IMPACT OF NELFINAVIR (NFV) AND ITS ACTIVE METABOLITE M8 TROUGH LEVELS (TL) ON VIROLOGIC RESPONSE FROM PRIMARY HIV-1 VERTICALLY INFECTED CHILDREN TREATED WITH STAVUDINE (D4T), DIDANOSINE (DDI) AND NFV IN THE PENTA 7 STUDY.

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ABSTRACT

Background : The impact of antiretroviral combination therapy with d4T, ddI and NFV was evaluated in 20 primary HIV-1 vertically infected children aged less than 3 months. Viral load decrease was 2.06 log at week 4 and was sustained up to week 12 but did not continue further. The incomplete viral suppression (HIV-1 RNA < 400 copies) in 70% of the infants even with high doses of NFV (150 mg/kg/day as powder or crushed tablets) and the presence of genotypic resistance mutations represent a great concern. Pharmacological issues may explain virologic response .
Objectives and methods : To investigate the relationship between virologic response at week 48 and early pharmacologic parameters, NFV concentrations and M8 from plasma samples taken through follow-up were analysed. M8/NFV "Metabolic ratio" (MR) was calculated. Samples taken between 0 and 1.5 hours and beyond 10.5 hours after dosing were considered as TL.
Results : Fourteen infants had 39 (range 1-5) TL up to week 12. At week 4, Mean (SD) NFV, M8 were 392 (416), 694 (745) in responders and 636 (455), 388 (432) in non responders. No significant differences in NFV and M8 were found between the two groups. Mean (SD) MR was 1.72 (0.09) and 0.62 (0.32) in responders and non responders respectively (p=0.005). Similar trend was observed when all TL between week 4 and week 12 were analysed.
Conclusions : In infants treated during HIV-1 primary infection, NFV TL and M8 were highly variable. MR values were different between responders and non responders at week 48. These findings even with a small number of infants reinforce the need to undertake further pharmacokinetic studies in very young children. The role of this metabolic ratio in virologic response needs to be elucidated.

BACKGROUND

In PENTA 7 we assessed the toxicity, tolerability, pharmacokinetics and activity of triple antiretroviral combination therapy with d4T, ddI and NFV in HIV-1 vertically infected children aged less than 3 months. A rapid decrease in plasma HIV-1 RNA occurred after 4 weeks of therapy (the median drop was 2.06 log) but although this decline was sustained beyond week 12, the decline did not continue further. The presence of incomplete viral suppression in 70% of the infants, associated with genotypic resistance mutations in 30% of them represents a great concern. Even with high doses of NFV (150 mg/kg/day) attaining undetectable viral load was difficult.

OBJECTIVES

To investigate the relationship between virologic response at week 48 and early pharmacologic parameters.

METHODS

❖ Infants initially received: stavudine (d4T) suspension (2 mg/kg/day in 2 divided doses), didanosine (ddI) suspension (200 mg/m2/day in 2 divided doses) and nelfinavir (NFV) powder/crushed tablets (120 mg/kg/day in 3 divided doses taken every 8 hours). The dose of nelfinavir was increased to 150 mg/kg/day after pre-planned PK studies performed on the first 4 infants showed low AUC. In addition, subsequent infants received nelfinavir twice daily after data within the study showed similar AUC and troughs with BID and TID dosing. Specific instructions on food requirements or not for different drugs were given to parents/carers.

❖ Weight, height, body area, doses of NFV, d4T and ddI, time of last drug intake and time of blood sampling were accurately recorded by doctors/nurses.

❖ Two ml venous blood samples were obtained and transferred to heparinized tubes. After centrifugation plasma samples were frozen at –20°C until analysis.

❖ Samples taken between 0 and 1.5 hours and beyond 10.5 hours after dosing were considered as trough levels (TL).

❖ NFV and M8 concentrations were measured by HPLC-MC.

❖ All plasma samples taken between W4 and W12 were analysed.

❖ TL at W4 were used as the early pharmacologic parameters. When not available, TL at W6 or W8 were used.

❖ Mean values for TL of NFV and M8 of each individual patient between W4 and W12 were analysed.

❖ NFV and M8 values below the limit of quantification (21.4 µg/l and 25 µg/l respectively) were considered as 0 µg/l.

❖ Metabolic ratio (MR) was calculated by dividing M8 by NFV concentration in the same sample. MR was analysed only when NFV was detectable.

❖ ***Statistics:*** comparisons in NFV, M8 and MR between responders (Viral load <400 copies/ml at W48) and non responders were analysed using the non parametric Mann-Whitney test (p values were 2-tailed).

