Age-Related Effects on Nelfinavir and M8 Pharmacokinetics: a Population Study with 182 Children

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As a relationship between nelfinavir antiretroviral efficacy and plasma concentrations has been previously established, nelfinavir pharmacokinetics was investigated in order to optimize the individual treatment schedule in a pediatric population. A population pharmacokinetic model was developed to describe the concentration-time course of nelfinavir and its active metabolite M8. Individual characteristics were used to explain the large interindividual variability in children. Data from therapeutic drug monitoring in 182 children treated with nelfinavir were analyzed with NONMEM. Then Food and Drug Administration (FDA) current recommendations were evaluated estimating the percentage of children who reached the target minimum plasma concentration (0.8 mg/liter) by using Bayesian estimates. Nelfinavir pharmacokinetics was described by a one-compartment model with linear absorption and elimination. Pharmacokinetic estimates and the corresponding intersubject variabilities for the model were as follows: nelfinavir total clearance, 0.93 liters/h/kg (39%); volume of distribution, 6.9 liters/kg (109%); absorption rate, 0.5 h−1; formation clearance fraction to hydroxy-tert-butylamide (M8), 0.025; M8 elimination rate, 1.88 h−1 (49%). Apparent nelfinavir total clearance and volume of distribution decreased as a function of age. M8 elimination rate was increased by concomitant administration of nevirapine or efavirenz. Our data confirm that the FDA recommendations for children from 2 to 13 years are optimal and that the dose recommended for children younger than 2 years is adequate for the children from 2 months to 2 years old. However, in children younger than 2 months, the proposed nelfinavir newborn dose of 40 mg/kg of body weight twice daily is inadequate and we suggest increasing the dose to 50 to 60 mg/kg administered thrice daily. This assumption should be further evaluated.

Nelfinavir is a protease inhibitor commonly used in a highly antiretroviral therapy to treat human immunodeficiency virus type 1 (HIV-1) infection. In children, the antiretroviral efficacy obtained with this drug was disappointing (18). However, this drug is still recommended as first-line therapy because it is well tolerated by children and few alternatives are available. Optimization of administration schedule, due to a better understanding of nelfinavir pharmacokinetics in children, could help at improving the efficacy of this drug.

Nelfinavir is metabolized via CYP2C19 (cytochrome P450 isoenzyme) in the liver into an active metabolite, hydroxy-tert-butylamide (M8), which is in turn metabolized via CYP3A4 (15). It has been reported that 2- to 13-year-old children demonstrate a two- to threefold increase in apparent oral clearance of nelfinavir compared to adult values (13) and that children younger than 2 years have lower nelfinavir concentrations (and higher apparent clearance) than older children (7). However, most studies were performed in small and heterogeneous groups of children and showed a very large variability in drug pharmacokinetic parameters (5, 8, 25).

The aim of the present study was to characterize the nelfinavir and M8 pharmacokinetics in children. This was achieved by (i) developing an integrated pharmacokinetic model to simultaneously describe the nelfinavir and M8 pharmacokinetics and (ii) using a pharmacostatistic model to identify the patient characteristics that can influence nelfinavir and M8 pharmacokinetics. Such results should be useful to optimize nelfinavir treatment since a significant relationship was demonstrated between nelfinavir antiretroviral efficacy/safety and minimum plasma concentration (6, 21, 24).

MATERIALS AND METHODS

Patients. The population included children receiving oral nelfinavir for treatment of HIV infection and whose antiretroviral drug plasma concentrations were monitored on a routine basis. Nelfinavir was administered according to body weight (BW), only as 250-mg tablets (never as powder), and tablets were crumbled in a small volume of water and added to milk or food when children could not swallow them. Nelfinavir powder was not used because of the large volume to administer, the unpleasant consistency, and the difficulties in dissolving it in milk or food (18).

Except newborns, children were outpatients. For outpatients, the dosing information was obtained by the clinician from the patient or the parents. For each child, if the time elapsed between drug administration and blood sampling times was less than 13 h, gender, BW, height, body mass index (BMI), body surface area (BSA), and age were carefully recorded, as well as combined treatments, particularly of other antiretroviral drugs. When low compliance was suspected by the clinician or by the pharmacologist (undetectable plasma concentrations of nelfinavir and M8), the data were not included in the analysis. When sample time was greater than 13 h and also nonadherence or error on the last administration time was highly probable, the records were not included in the data set. This included only 16 plasma samples (8%). Ethics committee approval and patient consent are not compulsory in France in order to use therapeutic drug monitoring data, and thus they were not obtained.

