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Intraspecies allometric equations derived using phase 1 clinical adult pharmacokinetic parameters for pediatric dosing of lamivudine, nevirapine, and zidovudine

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ABSTRACT

The aim of this study was to simulate pediatric pharmacokinetic parameters using data from a clinical trial in healthy adults who were administered a pediatric fixed-dose combination of lamivudine (3TC)/zidovudine (AZT)/nevirapine (NVP) (30/60/50 mg) granules for reconstitution and fast disintegrating tablets. Using the area under the curve (AUC) from noncompartmental analysis, the relative bioavailability of the test suspension and test tablet to the reference suspension was 93.7% and 104.5% for lamivudine, 82.9% and 97.9% for nevirapine, and 94.2% and 93.6% for zidovudine, respectively. The 90% CI for C_{max}, AUC_{0-t}, and $AUC_{t-\infty}$ were 85.69%–102.54%, 96.13%–117.79%, and 82.63%–106.72%, respectively, for lamivudine; 83.33%–109.15%, 99.94%–124.54%, and 98.22%–122.43%, respectively, for zidovudine; and 87.71%–109.20%, 89.31%–106.26%, and 85.95%–102.82%, respectively, for nevirapine. Pharmacokinetic parameters were generated using the pharmacokinetics (PK) PK™ module in GastroPlus® modeling and simulation software. Pediatric pharmacokinetic parameters were simulated using adult clinical data and pediatric physiologic variables as inputs to the PK™ module. The resulting virtual pediatric subjects' PK data were regressed against pediatric body weight (BW), body surface area (BSA), and postgestational age (PGA), respectively. Clearance and volume of distribution were linearly correlated with BW (R^2 = 1.000) but obeyed the polynomial equation of the third order with the PGA of the subjects (R^2 ubjects . Simulation of pediatric pharmacokinetic parameters using adult PK data and pediatric physiologic parameters as input produced pediatric PK total clearance and volume of distribution, which were linearly correlated with BW but polynomially correlated with the PGA of children. By making appropriate allowances for a specific enzyme's maturation rate and presence, allometric scaling of pediatric doses of antiretroviral drugs lamivudine, nevirapine, and zidovudine could be more reliably determined using a linear expression based on BW and BSA and polynomial expression based on child's PGA of up 12 years.

INTRODUCTION

The pediatric population comprises a special group in drug dosing. The US pediatric population is approximately 20% of the general population (U.S. Census Bureau, n.d). However, prior to the last decade before the US Food and Drug Administration (FDA) and European Medicine Agency passed the regulatory legislation enabling drug development in pediatrics, drugs safety and efficacy testing were not usually carried out in the pediatric population before marketing authorization and commercial distribution (Auby, 2008; Ziswoski *et al*., 2010). The general tendency for the low level of safety and efficacy testing in children has been attributed primarily to the ethical and moral obligations of submitting children for studies, the difficulties of taking samples by invasive procedures, and the limited numbers and volume of samples that could be obtained from a child (Ziswoski *et al*., 2010). These have resulted in a general lack of rich clinical pharmacology data in the pediatric population (Caparelli and Williams, 2007).

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In addition, the development of dosing strategies in children is generally more complex than in adults due to the much greater variation in pediatric physical and physiologic characteristics such as body weight (BW), age, ongoing growth and different patterns of disease progression, and maturation of organs, especially the organs of metabolism and excretion as well as the enzyme systems within them (Bartelink *et al*., 2006). Moreover, many biomarkers of disease and physiologic processes have age-dependent ranges. Although it has been clearly asserted that children are not small adults (Giacoia and Mattison, 2005), advances in knowledge of pediatric pharmacology indicate that some extrapolations can be made with a significant level of accuracy in drug dosing of children based on adult clinical information. Based on this assumption, the US FDA published the Guidance for Industry: General Considerations for Pediatric Pharmacokinetic Studies for Drugs and Biological Products (DHHS, 1998). Since, for ethical and logistic reasons, characterization of drug efficacy and safety in adults almost always precedes pharmacometric studies in children, the design of studies in children could benefit from the existing wealth of preclinical and clinical data in adults.

Literature information suggests that physiologic distribution and elimination pathways show commonalities across ages even though their relative contribution to the overall pharmacokinetics of drugs may differ (Caparelli and Williams, 2007). Similarly, enzyme presence and activity show a high degree of similarity across age groups. However, despite the existence of overall homology for a set of enzymes, some differences may lead to unexpected developmental changes in the pharmacokinetics of drugs (Caparelli and Williams, 2007). In the absence of pediatric-specific pharmacodynamic models, exposure-response surfaces, and models linking biomarkers to pediatric outcomes, the application of pharmacometrics appears to be the only feasible and most rational way of optimizing drug use in pediatrics (Trivedi *et al*., 2013). The procedure involves estimation of the impact of different levels of covariates on pharmacokinetics and pharmacodynamics with the potential application in dosing strategies. The large ranges of important dosing parameters such as age, BW, and surface area in children imply that these covariates would impact pharmacokinetics and pharmacodynamics in children more than in adults.

