Pharmacokinetics of nelfinavir in children: influencing factors and dose implications

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Objectives: The study describes the pharmacokinetics (PK) of the protease inhibitor nelfinavir and its active metabolite M8 in children and evaluates the influence of patient-related factors on nelfinavir plasma levels.

Methods: HIV-1-infected children treated with nelfinavir every 8 h (q8h) were eligible for inclusion in this retrospective study. 0–8 h intensive plasma pharmacokinetics (PK) sampling was performed at steady state. Nelfinavir maximum concentration (Cmax), area under the plasma concentration-time curve in 0–8 h (AUC 0-8), trough level at the 8 h time point (C8) and relative apparent oral clearance (Cl*r/kg) were calculated.

Results: Twenty-four children (median age: 4.5 years, median nelfinavir dose: 28 mg/kg q8h) were included. Nelfinavir PK were highly variable: 10/24 children had an AUC0-8 below the value of 12.5 mg/l*h, which has previously been associated with an increased virological failure rate in children. With children aged <2 years and a dose of 20 mg/kg q8h, a non-significant trend was observed to more AUC0-8<12.5 mg/l*h [odds ratio (OR) (95% CI): 2.44 (0.41–14.7) and 8.7 (0.79–95), respectively]. Nelfinavir C8 correlated strongly with AUC0-8 (r=0.89, P<0.001). C8 >0.69 mg/l predicted an AUC0-8 >12.5 mg/l*h with 71% sensitivity and 80% specificity. Dose of nelfinavir per body surface area was a better predictor of AUC0-8 than dose per body weight.

Conclusion: Nelfinavir PK show high interindividual variability in children. Children <2 years old tend to be at increased risk for low nelfinavir levels. These data show that the nelfinavir dose of 20 mg/kg q8h is inadequate in most children. Also, these data suggest that paediatric dosing of nelfinavir based on body surface area should be considered. Therapeutic drug monitoring (TDM) can detect abnormal plasma levels and is therefore useful in optimizing nelfinavir therapy in HIV-infected children. However, further research is needed to more firmly establish a therapeutic range for nelfinavir in children.

Introduction

With the introduction of highly active antiretroviral therapy (HAART), HIV infection has become a chronic disease with strongly improved survival. However, management of HIV infection is often complicated by several factors, such as adverse events related to medication and complex medication schedules; these can result in non-compliance and the emergence of resistant HIV mutants. HIV protease inhibitors, which are often a component of HAART, show highly variable pharmacokinetics (PK). Since plasma levels of protease inhibitors have been related to virological efficacy, this variability may have important consequences for the success of HIV treatment [1]. Insight on the PK of protease inhibitors and factors contributing to variability in their PK is valuable, e.g. for the correct application of therapeutic drug monitoring (TDM).

In children, additional factors, such as poor palatability of medication, absence of paediatric dose forms and changes in drug disposition due to physiological maturation, may complicate an optimal response to HAART. The protease inhibitor nelfinavir is frequently prescribed for the treatment of paediatric HIV infection. It has shown effective suppression of HIV combined with good tolerability in children >2 years old [2,3]. Despite its widespread use, data on the PK of nelfinavir in children, especially in those <2 years old, are sparse. Even less is known about the PK of M8, nelfinavir’s active metabolite, in the paediatric population. The major objective of this study was to describe the PK of nelfinavir and its active metabolite M8 in HIV-1-infected children. In particular, attention was paid to the PK in children <2 years old. Furthermore, the association between patient-related factors and low nelfinavir plasma levels has been investigated.
Materials and methods

Patients
HIV-infected children between 0–18 years old treated with nelfinavir every eight hours (q8h) and two nucleoside analogues were eligible for inclusion in this retrospective, observational two-centre study. Co-medication was allowed if it was not expected to interfere with the PK of nelfinavir. Informed consent was obtained from all patients or caregivers prior to starting antiretroviral therapy. Nelfinavir dose was calculated as mg nelfinavir/kg body weight. The standard adult nelfinavir dose of 750 mg q8h was not exceeded.