Analytical method. Nelfinavir and M8 plasma concentrations were measured by high-performance liquid chromatography. Briefly, the method involved the

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or, in the case of an inhibitory drug effect, (CLT). The mean population parameters of the parent compound were then
fraction (\(F\)). Distribution volume was not identifiable. The equation for the metabolite pharmacokinetics (\(CL_{MT}\)) is derived in the Appendix. All clearance and volume terms were
approximated additive model according to the following equation, using \(CL_T\), for example:
\[ CL_T = TV(CL_T) \times \text{AGE (median AGE)}^{\theta_{AGE}} \]  
where TV(CL_T) is the typical value of clearance for a patient with the median covariate value and \(\theta_{AGE}\) is the estimated influential factor for age.

Categorical covariates, including gender and combined antiretroviral drugs, were tested using an inducing drug effect, for example:
\[ CL_T = TV(CL_T) \times [1 + \theta_{\text{DRUG}} \times (\text{DRUG} = 0 \text{ or } 1)] \]  
or, in the case of an inhibitory drug effect,
\[ CL_T = TV(CL_T) \times [1 + \theta_{\text{DRUG}} \times (\text{DRUG} = 0 \text{ or } 1)] \]  
where \(\theta_{\text{DRUG}}\) is the estimated influential factor for the drug effect.

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Covariates were selected in the final population model if (i) their effect was biologically plausible, (ii) they produced a minimum reduction of 7 (\(P < 0.01\), one degree of freedom) in the objective function value (OFV), and (iii) they produced a reduction in the variability of the pharmacokinetic parameter, assessed by the associated intersubject variability. An intermediate multivariate model was then obtained including all significant covariates. In order to keep only those covariates with the largest contribution in the final multivariate model, a change of 11 (\(P < 0.001\), one degree of freedom) of the objective function was required for the retention of a single parameter during backward stepwise multiple regression analysis.

For evaluation of the goodness of fit, graphs of observed concentrations versus predictions (PRED), weighted residuals versus time, and weighted residuals versus PRED, as well as the corresponding graphs using individual predictions, were compared. Diagnostic graphics and distribution statistics were obtained using the R program (12).

### Bootstrap validation

The accuracy and robustness of the final population model were assessed using a bootstrap method, as previously described in detail (19). Briefly, this included the following steps: (i) from the original data set of \(n\) individuals, \(B\) bootstrap sets (\(B = 1000\)) of \(n\) individuals were drawn with replacement (resampling), (ii) for each of the \(B\) bootstrap sets, the population pharmacokinetic parameters were estimated; (iii) with the \(B\) estimates of each population pharmacokinetic parameter, the corresponding mean and standard deviation were estimated; and (iv) to validate the model, the parameters estimated from the bootstrap needed to be close to estimates obtained from the original population set.

### Individual minimum plasma concentrations

Individual pharmacokinetic parameters using the Posthoc option of NONMEM were used to calculate the daily dosage to obtain a minimum plasma concentration of 0.8 mg/liter (6). Three homogeneous groups of children were distinguished by age: younger than 2 months, 2 months to 2 years, and 2 to 13 years. Then the daily dosage to obtain a minimum plasma concentration of 0.8 mg/liter was calculated in the three age groups as the daily dose was given twice: every 12 h (i.e., twice daily [BID]) and every 8 h (i.e., thrice daily [TID]). For each category of age and regimen, a cumulated curve was drawn to show immediately for a given daily dose regimen which percentage of children would have a minimum plasma concentration above 0.8 mg/liter. Current Food and Drug Administration (FDA) nelfinavir dose recommendations (11), depending on drug regimen (every 8 or 12 h), were evaluated in each of the three age groups.

