# LOWER SCORES OF NELFINAVIR METABOLITE M8 WERE ASSOCIATED WITH VIROLOGICAL FAILURE VERTICALLY INFECTED CHILDREN IN THE PENTA 7 STUDY.

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## ABSTRACT :

**Background**: Early treatment with d4T+ddI+NFV administered to 20 HIV-1 infected infants (<=3 months) was associated with incomplete viral suppression (<400 cp/mL) in 70% of infants even with high doses of NFV (150 mg/kg/day).
**Objectives**: To investigate the relationship between virologic response and NFV and its metabolite M8.
**Methods**: Percentiles values of NFV and M8 for times H0, H1, H2, H4, H6, H8 and H12 were calculated from 3 PK studies performed in PENTA 7 at 3, 6 and 18 months of age. In addition, trough levels (TL) of NFV and M8 from plasma samples taken through 72 weeks of follow-up were analysed. Each TL was reported as 'acceptable' if it was above its respective 25th percentile value considered as the minimal target value. Thus for each infant, a score was calculated as the proportion of the number of 'acceptable' TL to the total number of TL. Scores were compared between responders and non-responders after 24 weeks and 48 weeks.
**Results**: 139 TL of NFV and M8 were analysed. NFV was lower in children under 6 months vs > 6 months whereas this trend was not observed for M8. Percentiles values were calculated for each time point from 27 PK studies in 14 infants. Scores of NFV in 9 responders and 11 non responders at week 24 were 0.71 and 0.54 respectively (P=0.23), with the same trend at week 48. However for M8, scores at week 24 were significantly different (0.80 vs 0.52; P=0.025). This trend in M8 was still observed in 6 responders and 14 non-responders at week 48 although with a non significant difference (0.78 vs 0.59; P=0.15).
**Conclusions**: In infants treated during HIV-1 primary infection, metabolite M8 appears to be associated with virologic failure at 24 weeks. Specificity of metabolism in infants may explain this finding.

## PENTA 7: SUMMARY

- 20 infants were enrolled between September 1999 and December 2000
- 1 died at week 60 (complications of prematurity,VL <50 cp at death)
- PK showed that high doses of NFV were needed (150 mg/kg bid)
- There was globally a good tolerability
- 14 (70 %) infants had Virologic Failure (VF) (2 consecutive HIV RNA-1 > 400cp/ml after week 24) by week 72
- 6 infants had acquisition of resistance mutations reported

## OBJECTIVE :

To investigate the relationship between virological response and plasma concentrations of NFV and its metabolite M8

## METHODS :

- Plasma concentrations of NFV, M8 were measured on week assessments (weeks 4, 6, 8, 12, 16, 20, 24, 32, 36, 48, 60, 72) at different times
- Percentile values of NFV and M8 were drawn from 3 PK studies (3, 6, 18 months of age) for times H0, H1, H2, H4, H6, H8, H12
- A plasma concentration was considered as acceptable if it was above its respective 25th percentile value (considered as a minimal target value)
- Score (by child) was defined as the proportion of acceptable plasma concentrations to the total number of plasma concentrations (comprised between 0 and 1)
- Scores were compared between responders and non-responders at weeks 24 and 48 using Non-parametric test (Mann-Whitney)

## RESULTS :

- 139 plasma concentrations of NFV and M8 were observed in 20 children. 114 measures with both NFV and M8 > Below Limit of Quantification (BLQ(*)); 18 with both NFV and M8 < BLQ; 4 with only NFV < BLQ and 3 with only M8 < BLQ. (Figures 1 and 2)
- Median (range) number of concentrations : 7 (1-11); one child with only one plasma concentration; 19 with at least 3 measures
- Percentiles values drawn for each time point from 27 PK studies in 14 children

(*) Limits of quantification were 21.4 µg/l for NFV and 25 µg/l for M8 respectively.

| | NFV | M8 |
|---|---|---|
| Non-VF (9) | 0.71 | 0.80 |
| VF (11) | 0.54 | 0.52 |
| *p* | *0.23* | *0.025* |

**Scores and VF at week 24**

| | NFV | M8 |
|---|---|---|
| Non-VF (6) | 0.68 | 0.78 |
| VF (14) | 0.59 | 0.59 |
| *p* | *0.6* | *0.15* |

**Scores and VF at week 48**

## DISCUSSION :

Early treatment with d4T+ddI+NFV in HIV-1 vertically infected children was well tolerated but associated with virological failure and emergence of resistance [1]. Problems related to adherence and drug metabolism in infants may explain such poor response. Pharmacokinetic studies in PENTA 7 showed that high doses of NFV were needed to achieve satisfactory AUC and confirmed the high variability intra and inter individual [2].

In this analysis, we observed that virological responders at week 24 had higher levels in metabolite M8 compared to non responders. This finding was not observed with NFV. It supports the idea of specificities in metabolism in infants and suggests that, in addition to NFV, metabolite M8 should be considered as an important pharmacological parameter to follow very young children.

## CONCLUSION :

- **Pharmacokinetic studies are indispensable tools during follow-up of HIV-1 infected patients, especially in very young children.**
- **In our study, scores of metabolite M8 were associated with virological failure at week 24.**
- **M8 seems to be a better pharmacological parameter than NFV in infants**

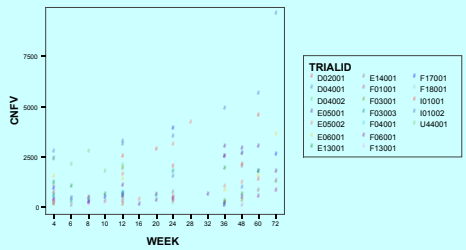


**Fig 1: NFV concentrations by week**

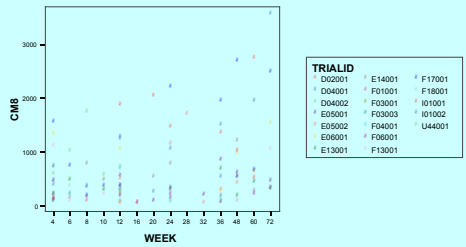


**Fig 2: M8 concentrations by week**

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