

# MAINTAINING THE NELFINAVIR TROUGH CONCENTRATION ABOVE 0.8 mg/L IMPROVES VIROLOGIC RESPONSE IN HIV-1-INFECTED CHILDREN

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Differences in virologic response were compared in 32 HIV-infected children with a nelfinavir trough concentration either below ( $n = 7$ ) or above ( $n = 25$ ) 0.8 mg/L. Virologic response at week 48 was observed in 29% of children with subtherapeutic nelfinavir troughs versus 80% in children with therapeutic nelfinavir troughs ( $P = .02$ ). (*J Pediatr* 2004;145:403-5)

Several studies have demonstrated that suboptimal pharmacokinetics of the HIV-1 protease inhibitor nelfinavir are related to the risk of virologic failure in HIV-1 infected adults.<sup>1-5</sup> For HIV-1-infected children, there is little information concerning the importance of maintaining plasma concentrations of nelfinavir above a certain threshold to optimize treatment. Therefore, there is a need for more data on the potential relation between plasma concentrations of nelfinavir and the virologic response in HIV-1-infected children.

## METHODS

This pharmacokinetic study was conducted as a substudy of the Pediatric European Network for Treatment of AIDS (PENTA) 5 trial. Details on PENTA 5 are provided elsewhere.<sup>6</sup>

A nelfinavir trough concentration was measured between week 20 and week 80 in the morning just before the next intake of medication. A nelfinavir trough concentration below 0.8 mg/L was considered subtherapeutic, based on a recent consensus document for target trough concentrations to be used in therapeutic drug monitoring services.<sup>7</sup>

Virologic response was defined as an undetectable viral load at week 24 or week 48 (Roche UltraSensitive assay version 1.5; lower limit of detection of 50 copies/mL).

Differences in virologic response between children with either subtherapeutic or therapeutic plasma concentrations of nelfinavir were compared by using the Fisher exact test for nominal and Mann-Whitney test for numerical data sets. A  $P$  value of  $< .05$  was considered statistically significant.

## RESULTS

A total of 44 children participated in this substudy. For various reasons, data from 12 children were not evaluable: insufficient sample volume ( $n = 1$ ), once-daily use of nelfinavir ( $n = 1$ ), inadvertent intake of nelfinavir before sampling ( $n = 6$ ), undetectable nelfinavir troughs, suggesting nonadherence ( $n = 4$ ) (Table).

A total of 7 children (22%) had a concentration below 0.8 mg/L, ranging from 0.10 to 0.57 mg/L. The remaining 25 children all had a nelfinavir trough concentration above 0.8 mg/L, with 5.3 mg/L as the highest observed value.

At weeks 24 and 48, 21 (66%) and 22 (69%) of the 32 evaluated children, respectively, had a viral load below 50 copies/mL. However, this proportion differed at

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**Table. Patient characteristics at baseline and at time of sampling**

	All patients (n = 32)	Patients with nelfinavir trough >0.8 mg/L (n = 25)	Patients with nelfinavir trough <0.8 mg/L (n = 7)	P value
At baseline				
Sex (n)				.86
Males	22	17	5	
Females	10	8	2	
HIV-1 RNA (Log <sub>10</sub> copies/mL), Median (range)	5.1 (4.1-6.6)	5.1 (4.3-6.4)	5.4 (4.1-6.6)	.45
At time of sampling				
Age (y), median (range)	6.7 (0.8-17.3)	8.3 (3.2-17.3)	3.8 (0.8-4.6)	.001*
Weight (kg), median (range)	23.2 (9.7-86)	25.8 (15.5-86)	13.8 (9.7-16.6)	< .001*
Daily nelfinavir dose (mg/kg)	94 (26-119)	96 (26-119)	91 (72-109)	.96
Nelfinavir dose frequency (n)				.96
TID	14	11	3	
BID	18	14	4	
Time between intake and sampling (h), median (range)	12.4 (8.5-17.0)	12.1 (8.5-17.0)	14.0 (9.0-16.5)	.20

Values are median range or numbers (n).