The use of combination therapy of two or more drugs has been found to provide significant viral suppression and inhibit drug resistance (Riska *et al*., 1990). Owing to these benefits, several fixed-dose combination therapies have been developed recently (Blum *et al*., 1988; vanLeeuwen *et al*., 1992). However, the biggest challenge for anti-HIV therapy in children is the lack of age-appropriate formulations that can be easily and accurately administered to the children population. There are over 20 antiretroviral drugs licensed worldwide for the treatment of adults, but many do not have appropriate formulations for children. The pediatric formulations currently in use are either poorly palatable liquids or tablets that cannot be crushed (Chokephaibulkit *et al*., 2011; French *et al*., 2002; Kayitare *et al*., 2009; Marier *et al*., 2007; Monif *et al*., 2009; Pujari *et al*., 2004). In addition, mother-to-child transmission of drug-resistant viruses or development of drug resistance due to prenatal treatment can also be a concern in developing formulations for children. There is therefore an urgent necessity to address three major challenges in pediatric antiretroviral therapy: determining the flexible and adaptable dosage form, establishing the parameters for dosage determination, and adopting appropriate strategies for stemming mother-to-child transmission.

Esseku *et al*. (2013) previously developed fixed-dose formulations of three drugs: 3TC, AZT, and ZDV. The fixed-dose combination of these drugs was bioequivalent to the coadministered single entities of reference products (Chokephaibulkit *et al*., 2011). The outcome of earlier clinical studies in pediatrics indicated significantly new information and pharmacokinetic differences between children and adults (Leeder *et al*., 2010). Several physiologic processes that affect the absorption, distribution, metabolism, and excretion of drugs differ significantly among neonates, children, and adults. For example, the activity of cytochrome P450 (CYP 450) is less in neonates but higher in children when compared to adults (Anderson, 2002). This variation in the activity of CYP 450 should be considered when developing formulations and doses for pediatric populations. However, there is significantly less clinical data available with regard to the pediatric population.

Generally, the first dose of the drug for an infant is calculated based on the established dose in adults by four methods: age-based categories, normalization of dose to BW, body surface area (BSA), and the allometric method. Each of these methods has its own limitations. Variability and progressive changes in body composition of a developing child imply potentials for significant differences in the processes of dosage form-dependent drug release for absorption, distribution, metabolism, and excretion known as liberation, absorption, distribution, metabolism, and excretion (LADME). Differences in the rate and extent of LADME will in turn impact the pharmacodynamics and therapeutic outcomes of the drug. Hence, knowledge of physiology-based pharmacokinetics with the help of a rationally determined allometric equation will significantly improve the quality of drug dosing in pediatrics. Although significant progress has been made since 1994 when the US FDA enacted the FDA Modernization Act (FDAMA) (Breitkreutz, 2008) encouraging pharmaceutical manufacturers to conduct pediatric clinical trials, there is still a long way before sufficient information would be available for routine clinical use. In the alternative, pharmacokinetic modeling has been recognized as a useful tool for predicting the pharmacokinetic parameters in children based on the data obtained from clinical trials in adults. It appears that such information is still not available in the literature for antiretroviral therapies. This study was therefore designed to simulate the pediatric parameters from the clinical trial data in healthy adults administered with a pediatric fixed-dose combination of lamivudine (3TC)/zidovudine (AZT)/nevirapine (NVP) at the levels of 30/60/50 mg per 5 ml, respectively, which were presented as granules for reconstitution or fast disintegrating tablets (Esseku *et al*., 2013). Existing pharmaceutical information on the drugs and projected physical and physiologic information in virtual pediatric patient populations would be used as input data into the pharmacokinetic modeling and simulation software.

MATERIALS AND METHODS

Pharmacokinetic parameters of lamivudine, nevirapine, and zidovudine were determined from a meta-analysis of the plasma-time profiles obtained from an open-label, randomized, two-way crossover study conducted on 24 healthy adults as previously

reported by Esseku *et al*. (2013). Drug physicochemical and molecular properties extracted from various literature, DrugBank, and other databases (Table 1) were entered into the GastroPlus® pharmacokinetic modeling and simulation software. For the respective drugs, Cp-versus-time profiles were entered into the model finding menu, and the drug dose, dosage form, and individual subject's BW were populated in the appropriate menu. The model solution was sought for one-, two-, and three-compartment models, respectively, using the Akaike information criterion and Schwarz criterion for indicating the best fitting model. Hooke and Jeeves's pattern search was selected, and the objective weighting was 1/Yhat. From the optimum solutions determined in GastroPlus®, the pharmacokinetic parameters [specifically clearance (CL)/F and Vc/F] associated with the solutions were extracted, plugged into an MS Excel spreadsheet, and used to generate the expected volume of distribution (Vd) and CL for a given age (months, after gestation), BW, and BSA (m^2) of virtual subjects, up to 12 years. A set of regression equations was generated by regressing CL/F against BW,

Table 1. Sources of variation in pharmacokinetics (PK) between children and adult.