Pharmacokinetic sampling
In all children, intensive PK sampling was performed at steady state (>1 week after starting nelfinavir). The procedure was part of standard patient care in our clinics. PK sampling was performed at the day care unit. Medication ingestion was directly observed and with food. For infants, medication was mixed with formula. Older children received medication with a meal. Blood samples were drawn at time points 0 (pre-dose), 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7 and 8 h post-ingestion. Within 24 hours after collection, samples were centrifuged and plasma was stored at −20 °C. Plasma concentrations of nelfinavir and M8 were determined by validated high performance liquid chromatography (HPLC) assay with ultraviolet (UV) detection (lower limit of quantification: 0.04 mg/l) [4].

Nelfinavir and M8 PK
Nelfinavir PK parameters were calculated using non-compartmental methods [5]. Nelfinavir plasma peak level (Cmax) and trough level at the 8 h time point (C8) were determined. Area under the plasma concentration-time curve 0–8 h (AUC0–8) was calculated using the trapezoidal rule. Apparent oral clearance of nelfinavir was calculated as dose (mg)/AUC0–8. Relative apparent oral clearance (Cl/kg*F) was calculated as dose (mg)/AUC0–8*body weight (kg). M8 plasma levels were also measured and Cmax, C8 and AUC0–8 of M8 were calculated. The association of different patient-related factors with nelfinavir PK parameters and with nelfinavir analogues was initiated between November 1997 and August 2000. Doses of nelfinavir were chosen upon the physician’s discretion. The median nelfinavir dose was 28 mg/kg q8h [interquartile range (IQR) 26–31 mg/kg q8h], with a maximum absolute dose of 750 mg q8h. Patients used nelfinavir either in tablets or in the powder formulation. Fourteen patients were naive to treatment with protease inhibitors and nine were non-naive; prior treatment was unknown for one patient. All protease inhibitor non-naive patients had been

Statistical methods
All statistical tests were performed using SPSS (SPSS, Chicago, IL, USA, version 10.0). Spearman’s rank correlation was calculated to evaluate the association between nelfinavir PK parameters and patient-related factors. A t test was used to test significance. Linear regression after logarithmic transformation of AUC0–8 and C8 was calculated. Receiver operating characteristic (ROC) curves were constructed to estimate sensitivity and specificity with which C8 or nelfinavir dose (mg/m2) could predict an AUC0–8 >12.5 mg/l*h. For this purpose, % sensitivity (% true positives) was plotted against % (1-specificity) (% false-positives) for patients with C8 or nelfinavir dose above a given value. Sensitivity was defined as the number of patients with an AUC0–8 >12.5 and C8 or dose above a given value/total number of patients with AUC0–8 >12.5. One-specificity was defined as % patients with AUC0–8 <12.5 and C8 or dose above a given value/total number of patients with AUC0–8 <12.5. Odds ratio (OR) calculation and Fisher’s exact test were performed to estimate the association of patient characteristics with nelfinavir AUC0–8 <12.5 mg/l*h. For this purpose, patient characteristics and the occurrence of nelfinavir AUC0–8 <12.5 mg/l*h were binary scaled. The Mann-Whitney U test and Kruskal-Wallis test were used to compare medians. A P-value of <0.05 was considered statistically significant.

Results
Twenty-four HIV-infected children between 5 months and 18 years of age were included. Patients using co-medication known to cause a pharmacokinetic interaction with nelfinavir and patients in whom intensive PK sampling was incomplete were excluded. Patient characteristics are given in Tables 1A and 1B. Treatment with nelfinavir q8h and two nucleoside analogues was initiated between November 1997 and August 2000. Doses of nelfinavir were chosen upon the physician’s discretion. The median nelfinavir dose was 28 mg/kg q8h [interquartile range (IQR) 26–31 mg/kg q8h], with a maximum absolute dose of 750 mg q8h. Patients used nelfinavir either in tablets or in the powder formulation. Fourteen patients were naive to treatment with protease inhibitors and nine were non-naive; prior treatment was unknown for one patient. All protease inhibitor non-naive patients had been
pretreated with the protease inhibitor indinavir. They had switched therapy to nelfinavir for several reasons (Table 1B). Two patients received the non-nucleoside analogues nevirapine (NVP) and efavirenz (EFV), respectively, in addition to their nelfinavir-containing regimen. Since earlier findings did not suggest NVP or EFV to markedly influence nelfinavir or M8 plasma levels, these PK data were not excluded from data analysis [7,8]. In all children, PK sampling was performed at steady state and nelfinavir and M8 plasma concentrations were determined. Overall PK parameters of nelfinavir and M8 are described in Table 2.

