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**Title:** Adherence to antiretroviral combination therapy in children: what a difference half a day makes...  
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SECTION II
Sample size, covariate distribution and predictive performance of pharmacokinetic models
Aim: Lamivudine is widely used as first-line therapy in HIV-infected children. Yet, the influence of developmental growth on drug exposure has not been fully characterised. Here we show how a comprehensive population pharmacokinetic model can be developed to account for the influence of demographic covariates on lamivudine exposure (i.e., AUC, Cmax).

Methods: Data from 3 trials including children between 3 months and 13 years old were used in conjunction with a stepwise covariate selection to describe the pharmacokinetics across the overall population. Modelling was performed using nonlinear mixed-effects as implemented in NONMEM v.6.2. A stepwise forward inclusion and backward elimination procedure was used for covariate model building.

Results: A one-compartment model with first-order elimination was found to best describe the pharmacokinetics of lamivudine in children. The effect of body weight on clearance and volume of distribution was characterised by an exponential function. The exponent for the effect of weight on CL and V was 0.705 and 0.635, respectively. The estimate of CL for a patient of 17.6 kg (median body weight) was 16.5 L/h (CI 15.2-17.7), while the estimate of volume of distribution for a patient of 17.6 kg was 46.0 L (CI 42.4-49.5). There were no pharmacokinetic differences between the two formulations (tablet and solution). The predicted steady-state AUC_{0-12} for twice daily dosing after a dose of 4 mg/kg ranged from 4.44 mg•h/L for children lighter than 14 kg to 7.25 mg•h/L for children heavier than 30 kg.

Conclusions: The use of a meta-analysis is critical to identify the correct covariate-parameter relationships, which must be assessed before a model can be applied for predictive purposes (e.g., defining dosing recommendations for children). In contrast to prior modelling efforts, we show that the covariate distribution in the target paediatric population must be considered.
**3.1. INTRODUCTION**

Lamivudine (3TC) is a nucleoside reverse transcriptase inhibitor (NRTI) widely administered as the nucleoside backbone in combination of highly active antiretroviral therapy to HIV-infected children. Lamivudine’s mechanism of action is based on the competitive inhibition of the HIV reverse transcriptase. It is phosphorylated to an active metabolite that competes for incorporation into viral DNA. According to the latest WHO guidelines (1), lamivudine is administered as pediatric first-line therapy in combination with abacavir (ABC), with either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI). In fact, given its excellent record of efficacy, safety and tolerability in HIV-infected children, lamivudine is contained in practically all recommended combinations in paediatric antiretroviral therapy. In addition, it is a frequent component of fixed-dose, including low-cost, drug combinations.

Lamivudine is rapidly absorbed after oral administration and it is excreted primarily in the urine as unchanged drug (2–6). The intracellular triphosphate has a long half-life of 16 to 19 hours, as compared to the plasma lamivudine half-life of 5 to 7 hours (7). Lamivudine is currently administered to HIV-infected children based on body weight according to the dose of 8 mg/kg/day for children lighter than 14 kg, 150 mg/day from 14 to 21 kg, 225 mg/day from 21 to 30 kg, and 300 mg/day thereafter, all given twice a day.

Over the last years, various attempts have been made to describe the effect of developmental growth on the pharmacokinetics of lamivudine in children. Tremoulet et al. performed an extensive population pharmacokinetic analysis in infants between 3 days and 3 years (8); Burger et al. also investigated the influence of age on lamivudine pharmacokinetics in HIV-infected children, showing that in children of 6 years of age and younger, the recommended dose of 4 mg/kg twice daily leads to exposure levels lower than those observed in children ≥ 7 years of age and adults (9). These findings have prompted additional evaluation of the effects of developmental growth on the pharmacokinetics of lamivudine. In this context, focus has been given to the use of allometric models to characterise the effect of body weight on clearance. Bouazza et al. described the covariate effects in large group of children (n=580) aged between 2 days and 18 years (10), whilst Zhang et al. developed a population pharmacokinetic model in young children between 0.5 and 4.5 years (11). In all these studies, either small populations (i.e., group size) or narrow age ranges (i.e., population inclusion criteria) were used or the relationship between parameter and covariate was fixed a priori.

