Background: Our main objectives were to study the population pharmacokinetics of efavirenz and to explore the adequacy of dosing guidelines.

Methods: A total of 33 HIV-1-infected patients were recruited from the Emma Children’s Hospital (Amsterdam, the Netherlands). Gender, age, drug formulation, the presence of the c.516G>T polymorphism in the CYP2B6 gene and the quantitation of liver enzymes alanine aminotransferase and aspartate aminotransferase at baseline were collected. A non-linear mixed effect pharmacokinetic model was developed.

Results: CYP2B6 genotype and drug formulation significantly influenced efavirenz pharmacokinetics. Clearance was 29.7% lower in children carrying the CYP2B6-516-G/T genotype compared with children carrying the G/G genotype. Relative bioavailability of the oral liquid compared with tablets or capsules was 46.6%. Children carrying the CYP2B6-516-G/G genotype had a 50–70% probability of developing a subtherapeutic trough level of efavirenz and only 1–3% probability of developing a trough level >4 mg/l. To reduce the probability of developing a subtherapeutic trough concentration, we propose to give an adult efavirenz dose to children weighing ≥25 kg and to allometrically scale doses for other weight levels a priori. The dose of the oral solution should be twice the dose of capsules.

Conclusions: Population pharmacokinetics of efavirenz in children were adequately described. Current dosing guidelines can result in subtherapeutic concentrations in children carrying the CYP2B6-516-G/G genotype and with the liquid formulation. A priori dose adaptations in the paediatric population seem feasible and need prospective validation.

Introduction

Optimal treatment of children with an HIV infection is a challenging task. Adherence to antiretroviral drugs is a key factor for successful therapy. However, adherence is a substantial problem in the paediatric population. A once daily regimen containing efavirenz is useful to tackle the problems of adherence and has been proven to be a safe, convenient and potent treatment for HIV type-1 (HIV-1) infection in children [1]. Apart from adherence, dosing is another challenge in the treatment of paediatric HIV-1 infection. Drug absorption, interactions and metabolism differ in children and change during growth. Pharmacokinetic guiding of efavirenz dosing by means of therapeutic drug monitoring (TDM) in the paediatric population is therefore considered important [2].

Efavirenz exposure has been well correlated with treatment outcome and target trough concentrations (C_{trough}) in plasma have been proposed to be between 1 and 4 mg/l [3–5]. Current paediatric efavirenz dosing guidelines for children >3 years are depicted in Table 1. Recommended dosages vary with weight, formulation and age. No efavirenz dosing strategies have been investigated in children <3 years of age. As it stands, there is only limited data on the pharmacokinetics of efavirenz in children. Recent findings of a high prevalence of subtherapeutic efavirenz plasma concentrations in children indicate that current paediatric dosing guidelines might not be sufficient and that a large proportion of children taking efavirenz need a dose increase [6–8]. However, these studies reporting the high prevalence of subtherapeutic drug concentrations of efavirenz were of observational nature and did not suggest alternative dosing regimes to prevent subtherapeutic efavirenz concentrations.
Several factors are known to influence efavirenz metabolism. Efavirenz is mainly metabolized by the cytochrome P450 enzyme CYP2B6. Efavirenz exposure is known to be influenced by polymorphisms in the CYP2B6 gene, resulting in a higher efavirenz exposure [9,10]. Unlike other CYP2B6*6 polymorphisms, the c.516G>T polymorphism has been shown to be the causal sequence variation for decreased expression and function of CYP2B6 [11]. Also, drug formulation has been shown to play a role; previous studies showed a relative bioavailability of the oral solution of 62% or 83% when compared with efavirenz administered as a tablet or capsule, respectively [3,12].

Because adequate exposure from the start of therapy (that is, the correct dose administered the first time) is desirable and because TDM might not always be available (for example, in resource-limited settings), we conducted a population pharmacokinetic study of efavirenz in children. Our main objective was to adequately describe the population pharmacokinetics of efavirenz in this population and to identify important covariates influencing the pharmacokinetics. Our secondary objective was to explore efavirenz exposure on the basis of the current paediatric guidelines and alternative dosing strategies using the developed model.