	Drug	Lamivudine (MW 229.26 g/mol)	Nevirapine (MW: 266.31 g/mol)	Zidovudine (MW: 267.24 g/mol	Comments: Age-dependence?
1	Solubility/permeability Characteristics and absorption				
	• Aq. Sol	70 mg/ml at 20°C	0.1 mg/ml	20.1 mg/ml at pH 1.2 to 6.8	
	• pKa	4.3	2.8	9.8	
	• LogP	0.06; −1.4 to −1.28	1.81; Highly lipophilic1	0.05	
	• cLogP	−0.9 to −0.88	2.65	0.04	
	• BCS class	III	II	I	
	• Transporter involved and type	human organic cation transporter 1 in kidneys	ABCB1, ABCC*12*, ABCC10rs2125739	A poor P-gp substrate	
	BA		BA from IR suspension, tablets and XR/CR: 82% to 106%	Oral absorption is rapid and complete; BA is 66% to 88%; subject to first pass	Lamividine absorption is age-dependent
	• Adult	82%			
	• Children	68%			
2	Distribution				
	• Volume of distribution (Vd)	1.3 l/kg	1.2 to 1.5 l/kg (Moffat *et al*., 2011)	1.3 l/kg	
	• Protein Binding	Albumin: 40%	Albumin: 60%	Albumin; 25%	
	• # of compartments	One-compartment	One-compartment	Two-compartment (bi-exponential)	
3	Metabolism				
	• % Metabolic clearance	5%–10%	Extensive (Moffat *et al*., 2011)	60%–70%	
	• Phase 1/phase 2?	Phase 1	Phase I: CYP450 oxidation and glucuronide conjugation (Riska *et al*., 1990)	Phase II	
	• Major mechanism/route	Intracellular phosphorylation by kinases to 3TCTP	CYP3A and CYP2B6; Nevirapine is an enzyme inducer; induces its own CYP3A and CYP2B6 metabolism, approximately 1.5- to 2-fold increase in the apparent oral clearance (CL/F) in course of therapy. T1/2: 40 to 45 hours	Glucuronidation by UGT2B7	
4	Excretion				
	• % Renal clearance	70%; 200 ± 55 ml/minute; GFR + active tubular secretion	Urinary excretion of glucuronidated metabolites	1% in parent form; 60%–70% as inactive metabolite	Lamivudine: For infant and children under 12 years, oral dose should be reduced to 2 mg/kg bid because of immature renal function.

postgestational age (PGA), and BSA, respectively. Similarly, Vc/F (and V2/F and CL2/F for drugs that showed a two-compartment model in GastroPlus®) were in turn regressed against BW, PGA, and BSA, respectively.

RESULTS AND DISCUSSION

At the end of 2020, about 1.7 million children around the world are living with HIV/AIDS, most cases of which were acquired through infection via mother-to-child transmission (available at https://www.unaids.org/en/keywords/children) (accessed January 03, 2022). Also, in 2020 there were 150,000 new HIV infections in children, mostly due to a lack of access to HIV testing and medication, especially in pregnant and breastfeeding women (available at https://www.unaids.org/en/keywords/children) (accessed January 03, 2022). Highly active antiretroviral treatment consisting of a combination of nonnucleoside reverse transcriptase, nucleoside reverse transcriptase, and protease inhibitors has been proven to suppress the replication of the HIV in the body. Some of the World Health Organization's recommended treatments consist of zidovudine (for infants 6 weeks–12 months) and nevirapine (0–12 months). However, these drugs either are not available in suitable dosage formulations or have not been studied at a considerable level in pediatric patients. The introduction of the FDAMA and various legislative initiatives encouraging drug manufacturers to evaluate the existing data that could support pediatric drug labeling resulted in pediatric studies on over 300 drugs and biological products. The studies showed some important pharmacokinetic differences between children and adults (Leeder *et al*., 2010). The outcome of the studies reinforced the previously held notion that drug dosing in this population requires critical consideration of the differences in the pharmacokinetics in relation to the pharmacology of a specific drug across the age range from a preterm newborn infant, newborn infant (birth–28 days), and infant (28 days–23 months) through a young child (2–5 years) to older child (6–11 years) and adolescent (12–18 years). It also emphasized the need for the provision of age-appropriate dosage forms in order to enhance product acceptance by children and provide the needed flexibility for a more accurate dosage determination for the pediatric population.