After stratification to dose groups of 20 (n=5), 30 (n=14) and 40 (n=5) mg/kg nelfinavir q8h, nelfinavir AUC0–8 showed a less than dose-proportional increase (median AUC0–8s of 8.7, 16.6 and 12.5 mg/l*h, respectively). Both Cmax and C8 of nelfinavir and M8 correlated strongly with the AUC0–8 of nelfinavir or M8, respectively (all P-values <0.001 and r>0.8). Linear regression (lnC8, lnAUC0–8) showed a nelfinavir C8 of 0.67 mg/l corresponding with an AUC0–8 of 12.5 mg/l*h. A C8 >0.69 mg/l predicted a nelfinavir AUC0–8 >12.5 mg/l*h with optimal sensitivity (71%) and specificity (80%) (Figure 2).

While median nelfinavir dose was similar in children below and above 2 years of age (medians 29 and 28 mg/kg q8h, respectively), the younger group showed a tendency to lower AUC0–8, Cmax and C8 of nelfinavir (Table 2). Also, CI/F*kg tended to be higher in children <2 years old than in older children (2.8 vs 1.9 l/h). None of these differences reached statistical significance (P-values all >0.1), except a significantly higher absolute CI/F of nelfinavir in older children. A non-significant trend to more lower AUC0–8s was also observed in younger children if 12.5 mg/l*h was used as a breakpoint for AUC0–8 (Table 3). In total, 10 out of 24 children (42%) had a nelfinavir AUC0–8 <12.5 mg/l*h, and these rates were 4/7 (57%) and 6/17 (35%), respectively, in children <2 and ≥2 years old.
A nelfinavir dose of 20 mg/kg q8h yielded the highest percentage of nelfinavir AUC0–8 <12.5 mg/l*h, although this difference was not significant (80% vs 29 and 40%, respectively, in dose groups of 30 and 40 mg/kg nelfinavir q8h P>0.1). OR (95% CI) for AUC0–8 <12.5 mg/l*h with a dose of 20 mg/kg q8h compared to higher doses was 8.7 (0.79–91) (not significant). While receiving a similar median nelfinavir dose in mg/kg, children with a nelfinavir AUC0–8 <12.5 mg/l*h received a statistically significant lower median nelfinavir dose in mg/body surface area (m²) than children with a nelfinavir AUC0–8 >12.5 mg/l*h (P=0.04) (Table 3). A nelfinavir dose >650 mg/m² predicted a nelfinavir AUC0–8 >12.5 mg/l*h with optimal sensitivity (79%) and specificity (67%). No apparent association was found between the occurrence of nelfinavir AUC0–8 <12.5 mg/l*h and gender.

Of the five children who received the maximum adult dose of 750 mg q8h, three (60%) had nelfinavir AUC0–8 below 12.5 mg/l*h vs. Seven out of 19 (37%) of children who had not reached the dose of 750 mg q8h [OR (95% CI) 2.57 (0.34–19.3)]. Patients’ M8/nelfinavir ratio ranged 0.1–0.8 (not shown in Table 2), except for two patients with plasma levels of M8 below the limit of quantification. No relation was found between M8/NFV ratio and dose of nelfinavir, age, gender, ethnicity or pretreatment (P-values all >0.1).

Twenty-two of 24 children completed 6 months of nelfinavir-containing therapy. The two remaining children had switched, at their parents’ request, to q12h regimens containing abacavir and lopinavir/ritonavir, respectively. Of the 22 children who completed 6 months of treatment with nelfinavir, sixteen (73%) showed virological response (viral load <500 copies/ml). Virological response rates at 6 months in nelfinavir dose categories of 20, 30 and 40 mg/kg q8h were 50, 71 and 100%, respectively (P>0.1). The virological response rate at 6 months was 80% in children with a nelfinavir AUC <12.5 mg/l*h, while a percentage of 71% was found in children with nelfinavir AUC0–8 >12.5 mg/l*h (P>0.1, Table 3). No serious adverse events were reported.