Methods

Patient recruitment
All patients were recruited from the Emma Children’s Hospital (Amsterdam, the Netherlands). All participated in an ongoing open-label study to evaluate the efficacy and safety of single daily treatment with efavirenz, abacavir, didanosine and lamivudine. HIV-1-infected children were eligible when they had a CD4+ T-cell count of <1,750 cells/µl (<1 year of age), <1,000 cells/µl (1–2 years of age), <750 cells/µl (3–6 years of age) or <500 cells/µl (>6 years of age). Previous exposure to antiretroviral therapy was allowed. Exclusion criteria were presence of mutations associated with efavirenz resistance or with two or more of the nucleoside reverse transcriptase inhibitors used. No restrictions were made with respect to ethnicity, gender, route of HIV acquisition or disease stage. The medical ethics committee approved the protocol and parents or caregivers provided written informed consent.

Dosing strategy
All children were dosed according to paediatric dosing guidelines listed in Table 1 and there were no restrictions considering food intake. For adherence, the children’s guardians were counselled regarding the importance of treatment adherence. Where appropriate, children were counselled accordingly. Adherence was monitored by telephone and at each follow-up clinic visit. TDM was applied throughout. The dose was increased when a child was exposed to subtherapeutic C_{min} of efavirenz (<1 mg/l). The dose was decreased when a child was suspected to have efavirenz-related side effects in combination with high efavirenz C_{min} (>4 mg/l).

Sampling and bioanalysis
All children were admitted to the hospital at the start of therapy. During this first day of treatment, a full pharmacokinetic curve during a dosing interval was assessed. Samples were drawn just before and after approximately 0–1, 1–2, 2–4, 4–7, 7–12 and 24 h after drug intake. Subsequently, after 2 and 6 weeks of treatment a trough sample (20–24 h after drug intake), and preferably a sample between 2–4 h after drug ingestion were taken. The efavirenz concentrations were quantified using a validated HPLC assay with UV detection. Validated concentration ranges were 0.05–15 mg/l. Intra- and interassay precision were <5.9%, whereas accuracies varied between -12.7 and 8.5% [13].

CYP2B6 genotyping
The presence of the c.516G>T polymorphism in the CYP2B6 gene was analysed using PCR and sequencing. DNA cycle sequencing was carried out essentially as described by the manufacturer (Applied Biosystems, Foster City, CA, USA). Genomic DNA was extracted from plasma using the QIAamp DNA mini kit (Qiagen, Inc., Valencia, CA, USA), following the manufacturer’s instructions. The methods used for the amplification of the CYP2B6 genes have been previously described by

<table>
<thead>
<tr>
<th>Body weight, kg</th>
<th>Liquid formulation (30 mg/ml)</th>
<th>Capsules/tablets dosage, mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age &lt;5 years dosage, ml</td>
<td>Age &gt;5 years dosage, ml</td>
</tr>
<tr>
<td>13&lt;15</td>
<td>12</td>
<td>9</td>
</tr>
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<td>15&lt;20</td>
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<td>25&lt;32.5</td>
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<tr>
<td>32.5&lt;40</td>
<td>–</td>
<td>17</td>
</tr>
<tr>
<td>&gt;40</td>
<td>–</td>
<td>24</td>
</tr>
</tbody>
</table>
Lang et al. [14]. After amplification and purification, sequences were analysed on an Applied Biosystems 3100-Avant DNA sequencer. For sequence alignment Seqscape version 2.1 (Applied Biosystems) was used.

Pharmacokinetic analysis

The nonlinear mixed effect modelling program (NONMEM) version VI was used to perform the analysis [15]. The model was fitted using the first-order conditional estimation procedure with interaction between interindividual, intraindividual and residual variability. The minimal value of the objective function (OFV, equal to minus twice the log likelihood) provided by NONMEM was used as goodness of fit characteristic to discriminate between hierarchical models using the log likelihood ratio test [15]. A $P$-value of 0.05, representing a decrease in OFV of 3.84 points was considered statistically significant. Furthermore, XPose and Perl speaks NONMEM (PsN) were used for graphical and statistical model diagnostics [16,17]. Conditional weighted residuals for model diagnosis were determined as described by Hooker et al. [18].

We used Piraña (interface to NONMEM, PsN and our cluster) for run deployment and analysis [19]. Precision of parameter estimates were estimated using the covariance step in NONMEM.