Bearing in mind the known issues associated with covariate selection when dealing with small datasets, we propose the use of a model-based meta-analysis for the analysis of the pharmacokinetics of lamivudine. Here we analyse data from three groups of HIV-infected children, focusing on the requirements for 1) accurately assessing the correlation between demographic covariates and pharmacokinetic parameters and 2) balance in the covariate distribution across the groups, without relying on a priori assumptions about the parameter-demographic covariate correlation.

Given the need for a scientifically driven dose rationale in paediatric diseases (12), it can be anticipated that the correct identification of influential covariates on drug disposition is essential when a population pharmacokinetic model is used for simulations and dosing recommendation purposes (13–15).

Dosing recommendations should be therefore obtained without introducing bias due to factors such as unbalanced distribution of the covariates, or due to the small sample size available for data analysis. Such a bias may result into suboptimal dosing across different groups in the population and consequently lead to increased risk of toxicity or reduced efficacy. A deep understanding of the correlation between the demographic covariates and pharmacokinetic parameters is still required to assess the implications of developmental growth on drug exposure and, as a consequence, on the efficacy of lamivudine.

**3.2. METHODS**

**Patients and samples**

This investigation was a retrospective pooled analysis of data obtained from three studies: PENTA (Paediatric European Network for the Treatment of AIDS) 13; PENTA 15 and ARROW (AntiRetroviral Research fOr Watoto). The primary objectives of these studies were to compare the pharmacokinetics of once daily versus twice daily lamivudine regimens in HIV type-1-infected children. PENTA 13 and PENTA 15 were conducted in European children aged from 2-13 years and from 3 months-3 years, respectively. The ARROW study was conducted in Uganda with children aged 3-12 years. The studies have been conducted in full conformance with the principles of the Declaration of Helsinki and with the local laws and regulations concerning clinical trials. The protocol and the informed consent documents for each study have been formally approved by the relevant research ethics committee of each clinical site and by a national ethics body. In total data from 77 paediatric patients were available (19 from PENTA 13 study (16), 18 from PENTA 15 study (17) and 40 from the ARROW trial (18)). The analysis population consisted of male and female patients across the age range between 3 months and 13 years (median age 5.79 years), and weight between 7.43 and 61.3 kg (median weight 17.6 kg). Demographic details are summarised in Table 1. In total 1184 blood samples were available for pharmacokinetic modelling, with 9 samples below the quantification limit.
Table 1 Summary of demographic characteristics

<table>
<thead>
<tr>
<th></th>
<th>Penta13</th>
<th>Penta 15</th>
<th>ARROW</th>
<th>Integrated analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUBJECTS</td>
<td>19</td>
<td>18</td>
<td>40</td>
<td>77</td>
</tr>
<tr>
<td>STEADY STATE</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>MEDIAN AGE (years)</td>
<td>5.79</td>
<td>1.91</td>
<td>7.56</td>
<td>5.79</td>
</tr>
<tr>
<td>MIN (years)</td>
<td>2.14</td>
<td>0.42</td>
<td>3.5</td>
<td>0.42</td>
</tr>
<tr>
<td>MAX (years)</td>
<td>12.84</td>
<td>2.81</td>
<td>12.57</td>
<td>12.84</td>
</tr>
<tr>
<td>MEDIAN WEIGHT (kg)</td>
<td>21.75</td>
<td>11.71</td>
<td>20.125</td>
<td>17.6</td>
</tr>
<tr>
<td>MIN (kg)</td>
<td>12.5</td>
<td>7.43</td>
<td>14</td>
<td>7.43</td>
</tr>
<tr>
<td>MAX (kg)</td>
<td>61.3</td>
<td>16.1</td>
<td>30</td>
<td>61.3</td>
</tr>
<tr>
<td>CREATININE CLEARANCE (mL/min)</td>
<td>81.72</td>
<td>59.9</td>
<td>63.89</td>
<td>95.59</td>
</tr>
<tr>
<td>MIN (mL/min)</td>
<td>41.25</td>
<td>31.99</td>
<td>50.43</td>
<td>31.99</td>
</tr>
<tr>
<td>MAX (mL/min)</td>
<td>199.59</td>
<td>87.58</td>
<td>168.32</td>
<td>199.59</td>
</tr>
<tr>
<td>ETHNICITY</td>
<td>17 black, 2 others</td>
<td>14 black, 4 others</td>
<td>40 black</td>
<td>71 black, 6 others</td>
</tr>
</tbody>
</table>

