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Neurodevelopmental and behavioural outcomes of HIV-exposed uninfected and HIV-unexposed children at 2–3 years of age in Cape Town, South Africa

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ABSTRACT

Successful vertical HIV transmission prevention programmes (VTP) have resulted in an expanding population of HIV-exposed uninfected (HEU) infants whose growth, health and neurodevelopmental outcomes could have consequences for future resource allocation. We compared neurodevelopmental and behavioural outcomes in a prospective cohort of 2–3 year old HEU and HIV-unexposed uninfected (HU) children.

Women living with and without HIV and their infants were enrolled within three days of birth from a low-risk midwife obstetric unit in Cape Town, South Africa during 2012 and 2013, under WHO Option A VTP guidelines. HIV-uninfected children aged 30–42 months were assessed using the Bayley scales of Infant Development-Third edition (BSID) and Strengths and Difficulties questionnaire (SDQ).

Thirty-two HEU and 27 HU children (mean birth weight 3048g vs 3096g) were assessed. HEU children performed as well as HU children on BSID cognitive, language and motor domains. Mean scores fell within the low average range. Mothers of HEU children reported fewer conduct problems but stunting was associated with increased total difficulties on the SDQ.

HEU and HU children's performance on the BSID was similar. In this low-risk cohort, HIV exposure did not confer additional risk. Stunting was associated with increased behavioural problems irrespective of HIV exposure.

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Introduction

There is increased recognition of the need to understand and improve the long-term neurodevelopmental outcome of HIV-uninfected children born to women living with HIV, particularly in low and middle-income countries (Evans, Jones, & Prendergast, 2016). In South Africa, the HIV vertical transmission rate has decreased to below 5% (Goga et al., 2015), but the high antenatal HIV prevalence has resulted in an expanding population of HIV-exposed uninfected (HEU) children with implications for their health, educational and social wellbeing (UNAIDS, 2018).

Evidence regarding neurodevelopmental outcome in HEU children remains conflicting. Studies from high-income countries found language delay and impairment in HEU toddlers and children respectively (Caniglia et al., 2016; Rice et al., 2013; Sirois et al., 2013). A meta-analysis reported poorer cognitive and motor performance in six of twelve cohorts of young HEU versus HIV- unexposed (HU) children tested on the Bayley Scales of Infant and Toddler Development, and lower cognitive and motor scores in HEU infants exposed to antiretroviral drugs (ARV). However, the six studies assessed as high quality, all in the United States, showed no difference in outcome between HEU and HU children (McHenry et al., 2018). Findings in Africa are mixed; a recent study described poorer cognitive and motor development in South African HEU infants (Le Roux et al., 2018) while poorer language outcomes were found in Kenyan toddlers (Alcock, Abubakar, Newton, & Holding, 2016) and children in the Democratic Republic of Congo (Van Rie, Mupuala, & Dow, 2008). Others

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found no difference between young HEU and HU children (Chaudhury et al., 2017; Ngoma et al., 2014) and no adverse effects from ARV exposure (Chaudhury et al., 2018). However methodologies vary with regards to inclusion criteria e.g., preterm infants, use of well matched control groups, and choice of child development assessment tools, while changing ARV regimes and other confounders may also influence findings.

There is limited information on behavioural outcomes in young HEU children. Most research has focused on school-going children and is confounded by social and educational factors (Kandawasvika, Gumbo, & Kuona, 2016; Sharp et al., 2014; Sherr, Skeen, Hensels, Tomlinson, & Macedo, 2016; Sherr et al., 2017; Sipsma et al., 2013). Detection of problems at a younger age provides an opportunity for earlier intervention (Holtz, Fox, & Meurer, 2015). Encouragingly, the South African government has prioritised investment in the first 1000 days (from conception to 2 years of age), adopting strategies to address modifiable factors, potentially enabling children to fulfil their cognitive and socio-emotional potential (Western Cape Government Department of Health, 2017).

We previously reported similar outcomes on Bayley Scales of Infant and Toddler Development-Third edition (BSID) in HEU and HU infants with subtle language and behavioural differences at 11–14 months (Springer et al., 2018). However significant deficits may only emerge at a later age (Smith, Puka, Sehra, Read, & Bitnun, 2017). Here we present the follow-up findings of a prospective cohort study comparing the neurodevelopmental and behavioural profile of HEU and HU children at age two to three years old. Secondary outcomes of interest included comparison of BSID scores (developmental trajectory) at one and three years of age and identification of factors associated with adverse outcomes.