Basic pharmacokinetic model

Data were described with a one-compartment model. The oral clearance (Cl/F, where Cl represents clearance in l/h and F represents the oral bioavailability) and volume of distribution (V/F) were allometrically scaled for body weight using two equations:

$\text{Cl/F} = \theta_1 \times (\text{weight}/70)^{0.75}$ and $\text{V/F} = \theta_2 \times (\text{weight}/70)^1$,

in which Cl/F and V/F represent the clearance and volume of distribution scaled to a person weighing 70 kg and $\theta_1$ and $\theta_2$ are the respective typical values of clearance and volume of distribution. Allometric scaling includes weight as a covariate in the model a priori, allowing exploration of other possible covariates independent of size. Scaling to a weight of 70 kg allows comparison of the pharmacokinetic estimates with adults [20–22].

The absorption phase was described using two transition compartments between the depot compartment and the central compartment, as described before by Kappelhoff et al. [23] for the determination of the mean absorption time (MAT). Autoinduction of clearance was accounted for by estimation of the proportional increase of clearance of efavirenz during the first 2 weeks of treatment.

Interindividual variability in the different pharmacokinetic parameters and interoccasion variability on relative bioavailability were estimated with an exponential error model as proposed by Karlsson et al. [24]. The residual variability was modelled with a combined additive and proportional error. The basic pharmacokinetic model is depicted schematically in Figure 1.

Covariate model building

Gender, age, drug formulation (liquid or solid), the presence of the c.516G>T polymorphism in the CYP2B6 gene and the liver enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST) at baseline were collected. The effect of body size was accounted for a priori by allometric scaling of Cl/F and V/F on body weight. When weight data of a patient were not...
available, a linear extrapolation of the weight was made on the basis of a previous and a later weight observation. All covariates were tested univariately (P<0.05) for their inclusion in an intermediate model: gender and age were tested on volume of distribution and clearance, drug formulation was tested on relative bioavailability, liver enzymes ALT and AST were tested on clearance and the presence of the c.516G>T polymorphism in the CYP2B6 gene was tested on reduction of clearance. The clearance for the group of extensive metabolizers (G/G genotype) was estimated. The decrease in Cl/F for the group of intermediate metabolizers (G/T genotype) and poor metabolizers (T/T genotype) was estimated separately. After inclusion of all significant covariates into the intermediate model, a stepwise backward elimination procedure was carried out. A parameter was retained in the model when the influence of this parameter was statistically significant with a P-value < 0.005, representing a decrease in OFV of 7.88.

Simulation study
The probability of developing a C\textsubscript{min} < 1 mg/l or >4 mg/l at 24 h after intake was estimated using the developed model. For each dose level, 1,000 virtual patients from the corresponding weight category were simulated and the probability of developing a C\textsubscript{min} < 1 mg/l or >4 mg/l for each weight category was expressed as a percentage of the number of simulated patients. Using this strategy, efavirenz exposure was evaluated using the current paediatric dosing guidelines. Alternative dosing options were explored as well. An alternative dose was considered acceptable if >75% of the patients had a efavirenz C\textsubscript{min} of at least 1 mg/l at steady state.

Results
Pharmacokinetic analyses
All patient characteristics have been previously described by Scherpbier et al. [1]. In the study by Scherpbier et al. a total of 36 children were included. In our study, 33 children were evaluable for pharmacokinetic analyses. The median age of these 33 children was 6.5 years (range 0.9–19 years), the median weight was 20.5 kg (range 8.7–83 kg), 16 of 33 patients were female and 11, 15 and 7 patients were wild type, heterozygous or homozygous mutant for the c.516G>T polymorphism, respectively. None of the children was previously exposed to efavirenz. A total of 30 full pharmacokinetic curves and 302 plasma concentrations at single time points were available. Samples without a known time after drug intake were excluded. Efavirenz was given as a liquid formulation in 95 out of a total of 329 dosing events. The median dose of all dosing events scaled to a person weighing 70 kg was 754 mg (interquartile range 636–901 mg).

Plasma concentrations of efavirenz were highly variable. On the first day of treatment the concentrations ranged from undetectable to approximately 5 mg/l. Maximum plasma concentrations were achieved 2–8 h after drug intake and declined gradually afterwards. As shown in Figure 2, most observed efavirenz concentrations during follow-up were within the therapeutic window of 1–4 mg/l (11% < 1 mg/l and 23% >4 mg/l), probably because of TDM-guided dosing interventions. Two children with efavirenz levels >4 mg/l had sleeping abnormalities. In one child, the dose was therefore reduced from 600 to 400, then to 200 mg once daily. One child developed grade 3 increases in liver enzymes, which led to the discontinuation of efavirenz.