Assay of lamivudine
For the PENTA13 and PENTA15 studies, plasma concentrations of lamivudine were determined by high performance liquid chromatography assay with UV detection (HPLC-UV) with a lower limit of quantification (LLOQ) of 0.015 mg/L (19). For the ARROW study, the high performance liquid chromatography assay with tandem mass spectrometry detection (HPLC-MS/MS) method was used, which had a LLOQ of 0.0025 mg/L.

Population pharmacokinetic analysis
The pharmacokinetic analysis was done in two steps:

1. Development of the population pharmacokinetic model using a subset of two studies (PENTA 13 and PENTA 15 studies) to allow for an initial assessment of model stability and predictive performance.
2. Integrated pharmacokinetic analysis of the patient data from all three studies, followed by model validation, as implemented by standard graphical and statistical methods.

Model Building
Nonlinear mixed effects modelling was performed in NONMEM version 6.2 (Icon Development Solutions, USA)(20). Model building criteria included: (i) successful minimisation, (ii) standard error of estimates, (iii) number of significant digits, (iv) termination of the covariance step, (v) correlation between model parameters and (vi) acceptable gradients at the last iteration (21).

Fixed and random effects were introduced into the model in a stepwise manner. A parameter value of an individual i (post hoc value) is therefore given by the following equation:

\[
\theta_i = \theta_{TV} \cdot e^{\eta_i}
\]

in which \(\theta_{TV}\) is the typical value of the parameter in the population and \(\eta_i\) is the variability between subjects which is assumed to follow a normal distribution with mean zero and variance \(\omega^2\). Residual variability, which comprises measurement and model error, was described with a proportional error model. This means for the \(j\)th observed concentration of the \(i\)th individual the relation

\[
Y_{ij} = F_{ij} + \varepsilon_{ij} \cdot W
\]

Where \(F_{ij}\) is the predicted concentration and \(\varepsilon_{ij}\) the random variable with mean zero and variance \(\sigma^2\). \(W\) is a proportional weighing factor for \(\varepsilon\).

Goodness of fit was assessed by graphical methods, including population and individual predicted vs. observed concentrations, conditional weighted residual vs. observed concentrations.
and time, correlation matrix for fixed vs. random effects, correlation matrix between parameters and covariates and normalised predictive distribution error (NPDE) (22). Comparison of hierarchical models was based on the likelihood ratio test. A superior model was also expected to reduce inter-subject variability terms and/or residual error terms.

**Covariate analysis**

Continuous and categorical covariates were tested during the analysis. The relationship between individual pharmacokinetic parameters (post-hoc or conditional estimates) and covariates was explored by graphical methods (plot of each covariate vs. each individual parameter). Relevant demographic covariates (body weight, age, height, creatinine clearance) were entered one by one into the population model (univariate analysis). Given that different lamivudine formulations were administered in the trials, formulation was also treated as a covariate. After all significant covariates had been entered into the model (forward selection), each covariate was removed (backward elimination), one at a time. The model was run again and the objective function recorded. The likelihood ratio test was used to assess whether the difference in the objective function between the base model and the full (more complex) model was significant. The difference in -2Log likelihood (DOB/JF) between the base and the full model is approximately $\chi^2$ distributed, with degrees of freedom equal to the difference in number of parameters between the two hierarchical models. Because of the exploratory nature of this investigation, for univariate analyses, additional parameters leading to a decrease in the objective function of 3.84 was considered significant ($p<0.05$). During the final steps of the model building, only the covariates which resulted in a difference of objective function of at least 7.88 ($p<0.005$) were kept in the final model.

