG 1018, 1052 protocols from United States plus v) PACTG 356 with ABC pharmacokinetic samples obtained predose as well as 1 to 3 hours and 4 to 6 hours postdose) from United States [15–20].

Zidovudine:

The dataset for zidovudine analysis consisted of pooled data from 5 studies. Four have already been published: i) therapeutic drug monitoring from France, ii) IMPAACT/PACTG 049, 152 and 1052 protocols from United Sates. One is unpublished: ACTG 245 from United Sates which was a phase 1 comparative study of combination antiretroviral therapy in children and adolescents with advanced HIV disease. Infants were treated with zidovudine in combination with didanosine with or without nevirapine. Three samples per patient were obtained from 0.5 to 4 hours postdose [21–25].

Analytical method

The analytical methods were previously described in details for all the published data (see above). Plasma abacavir concentrations for PACTG 356 were determined at Division of Bioanalysis and Drug Metabolism, Glaxo Wellcome, Inc., by a validated HPLC method [26] Plasma zidovudine concentrations for ACTG 245 were determined at the UCSD pediatric pharmacology laboratory using a validated radioimmune assays [21]

Modeling strategy and population pharmacokinetic model development

Data from the sources described above were analysed using the nonlinear mixed effect modelling software program Monolix version 4 (www.lixoft.eu) [27]. Parameters were estimated by computing the maximum likelihood estimator of the parameters without any approximation of the model (no linearization) using the stochastic approximation expectation maximization (SAEM) algorithm combined to a MCMC (Markov Chain Monte Carlo) procedure. Different error models were investigated (i.e. multiplicative, proportional and/or additive error models) to describe residual variabilities, and the between-subject variabilities (BSV or ω) were ascribed to an exponential model. The Likelihood Ratio Test (LRT) including the log-likelihood, the Akaike information criterion (AIC) and the bayesian information criterion (BIC) were used to test different hypotheses regarding the final model, i.e. i) covariate effect(s) on pharmacokinetic parameter(s), ii) residual variability model (proportional versus proportional plus additive error model) and iii) structure of the variance-covariance matrix for the BSV parameters. Main covariates of interest in the population were postnatal age (PNA) and bodyweight. Age-related change functions for CL or V have been described in detail [28]. Parameter estimates were standardized for a mean standard bodyweight using an allometric model: $P_i = P_{STD} \times (BW_i / BW_{STD})^{PWR}$ where P_{STD} is the standard value of parameter for a patient with the standard bodyweight value and P_i and BW_i are the parameter and bodyweight of the i^{th} individual. The PWR exponents may be estimated from the data. However, from allometric scaling theory and practice these are typically 0.75 for clearance parameters and 1 for volumes of distribution [28].

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For evaluation of the goodness-of-fit, the following graphs were drawn for the final model: observed and model predicted concentrations versus time, observed concentrations vs. population predictions (see Figure, Supplemental Digital Content 1), weighted residuals vs. time and weighted residuals vs. predictions. Similar graphs using individual predictive estimation were examined. Diagnostic graphics were obtained using the R statistical package [29].

Visual predictive check (VPC) validation.

Drug concentration profiles were simulated using the final models and compared with the observed data to evaluate the predictive performance of the model. Prediction-corrected visual checks were used as informative diagnostic tools to allow inspection of model appropriateness across time as well as across covariate values [30].

Dose simulations

From the final models, Monte Carlo simulations (500 replicates of each database) of current recommendation guidelines were performed in order to assess their ability to provide optimal exposure for each drug. For lopinavir, doses evaluated were the WHO guidelines i.e. 120 mg bid from 4 to 10 kg, 160 mg bid from 10 to 14 kg, 200 mg bid from 14 to 20 kg, and 240 mg bid from 20 to 25 kg and FDA approved doses i.e. 16 mg/kg bid for patients less than 6 months, 12 mg/kg bid for the less than 15 kg, and 10 mg/kg bid from 15 to 40 kg. For the nucleoside reverse transcriptase inhibitors and according to WHO guidelines, dose ratios of 2.67 and 2 were respectively used for LPV to 3TC and ZDV-ABC to 3TC.

The optimal exposure targets were defined as follows, for lopinavir: i) more than 75% of subjects with C_{min} greater than 3 mg/L [31], ii) more than 95% of subjects with C_{min} greater than 1.0 mg/L (recommended by TDM guidelines [32]) and iii) more than 75% of subjects with AUC_{0-12} greater than 55 mg.h/L (approximately adult mean – 1 SD [33]). For lamivudine, more than 75% of subjects had to get an AUC_{0-24} greater than 8 mg.h/L (approximately adult mean – 1 S.D [34]). For abacavir, more than 75% of subjects had to get an AUC_{0-24} greater than 8 mg.h/L (approximately adult mean – 1 S.D [35]), and for zidovudine i) more than 75% of subjects with AUC_{0-24} greater than 2 mg.h/L (approximately adult mean – 1 S.D [36,37].), ii) less than 25% of subjects with AUC_{0-24} greater than 8.4 mg.h/L (associated with mild anemia) [21] and iii) less than 5% of subjects with AUC_{0-24} greater than 19.2 mg.h/L (associated with neutropenia) [38]. These targets and proportions of subjects were fixed according to adults data. Abacavir and 3TC are well-tolerated drugs, thus only one target was considered to ensure efficacy for these ones. For ZDV, the toxicity is not negligible, so 3 targets were considered.

All the simulations were based on patients of 4 to 25 kg body weight and of at least 3 months of age.

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Results

Demographic data.

Table 1 summarizes patients age, weight and dosing for the entire population that served for the modeling and the subset that fell into the 4-25kg category that was used for simulations.

Population pharmacokinetics.

Lopinavir/Ritonavir

A one-compartment model described the data adequately. The estimated parameters were absorption rate constant (Ka), apparent clearance (CL/F) and volume of distribution (V/F) where F represents the unknown bioavailability (see Table, Supplemental Digital Content 2). Three residual variabilities were used and described by a proportional error model for TDM and P1030 and by an additive error model for P1038. An exponential error model was used for inter-subject variabilities of CL/F and V/F. The weight-based allometric scaling of clearance and volume parameters improved the goodness of fit. A significant effect of age on LPV bioavailability has been found also.

Lamivudine

A two-compartment model adequately described the data, thus the apparent parameters of the model were CL/F, the central volume of distribution (Vc/F), the peripheral volume of distribution (Vp/F), the inter-compartmental clearance (Q/F) and Ka (see Table, Supplemental Digital Content 3). Residual variability was best described by a proportional error model with a same residual error for P1056 and P1069. Inter-subject variabilities were described by an exponential error model and retained for CL/F, Vc/F, Q/F and Ka. The weight-based allometric scaling of the clearance and volume terms improved the goodness of fit. Thereafter, age had also a significant effect on clearance. A significant correlation of 0.88 was found between $\omega\text{-}_{CL/F}$ and $\omega\text{-}_{Q/F}$.

Abacavir

Abacavir pharmacokinetics was ascribed to a two-compartment model. Four residual variabilities were used and described by a proportional error model for P1018, P1052 and PENTA13, by a combined error model for TDM and by an additive error model for P352. Inter-subject variabilities were described by an exponential error model and retained for CL/F, Vc/F, Vp/F and Ka. After the inclusion of the weight-based allometric scaling, CL/F was found to increase slightly with age (see Table, Supplemental Digital Content 4).

Zidovudine

Zidovudine pharmacokinetics was ascribed to a one-compartment model. The estimated parameters were zero order absorption Tk0, CL/F, and V/F (see Table, Supplemental Digital Content 5). Residual variability was described by an additive error model for all studies except for twice daily administration data for which a proportional error model was used. An exponential error model was used for inter-subject variabilities for all parameters. The weight-based allometric scaling of clearance and volume

parameters improved the goodness of fit and a significant effect of age on ZDV clearance was found also.