RESULTS

❖ Demographic and baseline characteristics of the 14 infants are shown in table 1.

Male		7 *(50%)*
Age (months) : Median (range) in months		2.6 (0.9 to 4.0)
Ethnic origin :	Black	6 *(43%)*
	White	7 *(50%)*
	Other	1 *(7%)*
CDC disease stage:	N	8 *(57%)*
	A	4 *(29%)*
	B	2 *(14%)*
Weight (kg) : Median (range)		4.8 (1.7 to 6.0)
Height (cm) : Median (range)		56.6 (40.5 to 61)
CD4 % : Median (range)		38 (11 to 66)
Plasma HIV-1 RNA log_{10} copies/mL : Median (range)		5.5 (3.2 to 6.8)

Table 1: Demographic and baseline characteristics

❖ At W48, 11/14 were in virologic failure.

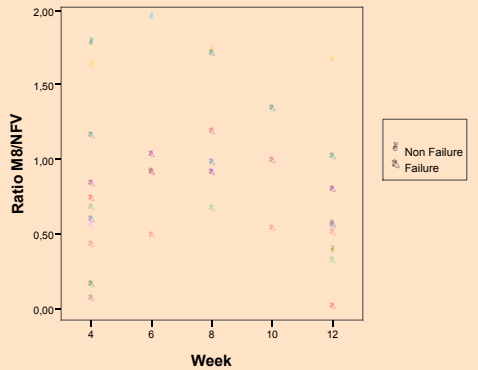
❖ Thirty-nine (range 1-5) TL up to W12 in 14 infants were analysed.

❖ All infants but one were on BID regimen. Median dose (range) of NFV was 147mg/kg/day (113-203). The infant in TID regimen received 121 mg/kg/day.

❖ Three out of 39 TL of NFV and 4 TL of M8 were below the level of detection (in 2 both NFV and M8 were indetectable).

❖ Median (range) dose of NFV at W4 was 150 mg/kg/day (121-150) in responders and 138 mg/kg/day (113-203) in non responders.This difference was not significant.

❖ Values of M8/NFV metabolic ratio (MR) between W4 and W12 of responders and non responders at W48 are shown in figure below.



❖ There were no differences in NFV and M8 between responders and non responders even if NFV was higher and M8 lower in non responders compared to responders. However both at W4 and between W4 and W12, the M8/NFV metabolic ratio was significantly higher in virological responders (Table 2).

VL (copies ARN/ml) at W48		< 400	> 400	p
W4	NFV	392 (416)	636 (455)	0.37
	M8	694 (745)	388 (432)	0.46
	MR	1.72 (0.09)	0.62 (0.32)	***0.005***
W4 - W12	NFV	400 (194)	566 (377)	0.66
	M8	608 (445)	359 (313)	0.29
	MR	1.54 (0.41)	0.66 (032)	***0.011***

Table 2: Mean (SD) of NFV, M8 and MR in responders and non responders

DISCUSSION

Virologic suppression with a d4T+ddI+NFV triple combination was difficult to obtain in infants treated during primary HIV-1 infection with, in addition, the emergence of genotypic resistance mutations in the majority of the infants.
Despite the increase in the dose of nelfinavir to 150 mg/kg/day BID, based on the subsequent PK studies performed on the PENTA 7 infants, more than two third of all the nelfinavir plasma concentrations measured through follow-up were below the target value of 700 µg/L (data not shown).
This could reflect problems related to drug intake due to poor adherence, or to poor absorption as a result of weaning or food restrictions. Low blood levels of the active metabolite of nelfinavir, M8, could also explain the high rate of virologic failure. Infants who failed seem to have lower levels of M8 than those who did not, although this difference was not significant. However, MR (M8/NFV) was significantly different in responders and non responders.
As NFV is extensively metabolised by cytochrome P450, with CYP3A4 and CYP2C19 being the predominant forms, our results may reflect the impact of both pharmacogenetic and development on drug metabolism in this age group. Since M8 has in vitro activity against HIV comparable to that of NFV, these results reinforce the need to consider M8 exposure in future studies analysing response in treated infants.
However, these results should be interpreted cautiously because the sample size is relatively small.

CONCLUSION

In infants treated during HIV-1 primary infection, NFV TL and M8 were highly variable. MR values were different between responders and non responders at week 48. These findings even with a small number of infants reinforce the need to undertake further pharmacokinetic studies in very young children. The role of this metabolic ratio in virologic response needs to be elucidated.

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