### Table 2. Pharmacokinetic parameters (median, IQR) overall and in age groups < and ≥2 years old

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>Age &lt;2 years</th>
<th>Age ≥2 years</th>
<th>Overall</th>
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<tr>
<td></td>
<td>n=7</td>
<td>n=17</td>
<td>n=24</td>
</tr>
<tr>
<td>Cmax (mg/l)</td>
<td>2.2 (1.3–4.8)</td>
<td>3.6 (2.7–4.5)</td>
<td>3.5 (2.2–4.5)</td>
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<tr>
<td>C0 (mg/l)</td>
<td>3.43 (0.36–0.73)</td>
<td>0.69 (0.50–1.44)</td>
<td>0.69 (0.43–1.4)</td>
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<tr>
<td>AUC0–8 (mg/l*h)</td>
<td>11.2 (8.9–20.0)</td>
<td>15.0 (7.9–20.1)</td>
<td>13.1 (8.8–20.2)</td>
</tr>
<tr>
<td>CI/F (l/h)</td>
<td>15.1 (8.4–27.4)</td>
<td>37.4 (24.4–71.5)</td>
<td>32 (19.6–52.3)</td>
</tr>
<tr>
<td>CI/F*kg (l/h)*kg</td>
<td>2.8 (1.4–3.4)</td>
<td>1.9 (1.5–3.1)</td>
<td>2.1 (1.5–3.2)</td>
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<tr>
<td>M8/nelfinavir AUC0–8 ratio</td>
<td>3.31 (0.21–0.43)</td>
<td>0.29 (0.20–0.43)</td>
<td>0.29 (0.20–0.44)</td>
</tr>
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</table>

*Statistically significant, n cases; Cmax, peak plasma level; C0, plasma level at 8 h time point; AUC0–8, area under plasma concentration-time curve 0–8 h; CI/F, apparent oral clearance; CI/F*kg, relative apparent oral clearance.

### Discussion

This study provides a description of the PK of nelfinavir in a relatively large number of children in whom intensive PK sampling was performed. In adults, nelfinavir plasma levels have been associated with virological efficacy [9–11]. In children, a target value of 10 mg/l*h has been used for nelfinavir AUC0–8; however, studies correlating nelfinavir levels with efficacy are limited [3,12]. In the present study, a nelfinavir AUC0–8 of 12.5 mg/l*h was used as a threshold in data analysis; at the time of the study this was the only reported PK cut-off value for virological response to nelfinavir in paediatric patients [6]. However, this value was derived from a naive population of HIV-infected children and has not yet been validated in pretreated patients.

**Risk factors for low nelfinavir levels**

Age <2 years and a dose of 20 mg/kg q8h both showed a trend to lower plasma concentrations of nelfinavir and higher rate of AUC0–8s below 12.5 mg/l*h. Also, children in whom the maximum (adult) dose of nelfinavir was reached tended to have higher rates of AUC0–8s below 12.5 mg/l*h. Although none of these differences was statistically significant, these findings are relevant for clinical practice.

Age <2 years has previously been associated with an increased risk of below average, possibly sub-therapeutic, nelfinavir plasma levels [6,12–14]. In infants <4 months old, even nelfinavir doses up to 40 mg/kg q8h have resulted in plasma levels far below adult values [14]. This may be explained by factors such as higher metabolic clearance in young children, impaired absorption and lower amount of α2-acid glycoprotein [15].

The very high rate of nelfinavir AUC0–8 <12.5 mg/l*h in the dose category of 20 mg/kg q8h nelfinavir, when compared to doses of 30 and 40 mg/kg q8h, suggests that the nelfinavir dose of 20 mg/kg q8h is insufficient and should not be used in children. The considerable rate of nelfinavir AUC0–8 <12.5 mg/l*h (60%) in children who had reached the adult nelfinavir dose indicates that, in some children, the adult
nelfinavir dose needs to be exceeded in order to normalize plasma levels of nelfinavir. At the time of enrolment in this study, the adult nelfinavir dose was recommended in children with body weight >23 kg. Currently, guidelines recommend the adult nelfinavir dose in children >13 years old, which corresponds with a higher body weight [16]. Nevertheless, in the present study, 2/3 children using 750 mg q8h nelfinavir and showing low nelfinavir AUC0–8 were <13 years old, suggesting that an actual age limit probably should be <13 years.