The superimposed Cp versus time of 12 volunteers who took the suspension dosage form containing lamivudine, nevirapine, and zidovudine are shown in Figures 1–3, respectively. The pharmacokinetic parameters of the three drugs are shown in Table 1. The area under the curve (AUC) from the noncompartmental analysis showed the relative bioavailability of the test suspension and test tablet to the reference suspension as 93.7% and 104.5% for lamivudine, 82.9% and 97.9% for nevirapine, and 94.2% and 93.6% for zidovudine, respectively (Table 2). The obtained bioavailability generally fell within the FDA acceptance criteria of −20 to +25% (i.e., 80 to 125%) of the reference formulation (DHHS, 1998). The 90% CI for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were 85.69%–102.54%, 96.13%–117.79%, and 82.63%–106.72%, respectively, for lamivudine; 83.33%–109.15%, 99.94%–124.54%, and 98.22%–122.43%, respectively, for zidovudine; and 87.71%–109.20%, 89.31%–106.26%, and 85.95%–102.82%, respectively, for nevirapine, indicating the bioequivalence of test to reference products.

The result of bioavailability/bioequivalence testing of the different fixed-dose combinations showed that the more soluble lamivudine (70 mg/ml, BCS Class III) and zidovudine (20 mg/ml; BCS Class 1) drugs generally followed the two-compartmental model while nevirapine (0.1 g/ml; BCS Class II) followed the one-compartmental model (Figs. 1–3).

Most literature models were determined in a relatively homogenous population of patients (Sabo *et al*., 2002). In order to capture the dependence of PK parameters on patient variables, the respective drug's adult pharmacokinetic parameters as a function of BW were regressed on virtual patient parameters obtained from the literature including PGA, BW, and BSA in the form of linear, exponential, power, and polynomial models in order to determine the model that best captures the parameter dependence most accurately across the developmental age ranges.

Clearance and Vd weighted on the bioavailability factor (F) per kg of subject BW was linearly correlated with the BW

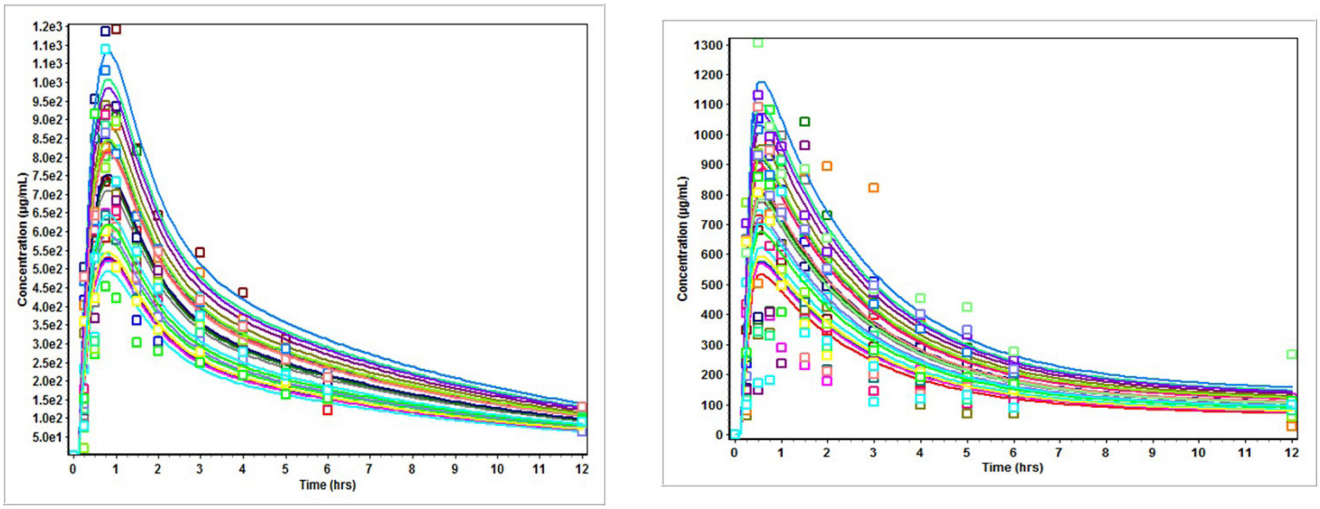

Figure 1. (a) Plasma concentration (Cp) versus time (t) profiles of subjects on lamivudine in three drug suspension formulations. (b) Plasma concentration (Cp) versus time (t) profiles of subjects on lamivudine oral disintegration tablets.