### RESULTS

#### Demographic data

A total of 182 children (95 boys, 87 girls) were available for pharmacokinetic evaluation. Table 1 summarizes the dosage regimens. A total of 742 nelfinavir concentrations (a median of three samples per patient) and 557 M8 concentrations (a median of two per patient) were collected. Sampling times were as follows: median was 3.5 h, 50% were between 12 and 13 h (Fig. 2). Median age was 8.2 years (from 2 mo (1.5–5 kg) BID 19 147 61
2 mo–2 yr BID 12 504 137
2–7 yr BID 24 233 89
>8 yr BID 53 655 131

TABLE 1. Dosage regimens

<table>
<thead>
<tr>
<th>Age (amt)</th>
<th>Frequency</th>
<th>No. of children</th>
<th>Mean dose/ administration (mg)</th>
<th>SD (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2 mo (1.5–5 kg)</td>
<td>BID</td>
<td>19</td>
<td>147</td>
<td>61</td>
</tr>
<tr>
<td></td>
<td>TID</td>
<td>6</td>
<td>130</td>
<td>70</td>
</tr>
<tr>
<td>2 mo–2 yr</td>
<td>BID</td>
<td>12</td>
<td>504</td>
<td>137</td>
</tr>
<tr>
<td></td>
<td>TID</td>
<td>24</td>
<td>233</td>
<td>89</td>
</tr>
<tr>
<td>2–7 yr</td>
<td>BID</td>
<td>29</td>
<td>416</td>
<td>108</td>
</tr>
<tr>
<td></td>
<td>TID</td>
<td>53</td>
<td>655</td>
<td>131</td>
</tr>
<tr>
<td>&gt;8 yr</td>
<td>BID</td>
<td>39</td>
<td>849</td>
<td>278</td>
</tr>
<tr>
<td></td>
<td>TID</td>
<td>53</td>
<td>655</td>
<td>131</td>
</tr>
</tbody>
</table>
3 days to 17 years), 25 children were younger than 2 months, 36 were 2 months to 2 years old, and 121 were older than 2 years. Median body weight was 21 kg (from 1.7 to 70 kg). Coadministered antiretroviral drugs known to influence plasma nelfinavir concentrations were efavirenz (n = 10, 53 samples), nevirapine (n = 33, 133 samples), ritonavir (n = 3, 11 samples), and saquinavir (n = 10, 48 samples). The subjects who took ritonavir were included in a first analysis, but the number of subjects was too small, producing an unstable model, so they were excluded in the final analysis. Plasma samples were generally collected at steady state, which means after at least 10 daily administrations of nelfinavir. Eighteen plasma samples were not at steady state, since they were obtained in children less than 10 days old.

**Population pharmacokinetics. (i) Nelfinavir pharmacokinetic model building.** A one-compartment pharmacokinetic model adequately described the data. Intersubject and residual variabilities were best described by exponential and additive error models, respectively. The available data were not sufficient to estimate an intersubject variability for \( K_e \), and exclusion of this random effect had no influence on the objective function value. Body size descriptors, BW, BSA, and BMI, had significant effects on CL\( _T \), resulting in an at least 44-U decrease of OFV. Because CL\( _T \) was proportional to BW and nelfinavir dosing is based upon BW, this effect was then fixed in the following step of the analysis.

\[
CL_T = TV(CL_T) \times BW \tag{4}
\]

\[
V = TV(V) \times BW \tag{5}
\]

The use of allometric principles suggests an exponent of 0.75 for the clearance, 1 for volume of distribution, and −0.25 for elimination constant rate (1, 22). With our data set, there were no significant differences in terms of OFV and goodness of fit when using an exponent of 1 for clearance and 1 for volume.

Age had a significant effect on CL\( _T \) and \( V \), resulting, respectively, in 93- and 13-U decreases in the OFV. This effect could be observed from the plot of nelfinavir apparent clearance (Fig. 3) and volume (data not shown) using maximum posteriori Bayes estimates from the base model versus age. Adding the same age effect on both \( V \) and CL\( _T \) resulted in a 101-U decrease in OFV. The following equations describe the final covariate model for nelfinavir:

\[
\text{Age effect} = (\text{AGE}/8.2)^{0.29} \tag{6}
\]

\[
CL_T = TV(CL_T) \times BW \times \text{age effect (liters/h/kg)} \tag{7}
\]

\[
V = TV(V) \times BW \times \text{age effect (liters/kg)} \tag{8}
\]

(ii) **M8 pharmacokinetic model building.** The M8 pharmacokinetics was modeled as a metabolite compartment. The nelfinavir pharmacokinetic parameters, including the effect of age on CL\( _T \) and \( V \), were fixed, and M8 parameters were estimated separately. The intersubject variability for \( F_{MT} \) was not significant, and exclusion of this random effect had no influence on the OFV. The covariate submodeling was then established for the M8 elimination rate constant \( K_{M0} \). Efavirenz and nevirapine are nonnucleoside inhibitors (NNI); both of them are inducers. Estimating the specific effect for each drug on \( K_{M0} \), we found that the inducer effects of efavirenz and nevirapine were not significantly different. We defined \( \theta_{NNI} \), which is the common influential factor used when one of these drugs is administered (the two drugs are never administered simultaneously).