Evaluation and validation.

The Prediction corrected visual predictive check plots show that the average prediction matches the observed concentration time-courses and that the variability is reasonably estimated for all the drugs (see Figure, Supplemental Digital Content 6). The 5^{th}, 50^{th} and 95^{th} percentiles of observed data are well included in the 90% confidence interval of the 5^{th}, 50^{th} and 95^{th} simulated percentiles.

Doses simulations for the fixed dose combination

Dose simulations based on WHO and FDA guidelines for lopinavir have been simulated through recommended weight bands. The figures 1a and 1b show the proportion of patients with a C_{min} above the 1 and 3mg/L targets respectively. In figure 1b, the WHO dose recommendations provided higher percentages of subjects reaching lopinavir efficacy targets, thus only WHO guidelines were simulated for NRTIs with the dose ratios of 0.375 for 3TC to LPV and 2 for ZDV-ABC to 3TC observed in the majority of weight bands.

For all nucleosides, simulations showed that more than 75% of subjects were above efficacy targets, i.e., 2 mg.h/L for ZDV and 8 mg.h/L for ABC and 3TC (data not shown).

Regarding ZDV, with these doses, patients were more likely to develop mild anemia and particularly neutropenia in the youngest age categories (from 4 to 6 kg) (Figure 2) suggesting that a lower dose would be preferable in this body weight range. To keep a single LPVr/NRTI ratio across weight bands, a lower LPV dose of 80mg bid (recommended by the WHO guidelines for 3 - 4 kg) was simulated in children weighing 4 to 6 kg. This lower dose resulted in more than 95% of patients with C_{min} above 1 mg/L (data not shown). However according to simulations this dose led to decrease the proportion of patients reaching the 3 mg/L target. This proportion was greater than FDA recommendations (Figure 3).

Regarding the efficacy of the NRTIs, the reduced doses of 30 mg bid for 3TC and 60 mg bid for ZDV and ABC provided a sufficient exposure with more than 75% of patients reaching the targets (data not shown). As shown in figure 4b, the risk of neutropenia was highly decreased using this lower dose of ZDV, i.e. from 40% to less than 10% in the 4-6 kg weight band. The risk to develop a mild anemia was also slightly reduced (Figure 4a).

Fixed dose combination

These simulations suggest that a formulation with a fixed dose of LPV/3TC/ZDV or ABC could be appropriate in children weighing 4 to 25 kg. According to the weight bands, i.e., 4-6kg, 6-10kg, 10-14kg, 14-20kg, 20-25kg children should receive respectively 2, 3, 4, 5, 6 units of this oral solid dose formulation twice daily. A single unit of this formulation corresponds to the following doses of active ingredients: LPV/RTV 40mg, 3TC 15mg, and ABC-ZDV 30 mg (see Table, Supplemental Digital Content 7).

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Discussion

This study describes lopinavir/ritonavir, lamivudine, abacavir and zidovudine pharmacokinetics in pediatric patients. The broad spectrum of ages allowed the investigation of the effect of growth (bodyweight) and maturation (age) on pharmacokinetic parameters. All the structural models were consistent with previous studies, i.e, a one-compartment model for lopinavir/ritonavir [8–11] and zidovudine [21,23,24] and a two-compartment model for lamivudine [13,14] and abacavir [16,39]. For zidovudine, the zero order absorption i.e. a rate of absorption independent of the dose administered, was preferred over the first order model (rate of absorption directly proportional to the dose) because the latter provided unlikely values corresponding to an instantaneous absorption (around 10 h^{-1}). Since all pharmacokinetic parameters do not change proportionally to body mass, allometric scaling was introduced to help distinguish variation due to growth and absorption or metabolic maturation as a function of age. The weight-based allometric scaling used for all drugs reflected fully mature adult values, i.e., the standardized clearance to 70kg were respectively 5.5 l/h, 34.9 l/h, 54.7 l/h, 137 l/h for LPV, 3TC, ABC, and ZDV; these values are fully consistent with previous studies in adults [36,40–42].

After weight-based allometric scaling, an effect of age on pharmacokinetic parameters was observed for all drugs. This age effect was found significant on the apparent clearance for all NRTIs and was best described by changes in bioavailability for lopinavir. Developmental changes in lopinavir clearance may also be occurring during the first year of life but were not detectable given the large increases in lopinavir bioavailability that occur concurrently. These age-related effects are consistent with previous studies in pediatric patients. According to the population modeling, the lopinavir bioavailability at birth corresponded to 38% of the adult value, and reached 90% after one year (see Figure, Supplemental Digital Content 8).

Lamivudine and zidovudine clearances increases reflect maturation of renal function and glucuronyl transferase activity reaching 90% of adult values within respectively 6 months and 1.5 years (see Figure, Supplemental Digital Content 8). These findings support that maturation due to age occurred mainly during the first weeks/months of life. For abacavir, the smaller number of patients under 2 years of age did not allow to describe as precisely the effect of maturation and thus explains the weak relationship found between clearance and age for that component (see Figure, Supplemental Digital Content 8).

For all drugs, the type of formulation (tablet, capsule or liquid) was evaluated during the covariate building process on bioavailability and this did not provide a significant decrease in the objective function value and did not decrease as well the between subject variability.

The simulations included only children weighing 4 to 25 kg over 3 months of age and should not be extrapolated beyond that population, especially in younger infants. Also these simulations assume similar bioavailability across formulations. The simulations indicated that the WHO dosing recommendations were generally appropriate. By definition the drug ratios for a fixed dose combination have to be constant across all weight bands. Because the original weight bands dosing for the different drugs from 4 to 10 kg did not provide constant ratios, the weight band dosing of either

LPV/r or NRTIs had to be modified. Using the original LPV/r dosage and the recommended drug ratios resulted in an overexposure of ZDV for the children in the 4-6 kg weight band, with an associated risk of neutropenia. Reducing the LPV/r dose in the lowest weight band significantly reduced ZDV exposure and thus the risk of neutropenia. This dosage reduction appears appropriate because it does not prevent children reaching optimal therapeutic targets. Moreover, this dosage fully corresponds to the WHO guidelines for all NRTIs and fulfills the blueprint of the dosage form of the pediatric oral combination.

Conclusion

These results show that a pediatric fixed-dose LPV/3TC/ZDV or ABC formulation can be developed to achieve targeted therapeutic effective and safe levels for all antiretroviral components. Each individual unit consists of 40 mg LPV, 10 mg RTV, 15 mg 3TC and 30 mg ABC or ZDV. According to the weight bands, i.e. 4-6 kg, 6-10 kg, 10-14 kg, 14-20 kg, 20-25 kg, therapeutic doses would be 2, 3, 4, 5, or 6 units twice daily of this formulation thus allowing the required flexibility of dosage and regimen in a broad pediatric population.

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Disclosure statement

All authors have nothing to disclose.

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DOI: 10.3851/IMP2876

Legends for figures

Figure 1

Percentage of children with LPV Cmin values above 1 mg/L (a) and 3 mg/L (b) as a function of bodyweight. The continuous curve corresponds to the FDA guidelines simulations (16 mg/kg bid for patients less than 6 months, 12 mg/kg bid for the less than 15 kg, and 10 mg/kg bid from 15 to 40 kg) and the dashed curve corresponds to WHO guidelines simulations (120 mg bid from 4 to 10 kg, 160 mg bid from 10 to 14 kg, 200 mg bid from 14 to 20 kg, and 240 mg bid from 20 to 25 kg). The horizontal lines represent the targets: 95% and 75% of patients that reach respectively 1mg/L (a) and 3mg/L (b).

Figure 2

Percentage of children with ZDV $AUC_{0\text{-}24h}$ values above 8.4 mg.h/L (a) and 19.2 mg.h/L (b) as a function of bodyweight using the following bid doses: 90mg for 4-10kg, 120mg for 10-14kg, 150mg for 14-20kg and 180mg for 20-25kg. The horizontal lines stand for the cutoffs: 25% and 5% of patients with $AUC_{0\text{-}24h}$ above 8.4mg.h/L (a) and 19.2mg.h/L (b).