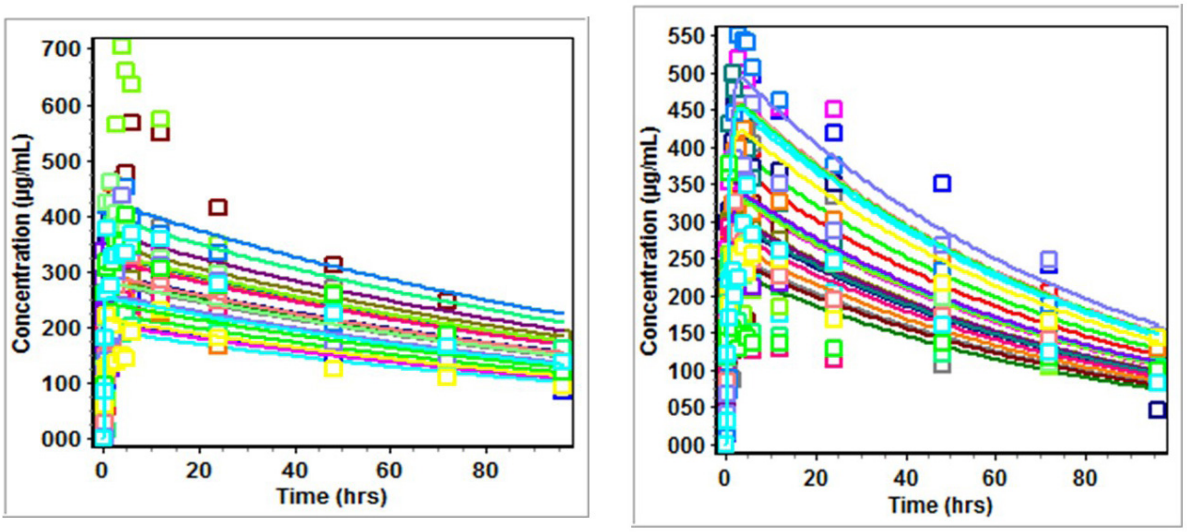

Figure 2. (a) Plasma concentration (Cp) versus time (*t*) profiles of subjects on nevirapine in three drug suspension formulations. (b) Plasma concentration (Cp) versus time (*t*) profiles of subjects on nevirapine oral disintegration tablets.

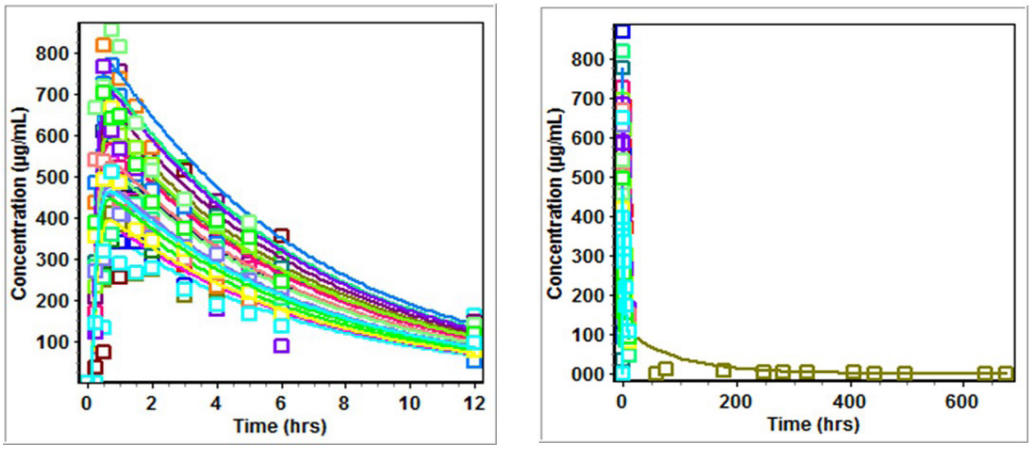

Figure 3. (a) Plasma concentration (Cp) versus time (*t*) profiles of subjects on zidovudine in three drug suspension formulations. (b) Plasma concentration (Cp) versus time (*t*) profiles of subjects on zidovudine oral disintegration tablets.

(R^2 = 1.000, Figs. 4 and 5) and exponent, n =1.0 (Anderson, 2002; Esseku *et al*., 2013). CL and Vd obeyed a power function with BSA according to the equation

$$\text{CL (or Vd)} = a^*(\text{BSA})^n,\ R^2 \geq 0.9987 \quad (1)$$

The factor "*a*" in the equation is drug substance-dependent and is highest for lamivudine, a BCS-III drug, essentially renally cleared by the glomerular filtration rate (GFR) and active tubular secretion (vanLeeuwen, 1992), and lowest for zidovudine, a BCS I drug, essentially metabolized with only 1% eliminated in the parent form (Blum *et al*., 1988). Agreement between pediatric pharmacokinetic parameters derived using adult clinical data and the predicted parameter values in the virtual children population provided the regression profiles shown in Figures 6–8 for lamivudine, nevirapine, and zidovudine, respectively.

According to Bartelink *et al*. (2006), BW provided the most predictive covariate for clearance, volume of distribution, and intercompartmental clearance and accounted for 65%, 75%, and 40% of the observed variability, respectively, in these parameters. The relationship between BW and clearance was best characterized using an allometric equation with a scaling exponent that changed with BW from 1.2 in neonates to 0.55 in young adults (Bartelink *et al*., 2006; Cella *et al*., 2012). For lamivudine and zidovudine, the renal system plays a crucial role in their elimination as either parent or metabolite form. Therefore, dosing should be carefully determined, especially during the postgestational and early childhood stages. Evidence abounds in the literature showing that, during the last months of gestation, GFR increases in parallel with gestational age until the 36th week due to an increase in both the number and size of nephrons and thereafter develops more slowly up to the time of birth. However, nevirapine CL/F has been shown

Table 2. Pharmacokinetic parameters from 24 healthy subjects in 3 × 3 randomized crossover study.