Interestingly, a significantly lower nelfinavir dose/body surface area was found in children with AUC0–8 <12.5 mg/l*h when compared to children with AUC0–8 >12.5 mg/l*h while both groups were receiving the same median dose per body weight. This suggests that, when nelfinavir dose is calculated per body weight, younger children with a relatively high body surface area are at increased risk for lower plasma levels. Body surface area has been described as a more accurate measure of metabolic activity and might, therefore, be more appropriate in children [15]. Our data indicate that a nelfinavir dose >650 mg/m2 q8h would be needed to obtain an AUC0–8 >12.5 mg/l*h. No association was found between gender and low nelfinavir plasma levels, which is in accordance with previous data [17]. Assuming that gender-related differences in PK of protease inhibitors are related to hormonal differences between males and females, they would be mainly expected after sexual maturation. These differences were difficult to distinguish in this relatively young paediatric population (median age 4.5 years) [15].

PK of nelfinavir and M8

A strong correlation was found for both nelfinavir and M8 between Cmax or C8 and AUC0–8. This correlation could largely simplify TDM by using one time point from a PK curve (such as C8) as a predictor of total exposure. Linear regression showed a C8 of 0.67 mg/l corresponding with a nelfinavir AUC0–8 of 12.5. Similarly, a C8 >0.69 mg/l predicted nelfinavir AUC0–8 >12.5 mg/l*h with optimal sensitivity and specificity. Both values are in accordance with efficacy thresholds for twice-daily nelfinavir in adults [9–11]. Earlier data found a strong correlation between the 2 h plasma concentration and AUC0–8 of nelfinavir [18]. However, these findings warrant further investigation.

While previous studies in paediatric and adult patients assumed a dose-proportional increase of nelfinavir AUC0–8, in the present study AUC0–8 showed a less than dose-proportional increase. The effect of a dosage increase can efficiently be monitored using TDM. However, these findings suggest that some patients with low plasma levels of nelfinavir might not benefit (i.e. experience sufficiently higher plasma levels) from a dosage increase.

In adults, the ratio between M8 and nelfinavir plasma levels is relatively constant at a nelfinavir dose of 1250 mg q12h; an M8/NFV ratio of 0.3 is in accordance with findings in adult patients [19,20]. In children, lower M8/nelfinavir ratios have also been reported, which we could not confirm [13].

Factors contributing to variability in nelfinavir PK

Nelfinavir absorption strongly improves when nelfinavir is taken with food [21]. In the present study, infants took their medication with formula, while older children received a standard meal. However, difficulties with ingestion of medication are common in children. For example, very young children who take medication with formula may be unable to take in the total medication dose at once; this may alter the time to peak level. While special attention was paid to complete medication ingestion in the presence of a substantial amount of food, interindividual variability of PK due to food effects and difficulties with medication ingestion could not totally be ruled out in this paediatric population. Nelfinavir is principally metabolized by cytochrome
enzymes (CYP) 3A4 and 2C19. Although CYP-inducing co-medication is known to decrease nelfinavir plasma levels, no other CYP-modifying co-medication was used in this study except by the two patients who used NVP or EFV [21]. While NVP and EFV are known to affect CYP3A4, the effect on nelfinavir metabolism appears absent for NVP and very slight for EFV. EFV, but not NVP, has been shown to slightly decrease M8 concentrations [7,8]. Interestingly, the child who used EFV showed a high AUC0–8 of nelfinavir (38 mg/l*h) and a M8/NFV AUC ratio of 0.14 while the child who used NVP showed a low AUC0–8 of nelfinavir (9 mg/l*h) and a M8/NFV ratio of 0.3. The relevance of these individual cases remains uncertain. Genetic polymorphism of CYP2C19 might have caused additional variability of nelfinavir and M8 PK. CYP2C19 polymorphism is especially found in Asians and Caucasians, with 18–22 and 2–6% of slow metabolizers, respectively [17]. However, the effect of CYP2C19 polymorphism was not likely in the study population, since most children were of African or mixed African origin and Asians and Caucasians were poorly represented (Table 1). It should also be remarked that CYP2C19 is not a unique pathway of nelfinavir metabolism and the impact of CYP2C19 polymorphism on nelfinavir plasma levels may be moderate. Furthermore, polymorphism in P-glycoprotein expression, of which nelfinavir is a substrate and possibly an inducer, may have influenced the PK of nelfinavir [22–24]. These factors were not examined but might also explain part of the observed variability of nelfinavir PK.