For the basic model, Cl/F at baseline scaled to a person weighing 70 kg was estimated to be 14.5 l/h. In the basic model, autoinduction could not be estimated. V/F scaled to a person weighing 70 kg was 523 l and MAT was 2.21 h. The results of the basic pharmacokinetic model are presented in Table 2.

The covariates of interest were introduced into the model separately and drug formulation (liquid formulation versus tablets or capsules) as well as CYP2B6 genotype significantly influenced efavirenz pharmacokinetics in the univariate analysis. The reduction in clearance of a heterozygous and a homozygous CYP2B6 c.516G>T mutation was 25.4% and 58.7%, respectively, indicating that the effect of a homozygous mutation was approximately twice the effect of a heterozygous mutation. Separate estimation of these effects did not improve the model (as judged by the graphical and statistical model diagnostics). Because more degrees of freedom resulted in model instability, the influence of a homozygous mutation was fixed to have twice the effect of a heterozygous mutation.

![Figure 2. Observed efavirenz concentrations during follow-up](image-url)
In the multivariate analysis both covariates were retained in the model. For the final model, Cl/F at baseline scaled to a person weighing 70 kg was estimated to be 13 l/h and increased by 21% during the first 2 weeks of treatment. V/F scaled to a person weighing 70 kg was 424 l and MAT was 1.96 h. The relative bioavailability for the efavirenz liquid formulation was only 46.6% and Cl/F was reduced by 29.7% due to a heterozygous G516T mutation in the CYP2B6 gene. A homozygous mutation was therefore estimated to reduce the Cl/F by 59.4% (twice the effect of a heterozygous mutation).

No additional age effect was found on clearance. The results of the final model are presented in Table 2. Figure 3A shows the goodness of fit plots of the final model. Figure 3B shows the observed concentrations versus individual predicted concentrations, indicating that individual efavirenz pharmacokinetics were well-described by the model. Lastly, Figure 3C shows the conditional weighted residuals versus time. All conditional weighted residuals were within ±3, indicating that the variability in efavirenz exposure was adequately captured by the model. Moreover, equal distribution of positive and negative conditional weighted residuals during time indicated the absence of bias in the model.

Results simulation study
Model-derived probabilities of developing a C_{min} <1 or >4 mg/l for each genotype and dosing schedule (tablets/capsules, oral liquid 3–<5 years old and oral liquid >5 years old) according to the manufacturer’s dosing guidelines are depicted in Table 3. Probabilities for each weight category were pooled due to similar results at each dose level. It can be noted that the group of extensive metabolizers and the group receiving the liquid formulation showed a high risk for subtherapeutic C_{min}. The probability of developing a C_{min} >4 mg/l was estimated to be relatively small, except in the group of poor metabolizers taking efavirenz as a capsule or tablet.

Alternative dosing options were explored on the basis of the group wild type for the c.516G>T CYP2B6 genotype, due to the high probability in that group of developing subtherapeutic concentrations. No additional age effect on pharmacokinetics was found in our model, therefore alternative dosing regimes were on the basis of weight only. We tested the regimen where one should give an adult dose of 600 mg to children weighing ≥25 kg. Doses for children weighing <25 kg should be allometrically scaled. Furthermore, a dose increase of 215% when switching from a solid efavirenz formulation to the oral solution because the diminished bioavailability of the latter was proposed. This regimen is shown in Table 4. Simulation derived probabilities of developing a C_{min} <1 or >4 mg/l for each genotype using the proposed alternative dosing regimen are shown in Table 5. As can be seen in this table, the risk for developing a subtherapeutic C_{min} has been highly reduced. However, children carrying the c.516G>T mutation in the CYP2B6 gene show an increased risk for developing a C_{min} >4 mg/l.

Discussion
We have successfully developed a population pharmacokinetic model for efavirenz in children. Weight was the main determinant for the development of clearance and volume of distribution and no additional age effect was found. In addition, drug formulation and the c.516G>T

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Basic model</th>
<th>RSE, %</th>
<th>Estimate</th>
<th>RSE, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAT, h</td>
<td>2.21</td>
<td>15.1</td>
<td>1.96</td>
<td>11.9</td>
</tr>
<tr>
<td>Cl/F at baseline, l/h</td>
<td>14.5</td>
<td>13.6</td>
<td>13.0</td>
<td>11.5</td>
</tr>
<tr>
<td>Autoinduction, %</td>
<td>–</td>
<td>–</td>
<td>21.0</td>
<td>4.54</td>
</tr>
<tr>
<td>V/F, l</td>
<td>523</td>
<td>14.5</td>
<td>424</td>
<td>8.87</td>
</tr>
<tr>
<td>Decrease in clearance due to c.516G&gt;T</td>
<td>–</td>
<td>–</td>
<td>29.7</td>
<td>19.4</td>
</tr>
</tbody>
</table>

Cl/F, oral clearance; F, oral bioavailability; MAT, mean absorption time; RSE, relative standard error; V/F, volume of distribution.

