

# Nelfinavir (NFV) Pharmacokinetics with an Increased Dose during the First Two Weeks of Life

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## Original Abstract

**Background:** The optimal postnatal antiretroviral (ARV) regimen to prevent mother to child HIV transmission (MTCT) in infants born to mothers with no ARV therapy during pregnancy is unknown. NICHD/HPTN 040/PACTG 1043 compares the efficacy of 3 infant ARV regimens to prevent MTCT in infants born to HIV+ mothers receiving no antepartum ARVs: zidovudine (ZDV) alone for 6 wks; ZDV for 6 wks plus 2 weeks of nelfinavir (NFV) and lamivudine; ZDV for 6 wks plus 3 doses of nevirapine during the 1st wk post birth. As a previous study of NFV pk in infants during the first weeks of life demonstrated inadequate exposure in around 1/3 of infants receiving 40 mg/kg bid, an increased NFV dose is being used in HPTN 040. This report describes NFV pharmacokinetics (PK) in infants with this increased dose.

**Methods:** A weight band-based NFV dosing regimen was used. BID dosing with 200 mg of birth weight (BW) > 3000 gm, 150 mg if BW 2001-2999 gm and 100 mg if BW 1500-2000 gm. Serial plasma samples for NFV concentration (conc) were obtained over 12 hrs at age 4-7 or 10-14 days. NFV conc was measured by HPLC, lower limit of detection was 0.04 ug/mL.

**Results:** 22 Brazilian infants (mean (SD) BW = 2994 (494) gm, mean gestational age = 38.7 (1.7) weeks) were studied. Median (range) per kg NFV dose was 58.3 (48.4-78.9) mg/kg. No PK parameter differed between infants studied on days 4-7 vs days 10-14. Median NFV AUC<sub>0-12</sub> was 25.9 (1.7-125.8) ug\*hr/mL, and median C<sub>12h</sub> was 1.4 (below quantitation-14.4) ug/mL. AUC<sub>0-12</sub> was < 15 ug\*hr/mL (the 10<sup>th</sup>ile for adults) in 9 infants (41%). C<sub>12h</sub> was < 0.8 ug/mL (the standard therapeutic drug monitoring [TDM] trough conc target for treatment) in 9 infants (41%) and was < 0.05 ug/mL (10 times the upper limit for wild type NFV IC<sub>50</sub>) in 2 infants (9%).

**Conclusion:** Infants receiving this weight band dosing regimen had a median dose of 58 mg/kg, and while overall median AUC<sub>0-12</sub> and C<sub>12h</sub> were equivalent to those observed in adults, interindividual variability in NFV exposure was large and NFV exposure was low in 41%. Given the wide range of variability in NFV exposure, a further increase in NFV dose would likely result in some infants with higher and potentially toxic conc while others would remain with low conc; thus, the dose was not increased in this study using NFV as part of a combination regimen for MTCT prophylaxis. For use of NFV for treatment of neonates found to be HIV-infected, TDM should be considered to ensure adequate exposure.

## Background

• When mothers receive no antiretroviral (ARV) therapy during pregnancy, the optimal composition and duration of postnatal ARV therapy to prevent mother to child HIV transmission is unknown.

• NICHD/HPTN 040/PACTG 1043 is an ongoing trial in Brazil, Argentina, South Africa and the US comparing the efficacy of 3 infant regimens in preventing mother to child HIV transmission in infants whose mothers receive no ARV therapy during pregnancy but may receive IV ZDV during labor:

- 6 weeks of ZDV alone
- 2 weeks of nelfinavir(NFV)/3TC plus 6 weeks of ZDV
- 3 doses NVP in 1st week plus 6 weeks of ZDV

• Previous studies of NFV pharmacokinetics during the first month of life have shown low NFV exposure in a significant number of infants:

- In adults, the standard NFV therapeutic drug monitoring [TDM] trough conc target is a C<sub>min</sub> > 0.8 ug/mL and the 10<sup>th</sup> percentile 12 hour AUC is 15 ug\*hr/mL.
- In Thai infants on day 14 of life receiving 45 mg/kg BID, 50% had a C<sub>min</sub> less than 0.8 ug/mL and 18% had an AUC below 15 ug\*hr/mL.
- In US infants on day 5-8 of life receiving 40 mg/kg BID, 30% had a C<sub>min</sub> less than 0.8 ug/mL and 27% had an AUC below 15 ug\*hr/mL.

## Objectives

• To describe infant NFV exposure during the first 2 weeks of life with administration of a BID weight band dosing regimen designed to provide 50-75 mg/kg doses.

