PHARMACOKINETICS OF NEVIRAPINE PROPHYLAXIS IN HIV-EXPOSED LOW BIRTH WEIGHT INFANTS

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Poster #758

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Introduction

- HIV-infected women are at high risk of delivering low birth weight (LBW) and premature (< 37 weeks gestation) infants[1]
- HIV-exposed LBW infants, < 2500 grams, require access to antiretroviral (ARV) post exposure prophylaxis
- Adequate pharmacokinetic (PK) data are available only for zidovudine in LBW infants[2]
- There are few PK and safety data for nevirapine (NVP) in LBW infants[3], who undergo developmental changes that influence PK[4]

Objective

- To describe the PK and safety of NVP in HIV-exposed LBW infants receiving NVP prophylaxis as part of routine care from birth to 24 weeks of life

Methods

- IMPAACT P1106 is a Phase IV study of the PK and safety in LBW infants receiving ARVs and tuberculosis medicines in their clinical care.
- Sites: Family Clinical Research Unit (FAM-CRU) in Cape Town and the Perinatal HIV Research Unit (PHRU) in Johannesburg, South Africa
- This study consists of six arms, of which arm 1 focused on NVP for prophylaxis of peripartum and breast milk HIV mother-to- child-transmission.
- Infants were stratified by birth weight:
  - <1400 g
  - 1400 g - <1800 g
  - 1800 g - <2500g
- NVP was dosed at 2 mg/kg once daily (birth to 14 days of age), followed by 4 mg/kg once daily
- Infant characteristics, PK samples and safety data were collected at study entry (week 1; day 7-14 of age) and at 4, 6, 10, 16 and 24 weeks of age. Plasma samples for NVP assay were collected pre-dose and 2 hours post dose at study entry and pre-dose at all other study visits
- Plasma samples were assayed for NVP by using liquid chromatography–mass spectrometry (lower limit of detection of 0.02 µg/ml)
- The NVP trough target was > 0.1 µg/ml. NVP trough concentrations were normalized to a 2 mg/kg dose for analysis
- Adverse events (AEs), potentially harmful to an infant, were classified as follows:
  Expected: events pre-identified as commonly associated with prematurity
  Unexpected: unanticipated events not commonly associated with prematurity

Results

- Arm 1 accrued 40 LBW infants between August 2015 and May 2016
  < 1400g: n = 12
  1400 – <1800g: n = 12
  1800 – 2500g: n = 16

Table 1. Baseline characteristics of LBW infants on NVP (n=40)

Characteristics	
Male gender (n, %)	18 (45)
Ethnicity (Black African) * (n, %)	38 (95)
Birth weight, g (mean, range)	1675 (950 – 2460)
Gestational age, weeks (mean, range)	33 (28-40)
Enrollment age, days (mean, range)	11 (8-14)

*2 infants were of mixed race

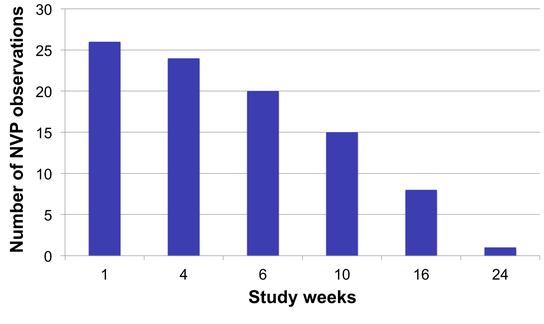
- In August 2016, 94 NVP trough concentrations were available for 27 infants.