**Model validation**

The validation of the final model was based on graphical and statistical methods. Given the importance of the validation procedures for the subsequent use of a model for simulation purposes, in this study we used different tools to validate the model. First, a bootstrap procedure was performed in PsN v2.30 (University of Uppsala, Sweden) (23). Bootstrap was used to identify bias, stability and accuracy of the parameter estimates (standard errors and confidence intervals). PsN does so by generating a set of new datasets by sampling individuals with replacement. The distribution of model-predicted AUC and Cmax values were presented for geometric mean, lower and upper boundaries of the 95% confidence intervals and compared to the findings from non-compartmental analysis in the two clinical studies. Model performance was demonstrated by the location of the original estimates across the predicted distribution (histograms).

### 3.3. RESULTS

**Population pharmacokinetic modelling**

The results shown in this paper are derived from the analysis of the combined datasets from three studies. A one-compartment pharmacokinetic disposition model with first order absorption was fitted to the plasma concentration vs. time data derived from the three populations. Inter-individual variability was identified for CL, V and Ka. In all three studies used in our investigation the patients received lamivudine according to once and twice daily dosing regimen. Therefore inter-occasion variability on CL and Ka was included in the model to quantify potential differences in parameter estimates between the two dosing regimens. The residual error was described using a combined model including a weighing factor for the variance estimate, which showed a better fit of the data compared with a simple combined error model. CL and V were found to increase with body weight. An exponential function best described the correlation between these pharmacokinetic parameters and body weight. The exponent for the effect of weight on CL was 0.705 and the exponent for the effect of weight on V was 0.635.

It should be pointed out that both body weight and age showed an influence on lamivudine clearance and volume of distribution. However, based on the magnitude of the changes in objective function (i.e., statistical criteria used for model building), body weight was found to be more influential than age on lamivudine pharmacokinetics. In addition to the statistical criteria, graphical diagnostics were used to assess the goodness-of-fit. As shown in figures 1, population and individual predictions are unbiased.

Although concentrations below the quantification limit were present at time 0 and 24h, the predicted mean concentrations did not significantly differ from the observed mean concentrations (0.081 mg/L vs. 0.098 mg/L at time 0 h and 0.059 mg/L vs. 0.061 mg/L at 24 hours after dose).
Chapter 3

Model validation
The validation procedure has been performed for twice daily and once daily data separately to ensure accurate characterisation of the data irrespective of the dosing regimen. The visual predictive check (VPC) (figure 1) indicated model stability and absence of significant bias in the estimates for fixed and random effects. Bootstrapping was also performed as part of the validation procedures. All runs carried out (n= 500) were successful. As shown in Table 2, the final parameter estimates and their confidence intervals were very similar to original fitting. Given that few patients between 3 to 24 months of age were included in the analysis (n=11), scatter plots of observed vs. model predicted AUC and Cmax for these subjects are shown to illustrate model performance in young children (figure 2). The predictive performance of the model in subsequent simulations was deemed critical to achieve the objective of our analysis. To this purpose, mirror plots were used to assess whether the variance and covariance structures have been well characterised. Mirror plots explore whether model parameters can accurately replicate the findings in the original study, enabling therefore further assessment of the covariate effects on dosing regimen and dose recommendations.

To complete the validation, a graphical summary of model performance across different weight ranges was used to assess the predicted distribution for the variable of interest [AUC₀₋ₜ]. As shown in figure 3, the predicted AUC distribution encompasses the exposure observed in the original dataset.

