The handle http://hdl.handle.net/1887/22077 holds various files of this Leiden University dissertation.

**Author:** Piana, Chiara  
**Title:** Adherence to antiretroviral combination therapy in children: what a difference half a day makes...  
**Issue Date:** 2013-10-31
Chapter 4

Population Pharmacokinetics of Abacavir in Infants, Toddlers and Children

Chiara Piana, Wei Zhao, Meindert Danhof, David Burger, Oscar Della Pasqua, Evelyne Jacqz-Aigrain

Br J Clin Pharmacol. 2013

Summary

Aims: To characterise the pharmacokinetics of abacavir in infants, toddlers and children, and assess the influence of covariates on drug disposition across these populations.

Methods: Abacavir concentration data from three clinical studies in HIV-infected children (n=69) were used for model building. The children received either a weight-normalised dose of 16 mg/kg/day or the WHO recommended dose based on weight-bands. A population pharmacokinetic analysis was performed using NONMEM v6. The influence of age, gender, body weight and formulation was evaluated. The final model was selected according to graphical and statistical criteria.

Results: A two-compartmental model with first-order absorption and first-order elimination best described the pharmacokinetics of abacavir. Body weight was identified as significant covariate influencing the apparent oral clearance and volume of distribution. Predicted steady-state Cmax and AUC0-12 of standard twice daily regimen were 2.5 mg/L and 6.1 mg•h/L for toddlers and infants, and 3.6 mg/L and 8.7 mg•h/L for children, respectively. Model-based predictions showed that equivalent systemic exposure was achieved after once and twice daily dosing regimens. There were no pharmacokinetic differences between the two formulations (tablet and solution). The model demonstrated good predictive performance for dosing prediction in individual patients and as such can be used to support therapeutic drug monitoring in conjunction with sparse sampling.

Conclusions: The disposition of abacavir in children appears to be affected only by differences in size, irrespective of the age of the patient. Maturation processes of abacavir metabolism in younger infants should be evaluated in further studies to demonstrate the potential impact of ontogeny.
Abacavir is well absorbed following oral administration and distributed into body tissues, including the central nervous system. It is extensively metabolized by the liver and less than 2% is excreted as unchanged drug in the urine. The two major catabolic pathways include oxidation by alcohol dehydrogenase (ADH) and conjugation by uridine diphosphate glucuronyltransferase (UGT), resulting in inactive carboxylate and glucuronide metabolites (3,4). The antiviral activity of abacavir results from its intracellular activation to carbovir triphosphate (CBV-TP). CBV-TP competes with the endogenous nucleotide 2’-deoxyguanosine triphosphate (dGTP) for incorporation into the nucleic acid chain and terminates the DNA chain by preventing addition of new bases (5). The endpoint for efficacy, as indicated by the change from baseline in viral load (plasma HIV-1 RNA) and T cells count rise was significantly correlated with area under the concentration–time curve (AUC) (6). The AUC_{0-12} value of 6.02 mg•h/L was set as target exposure both in adults and children (7).

The pharmacokinetics of abacavir has been previously investigated in children (8-15). However these studies were based on either a small number of patients, sparse sampling or narrow age range of the children, which renders difficult the assessment of the role of developmental factors on drug disposition. Accurate characterisation of these factors may allow not only further assessment of the individual dosing requirements across different age groups, but also insight into processes determining maturation and metabolic capacity, which may be deemed drug-independent. In this investigation, we make use of a model-based approach to analyse three different studies in children across a wide age range, with the objective of obtaining more reliable prediction of pharmacokinetic profiles in individual patients. In addition, given the availability of tablet and solution dosage forms, this analysis offered us the opportunity to explore the potential influence of formulation on paediatric pharmacokinetic parameters.