Methods

This neurodevelopmental study was nested in the Mother Infant Health Study (MIHS), primarily designed to compare infectious morbidity in HEU and HU infants. Study methods were described previously (Slogrove et al., 2017). Women living with and without HIV and their infants were enrolled within 72 hours of delivery at a low-risk midwife obstetric unit. All shared similar cultural and socioeconomic characteristics. Inclusion criteria were newborns weighing more than 2000 g, ≥34 weeks gestation with no perinatal complications.

Participants

Women from the MIHS cohort with children aged between 30 and 42 months were invited for a neurodevelopmental and behavioural assessment at Tygerberg Academic Hospital. A developmental paediatrician and an experienced tester performed the assessments blinded to the children's HIV-exposure status. They initially assessed children together, in order to reach consensus on scoring. A behavioural screening questionnaire was read to the caregiver in her preferred language (English, Afrikaans or isiXhosa) assisted by a translator, allowing time for clarification. Thereafter, the assessor documented her responses. Physical examination and anthropometry were performed after completion of developmental assessments. Appointments were rescheduled if the child was physically unwell or tired.

At the time, the vertical transmission of HIV prevention guidelines of the Western Cape (Option A) recommended that pregnant women living with HIV with a CD4 count ≤ 350/μl or WHO stage 3 or 4 disease received triple drug antiretroviral therapy (ART); the remainder received zidovudine (ZDV) monotherapy from 14 weeks gestation and single-dose nevirapine (NVP) at delivery, while newborns received NVP and ZDV for one week (South African National Department of Health; South African National AIDS Council, 2010).

Both MIHS and neurodevelopmental studies were approved by Stellenbosch University's Human Research Ethics Committee (N13/03/028 and S12/0/009) and the Children's and Women's Research Ethics Board at the University of British Columbia (H12-01181-A010).

Measures

Development was assessed using the cognitive, language and motor scales of the BSID (Bayley, 2006) with no adaptations to test materials. The BSID was administered in the child's home language using a translator. The United States BSID composite score norms classify developmental delay as moderate (70-85) and severe (<70). For this study, BSID composite scores below 85 (>1 standard deviation below the mean) were classified as "poorer neurodevelopmental outcome". Children with significant delays were referred to the appropriate developmental service.

Behaviour was assessed by direct interview using the pre-school version of the Strengths and Difficulties Questionnaire (SDQ) with Afrikaans and isiXhosa translations (Goodman, 1997). The instrument has 25 questions divided into five subscales: emotional symptoms, hyperactivity, conduct and peer relationship problems, and prosocial behaviour. The first four subscales combine to form internalising and externalising scores, and a summative Total Difficulties Score (TDS). The cut-off scores for the SDQ TDS and subscales have not been

validated for South African children, thus statistical analysis was limited to group comparison (Hoosen, Davids, de Vries, & Shung-King, 2018). Decisions regarding referral for formal evaluation were made in consultation with the caregiver.

Weight, height and head circumference were converted into standardised z-score anthropometric values utilising WHOAnthro (WHO, 2010) giving weight-for-age (WAZ), height-for-age (HAZ), weight-for-height (WHZ) and head circumference-for-age (HCZ) Z-scores. Children were further classified as underweight (WAZ < −2 Z), stunted (HAZ< −2 Z) and/or wasted (WHZ < −2 Z), macrocephalic (HCZ > 2Z) or microcephalic (HCZ < −2Z).

Baseline maternal sociodemographic information, maternal education, gestation, antenatal exposures, Centre for Epidemiological Depression (CES-D) scores at 12 months postpartum, newborn anthropometry, duration of breastfeeding, placental pathology, previous hospitalisation, and caregiver consistency were obtained from the MIHS database, direct interview and the child's immunisation record. Macroscopic and microscopic features of placentae were available on 46 participants (78%) (Kalk et al., 2017). Caregiver consistency indicated that the child had not been separated from their biological mother since birth. Mothers were also questioned regarding book-reading to their children.

Statistical analysis

Statistica 13 (TIBCO Software Inc.) was used for analysis. Cross tabulation with Chi-square test was used to compare categorical variables between groups (HEU vs HU). Effect size was reported using Cohen's d. For continuous measurements, one-way ANOVA was used for group comparison. When comparing neurodevelopmental scores at 12 and 30 months, mixed model ANOVA was performed with participants as random effect, and time, group and time*group interaction as fixed effects. Post-hoc testing was done using Fisher-LSD and Games-Howell testing where homogeneity of variants did not apply. Associations between poorer neurodevelopmental outcome and risk factors, including maternal education, antenatal exposures, placental pathology, breastfeeding and anthropometry, were assessed using a mixture of correlations and one-way ANCOVA.

