Therapeutic NVP Dosing in Infants

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Infant NVP Considerations

- **Very early antiretroviral treatment (ART) initiation in HIV infected newborns may limit the seeding of viral reservoirs and maintain immune responses.**
- **NVP safety and dosing are well established for prophylactic doses (2mg/kg) but this dose does not achieve therapeutic NVP concentrations (> 3 mcg/mL).**
- **Higher NVP doses are needed for newborn treatment.**

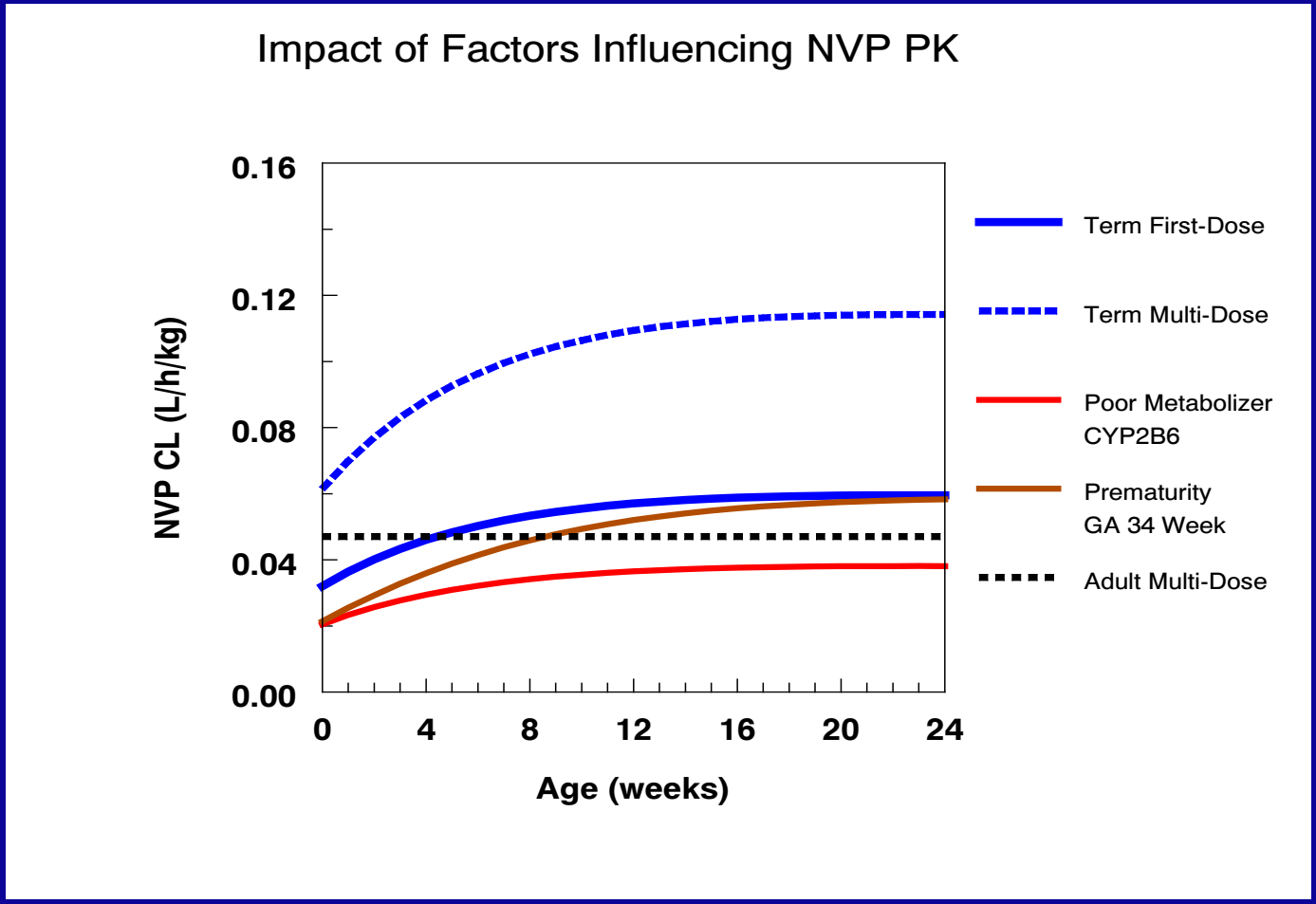
Nevirapine PK Issues

- **NVP induces its own metabolism**
- **Consistent and extensive absorption from gut**
- **Lead-in dosing impact on troughs compounded in infants with shorter half-life**
- **Developmental changes in NVP metabolism**
  - **Newborns with immature metabolism**
  - **Older infants have increased metabolism**
  - **Prematurity associated with reduced metabolism**
- **Higher CL/F and shorter $t_{1/2}$ in older infants and young children**
- **Polymorphism in CYP2B6 (516TT) associated with lower NVP CL and higher levels**