4.1. INTRODUCTION

Clinical trials
The data were obtained from three studies: PENTA (Pediatric European Network for the Treatment of AIDS) 13, PENTA 15 and a pharmacokinetic sub-study within the main ARROW (Antiretroviral Research for Watoto) trial (8-10). Briefly, the primary objectives of these studies were to compare the pharmacokinetics of once daily versus twice daily of abacavir and lamivudine in HIV type-1-infected children. The European studies PENTA 13 and PENTA 15 were conducted in children aged from 2-13 years and from 3 months-3 years, respectively. The ARROW pharmacokinetic sub-study was conducted in Uganda with children aged 3-12 years. In total, sixty-nine children were included in this population pharmacokinetic meta-analysis. The mean (SD) age was 5.74 (3.40) (range 0.42 – 12.84) years and the mean (SD) weight was 18.7 (8.0) (range 7.6 – 60.9) kg. Pharmacokinetic samples were obtained at steady-state at time T0 (immediately before administration) and T1, T2, T3, T4, T6, T8 and T12 h after administration for the twice daily regimen and an additional sample at T24 h for the once daily regimen. A summary of trial design, dosage regimens, and patient characteristics are presented in Table 1. 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.

Bioanalysis
For the PENTA13 and PENTA15 studies, plasma concentrations of abacavir were determined by high performance liquid chromatography assay with UV detection (HPLC-UV). The details of the analytical method have been reported (8,9). The lower limit of quantification (LLOQ) was 0.015 mg/L. Within-day and between-day variability were 1.1–1.9% and 0.16–2.3%, respectively. For ARROW study, plasma concentrations of abacavir were determined using validated HPLC/MS/MS method by GlaxoSmithKline (Research Triangle Park, NC, USA). The LLOQ was 0.0025 mg/L (10).

Pharmacokinetic modelling
Pharmacokinetic analysis was carried out using the nonlinear mixed effects modelling program NONMEM v6 (V2.0; Icon Development Solutions, USA) (16). First order conditional estimation (FOCE) method with interaction option was used to estimate pharmacokinetic parameters and their variability.
Inter-individual variability of the pharmacokinetic parameters was estimated using an exponential model and could be expressed as follows:

$$\theta_i = \theta_{TV} e^{\eta_i}$$

where $\theta_i$ represents the parameter value of the $i^{th}$ subject, $\theta_{TV}$ the typical value of the parameter in the population and $\eta_i$ the variability between subjects which is assumed to follow a normal distribution with a mean of zero and variance $\omega^2$.

Covariate analysis followed a forward and backward selection process. The stepwise covariate modelling (17,18) and likelihood ratio test was used to test the effect of each variable. Model validation was based on graphical and statistical criteria, including goodness-of-fit plots (19), mirror plots, bootstrap, visual predictive check (VPC) and normalized prediction distribution errors (NPDE) (20,21).

**Clinical application in therapeutic drug monitoring**

Given our interest in clinical application of model-based approaches, the performance of the final model to support therapeutic drug monitoring and dosing adjustment was tested via simulation scenarios. To assess its predictive value, we have extensively evaluated whether the final model could be used to accurately predict observed drug exposure with current dosing regimens. For this purpose, the time course of abacavir concentrations was simulated 100 times in each sub-population (infants, toddlers and children) and for each dosing regimen (once vs. twice daily). The area under the concentration vs. time curve (AUC 0-24) was selected as endpoint for the purposes of this evaluation and AUC 0-24 (2 × AUC 0-12 for twice daily) was calculated using trapezoidal rule. The simulated AUC0-24 was then compared with median observed AUC0-24.

The feasibility of a model-based approach in therapeutic drug monitoring was evaluated by considering two main scenarios in which pooled population data and sparse pharmacokinetic sampling are used as basis for predicting drug exposure in new patients:

1. To assess model performance in new patients, 10 children were randomly removed from the original dataset. The parameters for the remaining 59 children were re-estimated. The model parameters were then used to predict individually the pharmacokinetics of the 10 children excluded from the analysis, taking into account the effect of covariates in each patient. Predictions were compared to the observed data graphically by means of visual predictive check plots (1000 simulations/patient).

2. To assess the impact of empirical sparse sampling on model predictions, data from new patients using only three samples (T0, T1 and T3) were added in a stepwise manner to the dataset (i.e., initial population, n=59). Model parameters were then re-estimated for all 60 children (of which 59 had frequent sampling scheme). The new model was used to predict the full pharmacokinetic profile of single patients with sparse samples. Results were compared graphically with the original data using visual predictive check plots (1000 simulations/patient). This approach was selected as an initial step to the use of a full Bayesian analysis, in which model parameter values from a historical population (instead of the data) are used as priors to anchor the estimation of the parameters of interest for a new subject or population.