Figure 3

Percentage of children with LPV Cmin values above 3 mg/L as a function of bodyweight. The continuous curve corresponds to the FDA guidelines simulations (16 mg/kg bid for patients less than 6 months, 12 mg/kg bid for the less than 15 kg, and 10 mg/kg bid from 15 to 40 kg) and the dashed curve corresponds to the simulations of WHO guidelines modified for 4-6kg (80 mg bid from 4 to 6 kg, 120 mg bid from 6 to 10 kg, 160 mg bid from 10 to 14 kg, 200 mg bid from 14 to 20 kg, and 240 mg bid from 20 to 25 kg). The horizontal line represents the target above which 75% of patients are expected.

Figure 4

Percentage of children with ZDV $AUC_{0\text{-}24h}$ values above 8.4 mg.h/L (a) and 19.2 mg.h/L (b) as a function of bodyweight using the following bid doses: 60mg for 4-6kg, 90mg for 6-10kg, 120mg for 10-14kg, 150mg for 14-20kg and 180mg for 20-25kg. The horizontal lines stand for the cutoffs: 25% and 5% of patients with $AUC_{0\text{-}24h}$ above 8.4mg.h/L (a) and 19.2mg.h/L (b).

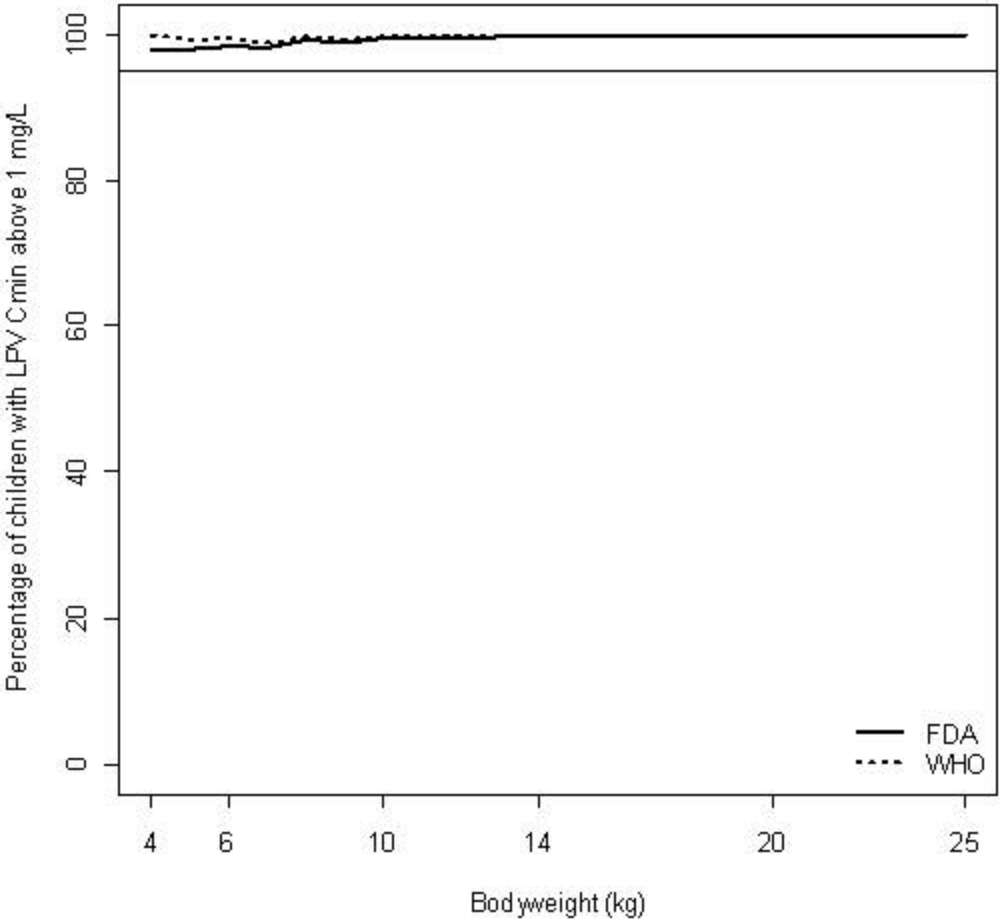
Publication: Antiviral Therapy; Type: Original article
DOI: 10.3851/IMP2876

Table 1. Characteristics of patients.

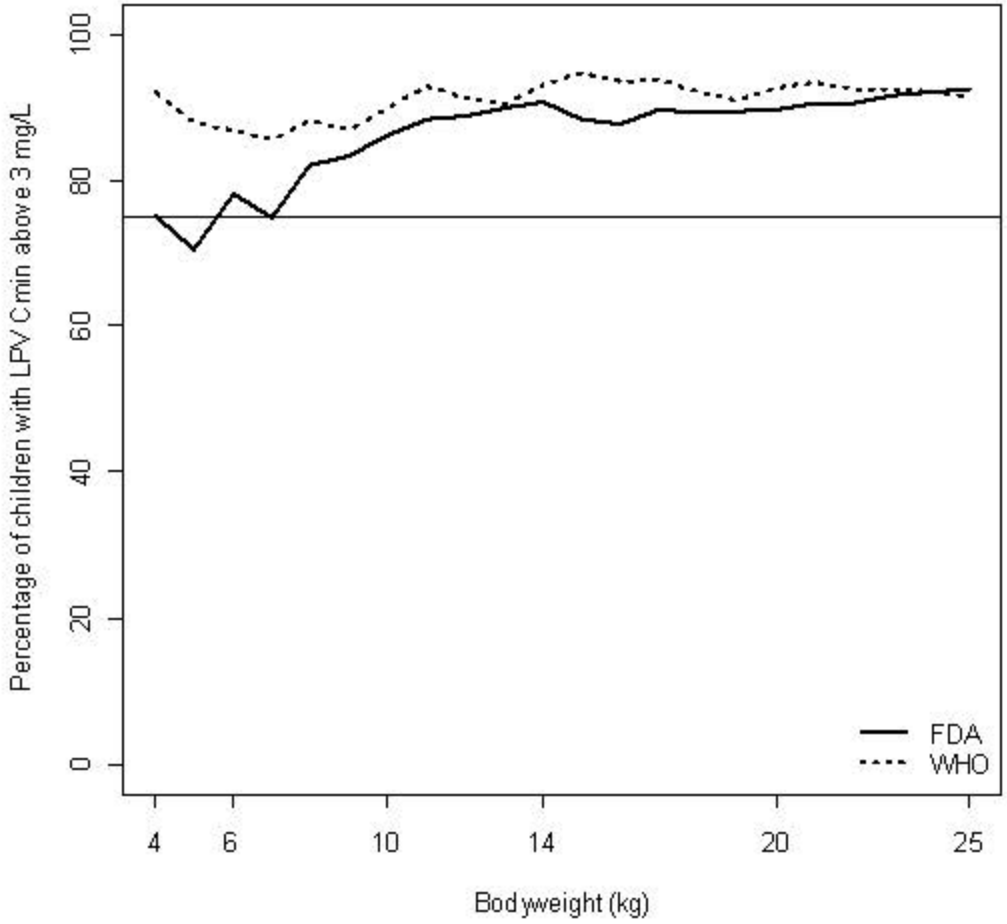
		Patients	Bodyweight (kg)	Age (years)	Dose (mg/kg)
		N (observations)		Median (IQR)	
Lopinavir	Total	338 (1394)	21.8 (8.5 - 37.9)	7 (1 - 12.4)	24.4 (18.5 - 30.1)
	4-25kg*	142 (613)	11 (8.2 - 19)	1.6 (1 - 5.6)	27.1 (24 - 30.9)
Lamivudine	Total	920 (3820)	18 (10.4 - 26.9)	5.4 (1.4 - 9.4)	7.7 (6.8 - 8.3)
	4-25kg*	590 (2347)	15 (10.7 - 20)	3.8 (1.5 - 6.6)	7.9 (7.3 - 8.4)
Abacavir	Total	187 (1231)	29.9 (18.6 - 53)	10.2 (5.5 - 14.7)	15.7 (12.8 - 16.4)
	4-25kg*	77 (488)	16.8 (13.7 - 20.7)	4.8 (2.2 - 6.8)	16.1 (15.4 - 16.9)
Zidovudine	Total	755 (3311)	16.9 (10.7 - 29.2)	4.7 (1.7 - 9.9)	12.9 (7.5 - 20.4)
	4-25kg*	508 (2225)	13.2 (9.6 - 18.2)	2.8 (1.4 - 5.1)	15.3 (7.1 - 22)