At this step, the following equation described the final covariate model:

\[
K_{M0} = TV(K_{M0}) \times [1 + \theta_{NNI} \times (\text{EFA} + \text{NEV})] \tag{9}
\]

Adding this covariate modeling resulted in a 42-U decrease in OFV.

(iii) **Nelfinavir-M8 pharmacokinetic model building.** Nelfinavir and M8 were simultaneously fitted to the parent-metabolite model with first-order administration and elimination, including the covariate submodelings, in order to verify and refine the parameter estimates. This step led to minor changes in the previous estimates. The addition of a covariance term between total clearance and M8 elimination rate led to a sig-
significant 11-U decrease in OFV. Then covariate deletion was performed to verify the nelfinavir-M8 pharmacokinetic model. Exclusion of each covariate of the model led to deterioration of the fit with OFV and ISV increase: respectively, 106 U and 15% on CLT, 7% on V for age, and 40 U and 5% on the elimination rate constant for NNI coadministration. At this final step, the following equations described the covariate elimination rate constant for NNI coadministration. At this final step, the following equations described the covariate elimination rate constant for NNI coadministration.

\[
\text{CL}_T = 0.93 \times BW \times (\text{AGE}/8.2)^{-0.29} \times (\text{CLF} - \text{K}_{\text{M0}}) \times (\text{EFA} + \text{NEV})
\]

\[
\text{V} = 6.86 \times (\text{AGE}/8.2)^{0.29} \times (\text{CLF} - \text{K}_{\text{M0}})
\]

\[
\text{K}_{\text{M0}} = 1.88 \times (\text{AGE}/8.2) \times 1 + 0.91 \times 12 \times (\text{CLF} - \text{K}_{\text{M0}})
\]

Table 2 summarizes the final population pharmacokinetic estimates.

(iv) Model performance. Final model performance could be appreciated by comparing the population predicted and observed plasma concentrations (Fig. 4). There was a correlation of \( r = 0.74 \) (\( P < 0.001 \)) and \( r = 0.79 \) (\( P < 0.001 \)) between individual predicted and observed concentrations for nelfinavir and M8, respectively, and the bias and precision were, respectively, \(-0.02 \pm 1.5\) and \(2.2 \pm 3.8\) for nelfinavir and \(-0.03 \pm 0.6\) and \(0.3 \pm 1.2\) mg/liter for M8.

Bootstrap assessment of the final population model. The final model obtained with the original data set was subjected to bootstrap analysis. As shown in Table 2, the mean, standard error, and variability of parameter estimates obtained from the bootstrap process, which entailed 1,000 runs, were very similar to the estimates previously obtained with the original data set.

Relevance of FDA recommendations. In children from 2 to 16 years (\( n = 121 \)), using the minimal doses currently recommended, 25 mg/kg of body weight TID or 50 mg/kg BID, the predicted concentration was above 0.8 mg/liter in 96% of children with a 25-mg/kg administration every 8 h and 91% of children with a 50-mg/kg administration every 12 h (Fig. 5). This large group was again split into two subgroups, 2 to 7 and 8 to 16 years, to refine the analysis: for the recommended doses, the percentages of children that had a trough concentration above 0.8 mg/liter were not significantly different between the two groups.

In children from 2 months to 2 years (\( n = 36 \)), using the minimal doses proposed, 40 mg/kg TID or 60 mg/kg BID, the predicted concentration was above 0.8 mg/liter in 100% of children with a 40-mg/kg administration every 8 h and in 89% of children with a 60-mg/kg administration every 12 h (Fig. 6). Thus, the daily dosage for children from 2 to 16 years should be 75 to 100 mg/kg, whereas the children from 2 months to 2 years should receive more, 120 mg/kg.

In children younger than 2 months (\( n = 25 \)), using 40 mg/kg every 12 h, the predicted concentration was above 0.8 mg/liter in 4% of children. For 50 and 60 mg/kg every 8 h, 88% and 100% of children, respectively, had a minimum plasma concentration above 0.8 mg/liter (Fig. 7) (between 0.7 and 2.1}
mg/liter for 50 mg/kg every 8 h and between 0.8 and 2.5 mg/liter for 60 mg/kg every 8 h).