Table 2 Summary of pharmacokinetic parameter estimates from the final model. Parameters are presented only for the final model and not for the initial model built using data from PENTA 13 and PENTA 15 studies.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Population Estimate</th>
<th>%CV</th>
<th>Bootstrap Mean (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clearance (CL)</td>
<td>CL/F = θ₁*(BW/med)^θ₂</td>
<td>16.5</td>
<td>16.3 (15.2-17.7)</td>
</tr>
<tr>
<td>(intercept) L/h</td>
<td>0.705</td>
<td>14.9</td>
<td>0.701 (0.498-0.911)</td>
</tr>
<tr>
<td>(exponent) L/h/kg</td>
<td>0.705</td>
<td>14.9</td>
<td>0.701 (0.498-0.911)</td>
</tr>
<tr>
<td>Volume (V)</td>
<td>V/F = θ₁*(BW/med)^θ₂</td>
<td>46.0</td>
<td>46.0 (42.4-49.5)</td>
</tr>
<tr>
<td>(intercept) L</td>
<td>0.635</td>
<td>14.0</td>
<td>0.625 (0.461-0.809)</td>
</tr>
<tr>
<td>(exponent) L/kg</td>
<td>0.635</td>
<td>14.0</td>
<td>0.625 (0.461-0.809)</td>
</tr>
<tr>
<td>Absorption rate constant (Ka) 1/h</td>
<td>3.68</td>
<td>15.9</td>
<td>3.86 (1.92-5.43)</td>
</tr>
<tr>
<td>ALAG1 h</td>
<td>0.755</td>
<td>4.5</td>
<td>0.755 (0.659-0.851)</td>
</tr>
</tbody>
</table>

1. Population parameter point-estimates for the full one-compartment model and 95%CI and %CV from a non-parametric bootstrap are presented.
2. Value in parentheses represents the interindividual variability of the pharmacokinetic parameters calculated as the square root of Ω x 100%.
3. Value in parentheses represents the inter-occasion variability of the pharmacokinetic parameters calculated as the square root of the Ω x 100%

Figure 1 (a) Goodness-of-fit (Left). Left upper panel shows the population prediction (PRED) vs. observed concentration values (DV). Right upper panel shows individual predictions (IPRE) vs. observed concentration values (DV). Left lower panel shows conditional weighted residuals (CWRES) vs. population predictions (PRED). Right lower panel shows conditional weighted residuals (CWRES) vs. time (TIME). Solid line represents the identity line. (b) Visual predictive check (VPC) of the population PK model for lamivudine (Right). The dots represent observed concentrations, the dotted lines represent the 5th and 95th percentiles of the simulated values. The solid blue line represents the median of the simulated profiles. The VPC is presented for the data following twice daily (upper panel) and once daily (lower panel) dosing.
Figure 2 Scatter plots of observed vs. model predicted AUC$_{0-24}$ (top panels) and Cmax (bottom panels) for children younger than 24 months. Left panels show children from 0 to 12 months, whereas children from 12 to 24 months are shown on the right panels.

Figure 3 Distribution of the model-predicted area under the plasma concentration vs. time curve [AUC$_{0-\infty}$] (1000 replicate trials) compared to the original dataset. The left panels show AUC$_{0-\infty}$ predictions for children weighing less than 14 kg, middle panels show AUC$_{0-\infty}$ predictions for children from 14 to 21 kg and right panels show AUC$_{0-\infty}$ predictions for children weighing more than 21 kg. These weight boundaries were defined according to dosing recommendations available in the approved label. Predictions for twice and once daily doses are shown in the upper and lower panels, respectively. The solid line represents the geometric mean of the observed AUC$_{0-\infty}$ in the three sub-groups for each dosing regimen. AUC$_{0-\infty}$ = AUC$_{0-12}$ for twice daily dosing and AUC$_{0-\infty}$ for once daily.
3.4. DISCUSSIONS AND CONCLUSIONS