* Data are summarized for patients weighing 4 to 25 kg and aged more than 3 months.

a)


Percentage of children with LPV Cmin above 1 mg/L
0
20
40
60
80
100
4
6
10
14
20
25
Bodyweight (kg)
FDA
WHO

b)


Percentage of children with LPV Cmin above 3 mg/L
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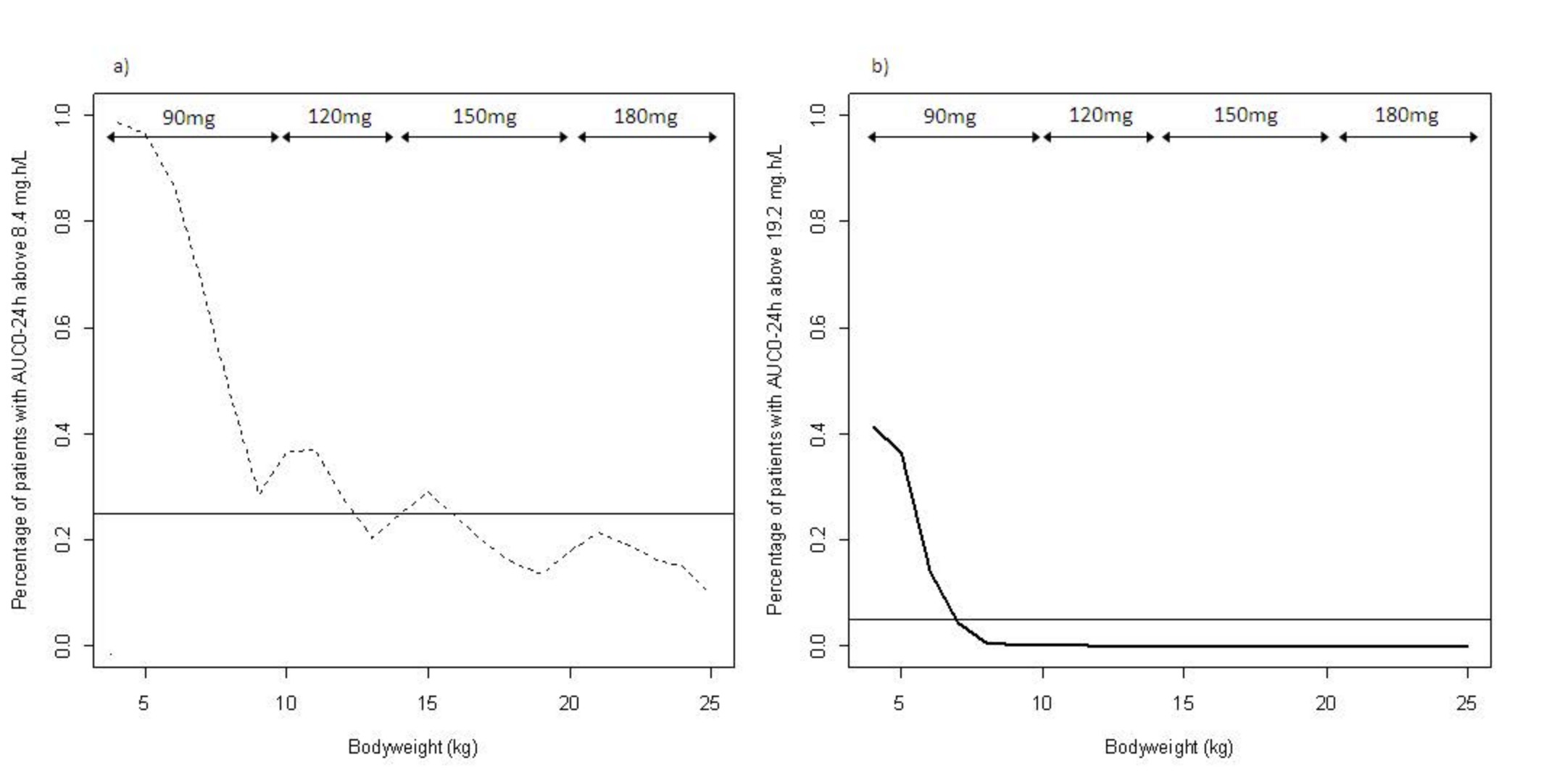
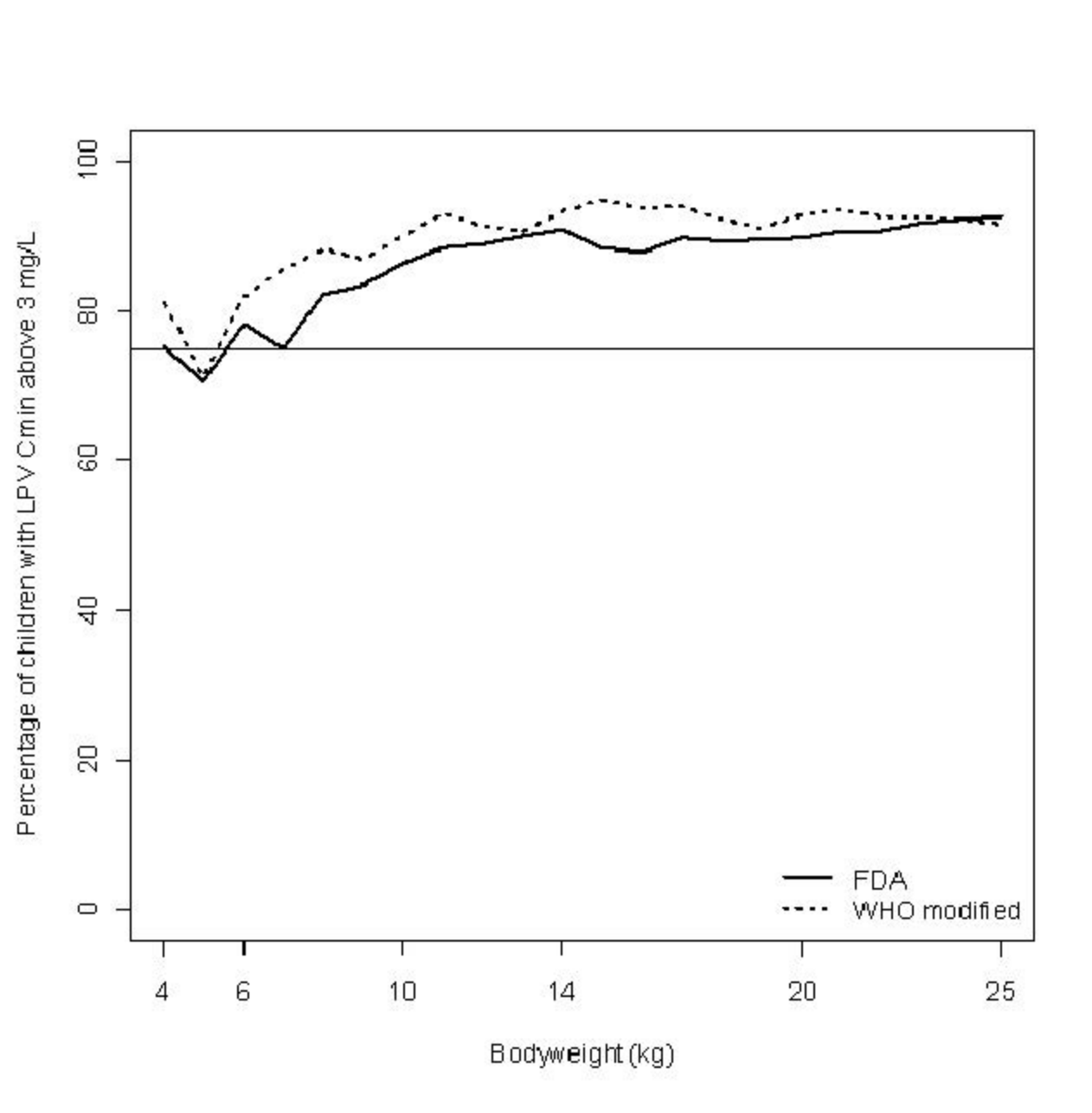
60
80
100
4
6
10
14
20
25
Bodyweight (kg)
FDA
WHO