Whichever age, the percentage of children with a minimum plasma concentration above 0.8 mg/liter was higher with an administration every 8 h than with an administration every 12 h, corresponding to better TID than BID FDA-recommended doses (11).

**DISCUSSION**

The nelfinavir-M8 pharmacokinetics was satisfactorily described by the proposed compartmental model. The present study showed a great consistency in the final nelfinavir-M8 population model derived from sequential analyses of nelfinavir and M8, confirming the robustness of the process. The basic one-compartment model was already used in adults for nelfinavir (21). The pharmacokinetics of the metabolite produced from the parent compound should be described by a two-exponential equation, but the sparse data set (a median of only two M8 concentration-time samples per child) did not allow the identification of two exponential components. So only an integrated modeling of parent-metabolite pharmacokinetics could provide a reliable estimate of M8 elimination, since the information for the fast exponential decay is provided by nelfinavir data. Indeed, in this approach, data on the metabolite may add information to the observations on the parent and vice versa.

The following observations support the use of the proposed pharmacokinetic model. (i) Nelfinavir mean plasma clearance (\(CL_{\text{T/F}} = 0.92 \pm 0.04\) liter/h/kg) was consistent with previously reported values: 1.0 to 1.3 liters/h/kg in 18 children (2.1 to 10.8 years) (25) and 1.57 liters/h/kg in 26 children (0.6 to 16 years) (8). (ii) Nelfinavir apparent plasma clearance and volume (\(CL_{\text{T/F}}, V/F\)) decreased with age, being much higher in children younger than 2 years, in agreement with previous studies. Bergshoeff et al. (5) showed that the clearance in children aged
<2 years was 1.5 times higher than in older children (2 to 18 years). Very high clearance in infants was reported by Lalitien et al. (4.2 liters/h/kg for children from 2.3 to 8.5 months) (16), Capparelli et al. (2.7 liters/h/kg in infants between 15 days and 2 years) (7), Payen et al. (2.13 liters/h/kg for children younger than 2 years) (20), and Mirochnick et al. (2.1 liters/h/kg at weeks 1 and 6 of life) (17). (iii) Finally, the goodness of fit, depicted in Fig. 4, was also a factor.

The residual error, 1.65 μg/ml, was probably overestimated because it included some part of interoccasion variability that could not be estimated here, since only one sample was available at each occasion. If there was a significant interoccasion variability in the nelfinavir pharmacokinetics, it could result in an underestimation of the ISVs, including CLT intersubject variability.

A major aim of population pharmacokinetics is to determine which measurable pathophysiological factor can cause changes in the dose-concentration relationship and to estimate the degree to which they do so, such that an appropriate dose adjustment can be made. This is particularly relevant for drugs that exhibit an appreciable degree of intersubject variability, such as nelfinavir, in children.

In the present study, age and the NNI drugs influenced the nelfinavir-M8 pharmacokinetics.

As shown, CLT and V normalized to BW decreased as an inverse function of age. CLT and V were apparent parameters (CLT/F and V/F). In our model, the same age effect was added to increase both V and CLT in the younger children, as we supposed that the age effect was due to a decrease in bioavailability (F).

A number of factors may explain the decrease of the bioavailability in infants. For instance, a diet which differs in content and calories from that of older children may play a role, as the influence of diet on the bioavailability of nelfinavir is well established (16). Moreover, newborns have an alkaline gastric pH (pH 6 to 8) and gastric acid production increases over the next 24 to 48 h before declining and remains relatively low in the first months of life. This high gastric pH in the newborn and young infant may reduce the bioavailability of weakly acidic compounds such as nelfinavir. Also, a smaller absorption area and binding of nelfinavir to a baby’s inner side bottle may also be suggested. In these young children, an increase in the metabolism did not seem relevant. There is no argument in favor of an overexpression of the P glycoprotein in infants. Moreover, CYP2C19, which metabolizes nelfinavir to M8 (16), has a low activity during the first year of life (30% of the adult activity) (23).

The plasma M8 concentrations were 1.9-fold lower in patients treated with efavirenz or nevirapine, consistent with an induction of CYP3A4 by these drugs, with M8 being metabolized via CYP3A4 (2). Furthermore, very high plasma M8 concentrations were observed in all samples (n = 11) from three children who received ritonavir, a known CYP3A4 inhibitor (14), but these data were too scanty to reach statistical significance.