Drug	Dosage form	Pharmacokinetic parameters								
		CL/*F* (kg^{-1}) l/hour	Vc/*F* (kg^{-1}) l	C_{max} µg/ml	$T_{1/2}$ (hour)	AUC (1–Compt. analysis)	K_a ($hour^{-1}$)	T_{lag} (hour)	R^2	BA_R (%)
Lamivudine	Suspension (REF)	6.342×10^{-4} −179.71	2.274×10^{-3} −167.41	8.054	7.044 0	5.47×10^{3}	4.923 −272.13	0.188 −86.39	0.672	-
	Suspension (TEST)	7.038×10^{-4} −111.08	1.164×10^{-3} −1,598.93	7.193	5.197 0	5.13×10^{3}	1.404 −1,328.4	0.1468 −254.25	0.719	93.8
	Tablet (TEST)	3.344×10^{-4} −2,556.16	2.933×10^{-3} −81.58	7.848	32.52 0	5.72×10^{3}	8.348 −206.79	0.1764 −123.92	0.5885	104.6
Nevirapine	Suspension (REF)	1.118×10^{-4} −143.85	0.01 −59.27	2.517	63.02 −155.58	2.64×10^{4} −211.89	1.666 −324.11	0.041 −2,469.36	0.472	-
	Suspension (TEST)	8.552×10^{-5} −250.93	0.013 −50.27	2.139	102 −255.91	2.19×10^{4} −358.41	56.26 −1,033.3	7.806×10^{-4} −10,084.4	0.2959	82.9
	Tablet (TEST)	1.186×10^{-4} −138.29	0.01 −58.04	2.487	60.5 −149.97	2.58×10^{4} −204	1.455 −176.94	0 0	0.481	97.9
Zidovudine	Suspension (REF)	5.569×10^{-4} −2,608.46	5.299×10^{-3} −157	4.315	19.95 0	4.50×10^{4}	6.401 −1,015.78	0.1048 −1,253.79	0.6593	-
	Suspension (TEST)	9.581×10^{-4} −81.28	6.31×10^{-3} −60.81	3.851	4.565 −101.51	4.24×10^{3} −130.04	7.112 −784.77	0.132 −706.62	0.5752	94.2
	Tablet (TEST)	3.278×10^{-4} −528.28	5.93×10^{-3} −88.93	3.884	64.67	4.21×10^{3}	5.536 −334.33	0 0	0.5756	93.6

BA_R, Relative bioavailability.

to be insignificantly affected by patient demographics (age, gender) and only minimally affected by patient weight (Sabo *et al*., 2002).

The GFR is low in preterm infants at birth and varies with gestational age. The stage of renal development may be critical for lamivudine and nevirapine elimination in these neonates. Postnatal GFR develops slowly until 34 to 36 weeks of gestation. Thereafter, GFR increases rapidly, like postnatal GFR in term neonates, and GFR measured by inulin clearance at birth is almost 20 ml/minute/1.73 m^2 in term neonates (van der Heijden *et al*., 1988). There is a large increase in GFR during the first 2 weeks after birth in term infants, which has been associated with a postnatal increment in gestational age, BW, and renal hemodynamic changes reaching 50 ml/minute/1.73 m^2. Renal hemodynamics is independent of gestational age and BW (Otukesh *et al*., 2012). All these data support the need for pharmacokinetic monitoring of drug clearance in this population to ensure an optimal outcome and minimal adverse drug event.

Regression of CL and Vd, respectively, on PGA of subjects followed a polynomial with the highest R^2 at the third order according to the equations

$$CL_{Nev} = 2^{-09}(Age)^3 - 4^{-07}(Age)^2 + 5^{-05}(Age) - 0.0001 \quad (2)$$

($R^2 = 0.9948$),

$$CL_{Lam} = 1^{-08}(Age)^3 - 4^{-06}(Age)^2 + 4^{-04} - 0.001 \quad (3)$$

($R^2 = 0.9948$),

$$CL_{Zid} = 2^{-12}(Age)^3 - 4^{-10}(Age)^2 + 4^{-08}(Age) - 1^{-07} \quad (4)$$

($R^2 = 0.9948$).