## Methods

• Infants assigned to the NFV arm of NICHD/HPTN 040/PACTG 1043 received NFV BID according to the following weight based dosing regimen:

- If birth weight ≥ 3000 gm, each dose was 200 mg
- If birth weight 2001-2999 gm, each dose was 150 mg
- If birth weight 1500-2000 gm, each dose was 100 mg

• NFV was administered as powder (1 scoop = 1.25 ml = 50 mg) mixed with water or formula.

• Plasma samples were obtained from 25 infants in Brazil between either days 4-7 or days 10-14 of life

- Samples were collected prior to a dose and at 1, 2, 4, 8 and 12 hours after dosing

• Plasma NFV concentrations were determined by a validated HPLC assay with a lower limit of quantitation of 0.04 ug/mL.

• Pharmacokinetic calculations were performed using WinNonlin (Pharsight Corporation, Mountain View, CA) and Excel (Microsoft Corporation, Redmond, WA)

• NFV exposure targets were a 12 hour AUC above 15 ug\*hr/mL (the 10<sup>th</sup> percentile for adults) and 12 hour concentration above 0.8 ug/mL (the standard therapeutic drug monitoring [TDM] trough concentration target)

## Results

### Patient Population

• 25 Brazilian infants studied

- 9 females, 16 males
- Median (range) birth weight = 3120 (1775-3900) gm
- Median (range) gestational age = 39 (34-42) weeks
- Born to mothers with:
  - Median (range) age = 25 (15-42) years
  - Median (range) HIV viral load = 8622 (224-538773) copies/ml
  - Median (range) CD4 cell count = 704 (143-1711) cells/mm3

• 14 infants studied at age 4-7 days, 11 studied at age 10-14 days

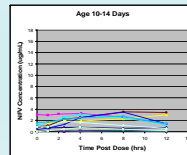
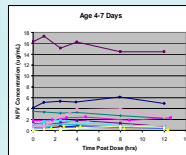
• NFV dosing:

- 13 received 200 mg BID, 11 received 150 mg BID, 1 received 100 mg BID
- Median (range) per kg NFV dose = 58.3 (48.4-78.9) mg/kg BID

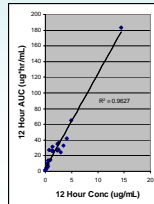
## NFV Exposure Parameters

	Days 4-7 (n=14)	Days 10-14 (n=11)	Combined (n=25)
Median (range) 12 hr AUC (ug*hr/mL)	20.6 (3.43 - 183.54)	26.22 (1.66 - 41.72)	26.22 (1.66 - 183.54)
# (%) with 12 hr AUC < 15 g*hr/mL	7 (50%)	4 (36%)	11 (44%)
Median (range) C <sub>12h</sub> (ug/mL)	0.81 (0.18 - 14.44)	1.37 (<0.04 - 4.06)	1.29 (<0.04 - 14.44)
# (%) with C <sub>12</sub> < 0.8 ug/mL	7 (50%)	4 (36%)	11 (44%)
# (%) with C <sub>12</sub> < .04 ug/mL	0	2 (18%)	2 (8%)

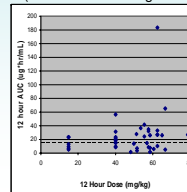
## NFV Concentration-Time Plots



## NFV AUC vs Trough Concentration



## NFV AUC vs Dose in PACTG 353<sup>2</sup> and HPTN 040 (Dashed line = 15 ug\*hr/mL)



## Conclusion

• Infants dosed according to this weight band dosing regimen received a median dose of 58.3 mg/kg BID, increased from the 40-45 mg/kg BID doses used in previous studies.

• While median AUC and C<sub>min</sub> in these infants were above the exposure targets, interindividual variability in NFV exposure was large and NFV exposure failed to meet the targets in 44% of the infants.

• The 12 hour post dose NFV concentration did exceed 0.04 ug/ml (10 times the upper limit for wild type NFV IC<sub>50</sub>) in all but 2 infants.

• Given the large amount of interpatient variability in NFV exposure, a further increase in NFV dose size would likely result in high and potentially toxic NFV concentrations in some infants with suboptimal NFV concentrations in others; therefore the dose was not increased in this study of prophylactic regimens to prevent mother to child transmission of HIV.

• If this NFV dosing regimen is to be used in treatment of HIV infected neonates during the first weeks of life, therapeutic drug monitoring should be used to ensure appropriate NFV exposure.

## References

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