a)
90mg
120mg
150mg
180mg
Percentage of patients with AUC0-24h above 8.4 mg.h/L
0.0
0.2
0.4
0.6
0.8
1.0
5
10
15
20
25
Bodyweight (kg)
b)
90mg
120mg
150mg
180mg
Percentage of patients with AUC0-24h above 19.2 mg.h/L
0.0
0.2
0.4
0.6
0.8
1.0
5
10
15
20
25
Bodyweight (kg)


Percentage of children with LPV Cmin above 3 mg/L
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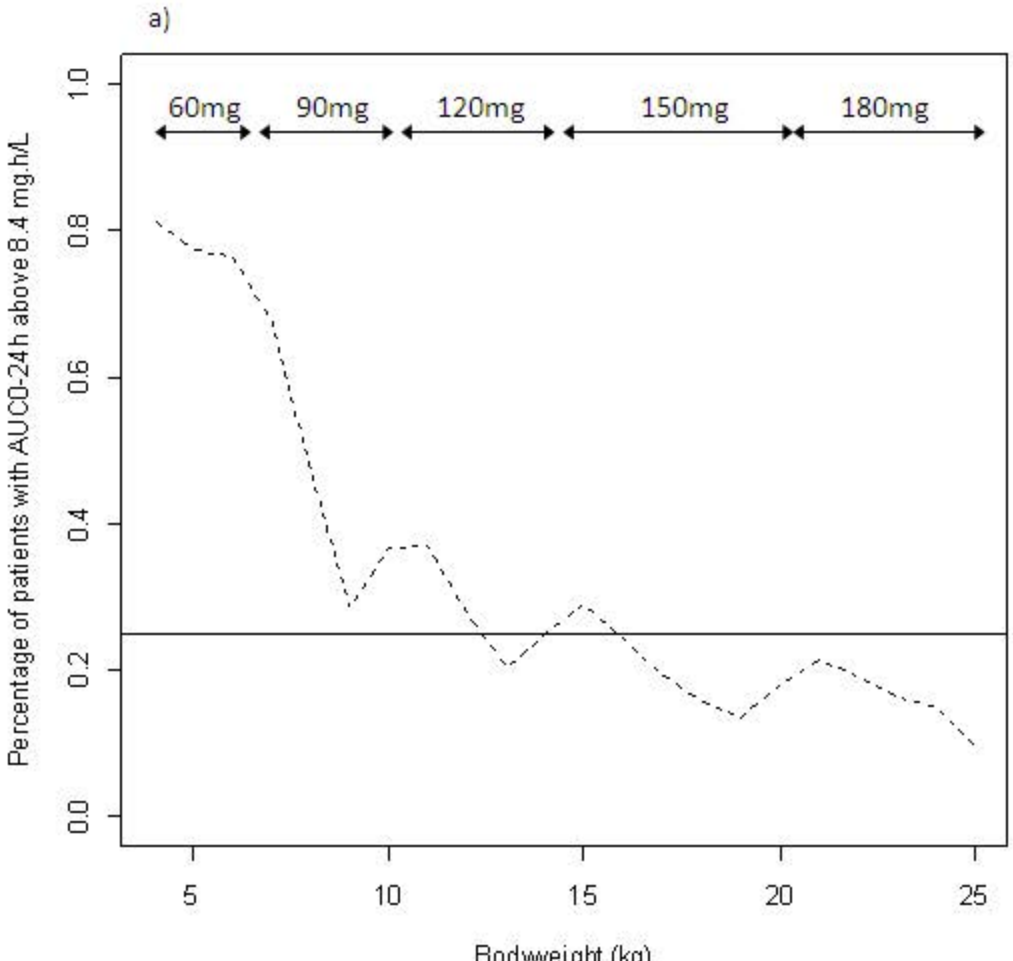
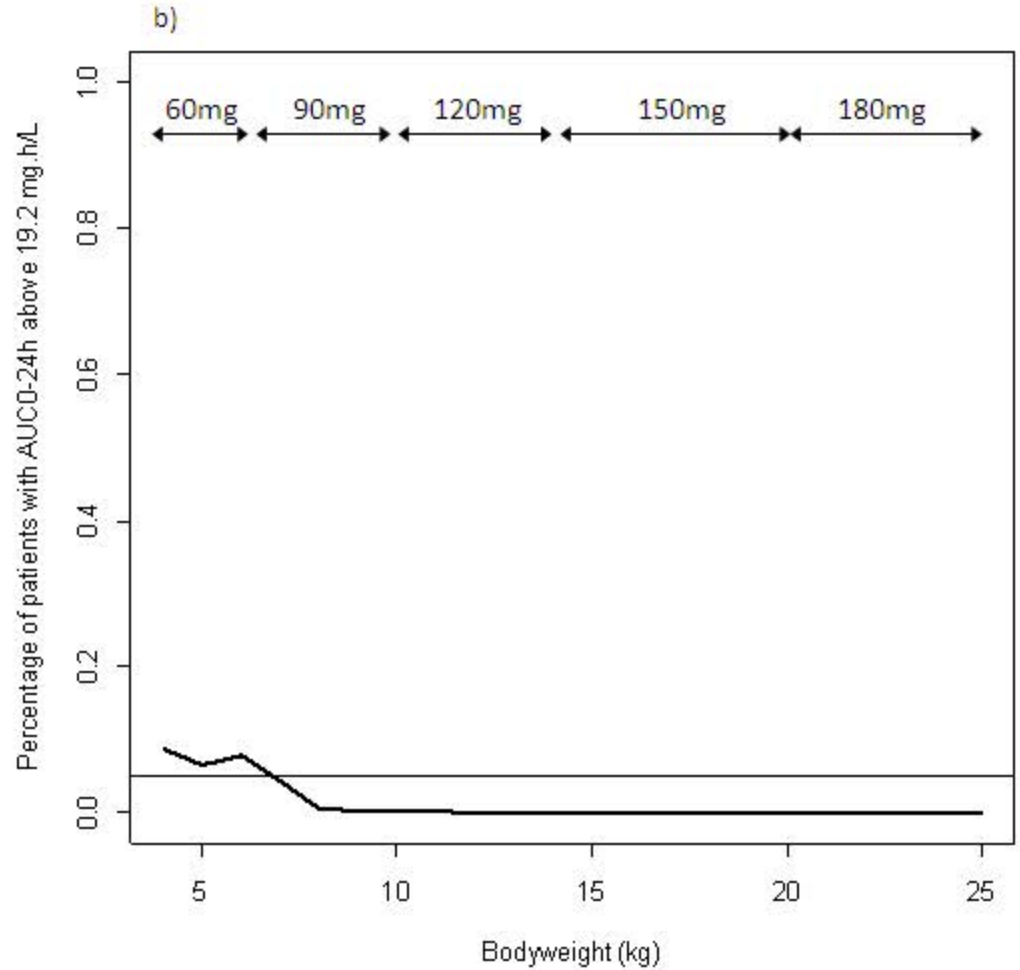
20
40
60
80
100
4
6
10
14
20
25
Bodyweight (kg)
FDA
WHO modified