Nevirapine Pharmacodynamics

- Target NVP trough for prophylaxis is 100 ng/mL (0.1mcg/mL) based on IC50.
- NVP treatment troughs < 3 mcg/mL associated with clinical failures (de Vries Sluijs et al Clin PK 2003).
- Rash seen in 47% of adults in Phase I study with 400mg qd -rationale for lead-in & bid dosing.
- In African women Gr3+ rash is associated with higher NVP troughs (8.7 vs. 7.2 mcg/mL) (Dong et al AIDS 2012).
- 12 hydroxy-metabolite may be responsible for hepatotoxicity
- Most studies show no association between NVP levels and liver toxicity in patients without hepatitis.

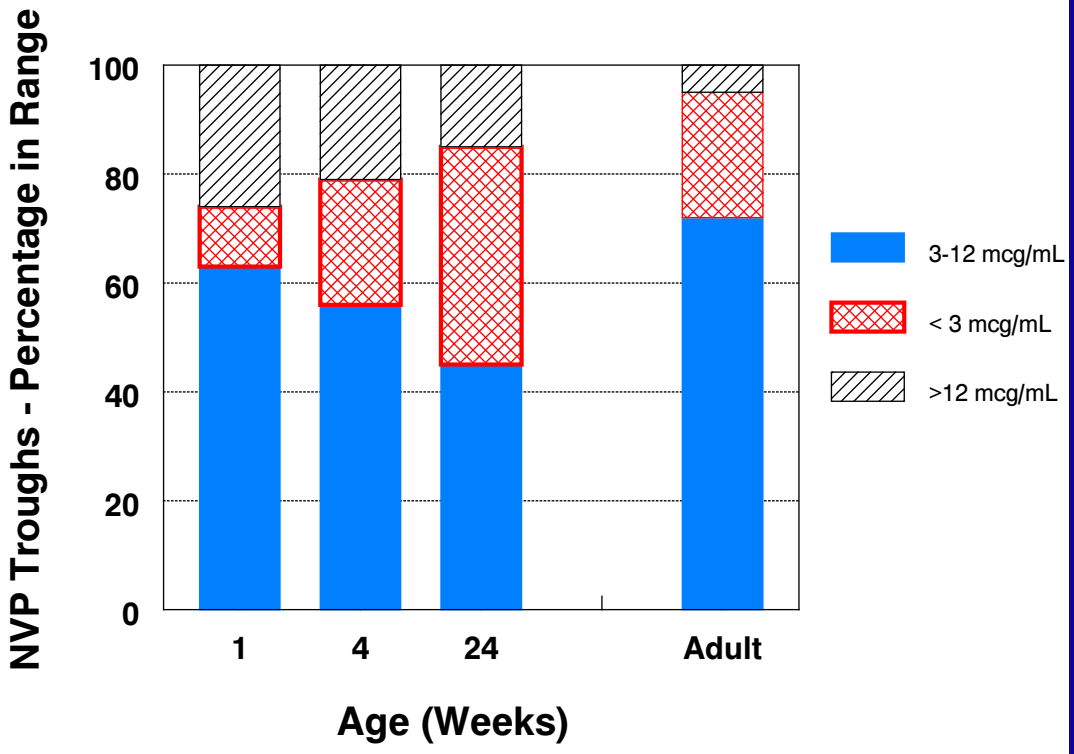
Pop PK Model of NVP in Infants



Mirochnick et al. CROI 2016

Predicted NVP Levels in Infants with 6 mg/kg

Based on PopPK Model – Mirochnick et al CROI 2016

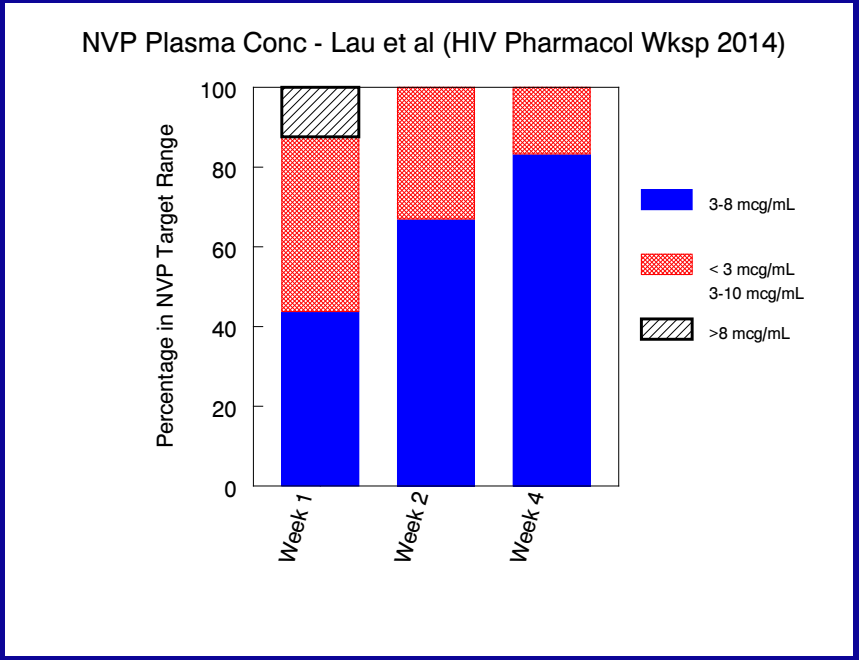


NVP in Early HIV Treatment Studies

- **Retrospective – Lau et al 150mg/m^2 with lead-in**
- **The Early Infant Treatment Study in Botsawna (BHP 074 R. Shapiro et al) – 6mg/kg bid:**
  - **NVP PK results after 1 and 2 weeks of treatment on first 6 subjects presented at CROI 2016 (Capparelli Abs#815)**
