Developmental & Cognitive Effects of Type of Antepartum and Postpartum ARV Exposure for Ugandan and Malawian PROMISE HIV-Exposed vs. Unexposed Children at age 12, 24, 48, and 60 Months

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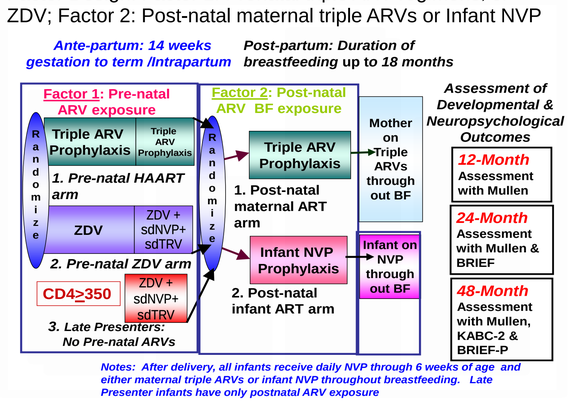
BACKGROUND

- 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*.

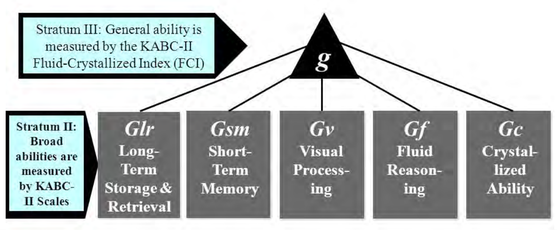
Figure 1. Assessing Developmental Outcomes among ARV exposed Uninfected Infants in PROMISE 1077 BF Using a 2-Factor Design: Factor 1: Prenatal triple ARV regimens, or ZDV; Factor 2: Post-natal maternal triple ARVs or Infant NVP



OBJECTIVE: To determine if developmental and cognitive performance of HIV/ARV-exposed uninfected children in Malawi and Uganda differed on the basis of ante-natal and post-natal ARV treatment arms within the PROMISE clinical trial of PMTCT.

Figure 2. Mullen Scales of Early Learning administration kit (left) and child during testing (right)

Figure 3. Cognitive domains evaluated with Kauffman Assessment Battery for Children II



DESIGN/METHODS

During pregnancy, HIV-infected mothers were randomized to either:

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.

Child assessments

Mullen Scales of Early Learning (MSEL): Used to assess development in children at 12, 24 and 48 months of age

The Kaufman Assessment Battery for Children (KABC-II): Used to evaluate cognition at 48 and 60 months of age.

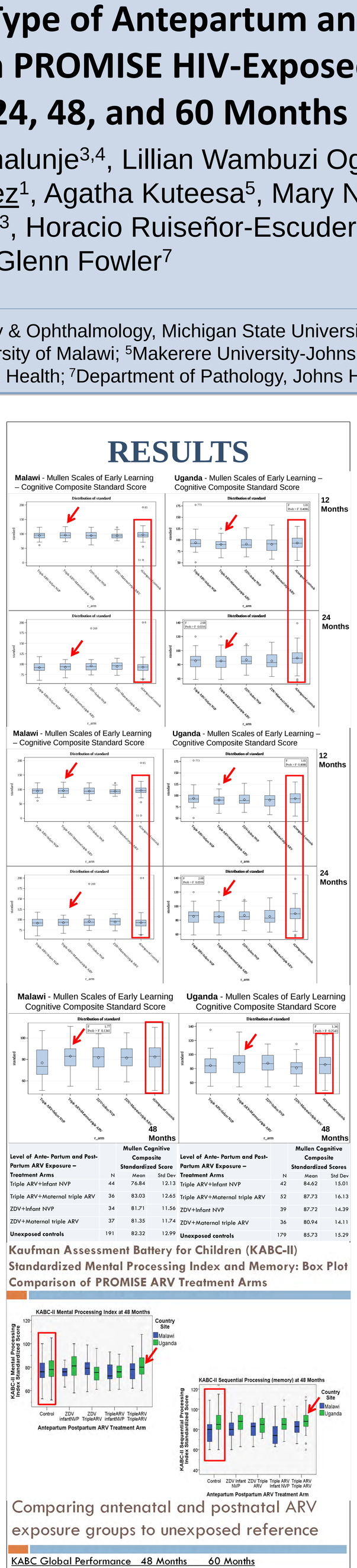
When controlling for WHO Standardized Height-for-Age (LAZ) as a time-varying covariate

- **MSEL composite was significantly related LAZ (p<.01);** overall differences by exposure at 48 months were attenuated (p=.07);
- **Gross motor and visual reception scores were significantly related to LAZ (p<.01);** no changes in the results (no significant differences by exposure).
- **Fine motor score was significantly related to LAZ (p<.01)**
- **Expressive language score was not related to LAZ**, and controlling for LAZ did not change the results (no differences by exposure).
- **Receptive language score was significantly related to LAZ (p<.01);** and LAZ mediates differences in receptive language by exposure.