a)
60mg
90mg
120mg
150mg
180mg
Percentage of patients with AUC0-24h above 8.4 mg.h/L
0.0
0.2
0.4
0.6
0.8
1.0
5
10
15
20
25
Bodyweight (kg)


b)
60mg
90mg
120mg
150mg
180mg
Percentage of patients with AUC0-24h above 19.2 mg.h/L
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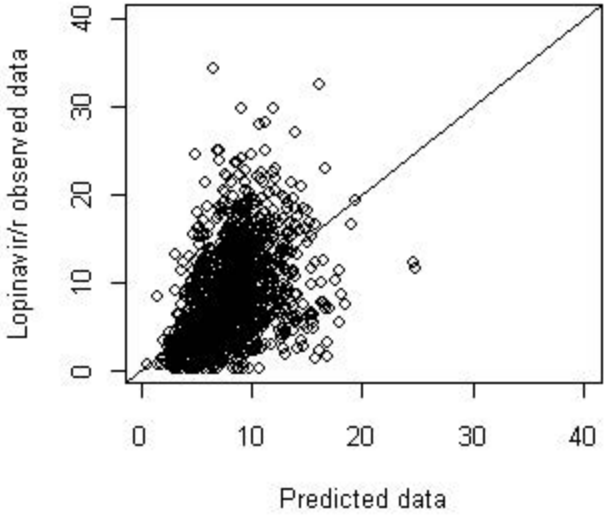
0.8
1.0
5
10
15
20
25
Bodyweight (kg)


Lopinavir/r observed data
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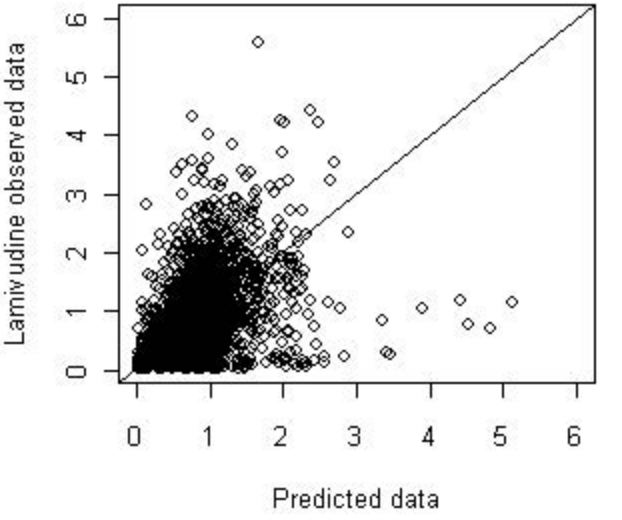
10
20
30
40
Predicted data


Lamivudine observed data
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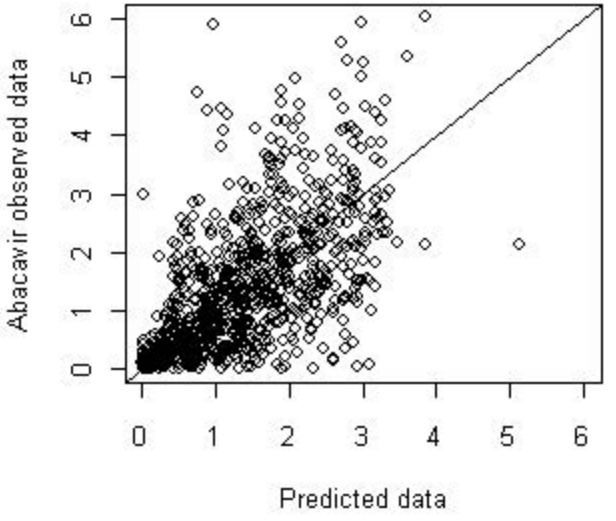
2
3
4
5
6
Predicted data


Abacavir observed data
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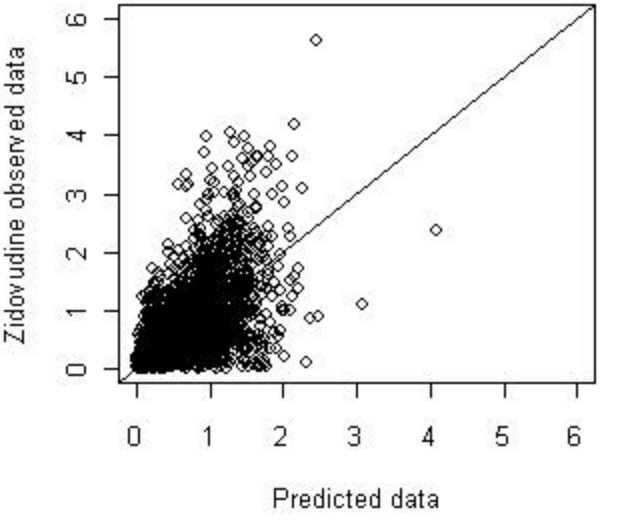
1
2
3
4
5
6
Predicted data


Zidovudine observed data
0
1
2
3
4
5
6
Predicted data

Supplemental Data File 2. Population pharmacokinetic parameters of lopinavir

	parameter	r.s.e.(%)
ka (h^{-1})	0.26	25
CL/F (L/h/70kg)	5.51	3
V/F (L/70kg)	105	18
Matb	0.375	10
yr50 (yr)	0.36	23
Between subject variabilities		
ω-CL/F	0.39	6
ω-V/F	0.59	16
Residual variabilities		
σ proportional (TDM)	0.43	3
σ proportional (P1030)	0.56	5
σ additive (mg/L) (P1038)	2.32	8

RSE, relative standard error (standard error of estimate/estimate x 100); CL/F, apparent elimination clearance; V/F, apparent volume of distribution; ka, absorption rate constant; F, bioavailability; Matb, is the value of F at birth; yr50 is the age needed to reach 50% of adult mature F; ω, intersubject variability estimate; σ, residual variability estimate.

$$F = Matb + (1-Matb) \times (1-\exp(-age \times 0.693/yr50))$$

Supplemental Data File 3. Population pharmacokinetic parameters of lamivudine

	parameter	r.s.e.(%)
ka (h-1)	0.573	3
CL/F (L/h/70kg)	34.9	2
Vc/F (L/70kg)	79.3	5
Q/F (L/h/70kg)	8.39	6
Vp/F (L/70kg)	523	16
Matb	0.174	8
yr50 (yr)	0.18	9
Between subject variabilites		
ω-ka	0.128	17
ω-CL/F	0.375	4
ω-Vc/F	0.72	6
ω-Q/F	0.851	7
corr(CL,Q)	0.885	3
Residual variabilities		
σ proportional (P1056 and P1069)	0.202	4
σ proportional (TDM, P300, P353, P356, P386)	0.474	2

RSE, relative standard error (standard error of estimate / estimate*100); ka, absorption rate constant; CL/F, typical value of apparent elimination clearance; Vc/F, typical value of apparent central volume of distribution; Vp/F, typical value of apparent peripheral volume of distribution; Q/F, typical value of intercompartmental clearance; F, bioavailability; Matb, is the fraction of typical value at birth; yr50 is the age needed to reach 50% of adult mature CL/F; ω, intersubject variability estimate; corr(CL,Q) covariance between CL/F and Q/F variabilities; σ, residual variability estimate.