  - **NVP PK at Weeks 1 and 2 looked similar**
    - **median trough 3.6 mcg/mL all < 11 mcg/mL**
- **P1115 - Very Early Intensive Treatment of HIV-Infected Infants to Achieve HIV REMISSION: A Phase I/II Proof of Concept Study (Y Bryson / E Chadwick et al) – Term (GA ≥37 wk) 6mg/kg bid / (GA 34-<37 wk) 4mg/kg bid**

NVP PK in Newborns Receiving Treatment Dosing – Lau et al

- Retrospective study of 22 infants – median GA 37 weeks; BWT 2.9 kg.
- Initial NVP dose 150 mg/m^2 (~10 mg/kg) bid with 14 day qd lead- in.
- TDM applied of achieve NVP 3-8 mg/mL.
- Median (range) NVP troughs:
  - Week 1 – 9.2 (1.6 – 25.4)
  - Week 2 – 4.1 (1.6 – 26.1)
  - Week 4 – 3.8 (0.2 – 17.1)



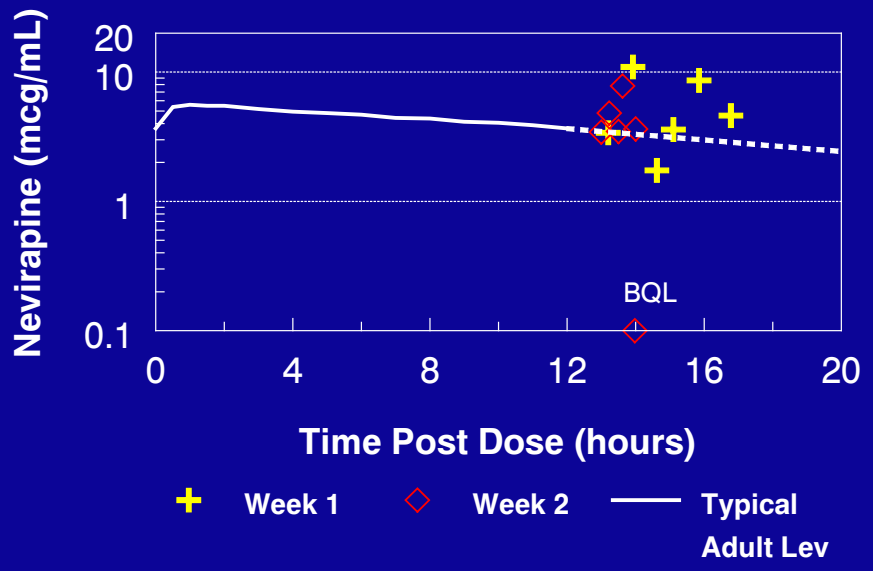
BHP 074 PK Results and Conclusions

- Pharmacokinetic (PK) evaluations performed in the first 6 infants
- PK samples at 1 and 2 weeks of treatment analyzed

- Subject Characteristics
  - Median GA at birth: 37.0 ± 1.9 weeks
  - Median age at start of ART: 2.8 ± 1.7 days
- No drug toxicities identified

