Neurodevelopmental effects of type of ante- & postpartum PMTCT ARV exposure on Ugandan and Malawian PROMISE HIV-exposed children at age 12, 24, and 48 months

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BACKGROUND

- Despite WHO guidelines recommending antepartum and postpartum (if breast feeding) **Triple-ARV** for the prevention of mother-to-child transmission (**PMTCT**) of HIV, neurodevelopmental risk to infants for such exposure is unknown.
- Children in the clinical trial Promoting Maternal and Infant Survival Everywhere (**PROMISE**) Blantyre Malawi (N=188) and Kampala Uganda (N=208) sites were *evaluated on the basis of ARV pre- and post-natal treatment arm*.
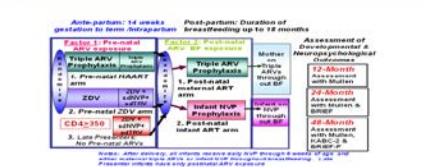
OBJECTIVE: To determine if the developmental (MSEL) and cognitive (KABC-II) performance of HIV/ARV-exposed uninfected African children from Malawi and Uganda differed on the basis of ante-natal and post-natal mono- versus triple-ARV treatment arms within the PROMISE clinical trial of PMTCT.

Assessments – Mullen Test

- Mullen Scales of Early Learning
  - Gross Motor
  - Visual Reception
  - Fine Motor
  - Receptive Language
  - Expressive Language
- Mullen Early Learning Scales Composite (global cognitive score)
- Administered 1, 2, and 4

KABC-II : Summary
- Covers an extended age range: 3-18
- Provides measurement of 5 Scales
  - Learning/Glr
  - Sequential/Gsm
  - Simultaneous/Gv
  - Planning/Gf
  - Knowledge/Gc
- Uses Luria or CHC Theories
- Conormed with KTEA-II

DESIGN/METHODS

At 12, 24, and 48 months of age, the **Mullen Scales of Early Learning (MSEL)** was used for developmental assessment. **The Kaufman Assessment Battery for Children (KABC-II)** was also used at the 48 month assessment.

During pregnancy, HIV-infected mothers were randomized to

1) Triple-ARV prophylaxis (3TC-ZDV/LPV-RTV; N=178) or FTC-TDF/LPV-RTV; N=37) or

2) Zidovudine (ZDV: N=178).

Postpartum: mother/newborn dyads were then randomized to either

1) Maternal Triple-ARV (MSEL available for N=186) or

2) Infant Nevirapine (NVP; N=186), continuing on their trial arm regimen throughout breast feeding.

Table 1. MSEL Ante- & Postpartum

RESULTS

- Antepartum ARV regimen did not differ significantly on MSEL composite cognitive ability at age 12 months (p=0.89), but did at 24 months (p=0.02), with FTC-TDF/LPV-RTV exposed children doing significantly more poorly than Zidovudine (Table 1).

- MSEL expressive language differences were not significantly different among treatment arms at 12 (p=0.84) or 24 (p=0.27) months, but were at 48 months (p=0.03), with antepartum 3TC-ZDV/LPV-RTV doing more poorly (Table 1).

- For antepartum by postpartum treatment-arm interaction effects, antepartum FTC-TDF/LPV-RTV, followed by postpartum maternal triple ARV, produced the worst, and ZDV followed by infant Nevirapine produced the best mean MSEL composite cognitive performance scores at 24 months (p<0.01).

- **KABC-II:** best outcomes for triple ARV followed by maternal triple ARV (Table 2).

Table 2. KABC-II Ante- by Postpartum

Outcome	Triple ARV, Infant NVP Mean (SE)	Triple ARV, Maternal triple ARV Mean (SE)	Zidovudine, Infant NVP, Mean (SE)	Zidovudine, Maternal triple ARV Mean (SE)	P-value for interaction of trial arms
Mental Processing Index	77.02 (1.58)	81.90 (1.48)	78.97 (1.61)	77.12 (1.51)	0.03
Non-verbal Index	72.04 (1.83)	77.11 (1.73)	74.88 (1.87)	73.36 (1.75)	0.06
Sequential Processing	76.40 (2.14)	84.90 (2.17)	83.02 (2.38)	80.71 (2.22)	0.02
Simultaneous Processing	70.59 (2.09)	75.45 (1.96)	74.04 (2.14)	70.40 (2.00)	0.04
Learning	84.01 (2.79)	87.60 (2.61)	88.09 (2.86)	80.62 (2.68)	0.04
Conceptual Thinking	6.72 (0.23)	6.74 (0.24)	6.73 (0.24)	6.53 (0.22)	0.62

CONCLUSIONS

- The combination of ante-partum followed by post-partum triple-ARV exposure did not consistently result in significantly poorer developmental outcomes with the MSEL at age 12, 24, 48 months.

- The combination of ante-partum followed by post-partum triple-ARV exposure did not result in significantly poorer cognitive ability outcomes with the KABC-II at 48 months of age.

- Despite these encouraging preliminary results as to the neurodevelopmental safety of prolonged triple-ARV exposure in African children, we are continuing to monitor cognitive performance of HEU treatment arms at 54/60 months of age with the KABC-II test battery.