Individual clearance (CL/F_i) is defined according to the equation below:

$$CL/F_i = 34.9 \times (WT/70)^{0.75} \times [Matb + (1-Matb) \times (1-\exp(-age \times 0.693/yr50))]$$

Supplemental Data File 4. Population pharmacokinetic parameters of abacavir

	parameter	r.s.e.(%)
ka (h-1)	0.686	4
CL (L/h/70kg/18 yr)	54.7	4
Vc (L/70kg)	32.4	16
Q(L/h/70kg)	4.76	10
Vp(L/70kg)	37.9	42
t.age	0.0906	26
Between subject variabilites		
ω-ka	0.226	13
ω-CL	0.39	7
ω-Vc	1.14	12
ω-Vp	2.02	33
Residual variabilities		
σ additive (mg/L) (**P352)**	0.79	10
σ proportional (P1052)	0.187	6
σ proportional (P1018, PENTA13)	0.393	1
σ additive (mg/L) **(TDM)**	0.02	14
σ proportional (TDM)	0.594	4

RSE, relative standard error (standard error of estimate / estimate*100); ka, absorption rate constant; CL/F, typical value of apparent elimination clearance; Vc/F, typical value of apparent central volume of distribution; Vp/F, typical value of apparent peripheral volume of distribution; Q/F, typical value of intercompartmental clearance; F, bioavailability; t.age, factor for CL/F maturation due to age; ω, intersubject variability estimate; σ, residual variability estimate.
Individual clearance (CL/F_i) is defined according to the equation below:

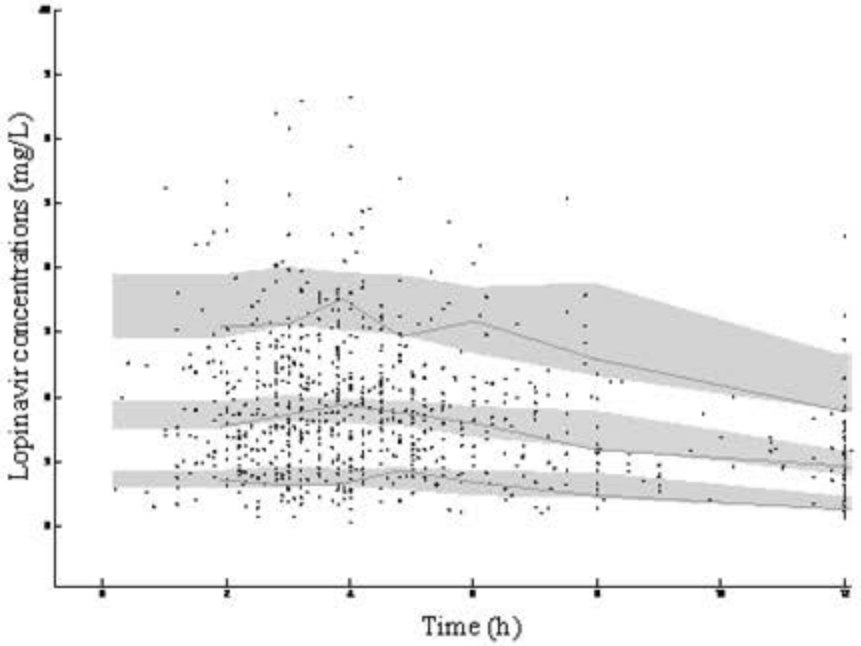
$$CL/F_i = 54.7 \times (WT/70)^{0.75} \times (age/18)^{t.age}$$

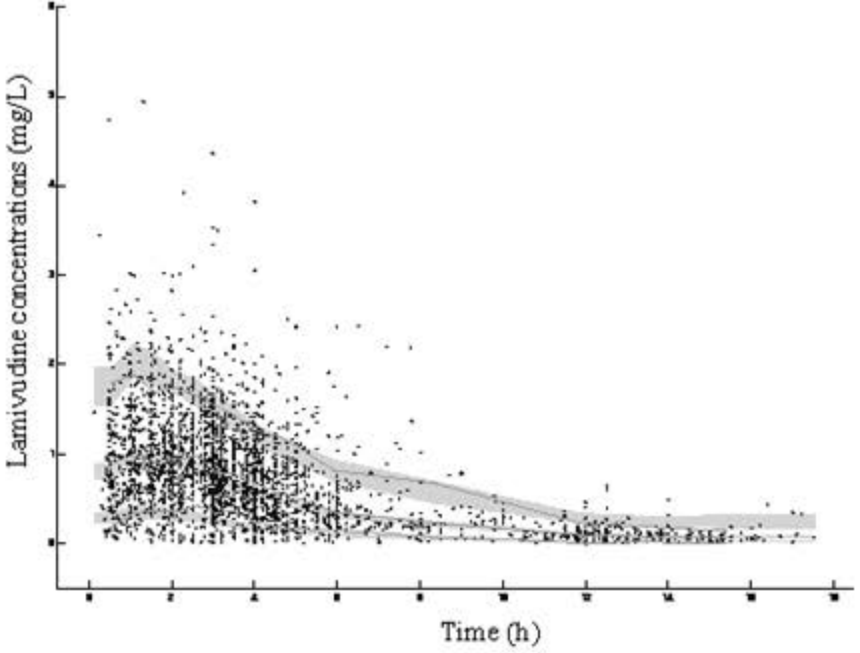
Supplemental Data File 5. Population pharmacokinetic parameters of zidovudine

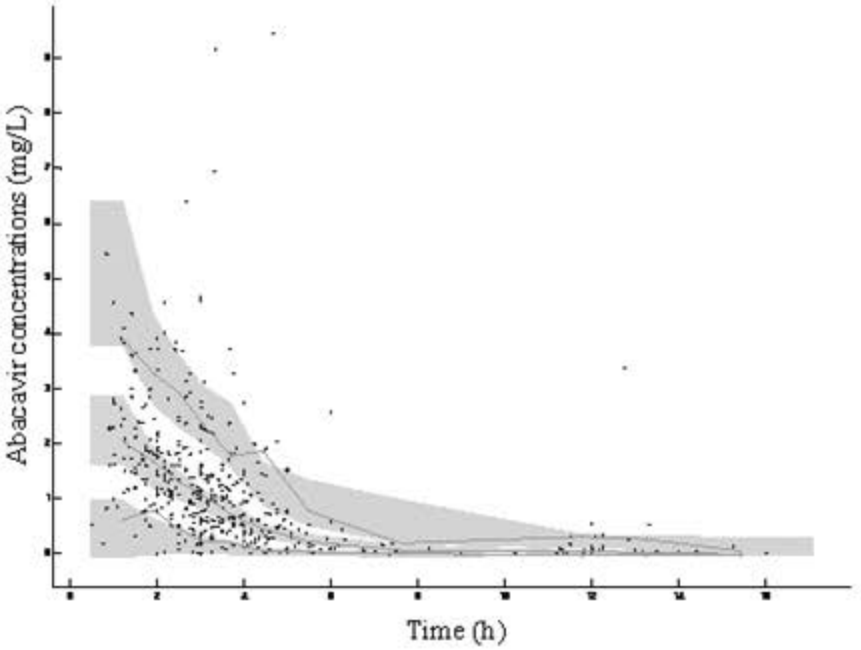
	parameter	**r.s.e.(%)**
Tk0 (h)	0.382	10
V (L/70kg)	257	3
CL (L/h/70kg)	137	2
Matb	0.171	37
yr50 (yr)	0.45	15
Between subject variabilites		
ω _Tk0	0.866	10
ω _V70	0.535	6
ω _CL70	0.33	6
Residual variabilities		
σ additive (mg/L)	0.382	2
σ proportional (twice daily administrations)	0.544	1