\*Significant.

both week 24 and 48 between children who had a plasma nelfinavir trough concentration below or above 0.8 mg/L ( $P = .02$  at week 48; [Figure](#)).

## DISCUSSION

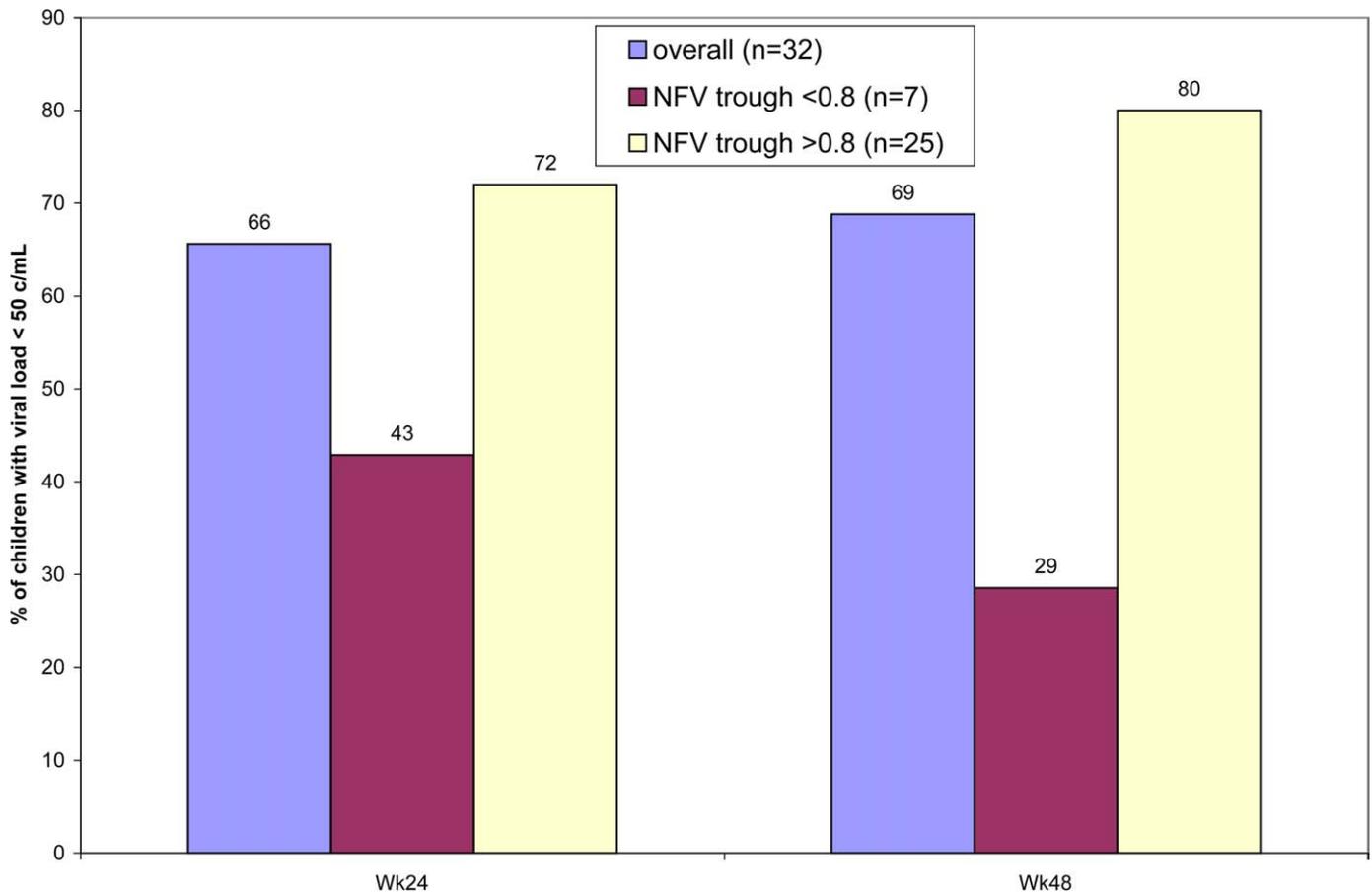
This pharmacokinetic substudy of PENTA 5 in treatment-naïve HIV-infected children confirms previous observations of a positive association between nelfinavir plasma levels and virologic response in HIV-infected adults.<sup>1-4</sup> Children who had a nelfinavir trough concentration >0.8 mg/L had a better virologic response than children with a value below this threshold ([Figure](#)). These data are consistent with the concept that the advised target concentration of 0.8 mg/L for a nelfinavir trough concentration as derived from treatment-naïve adult patients, and published in a recent consensus document,<sup>7</sup> is also valid for treatment-naïve children. It should be noted that we cannot extrapolate these findings to children who have been exposed to treatment before starting with nelfinavir.