### 4.3. RESULTS

**Population pharmacokinetic modelling**

A total of 1065 plasma abacavir concentrations were available for population modelling. Data fitted a two-compartment model with first order absorption and elimination. Inter-individual variability was best described by an exponential model and was then estimated for Q/F, $V_1/F$, $V_2/F$ and CL/F. Inter-occasion variability on CL/F was coupled to inter-individual variability by an additive model, respectively. Residual variability was best described by a proportional model.

#### Table 1: Summary of three pharmacokinetics studies and characteristics of patients

<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>14</td>
<td>18</td>
<td>37</td>
<td>69</td>
</tr>
<tr>
<td>STEADY STATE</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>MEDIAN AGE (years)</td>
<td>5.10</td>
<td>1.93</td>
<td>7.61</td>
<td>5.74</td>
</tr>
<tr>
<td>MIN (years)</td>
<td>2.14</td>
<td>0.42</td>
<td>3.62</td>
<td>0.42</td>
</tr>
<tr>
<td>MAX (years)</td>
<td>12.84</td>
<td>2.81</td>
<td>12.54</td>
<td>12.84</td>
</tr>
<tr>
<td>MEDIAN WEIGHT (kg)</td>
<td>19.2</td>
<td>11.6</td>
<td>20.5</td>
<td>17.6</td>
</tr>
<tr>
<td>MIN (kg)</td>
<td>14.0</td>
<td>7.6</td>
<td>14</td>
<td>7.6</td>
</tr>
<tr>
<td>MAX (kg)</td>
<td>60.9</td>
<td>15.8</td>
<td>29.8</td>
<td>60.9</td>
</tr>
</tbody>
</table>
During covariate model building, the inclusion of age, weight and formulation on CL/F, and weight on V₁/F all separately produced a significant decrease in objective function (OFV). However, following the backward exclusion process, only the effect of weight on CL/F and V₁/F was found to be significant (ΔOFV > 7.88 (p<0.005, χ² distribution)). Therefore, the influence of weight on CL/F and V₁/F was retained in the model as follows:

\[
\frac{CL/F_i}{CL/F_{ref}} = (WT_i / WT_{ref})^{θ_1} \\
\frac{V₁/F_i}{V₁/F_{ref}} = (WT_i / WT_{ref})^{θ_2}
\]

Where CL/F, and V₁/F, are, respectively the CL/F and V₁/F of the i⁰ individual, WT, the weight of the i⁰ individual, WTₜᵣₑᶠ, the reference weight. The subscripts “ref” indicates the individual with a reference weight. In our study, the reference weight was the median value of our population 17.6 kg. The allometric exponents were estimated to be 0.802 for CL/F and 0.810 for V₁/F.

Model diagnostics indicated acceptable goodness-of-fit for the final model. As shown in figure 1a, population and individual predictions are unbiased. In addition, the mean parameter estimates resulting from the bootstrap procedure very closely agreed with the respective values from the final population model, indicating that the estimates for the population pharmacokinetic parameters in the final model were accurate and that the model was stable. The results of 1000 bootstrap replicates are summarised in table 2.

Mirror plots reveal that the variance-covariance structure was well characterised, as the simulated datasets reproduce the similar dispersion pattern observed in the original data (results not shown). The NPDE distribution and histogram indicates that the assumption of normal distribution of the differences between individual predictions and observed data is acceptable (figure 1b). No trends were observed on the diagnostic plots of NPDE versus time. The VPC (figure 2) of the final model with all patients shows that observed concentrations were well predicted by the model (Exact Binomial Test, 7.4% out of limits observed, 95% confidence interval [5.9% – 9.2%]). VPCs for each sub-population (infants, toddlers and children) and each dosing regimen (once and twice daily) are also shown in figure 2.