It was previously shown that the antiretroviral response was improved in children with a minimum plasma concentration above 0.8 mg/liter (6). Using a Bayesian approach, we showed that this target concentration was reached more often with an administration every 8 h than an administration every 12 h (Fig. 5 to 7). This is in agreement with a previous study which showed that a significantly higher percentage of children in the twice-daily group had subinhibitory minimum plasma concentrations of nelfinavir than the thrice-daily regimen (9). Nelfinavir has a short half-life (5.5 h), which explains why an administration every 8 h maintained a higher trough concentration than an administration every 12 h. This difference in minimum plasma concentration between administrations every 8 or 12 h is more important in the youngest children. The youngest children, who have a smaller absorption area, may have a better bioavailability with a small dose administered thrice daily than with a higher dose administered twice daily. Therefore, the thrice-daily regimen should be preferred to the twice daily regimen, especially in this group. FDA-recommended doses for nelfinavir were then simulated as doses given with uniform intervals (every 8 h TID and every 12 h BID); however, nelfinavir is taken during a meal to increase bioavailability and children do not eat exactly every 8 or 12 h.

For children from 2 to 13 years, we showed that the new current FDA recommendations, 25 to 35 mg/kg TID or 50 to 60 mg/kg BID, were optimal. We confirmed also that the proposed nelfinavir doses for children younger than 2 years, 40 to 50 mg/kg TID or 60 to 75 mg/kg BID, are optimal for children from 2 months to 2 years. However, more children had a trough concentration above 0.8 mg/liter with the TID than with the BID recommended regimen. For children younger than 2 months, a 40-mg/kg dose of nelfinavir administered twice daily is inadequate. We recommend a nelfinavir dose between 50 and 60 mg/kg administered thrice daily. Mirochnick et al. also proposed further investigations of larger doses, such as 75 mg/kg twice a day for infants younger than 6 weeks (17). As stated above, the predicted trough concentrations that served to determine this drug dosage recommendation were obtained from a Bayesian approach, and because the residual variability was rather high, these predictions are likely to be close to the mean population trough values. However, the main consequence, i.e., the need to increase dosage in the youngest children, is also supported by direct examination of their observed concentrations at various times after administration that were mainly lower than 0.8 μg/ml. These data confirm the FDA dosage recommendations for children older than 2 months. However, in younger children, it is suggested to increase the dosage and to give it thrice daily. Nevertheless, the results of this population pharmacokinetic analysis should be confirmed by a prospective analysis.

APPENDIX

The differential system connected with the model depicted in Fig. 1 is:

\[ dG/dt = -K_g D, \quad G = D \quad \text{at} \quad t = 0 \quad (A1) \]

\[ d(\text{nelfinavir})/dt = K_g G - CL_{Tg}/V (\text{nelfinavir}), \]

where \( (\text{nelfinavir}) = 0 \) at \( t = 0 \) \quad (A2)

\[ d(M8)/dt = F_{MT} \times CL_d/V (\text{nelfinavir}) - K_{sof}(M8), \]

where \( (M8) = 0 \) at \( t = 0 \) \quad (A3)

where \( G \) corresponds to the gut compartment, \( (\text{nelfinavir}) \) to nelfinavir amount and \( (M8) \) to the metabolite’s amount, \( K = CL_{Tg}/V \) is the total nelfinavir constant rate, \( F_{MT} \) is the nelfinavir-to-M8 forma-
tion clearance fraction (fraction between 0 and 1), and $K_{\text{M0}}$ is the MS elimination rate constant ($K_{\text{M0}} = \frac{\text{CL}_{\text{M0}}}{V_{\text{M0}}}$ with $V_{\text{M0}} = 1$).

The solution giving the profile of the metabolite ($m = \text{MS}$) compartment is:

$$C_m(t) = \frac{K_{\text{D}} F_{\text{MS}} \text{CL}_{\text{E}}}{V} (1 - e^{-K_{\text{M0}} t}) (K_{\text{M0}} - K_{\text{E}}) e^{-K_{\text{E}} t} + (1 - e^{-K_{\text{M0}} t})(K_{\text{M0}} - K_{\text{E}}) + (1 - e^{-K_{\text{M0}} t})(K_{\text{M0}} - K_{\text{E}}) e^{-K_{\text{M0}} t}$$

(A4)

where $t$ is the time elapsed between drug administration and blood sampling and $T$ is the time interval between two administrations.

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