Table 2. Final parameter estimates of the basic and final pharmacokinetic model for efavirenz

Table 3. Simulation derived probabilities of developing a C_{min} <1 or >4 mg/l for each genotype and dosing schedule (tablets/capsules, oral liquid 3–<5 years old and oral liquid >5 years old) according to the manufacturer’s dosing guidelines.
polymorphism were found to have a large effect on the $C_{\text{min}}$ of efavirenz in our cohort. Our data suggests that an unexpected Cl/F is the main determinant of decreased efavirenz exposure in children. The Cl/F in a child wild type for the c.516G>T CYP2B6 genotype scaled to a person of 70 kg was 13 l/h, and increased by 21% to 15.7 l/h during the first 2 weeks of treatment due to autoinduction. The MAT was 1.96 h. In the final model the V/F scaled to a person weighing 70 kg was 424 l. The V/F is comparable with previously found V/F in population pharmacokinetic analyses in adults ranging from 150 to 418 l [23,26–28]. However, the Cl/F of 15.7 l/h in children wild type for the c.516G>T CYP2B6 polymorphism is higher than the previously reported 9.4 l/h in adults wild type for this genotype [28].

Drug formulation had a large effect on the bioavailability of efavirenz. The estimated relative bioavailability of the oral liquid compared with solid liquid formulations was 46.6%. This finding conflicts with the 20% dose increase suggested by the manufacturer when switching from a solid formulation to the liquid. This dose increase was based on a single dose study in healthy adults [12]. A previous pharmacokinetic study of the efavirenz liquid formulation in HIV-infected children showed that its relative bioavailability was 62%, which supports our conclusion that a 20% dose increase is not sufficient [3]. This could indicate that there is a physiological difference between healthy adults and HIV-infected children that could influence drug absorption. Moreover, the absence of food restrictions might also have influenced the relative bioavailability because simultaneous food intake is known to increase efavirenz exposure [12].

Efavirenz Cl/F was reduced markedly in children by the c.516G>T polymorphism in the CYP2B6 gene. A heterozygous mutation resulted in a 29.7% decrease in clearance. CYP2B6 genotype has been previously shown to significantly decrease efavirenz clearance in adults as well as children. Haas et al. [9] showed an increase of efavirenz exposure of approximately 36% in heterozygous patients and even a threefold increase in patients who were homozygous for the CYP2B6 c.516G>T mutation. A study by Saitoh et al. [10] investigating the influence of CYP2B6 on efavirenz pharmacokinetics in children showed similar results. Our study confirms the importance of the CYP2B6 genotype in the clearance of efavirenz in children.

The mean administered dose scaled to a person weighing 70 kg of 754 mg already indicated that, in our population, normal efavirenz dosing (600 mg once daily allometrically scaled to a person weighing 70 kg) would result in inadequate exposure. Using a simulation study, it was confirmed that current paediatric dosing guidelines leaves certain populations (children

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**Figure 3. Goodness of fit in the final pharmacokinetic model**

(A) Observed concentrations versus population predicted concentrations.
(B) Observed concentrations versus individual predicted concentrations.
(C) Conditional weighted residuals versus time.
Pharmacokinetics of efavirenz in children

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Table 3. Simulation-derived probabilities of developing a trough level <1 or >4 mg/l for each genotype using current paediatric dosing guidelines

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Tablets/capsules</th>
<th>Oral liquid 3–5 years</th>
<th>Oral liquid &gt;5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Probability of $C_{\text{min}}&lt;1$ mg/l, %</td>
<td>Probability of $C_{\text{min}} &gt;4$ mg/l, %</td>
<td>Probability of $C_{\text{min}}&lt;1$ mg/l, %</td>
</tr>
<tr>
<td>Extensive metabolizer (c.516G&gt;T wild type)</td>
<td>49</td>
<td>3</td>
<td>64</td>
</tr>
<tr>
<td>Intermediate metabolizer (c.516G&gt;T heterozygote)</td>
<td>24</td>
<td>11</td>
<td>43</td>
</tr>
<tr>
<td>Poor metabolizer (c.516G&gt;T homozygote)</td>
<td>5</td>
<td>43</td>
<td>14</td>
</tr>
</tbody>
</table>