Figure 1 (a) Goodness-of-fit. Left upper panel shows the population prediction (PRED) vs. observed concentration values (DV). Right upper panel shows conditional weighted residuals (CWRES) vs. time (TIME). Left lower panel shows individual predictions (IPRE) vs. observed concentration values (DV). Right lower panel shows conditional weighted residuals (CWRES) vs. population predictions (PRED). Solid line represents the identity line. (b) Normalized Prediction Distribution Errors (NPDE) analysis. Upper panel shows the histogram of the distribution of the NPDE, with the density of the standard Gaussian distribution overlaid. Lower panel shows NPDE versus time (TIME)

Figure 2 VPC in infants and toddlers (a), children (b), following once daily (c) and twice daily dosing regimen (d): observed data are plotted using a circle (○). The dashed lines represent the 5th, and 95th percentiles of simulated data (n=1000). The solid lines represent the 50th of simulated data (n=1000).
**Table 2 Population pharmacokinetic parameters of abacavir and bootstrap validation**

<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></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$CL/F = \etaCL\cdot (BW/med)^q$</td>
<td>2.0</td>
<td>3.8</td>
<td>20.1 (18.7-21.4)</td>
</tr>
<tr>
<td>(intercept) L/h</td>
<td>0.802</td>
<td>11.6</td>
<td>0.796 (0.651-0.954)</td>
</tr>
<tr>
<td>Inter-compartmental Clearance (Q)</td>
<td>2.0</td>
<td>9.9</td>
<td>0.796 (0.651-0.954)</td>
</tr>
<tr>
<td>Inter-compartmental Clearance (Q)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central Volume of distribution ($V_1$) L</td>
<td>13.0</td>
<td>11.7</td>
<td>12.8 (9.3-15.5)</td>
</tr>
<tr>
<td>(intercept) L/kg</td>
<td>0.810</td>
<td>23.3</td>
<td>0.793 (0.330-0.954)</td>
</tr>
<tr>
<td>Peripheral volume of distribution ($V_2$) L</td>
<td>13.5</td>
<td>10.7</td>
<td>0.796 (0.651-0.954)</td>
</tr>
<tr>
<td>Absorption rate constant ($K_a$) 1/h</td>
<td>0.913</td>
<td>4.0</td>
<td>0.909 (0.842-0.985)</td>
</tr>
<tr>
<td>Interindividual variability</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\etaCL$ variance</td>
<td>42.5%</td>
<td>4.1</td>
<td>41.0 (27.5-62.1)</td>
</tr>
<tr>
<td>$\etaV_1$ variance</td>
<td>47.7%</td>
<td>3.9</td>
<td>46.2 (29.7-66.4)</td>
</tr>
<tr>
<td>$\etaV_2$ variance</td>
<td>57.5%</td>
<td>4.0</td>
<td>55.8 (38.3-76.4)</td>
</tr>
<tr>
<td>Inter-occasion variability</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OCCCCL</td>
<td>20.4%</td>
<td>2.5</td>
<td>20.2 (15.7-24.8)</td>
</tr>
<tr>
<td>Residual Error</td>
<td>38.2%</td>
<td>8.2</td>
<td>38.1 (35.7-40.9)</td>
</tr>
</tbody>
</table>

1. Population parameter point-estimates for the full two-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 the % CI.
3. Value in parentheses represents the inter-occasion variability of the pharmacokinetic parameters calculated as the square root of the % CI.

**Predictive performance in clinical applications**

To assess the performance of the final model for therapeutic drug monitoring and dose adjustment, pharmacokinetic parameter estimates were also used to simulate drug exposure, expressed as area under the concentration vs. time curve $AUC_{0-24}$ in different sub-populations (infants and toddlers $n=21$, age range: 0.42-2.81; children $n=48$, age range: 3.58-12.84) and for currently used dosing regimens (once and twice daily dosing). As shown in figure 3, considerable overlap was observed in the simulated and observed $AUC_{0-24}$ values in infants and toddlers, and children. Model predicted $C_{max}$ and $AUC_{0-24}$ (geometric mean) of standard dose regimen (8mg/kg twice daily) were 2.5 mg/L and 6.1 mg•h/L in toddlers and infants, and 3.6 mg/L and 8.7 mg•h/L in children, respectively. These values were in agreement with the observed values in the original studies. In fact, the observed $C_{max}$ and $AUC_{0-24}$ (geometric mean) were respectively 2.3 mg/L and 5.8 mg•h/L in toddlers and infants, and 3.6 mg/L and 8.2 mg•h/L in children. Similarly, drug exposure was not different after once or twice daily doses of abacavir.

