Background: Early treatment of HIV-infected neonates may sufficiently reduce viral load to enable HIV remission after cessation of combination antiretroviral therapy (cART). However, there are limited data on therapeutic concentrations of antiretrovirals achieved in neonates.

Methods: IMPACT P115 is an ongoing multinational trial investigating early cART and HIV remission in infected neonates. Pharmacokinetic (PK) modeling from prior neonatal NVP (nevirapine) prophylaxis data suggested that NVP dosing of 6 mg/kg/dose twice daily (DDI) would maintain concentrations between 0.3-3 mcg/mL, just above the established therapeutic range for infant NVP dosing. However, the success of early NVP dosing in infants is limited by the wide interindividual NVP PK variability and toxicities that are generally tolerable in older children due to maturation of metabolism and auto-induction (van de Water et al. JID 2015). Dr. Jennings et al. (JID 2015) recently reported low plasma NVP concentrations and high failure prevalence among neonates treated with a prophylaxis dose of 6 mg/kg twice daily. This PK dataset was then used as an input in a nonlinear mixed-effects model to predict NVP concentrations if cART is initiated on the day of birth. Simulations were compared to a baseline NVP dose of 6 mg/kg twice daily.

Background: The study was presented at the 21st International AIDS Conference (21IACS) in Durban, South Africa, in 2016. The authors acknowledge the support of various institutions and organizations, including the FAMCRU, Stellenbosch University, Tygerberg, South Africa, Rush University Medical Center, Chicago, IL, USA, and the John Hopkins University, Baltimore, MD, USA. The content of this presentation is solely the responsibility of the authors and does not necessarily represent the official views of the authors or their institutions.

Results: Among 30 neonates with ≥ Grade 2 Toxicities Through Week 2 at cART initiation, 19 (63.3%) had at least one toxicity related to cART (ZDV, 13; 43%; FTC, 2; 6.7%; and ABC, 2; 6.7%). Of these, 13 (43%) were severe toxicities (Grade 3 or 4) and 8/13 (61.5%) were possibly related to cART. The median (range) birth weight was 3.1 (2.8-3.3) kg; 20 boys/10 girls. Within the group, the median (range) birth weight was 3.1 (2.8-3.3) kg; 20 boys/10 girls. Median (range) gestation was 38.7 (36-40) weeks. Median (range) weight at birth was 2.8 (2.3-3.2) kg. The majority of neonates were born at ≥ 37 weeks gestation, and 25/28 (89%) neonates ≥ 37 weeks gestation were examined among enrolled neonates ≥ 37 weeks gestational age. Target hematologic toxicities included rashes (9/30; 30%) and elevated transaminases (8/30; 26.7%). The median (range) age at cART initiation was 20.4 (17.4-23.5) weeks.

Discussion: 
• A lower NVP dose of 4 mg/kg/dose is preferred to better maintain target plasma concentrations of 3-10 mcg/mL (Patel et al. JID 2011) with less risk of virologic rebound and NVP resistance. In addition, NVP concentrations are known to fall rapidly in the first weeks of life. Target concentrations ≥ 3 mcg/mL can be achieved if NVP is administered >2 weeks of age, underscoring the challenge of NVP dosing in neonates.
• The strategy of dosing at NVP 6 mg/kg/dose appears to be safe and minimizes sub-therapeutic NVP exposures; these results underscore the need for continued study of this NVP dosing regimen to treat neonates.

References

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