Virological outcome
An overall virological response of 73% was measured after 6 months of nelfinavir-containing HAART. Both similar and considerably lower success rates have been reported in children using protease inhibitor-containing treatment [2,3,23–30]. The difference between virological responses in the dose group of 20 as compared to 30 and 40 mg/kg nelfinavir q8h would be in accordance with the high rates of AUC0–8 <12.5 mg/l*h in the lowest dose category. Meanwhile, no significant relationship was found between plasma levels of nelfinavir and virological efficacy in this study. Response rates were not significantly different between children with an AUC <12.5 mg/l*h and those with an AUC >12.5 mg/l*h. However, it should be noted that children naive and non-naive for protease inhibitors were not equally distributed between these groups. Most children with a nelfinavir AUC <12.5 mg/l*h and those with an AUC >12.5 mg/l*h. Taking into account that naive patients tend to respond better to antiretroviral therapy than pretreated patients, this may have biased our findings. Finally, as stated before, the cut-off value of 12.5 mg/l*h for AUC0–8 of nelfinavir has been proposed for naive children; a different cut-off value may be needed for non-naive children depending on, for example, the presence of viral resistance and differences in clinical condition in these patients.

**Conclusion**
Nelfinavir PK in children showed high interindividual variability in this population heterogeneous with regard to pre-treatment, age and dose. Children <2 years old tend to be at higher risk for low plasma levels of nelfinavir. A nelfinavir dose of 20 mg/kg q8h yielded a low plasma levels in most of the children. Although these findings were not statistically significant, they suggest that children using nelfinavir should be closely monitored by TDM. Also, the dose of 20 mg/kg q8h nelfinavir is insufficient and should not be used. The strong correlation between C8 and nelfinavir AUC0–8 could simplify PK sampling. The maximum dose of 750 mg q8h is frequently sub-optimal and needs to be

<table>
<thead>
<tr>
<th>Age (years) median (IQR)</th>
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<tr>
<td>Female (n)</td>
<td>4/10</td>
<td>5/14</td>
</tr>
<tr>
<td>Dose (mg/kg) median (IQR)</td>
<td>28 (17–39)</td>
<td>30 (28–37)</td>
</tr>
<tr>
<td>Dose (mg/m²) median (IQR)</td>
<td>551 (391–835)</td>
<td>727 (628–809)</td>
</tr>
<tr>
<td>Body weight (kg) median (IQR)</td>
<td>12 (6–40)</td>
<td>14 (9–23)</td>
</tr>
<tr>
<td>BSA (m²) median (IQR)</td>
<td>0.56 (0.38–1.25)</td>
<td>0.63 (0.42–0.89)</td>
</tr>
<tr>
<td>HIV RNA median baseline (IQR)</td>
<td>77,350 (13920–750000)</td>
<td>106,150 (6955–578250)</td>
</tr>
<tr>
<td>Protease inhibitor-naive (n)</td>
<td>8/10</td>
<td>6/14*</td>
</tr>
<tr>
<td>Virological response week 48</td>
<td>8/10 (80)</td>
<td>10/14 (71)</td>
</tr>
</tbody>
</table>

Table 3. Patient characteristics of children with nelfinavir AUC0–8 < vs >12.5 mg/l*h

*Of one patient, no data available; † statistically significant; n, cases; IQR, interquartile range; BSA, body surface area.
exceeded in children. Nelfinavir dose based on body surface area, rather than body weight, should be considered in children. While low plasma levels of nelfinavir have been related with virological outcome in adults, we were not able to find such an association in this highly heterogeneous paediatric study population. Meanwhile, nelfinavir TDM in children is expected to be of similar importance as in adults, since it can detect abnormal plasma levels and allows handling in order to prevent toxicity or virological failure. However, further research is strongly needed to more firmly establish a therapeutic range for nelfinavir in children.

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