As far as we know, there have been two other reports dealing with potential relations between nelfinavir pharmacokinetics and virologic response in HIV-infected children. Hsyu et al<sup>8</sup> found a significant relation between nelfinavir area under the curve and virologic response in protease inhibitor-naïve children participating in clinical trials with nelfinavir TID. In clinical practice, however, it may be impractical to obtain a full area under the curve in every child, and sparse sampling (for instance, a trough sample) is much more convenient. Furthermore, most children use nelfinavir BID these days, and it is unknown whether these data can be extrapolated from TID to BID regimens.

In contrast to our observations and those from Hsyu et al, in a recent study by Gatti et al<sup>9</sup> there was a detectable relation between nelfinavir trough plasma concentrations and virologic response in 25 children. There may be several explanations for this discrepancy. First, the large majority of the children in that study had been pretreated with nucleoside reverse transcriptase inhibitors. Second, in that study, virologic response was evaluated at week 24, whereas in this substudy of PENTA 5, both week 24 and week 48 responses were evaluated (and the difference became statistically significant only at week 48). Finally, Gatti et al used a different threshold for the nelfinavir trough concentration (1.0 mg/L), a different outcome measure for virologic response (decline in viral load between baseline and week 24), and did not exclude patients with undetectable nelfinavir plasma concentrations; this all may have influenced their results.

One aspect that all pediatric studies with nelfinavir have in common is the huge interpatient variability in the plasma concentrations of this drug. In this study, the coefficient of variation in the morning nelfinavir trough concentration was 65.8% and 90.0% for the BID and TID dosing regimens, respectively. Previous research indicated that especially younger children were at risk for having subtherapeutic nelfinavir plasma concentrations.<sup>10</sup> This is confirmed by our data, as there was a significant difference in age (and body weight) between children with subtherapeutic versus therapeutic plasma concentrations ([Table](#)).

Although a strong relation between nelfinavir trough concentrations and virologic response was observed in this study, it is clear that other factors may also play a role. First, and most important, is adherence to a regimen. The study design had its limitations because we had only one nelfinavir



**Figure.** Proportion of children with undetectable viral load at week 24 and week 48. The difference between the subgroups with a nelfinavir trough concentration above or below 0.8 mg/L is statistically significant at week 48 ( $P = .02$ ). This figure can be viewed in color online at [www.us.elsevierhealth.com/jpedis](http://www.us.elsevierhealth.com/jpedis).

plasma level determined at a variable time point after start of the study. As a result, we do not have information on inpatient variability. A randomized, controlled clinical trial of therapeutic drug monitoring of antiretroviral agents, including nelfinavir, is currently in preparation (PENTA 14).

In conclusion, we have demonstrated that as in adults, suboptimal pharmacokinetics of nelfinavir are related to virologic failure in HIV-infected children. Maintaining the nelfinavir trough concentration >0.8 mg/L significantly improves virologic response in treatment-naïve children 48 weeks after treatment initiation. Research is needed particularly for children younger than 5 years because all subtherapeutic plasma levels of nelfinavir occurred in children of this age.

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