Table 2. Characteristics of LBW infants on NVP at time of PK sampling (n=27)

Characteristics	Mean and (range)
Birth weight, g	1383 (950-2390)
Current weight, g	2147 (965-6050)
Gestational age, weeks	31 (28-38)
Postmenstrual age, weeks	37 (29-56)
NVP dose, mg/kg	3.4 (1.38-5.7)

- **Figure 1. 94 NVP trough concentrations across study visits from day 7 to week 24.**

Figure 1

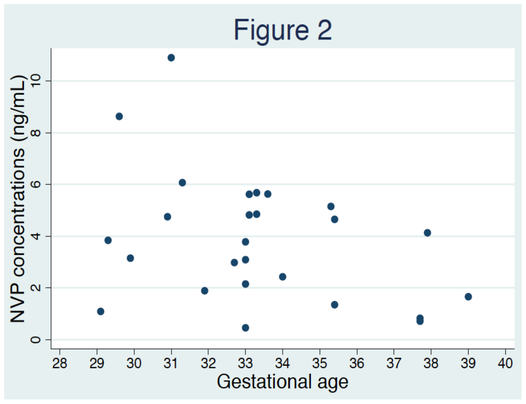


Results

- NVP was administered for a mean duration of 10 weeks (range of 1.5 – 18.8 weeks)
- The mean NVP trough concentration across all visits was 1.87 µg/mL (range < 0.02 - 10.69 µg/mL); 6/94 (6%) observations were < 0.1 µg/ml (NVP prophylaxis target)
- Below target samples were all from later visits (median postmenstrual age 44 weeks; median weight of 3903g) when at home and receiving NVP from caregiver.

- **Figure 2. Observed NVP trough concentrations versus gestational age at initial visit (n=26)**

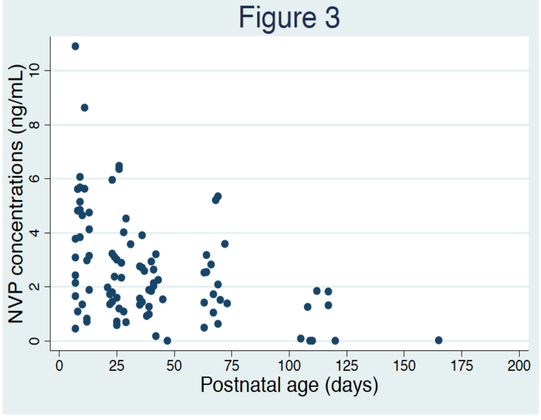
Figure 2



- At the initial visit, lower gestational age was associated with higher NVP trough concentration normalized for dose (r = - 0.47; p=0.02)

- **Figure 3. Observed NVP concentrations versus postnatal age in days over study period (n=94)**

Figure 3



- Across all visits, NVP trough concentrations normalized for dose were inversely related to infant postnatal age (r = - 0.45; p<0.001)

Safety results

- All AEs were unrelated to NVP
- Three infants died during the study period:
  2 sudden unexpected death in infancy (SUDI) at 7 and 17 weeks of age
  1 *Acinetobacter baumannii* sepsis at 4 weeks of age
- 10 had Grade 3/4 unexpected AEs, most common being pneumonia (n=4)
- 9 infants had Grade 3/4 expected AEs that commonly occur in premature infants, the most frequent being presumed or confirmed sepsis (n=6)
- The majority of grade 3/4 AEs resolved or were downgraded to a Grade 1/2 by study end

Conclusions

- The NVP dosing regimen achieved trough concentrations above the 0.1 µg/mL prophylaxis target
- NVP trough concentration at the initial visit increased with decreasing gestational age
- Subsequent NVP concentrations decreased with increasing postnatal age
- No treatment related adverse events were observed

References

1. Fowler MG, Qin M, Fiscus SA, Currier JS, Flynn PM, Chipato T, et al. Benefits and Risks of Antiretroviral Therapy for Perinatal HIV Prevention. N Engl J Med. 2016 Nov 3;375(18):1726-1737.
2. Capparelli EV, Mirochnick M, Dankner WM, Blanchard S, Mofenson L, McSherry GD, et al., Pharmacokinetics and tolerance of zidovudine in preterm infants. J Pediatr. 2003 Jan;142(1):47-52.
3. De Waal R, Kroon SM, Holgate SL, Horn AR, Tooke LJ, Norman J, et al. Nevirapine concentrations in preterm and low birth weight HIV-exposed infants: implications for dosing recommendations. Pediatr Infect Dis J. 2014 Dec;33(12):1231-3.
4. Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE. Developmental pharmacology-drug disposition, action, and therapy in infants and children. N Engl J Med. 2003;349(12):1157-67.

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