Figure 3 Simulated AUC distribution and median (continuous line) and 5th and 95th percentiles (dashed lines) of the observed AUC in infants and toddlers (a), in children (b), following once daily dosing (c) and twice daily dosing (d)
Moreover, the assessment of the predictive performance of the model included scenarios in which drug exposure was predicted in new patients taking sparse sampling schemes into account. In both cases, estimates of parameter accuracy and precision were acceptable. As shown in figure 4, accurate predictions can be made of individual patient profiles using this model, despite some evidence of over-estimation of residual variability.

Figure 4 Individual VPC for new patients. Scenario (a): VPC for 10 new patients. Scenario (b): VPC for 1 patient with sparse sampling. Open circles (○) represent the observed data, whilst dashed lines depict the 5th and 95th percentiles of the simulated data (n=1000). The solid lines indicate the median obtained from the simulated data (n=1000).

4.4. Discussions and Conclusions

In the present study, we have shown the use of population pharmacokinetic meta-analysis of abacavir based on data obtained by a rich sampling strategy in 69 children from three pharmacokinetic studies. We believe that pooling of data offers the opportunity to evaluate drug disposition across a wide age and body weight range. Such an evaluation may be essential to assess the suitability of dosing recommendations for children. Even though our analysis is limited to abacavir data, we anticipate that such considerations are necessary and applicable to most if not all compounds for paediatric indications.

From a methodological perspective, meta-analytical concepts are required to ensure thorough understanding of the implications of developmental growth on pharmacokinetics in paediatric patients. Despite attempts to describe changes in drug disposition by allometric models, it should be clear that the paediatric population encompasses a very heterogeneous group of patients. Inferences about pharmacokinetics in individual patients may be challenging with data arising from a very limited number of patients, especially when the objective is to predict individual exposure in prospective patients or to adjust dosing regimens in chronic treatment, as in the case of therapeutic drug monitoring. The scope of population pharmacokinetic modelling is to enable the description and prediction of ADME processes in a parametric manner, so that hierarchical parameters can be derived that can discriminate population from individual patient characteristics. In paediatric pharmacokinetics, however, discrimination between population and individual differences is further confounded by the role of maturation and other factors associated with developmental growth, including changes in metabolic capacity. In a previous work (7), Cella et al. have shown that a model-based approach offers a suitable basis for estimation of pharmacokinetic parameters even when only sparse samples may be available. However, such models do not necessarily permit accurate prediction of the differences in pharmacokinetics for individuals whose characteristics are not represented in the population used during model building and validation. As shown in a previous analysis (23), a model developed using data in older children cannot reliably predict exposure in infants and toddlers, and vice versa. This lack of predictive performance is partly explained by the fact that covariate-parameter correlations may not remain constant beyond the range of observations. Estimation of covariate effects is therefore not sufficient to allow accurate extrapolation of pharmacokinetics from a reference population to another population.

Our results indicate that it is not the overall number of patients that determines the predictive performance of a model, but rather the availability of data from the overall population, so that parameter distributions can be accurately estimated and imputations can be made about individuals belonging to any part of the population with adequate precision. Our results show that good predictive performance of a model can be achieved with a considerably limited number of individuals as long as the covariate distribution in the subjects used for model building represents...
the covariate distribution in the population described by the model. This is critical to ensure that differences driven by covariates are not captured as random effects, nor random effects are wrongly associated with covariates. This is illustrated by the difference in the magnitude of parameter estimates in our analysis and in estimated parameters from single trials (table 3).

Table 3 Covariate-parameter relationships identified for abacavir in previous population pharmacokinetic analyses.