Pharmacokinetic Model for the Paediatric Population

A model-based approach has been applied in our study to describe the pharmacokinetics of lamivudine in HIV-infected children across a wide age range. A one-compartment model with first order absorption was found to best describe lamivudine pharmacokinetics, which is consistent with previous studies in adults and children (5, 8). In our analysis body weight was the only covariate found to influence lamivudine apparent clearance and volume of distribution, which is also in agreement with earlier investigations (5, 8, 10). However, differently from the study in adults, creatinine clearance was not found to have an effect on lamivudine apparent clearance, probably because its effect was confounded by body weight. Apparent clearance estimates in our study were very similar to literature findings in children (16.5 vs. 16.9 L/h). In addition, it was not possible to find a significant effect of the formulation on relevant pharmacokinetic parameters or to estimate a relative bioavailability of the two formulations. Similar results were reported previously by Bouazza (24), whereas Kasirye et al. (25) showed in a study with 19 children (aged 1.8 to 4 years) that lamivudine exposure was 55% higher after administration of the solid dosage form (i.e., tablet) as compared to the liquid formulation. Such differences may be partly due to dose approximation in scored tablet as compared to the precise dose administration of the solution.

Identification of covariates in lamivudine pharmacokinetics in children

Our meta-analysis using three groups of HIV-infected children (see Table 1) included model building and validation steps to ensure predictive performance in subsequent application of the model, as e.g., in clinical trial simulations.

In contrast to common practice, an integrated analysis of the full population was performed after preliminary model-building based on a subset of the full population. Such a method was chosen to assess model stability and confirm the selection and magnitude of the effect of influential covariates. This approach can be particularly useful in paediatric studies, given the difficulties in identifying the correct demographic covariates, which are often highly correlated with each other (13, 14, 26). Given that a wrong decision in covariate selection may affect future dosing recommendation, special attention should be paid to covariate model building. As shown in a previous study, the stepwise approach commonly used for covariate selection may introduce selection and omission bias in the model when the dataset used during the analysis is small (27). In fact, in small datasets the distribution of the covariates may not allow identification of a correlation between the covariate and the pharmacokinetic parameters.

In our analysis, the initial lamivudine model accurately predicted the pharmacokinetic profiles of the group which was not used for initial model building (results not shown). The same parameter-covariate correlations were identified when the model was re-evaluated using the full paediatric population. It is important to point out that the correlation between clearance and body weight is exponential. For example, the apparent clearance has a median value of 9.33 L/h for a child weighing 10 kg. It increases to 16.55 L/h in children whose weight is 20 kg, but only increases by an additional 1.27 L/h in children of 30 kg (17.82 L/h).

A separate analysis of the data from the ARROW trial (age range 3 to 12 years) was also performed and a one-compartment model with first order absorption and elimination was identified to best describe this subset of data. Very interestingly, none of the demographic covariates available was found to be significantly correlated to the pharmacokinetic parameters. Furthermore, diagnostic measures, such as the visual predictive check of the model, were not able to show any inaccuracy or bias in model-based predictions of the data (figure 5). These results suggest that the model could be used subsequently for dosing recommendation purposes. However, its use would yield incorrect model-based predictions in a different population since the correct parameter-covariate relationship was not identified during covariate model building. This finding strongly underlines the importance of an integrated data analysis and the risk of inaccurate covariate selection when only a part of the full population is available for analysis.