- Median NVP trough concentration = 3.6 mcg/mL

Nevirapine Levels withTreatment Dosing

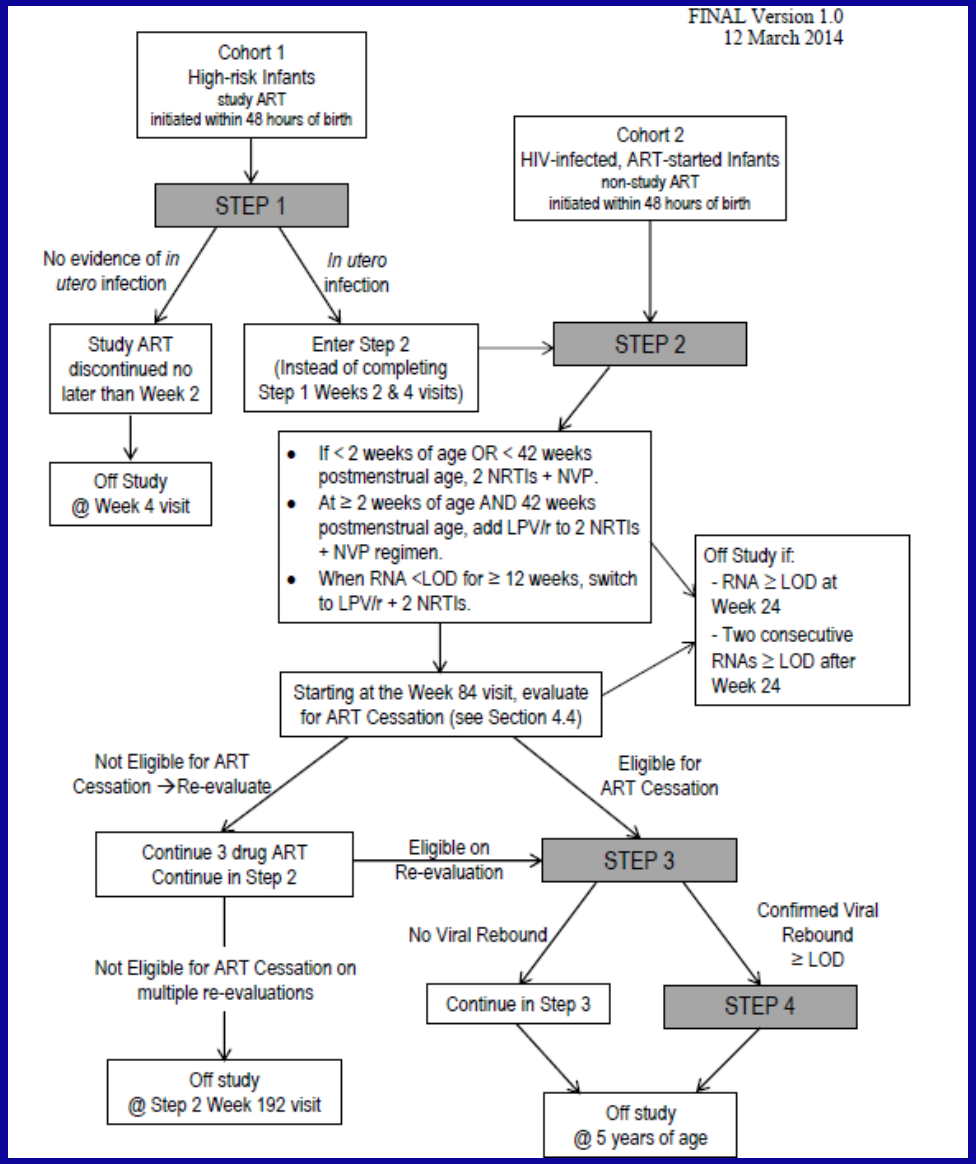


Conclusions

- **Values consistent with typical adult NVP concentrations**
- **This dosage worthy of further study to determine safety and activity**

P1115 PK Elements

- 2 Cohorts
  - Cohort 1: High Risk
  - Cohort 2: HIV Infected
- Dose
  - >=37 wk GA: 6mg/kg bid
  - 34-<37 GA: 4mg/kg bid
- Sparse Plasma and DBS collected at WK 1 & 2 in first 30 Cohort 1 participants.
- DBS collected at regular intervals while receiving NVP.
- Target NVP 3-10 mcg/mL.
- Goal: <20% above and <20% below NVP target. (within subject mean).



Stay Tuned

- P1115 initial NVP results to be presented at IAS, summer 2016.