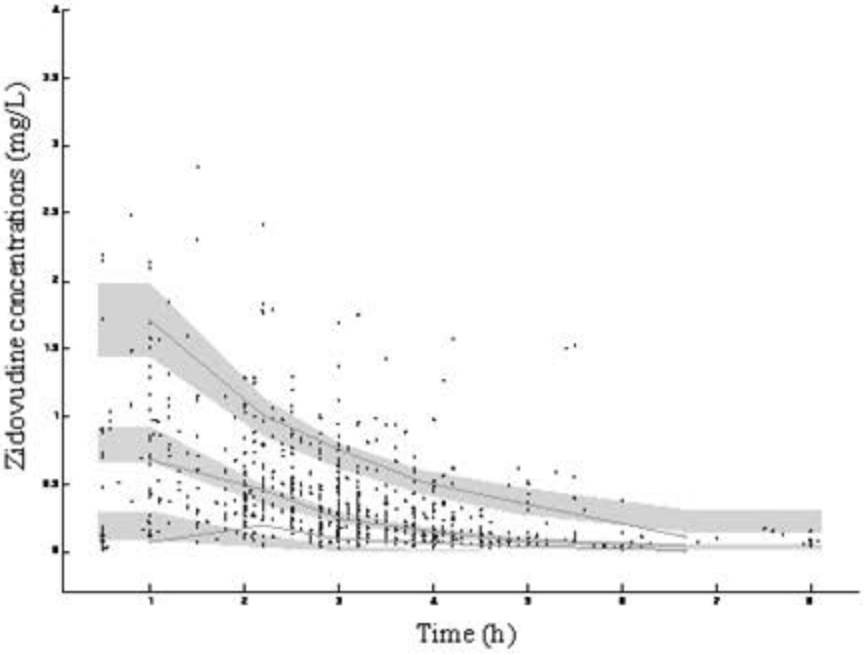
RSE, relative standard error (standard error of estimate / estimate*100); Tk0, zero-order absorption rate constant; CL/F, typical value of apparent elimination clearance; V/F, typical value of apparent volume of distribution; F, bioavailability; Matb, is the fraction of typical value at birth; yr50 is the age needed to reach 50% of adult mature CL/F; ω, intersubject variability estimate; σ, residual variability estimate.
Individual clearance CL/F_i is defined according to the equation below:

$$CL/F_i = 137 \times (WT/70)^{0.75} \times [Matb + (1-Matb) \times (1-\exp(-age \times 0.693/yr50))]$$


Lopinavir concentrations (mg/L)
Time (h)


Lamivudine concentrations (mg/L)
Time (h)

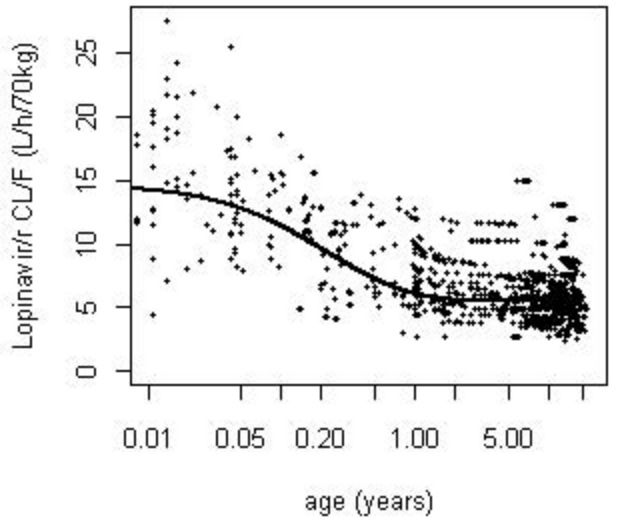

Abacavir concentrations (mg/L)
Time (h)

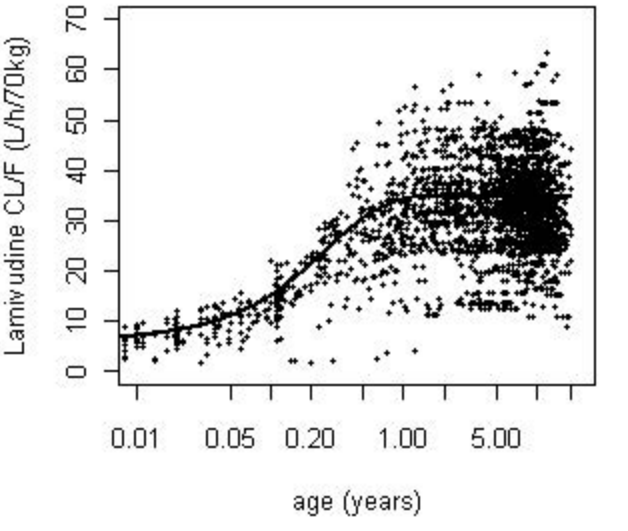

Zidovudine concentrations (mg/L)
Time (h)

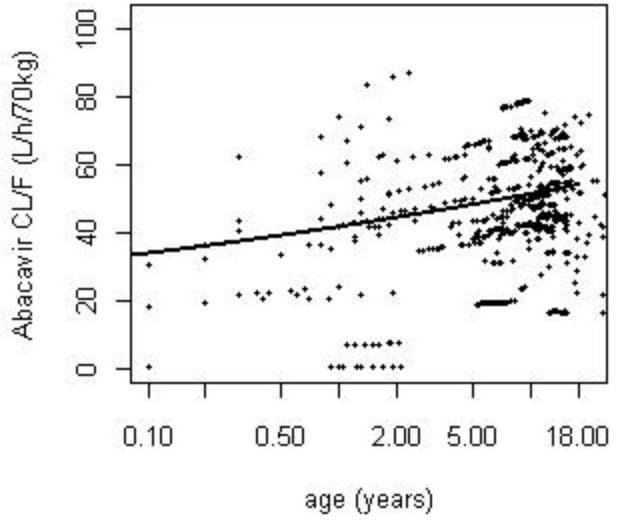
Supplemental Data File 7. Fixed dose combinations.

Weight bands	Lopinavir (mg)	Lamivudine (mg)	Abacavir - Zidovudine (mg)	Number of units BID*
4 - 6 kg	80	30	60	**2**
6 - 10 kg	120	45	90	**3**
10 - 14 kg	160	60	120	**4**
14 - 20 kg	200	75	150	**5**
20 - 25 kg	240	90	180	**6**

* A unit corresponds to a formulation with the following doses: LPV 40mg, 3TC 15mg, and ABC-AZT 30 mg


Lopinavir/r CL/F (L/h/70kg)
0
5
10
15
20
25
0.01
0.05
0.20
1.00
5.00
age (years)


Lamivudine CL/F (L/h/70kg)
0
10
20
30
40
50
60
70
0.01
0.05
0.20
1.00
5.00
age (years)


Abacavir CL/F (L/h/70kg)
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20
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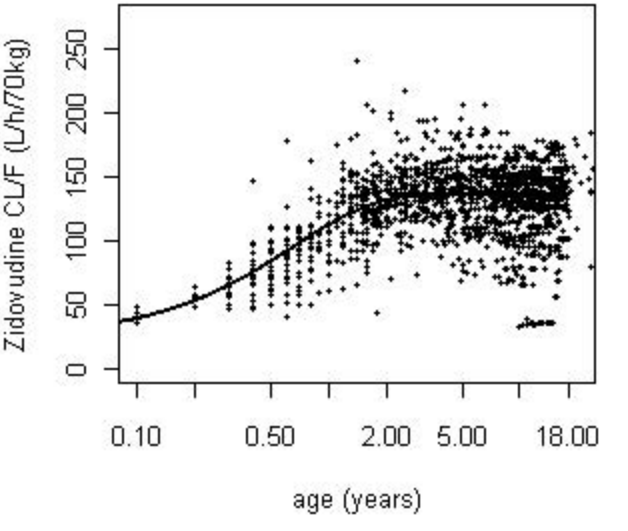
60
80
100
0.10
0.50
2.00
5.00
18.00
age (years)


Zidovudine CL/F (L/h/70kg)
0
50
100
150
200
250
0.10
0.50
2.00
5.00
18.00
age (years)