Table 4. Alternative efavirenz dosing regimen

<table>
<thead>
<tr>
<th>Body weight, kg</th>
<th>Capsules/tablets dose, mg</th>
<th>Oral liquid dose of 30 mg/ml, ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>13&lt;15</td>
<td>400</td>
<td>29</td>
</tr>
<tr>
<td>15&lt;20</td>
<td>450</td>
<td>32</td>
</tr>
<tr>
<td>20&lt;25</td>
<td>500</td>
<td>36</td>
</tr>
<tr>
<td>&gt;25</td>
<td>600</td>
<td>43</td>
</tr>
</tbody>
</table>

Table 5. Simulation derived probabilities of developing a trough level <1 or >4 mg/l for each genotype using the proposed alternative dosing regimen

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Tablets/capsules</th>
<th>Oral liquid</th>
</tr>
</thead>
</table>

|                                 | Probability of $C_{\text{min}}<1$ mg/l, % | Probability of $C_{\text{min}} >4$ mg/l, % | Probability of $C_{\text{min}}<1$ mg/l, % | Probability of $C_{\text{min}} >4$ mg/l, % |
|---------------------------------|------------------|-------------|
| Extensive metabolizer (G516T wild type) | 22               | 13                      | 24                   | 16                    |
| Intermediate metabolizer (G516T heterozygote) | 9                | 30                     | 11                   | 31                    |
| Poor metabolizer (G516T homozygote) | 1                | 59                     | 2                    | 58                    |

C$_{\text{min}}$, trough level.

wild type for the c.516G>T mutation as well as children dosed with the liquid formulation) at risk for obtaining subtherapeutic efavirenz $C_{\text{min}}$. This is in concordance with results of earlier observational studies, reporting a high incidence of subtherapeutic efavirenz concentrations or a high incidence of TDM-guided dose increases in children [6–8].

Currently, CYP2B6 genotyping is not part of the standard of care. The reported allele frequency of the c.516G>T mutation in the CYP2B6 gene is reported to be 20–50%, with the higher frequencies mainly reported in patients of African origin [9,14,28,29]. We have shown that the group wild type for the CYP2B6 c.516G>T mutation is at high risk of developing subtherapeutic concentrations. This is approximately 50–80% of all children. TDM should be standard of care but it might not always be available, for instance in resource-limited settings. Adequate drug exposure from the start of therapy is desirable to minimize the chance of developing resistance against efavirenz. Side effects due to high efavirenz exposure are reversible, however, drug resistance is not. Although it increases the probability of developing $C_{\text{min}}>4$ mg/l in patients heterozygous or homozygous for the CYP2B6 c.516G>T mutation, we propose to increase the dose of efavirenz $a$ priori when the presence of the c.516G>T polymorphism is unknown or known to be absent. Furthermore, when administered as the liquid formulation, the efavirenz dose should be increased at least twofold, instead of 20% as proposed by the manufacturer.

Two previous pharmacogenetic studies of efavirenz in adults proposed an $a$ priori efavirenz dose decrease in patients with the CYP2B6 c.516G>T genotype, but did not report subtherapeutic concentrations in patients...
wild type for this genotype [28,30]. This underlines our finding that the paediatric population is a different population than the adult population taking efavirenz. Our model adequately described the population pharmacokinetics of efavirenz in children, but additional data are needed to fully describe the development of efavirenz pharmacokinetics from infancy to adulthood.

Our study is limited by the number of children included. However, this is the largest study of its kind performed so far. Although there was thorough monitoring of compliance, non-compliance could not be ruled out and could have influenced the results.

In conclusion, we have successfully developed a population pharmacokinetic model of efavirenz in children. Weight, CYP2B6 genotype and drug formulation were important covariates influencing efavirenz pharmacokinetics and using current paediatric dosing guidelines, a large group is at risk for developing subtherapeutic efavirenz concentrations. An a priori dose increase in children seems therefore feasible and needs prospective validation.

Acknowledgements

Ron Keizer is greatly acknowledged for technical assistance, Atie van der Plas and Marleen Kemper are acknowledged for their help in gathering clinical information and Valerie Doodeman is acknowledged for her help genotyping the samples.

Disclosure statement

The authors declare no competing interests.

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Accepted for publication 9 June 2008