<table>
<thead>
<tr>
<th>Study</th>
<th>Ref.</th>
<th>Number of children</th>
<th>Age range (years)</th>
<th>Significant covariates in the model</th>
<th>Covariate-parameter relationship</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penta 13</td>
<td>[7]</td>
<td>14</td>
<td>2.14-12.84</td>
<td>Weight on CL and V</td>
<td>CL/F (L/h) = 37.2 • (BW/23.8)0.553 ( V/F (L) = 64.8 • (BW/23.8)0.537 )</td>
</tr>
<tr>
<td>Penta 15</td>
<td>[12]</td>
<td>18</td>
<td>0.42-2.81</td>
<td>Weight on CL</td>
<td>CL/F (L/h) = 13.4 • (BW/12)1.14</td>
</tr>
<tr>
<td>Penta 13+Penta 15+ARROW</td>
<td>This article</td>
<td>69</td>
<td>0.42-12.84</td>
<td>Weight on CL and V1</td>
<td>CL/F (L/h) = 20.1 • (BW/17.6)0.802 ( V1/F (L) = 13.0 • (BW/17.6)0.810 )</td>
</tr>
<tr>
<td>Therapeutic drug monitoring data</td>
<td>[11]</td>
<td>105</td>
<td>0.0685-16</td>
<td>Weight on CL and V</td>
<td>CL/F (L/h) = 24.3 • (BW/25)1.0 ( V/F (L) = 42.9 • (BW/25)0.95 )</td>
</tr>
</tbody>
</table>

Whereas the focus of previous publications was on the use of modelling as the basis for drug development (i.e., early paediatric trials), little attention has been paid to the implications of similar modelling requirements for accurate dosing adjustment and therapeutic drug monitoring in clinical practice (24, 25). In the present study, we have assessed the predictive performances of the final model using several simulation scenarios in which potential differences in individual exposure are evaluated. Our results indicated that the final model can accurately predict drug exposure with currently used dosing regimens in new patients, even in case of sparse sampling.

Population pharmacokinetic and/or pharmacodynamic model validation is another key-issue to consider when models are to be used for simulation purposes (i.e. dosage optimisation or clinical trial simulation). Validation procedures are lacking in many publications reporting the development of population pharmacokinetic and/or pharmacodynamic models (26). In fact, advanced internal evaluations were performed on merely 16% of the models in children (27). In the present study, five evaluation/validation criteria were included: 1) Standard goodness-of-fit plots, which inform on model misspecification and allow assessment of trends or bias in the model predictions. 2) Mirror plots, which allow comparison of the variance structure between simulated and observed data. 3) Bootstrap, which provides information on the stability of the final model. A robust model is not affected by the contribution or influence of specific individuals in the data set. 4) Visual Predictive check, which yields information on the presence of systemic bias or deviations (trends) in model predictions. 5) NPDE, which provides details on the distribution of the differences between predictions and observations. It is an important criterion for the validation of a model for subsequent simulation purposes. Even though each of the aforementioned diagnostic tools reveals different aspects of model performance, it is critical to point out that there is no guarantee that model predictions will be accurate unless the relevant covariates are included in the initial model.

Limitations

During this investigation only body weight, age, gender and formulation were tested as potentially influential covariates on pharmacokinetic parameters. Information on ethnicity and other potential demographic factors were not available. Given that abacavir is metabolised primarily through alcohol dehydrogenase or glucuronyl transferase, metabolic information would have been useful to describe abacavir pharmacokinetics. Further studies are required to evaluate the ontogeny of abacavir metabolism.

In summary, we have shown that abacavir pharmacokinetics in children can be characterised by a two-compartment model with first order absorption. Body weight was identified as the primary covariate influencing the apparent oral clearance and volume of distribution. The availability of data across a wide range of ages and consequently across body weights enabled the identification of the accurate relationships between pharmacokinetic parameters and covariates in the paediatric population. These relationships may not be evident or even missed when analysing small datasets or when the relevant range of values for the influential covariates is not included in the overall population. The use of an integrated, meta-analytical approach is therefore essential to ensure accurate prediction of drug exposure in new patients or in clinical conditions different from the original trial setting.
References