Knowledge of PK of drugs is being used in the calculation of the first in-human dose (Jones *et al*., 2011; Rowland *et al*., 2011). Pending the availability of more extensive pharmacokinetic data of most drugs in pediatrics, allometric estimation of a child's doses based on adult human clinical data provides a rational basis for age- and BW-dependent adjustments in antiretroviral medication, once the role of enzymes and transporters has been carefully considered. Thus, by selecting the most fitting equations (Figs. 4 and 5), more accurate age-appropriate doses can be determined for the pediatric population, from infant to age 12, using adult human PK data. The model fitness evaluated as a function of predicted versus observed Cp in virtual pediatric patients of postgestation to age 12 years is shown in Figures 6 and 7, with regression coefficients of 0.7084, 0.4822, and 0.5829, respectively, for lamivudine, nevirapine, and zidovudine. Allometric scaling is a well-established method for relating physiological or pharmacokinetic parameters to BW, and it is currently used for the prediction of human dose by extrapolation from preclinical animal studies and for dose estimation for other animal species. Fixed-exponent scaling from human adult pharmacokinetic data provides a more practical alternative to conventional interspecies scaling (Anderson and Holford, 2008; Holford *et al*., 2013; Tod *et al*., 2008). However, the validity of fixed exponents such as ⅔ or ¾ has been questioned under changing physiologic or disease states, conditions of immature clearance mechanisms, extreme of ages, and immunocompromised

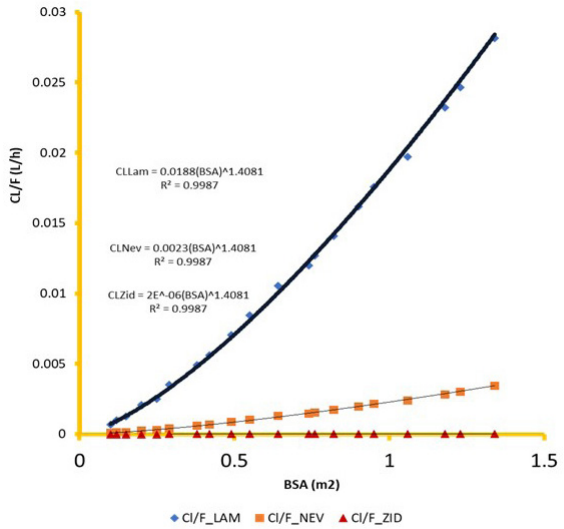

Figure 4. Regression of drug clearance on BSA of subjects.

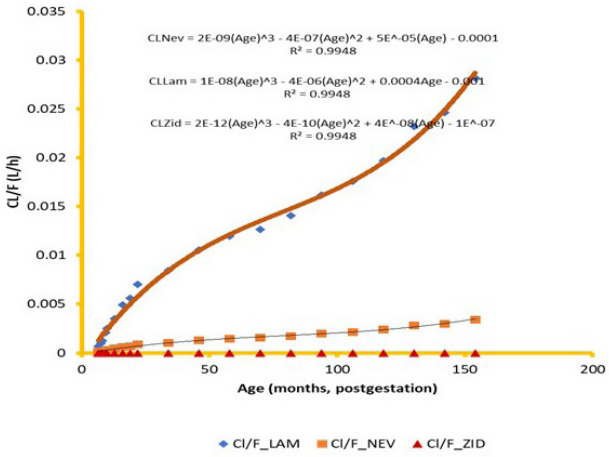

Figure 5. Regression of CL/F on age postgestation (6 months–12 years) of subjects.

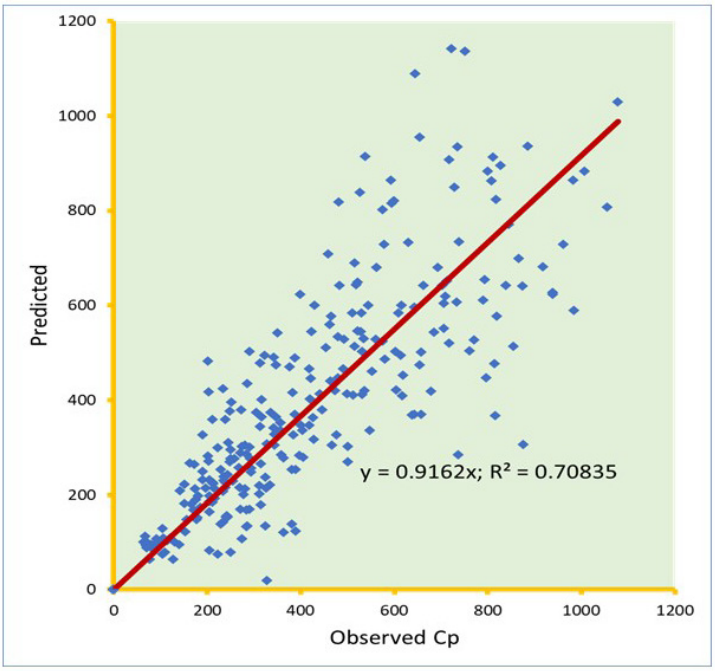

Figure 6. Predicted versus observed Cp (μg/ml) of lamivudine on administration in three drug suspension formulations.

patients (Holford, 1996; Johnson, 2008; Mahmood, 2006). The polynomial allometric equations developed in this study could provide more reliable indices of dosage determination across age ranges to assist with first-dose determination of these antiretrovirals in children. Once the first dose is administered, monitoring of the usual outcomes together with patient-specific pharmacokinetic parameters determination can be applied for optimization of therapeutic outcomes in the patient.