When controlling for WHO Standardized Height-for-Age (HAZ) as a time-varying covariate

- **KABC Mental Processing Index (MPI) and non-verbal index (NVI) were significantly related to HAZ (p<.01);** no changes in the results (no significant differences by exposure group).
- **Sequential processing (working memory) was significantly related to HAZ (p=.04);** no changes in the results (no significant differences by exposure group).
- **Simultaneous processing score (visual-spatial analysis) was significantly related to HAZ (p<.01);**
- **Learning was not significantly related to HAZ, but controlling for HAZ attenuated exposure group differences at 48 months (p=.06, was .04).**

RESULTS



Level of Ante- Partum and Post-Partum ARV Exposure – Treatment Arms	N	Mullen Cognitive Composite Standardized Score Mean	Std Dev
Triple ARV+Infant NVP	44	76.84	12.13
Triple ARV+Maternal triple ARV	36	83.03	12.65
ZDV+Infant NVP	34	81.71	11.56
ZDV+Maternal triple ARV	37	81.35	11.74
Unexposed controls	191	82.32	12.99

Level of Ante- Partum and Post-Partum ARV Exposure – Treatment Arms	N	Mullen Cognitive Composite Standardized Scores Mean	Std Dev
Triple ARV+Infant NVP	42	84.62	15.01
Triple ARV+Maternal triple ARV	52	87.73	16.13
ZDV+Infant NVP	39	87.72	14.39
ZDV+Maternal triple ARV	36	80.94	14.11
Unexposed controls	179	85.73	15.29

Kaufman Assessment Battery for Children (KABC-II) Standardized Mental Processing Index and Memory: Box Plot Comparison of PROMISE ARV Treatment Arms

Comparing antenatal and postnatal ARV exposure groups to unexposed reference

KABC Global Performance	48 Months	60 Months
Mental Processing Index	P=0.81	P=0.89
Nonverbal Index	P=0.84	P=0.63
Sequential Processing	P=0.40	P=0.55
Simultaneous Processing	P=0.39	P=0.93
Learning	**P=0.04***#	P=0.79

- *antenatal Triple ARV/postpartum NVP $P<0.05$ below Reference Group
- #antenatal ZDV/postpartum Triple ARV $P<0.05$ below Reference Group

Note: Results adjusted for data collection site (Kampala – Uganda, Blantyre – Malawi)

PROMISE Neurodevelopmental Study of ARV Exposure: Unadjusted Standardized (American Norms) Group Means and Standard Deviations for KABC-II Global Scales (48, 60 months) and MSEL Composite Cognitive Score (12, 24, 48 months)

Characteristic	Time, months	Maternal Triple ARV+ infant NVP, N (%) or Mean (SD)	Maternal Triple ARV+ maternal triple ARV, N (%) or Mean (SD)	Maternal Zidovudine+ infant NVP, N (%) or Mean (SD)	Maternal Zidovudine+ maternal triple ARV, N (%) or Mean (SD)	HIV-unexposed Reference Group, N (%) or Mean (SD)	P-value for comparison of all groups
KABC Mental processing index	48	77.48 (10.49)	79.11 (11.39)	79.65 (10.83)	77.42 (9.44)	78.22 (10.52)	.60
	60	72.63 (11.60)	75.56 (11.25)	72.91 (9.68)	73.43 (10.72)	74.68 (10.81)	.51
Non-verbal index	48	72.31 (12.52)	73.82 (13.70)	74.40 (11.74)	73.59 (11.02)	73.11 (12.74)	.85
	60	69.52 (13.22)	71.53 (12.70)	70.23 (12.10)	71.73 (13.28)	72.80 (12.97)	.45
Sequential processing	48	80.15 (17.28)	84.57 (12.49)	83.75 (10.51)	82.44 (14.84)	82.18 (14.55)	.30
	60	78.00 (10.97)	82.56 (11.11)	79.10 (9.72)	80.25 (11.33)	81.40 (13.05)	.26
Simultaneous processing	48	72.33 (14.42)	74.33 (12.20)	76.00 (9.47)	72.45 (12.81)	73.50 (11.68)	.31
	60	70.63 (12.68)	71.55 (14.31)	71.23 (11.49)	71.79 (12.87)	72.47 (12.87)	.89
Learning	48	84.21 (18.99)	86.93 (14.97)	89.08 (11.51)	83.63 (18.57)	87.96 (15.73)	.08
	60	82.33 (11.97)	85.03 (12.93)	82.11 (10.15)	81.42 (10.80)	82.17 (12.69)	.56
MSEL							
Standardized composite	12	94.21 (15.00)	92.80 (13.15)	92.84 (14.28)	91.95 (14.08)	95.20 (14.54)	.23
	24	88.16 (11.94)	88.27 (12.64)	91.04 (14.77)	89.84 (12.15)	91.07 (12.91)	.14
	48	80.64 (15.00)	85.81 (14.91)	84.92 (13.41)	81.15 (12.88)	83.97 (14.22)	.06

CONCLUSIONS

- Ante-partum followed by post-partum triple-ARV exposure did not result in significantly poorer outcomes with the MSEL at age 12, 24, 48 months compared to the unexposed reference group.
- Ante-partum followed by post-partum triple-ARV exposure did not result in significantly poorer cognitive ability outcomes with the KABC-II at age 48 and 60 months compared to the unexposed group.
- Monthly clinic visits lead to better nutritional support (e.g., treatment for anemia, micronutrient support).
- Maternal antepartum and postpartum triple ARV results in better health and functionality for moms; enhanced caregiving versus infant exposure risk.

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