Limitations of current approaches in paediatric dosing

Many examples are available in literature of population pharmacokinetic analyses based on less than 40 patients (28–31). In such small populations an unbalanced covariate distribution may lead to the identification and selection of wrong covariate-parameter relationships and, in turn, to wrong model-based predictions when applying the model to a different population (i.e., extrapolation). Many experts in paediatric pharmacology claim to be able to define the type and magnitude of the effect of a covariate on pharmacokinetic parameters; however they do not take into account that the parameter-covariate correlation may be biased by the covariate distribution in that particular group of children and as such should not be used in a different population. In these circumstances, one should talk about a data-driven approach, in the sense that the model is able to correctly describe the data (as shown in our analysis by the visual predictive check in figure 4), but is not able to predict correctly the variable of interest in a different population. It is also worth mentioning that such a hidden bias is not addressed by simply increasing the sample size as often is the case in pooled analysis of patients undergoing therapeutic drug monitoring. Meta-analyses should therefore be the preferred method in paediatric pharmacokinetics to avoid model misspecification and consequently expose children to suboptimal drug levels or to a higher risk of toxicity. When sufficient paediatric data are not available, one should consider overcoming the limitations of small populations by incorporating prior information from pharmacokinetic parameters in adults and include them in the model, as suggested by Celia et al (12). There are also other research groups, who choose not to use pharmacokinetic modelling for the analysis for drug exposure and dose selection in children. Instead, they prefer to solely rely on non-compartmental analysis, ignoring the issues highlighted above. The use
of a model-based approach presents significant advantages compared to non-compartmental analysis, which cannot be overlooked from a scientific and ethical point of view.

Clinical implications of an integrated population analysis for accurate dosing recommendation

Given that drug exposure drives efficacy, it should be clear that model misspecification may lead to incorrect dosing recommendations. The identification of the correct covariate-parameter relationships is therefore crucial to accurately predict drug exposure across different groups in the paediatric population. Yet, this issue is further compounded by current prescription practices.

The role of covariate-parameter correlations is apparently even more important when exploring changes in dosing regimen. For instance, we could not investigate the effect of obesity in this population. However, given the low lipophilicity of lamivudine (which is water soluble), we anticipate no major impact of obesity on its pharmacokinetics. It is conceivable that doses based on lean body mass might be required for very obese patients, as drug distribution and metabolism would not increase proportionally to total body weight.

How to dose a drug in children remains a very debatable subject. Whereas normalisation of the dose by body weight makes prescription easy and reduces the risk for prescription errors, deriving dose recommendations without a thorough understanding of drug disposition in children has been proven to be unsafe and harmful (32). Clearly, the effect of developmental growth on pharmacokinetics is a nonlinear phenomenon and as such can be best described by a model-based approach. However, modelling and simulation techniques should be used with caution. Too little attention has been paid so far to the implications of unbalanced covariate distributions on pharmacokinetic analyses outcome, as shown by the elevated number of examples available in literature. We are fully aware of the challenges in performing paediatric trials and in collecting clinical data in children. These difficulties must not prompt us to neglect the problems caused by small datasets, which may lead to the wrong dose selection. The use of meta-analyses, i.e., combined datasets from available clinical trials in children is strongly encouraged to avoid erroneous predictions of the paediatric dose.

Limitations in our approach

It is important to mention that lamivudine plasma concentrations represent a limited marker of drug exposure, as it is the intracellular lamivudine triphosphate metabolite that becomes pharmacologically active. Unfortunately adequate sampling for determination of intracellular concentrations of nucleoside transcriptase inhibitor triphosphate is logistically and technically difficult (33). Furthermore the volume of blood needed to measure intracellular lamivudine triphosphate concentrations with current technology makes serial evaluations impractical for paediatric patients.
Conclusions
The clinical relevance of a pharmacokinetic model depends on the generalisability of the covariate model across the overall population. Here we have shown that covariate effects may be under or overestimated if the available data do not support accurate identification of the correlation between pharmacokinetic parameter and covariate. Unbalanced distribution of covariates may result in hidden bias and yield inaccurate dosing recommendations in children. In addition, our work shows that the concept of pharmacokinetic bridging has been met for lamivudine, in that the dosing corrected by body weight does account for developmental growth, yielding comparable systemic exposure throughout the population older than 3 months of age.

References