During the past decade, understanding of the effects of pharmacogenomics, allometry of metabolizing enzymes, and drug transporters has increased significantly. This information would provide the appropriate framework for pharmacokinetic adjustment of a dosage regimen in pediatrics following a more accurate determination of the starting dose using the pharmacokinetics-derived polynomial allometric equations reported in this study.

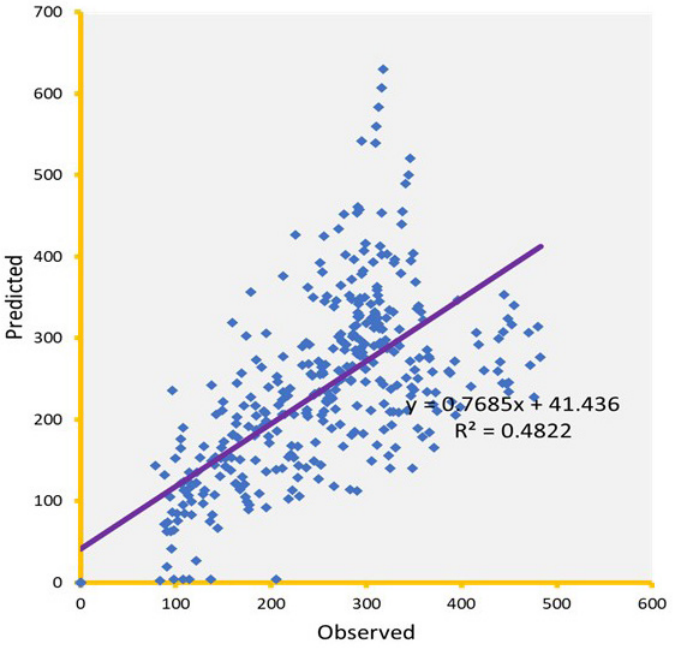

Figure 7. Predicted versus observed Cp (µg/ml) of nevirapine on administration in three drug suspension formulations.

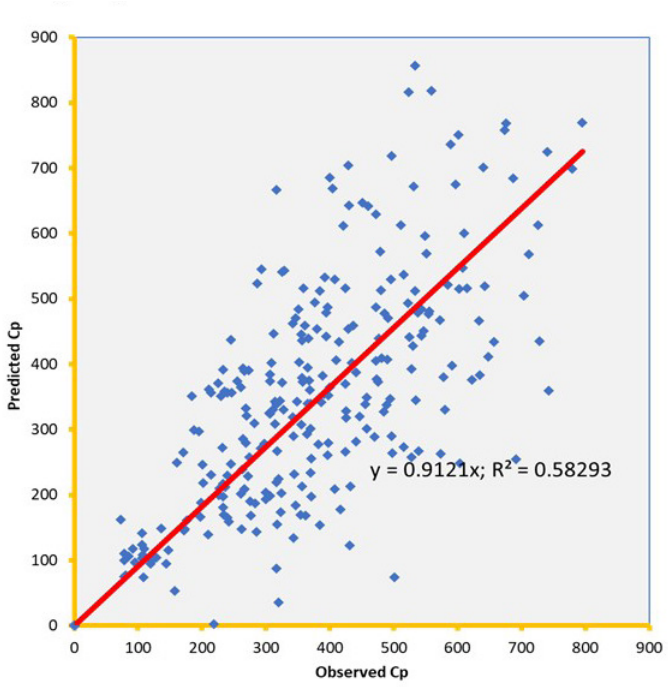

Figure 8. Predicted versus observed Cp of zidovudine on administration in three drug suspension formulations.

CONCLUSION

Using adult human clinical data, we were able to generate equations for the determination of pediatric pharmacokinetic parameters for combination antiretroviral drugs lamivudine, nevirapine, and zidovudine. Model evaluations showed that drug clearance, a major parameter for dose and dosage regimen determination, and the volume of distribution were linearly dependent on BW and exponentially dependent on BSA and showed a polynomial relationship with PGA.

Although pharmacokinetic dose determination has been widely recognized as the hallmark of pediatric dosage determination, significant variability in patient characteristics due to the rapidly developing systems as well as the drug physical–chemical and pharmacokinetic properties implies a significant complication in first-dose determination. Unlike the fixed-exponent allometric equations which correlate clearance and Vd to BW or BSA, the polynomial allometric equations developed in this study could be used for rational determination of age-dependent first in-pediatric doses which will provide a more realistic basis for the subsequent patient monitoring and individualized pharmacokinetic adjustment.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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CONSENT TO PARTICIPATE

For this type of study, formal consent is not required.

ETHICAL APPROVAL

This article does not contain any studies with human participants or animals performed by any of the authors.

AUTHORS' CONTRIBUTIONS

AA contributed to conceptualization and methodology. AA and RP contributed to formal analysis and investigation. RP and AA contributed to writing and original draft preparation and review and editing.

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