Safety and Efficacy of Starting Antiretroviral Therapy in the First Week of Life

Roger Shapiro,1,2,3 Kara Bennett,1 Michael Hughes,1 Kenneth Maswabi,2 Gbolahan Ajibola,2 Patrick Jean-Philippe,4 Edmund Capparelli,5 Sikhuille Moyo,6 Terence Mohammed,2 Oganne Batling,2 Shahin Lockman,2 Max Essex,2,4 Joseph Mahkema,2 Mathias U Fletcher,2,4 Daniel R. Kutzke6


Background

• Antiretroviral therapy (ART) started in the first week of life may limit HIV viral reservoir and improve treatment outcomes
• WHO supports early infant diagnosis and recommends ART initiation without delay
• Few antiretrovirals are available during neonatal period • ZDV, 3TC, NVP, LPV/r (from 2 weeks), RAL
• Little information is available about safety, viral efficacy, and pharmacokinetics (PK) of ART in early infancy

Methods

• The EIT Study (U01AI114235) enrolled HIV+ infants < 7 days of age, > 35 gestational weeks, and > 2000g
• Treatment doses of NVP, ZDV, and 3TC started as initial ART, and changed to LPV+r, ZDV, 3TC after 2-5 weeks • Switched to LPV+r when > 2 weeks of life and > 40 gestational weeks age equivalent • Dosing: NVP – 6mg/kg BID; ZDV – 4 mg/kg BID (0-4 wks), 8mg/ kg BID 4-6 wks, then by WHO weight band; 3TC – 2 mg/kg BID (0-4 wks), 4 mg/kg BID (4-6 wks), then by WHO weight band; LPV/r – by WHO weight band • Study visits and HIV RNA testing at wks 0, 1, 2, 4, 8, 12 • PK testing of NVP trough values at weeks 1 and 2

Results

Enrollment:
• From April 2015-July 2018, 40 HIV+ infants were enrolled
• Median age at HIV screening was 1 day after birth (range 0, 4 days)
• Median age of enrolled infants at ART initiation was 2 days after birth (range 1, 5)
• Median change from NVP/ZDV/3TC to LPV/r/2dd/3TC was after 2.7 weeks (range 2, 1.5-9 weeks)

Pharmacokinetics at Weeks 1 and 2:
• Median NVP trough concentration was 3.3 mcg/mL at 1 week and 2.7 mcg/mL at 2 weeks (at a median of 15.6 and 14.5 hours from last dose, respectively) (Figure 1)
• 15 (50%) of 30 infants tested were below therapeutic target of 3.0 mcg/mL at 2 wks (including 2 BLO, indicating non-adherence)
• NVP concentrations did not correlate with the magnitude of decline in HIV RNA logs copies/mL at either 2 or 4 weeks

Safety through 12 weeks of ART:
• No deaths or loss to follow-up
• 1 Grade 3 neutropenia
• No modification of ART for toxicity
• No Grade 3/4 anemia

Viral Suppression:
• Infant plasma HIV RNA declined from a median of 4.05 log copies/mL at baseline (IQR 2.79, 4.86 log copies/mL) to 2.54 log copies/mL at 2 wks (IQR 1.86, 3.21) and <1.60 log copies/mL at 12 wks (IQR <1.60, 1.93 log copies/mL) (Figure 2) – HIV RNA response at 12 weeks did not differ by baseline HIV RNA, or other factors

In the 4-week period following transition to LPV-r-based ART, 9 (22.5%) had transient increases in HIV RNA thought to be adherence-related (spitting out LPV-r)

After 12 weeks of ART, 22 (55%) had HIV RNA < 40 copies/mL, and only 3 (8%) had HIV RNA > 400 copies/mL

Conclusions

• NVP, ZDV, 3TC started in the first week of life was safe and effective, even among the 50% of infants with NVP levels below the ideal therapeutic PK target
• All infants were successfully transitioned from NVP to LPV-r at 2-5 weeks. However, poor LPV/r tolerability may have contributed to transient viral increases following this transition in over 20% of infants
• By 12 weeks of life, almost all children (93%) were able to achieve HIV RNA declines to < 400 copies/mL

Figures:

Figure 1: NVP trough concentrations at 1 and 2 weeks

Figure 2: Median HIV RNA log copies/mL and percentage of infants < 40 copies/mL after 0, 1, 2, 4, 8, and 12 weeks on ART

Acknowledgments

The EIT Study participants and staff, and the Botswana Harvard AIDS Institute Partnership (BHAP) participants, were key contributors to this study. We gratefully acknowledge the EIT DSMB Members, and the NIH (R01 AI066470, R01 AI066470-02, R01 AI066470-03) for funding this study. We gratefully acknowledge the EIT DSMB Members, and the NIH (R01 AI066470, R01 AI066470-02, R01 AI066470-03) for funding this study.

Table 1: Baseline Characteristics of Infants (N=40)