Results

Of the original 176 mother-infant dyads (94 HEU and 82 HU) in the MIHS on whom baseline data were available, 96 (58 HEU and 38 HU) infants had neurodevelopmental assessments at age 12 months (Springer et al., 2018) and 59 children (32 HEU and 27 HU), were assessed at age 30–42 months. The proportion of HEU and HU infants either retained or not retained for neurodevelopmental assessment had similar baseline characteristics except for lower median birth weight in those with neurodevelopmental assessments compared to those not retained (3070 g vs 3199 g, $p = 0.03$). Of the 59 participants in the neurodevelopmental study, 29 HEU and 24 HU children had previous BSID evaluations at age 12 months.

Maternal and child characteristics are shown in Tables 1 and 2. In total, 58 children were accompanied by their biological mothers and one by the grandmother. Mothers of HEU children were older, attained a lower grade of schooling, and were less likely to have planned their pregnancy or breastfed than mothers of HU children (Table 1). Only one mother of an HEU child reported illicit antenatal drug use. Thirteen (40.6%) HEU children were exposed in utero to combined antiretroviral therapy (cART), and 19 (59.4%) to zidovudine.

All except one HU child were primarily cared for by their mothers and caregiver consistency amongst the two groups was similar (HEU 81% vs. HU 89%, $p = 0.41$). Mothers read books to six (18.7%) HEU and four (14.8%) HU children, however only eight (four HEU and four HU) children were read to more than once a week. Eight (25%) HEU and three (11%) HU children required hospitalisation after one year of age ($p = 0.52$), without reported neurological sequelae. The HU group had lower WHZ ($p = 0.04$), but none were underweight. However, two HEU (6%) and four HU (14.8%) children were stunted.

Four HEU children had macrocephaly (12.5%), absent at birth, but documented in three of the children at both 12 months and 30–42 months. Two macrocephalic children had moderate language delay, one with *in utero* ZDV exposure, and the other with ART exposure; the latter had normal neuroimaging and tested negative for glutaric aciduria (Govender, Mitha, & Mubaiwa, 2017). No child had microcephaly.

Results of the neurodevelopmental and behavioural assessments are shown in Table 3. All 59 children completed BSID assessments. There was no significant difference between HEU and HU infants for cognitive, language, or motor domains after adjustment for stunting and maternal education. No child had severe delay in any BSID domain. HEU children with *in utero* ART exposure performed as well as those with single ARV exposure (data not shown).

All caregivers completed the SDQ. Mothers of HEU children reported fewer behavioural problems. However after adjustment for stunting and maternal education, only conduct problems (Cohen's $d = 0.54$, $p = 0.02$,)

Table 1. Maternal and perinatal characteristics of HIV-exposed uninfected and HIV-unexposed children at the 2 year follow-up visit of the MIHS cohort.

Characteristic	HIV exposed uninfected ($n = 32$)	HIV unexposed ($n = 27$)	p-value
Maternal age at delivery (years) mean (SD)	28.2 (5.2)	25.3 (5.2)	0.04
Maternal home language N (%)			
Afrikaans	3 (9.4)	4 (14.8)	0.54
isiXhosa	26 (81.2)	21 (77.8)	
Other African language	3 (9.4)	2 (7.4)	
Ethnicity N (%)			
Black African	29 (90.6)	23 (85.2)	0.55
Mixed ancestry	3 (9.4)	4 (14.8)	
Maternal marital status N (%)			
Married	8 (25.0)	8 (29.6)	0.86
Never married	21 (65.6)	19 (70.4)	
Widowed/divorced/ separated	3 (9.4)	0 (0.0)	
Maternal education			
Years of education – mean (SD)	10.3 (1.7)	11.1 (1.3)	0.04
≥Grade 12 *N* (%)	11 (34.7)	14 (51.8)	
Grades 10–11 *N* (%)	12 (37.4)	11 (40.7)	
Grades 8–9 *N* (%)	7 (21.8)	1 (3.4)	
≤Grade 7 *N* (%)	2 (6.3)	1 (3.4)	
Primiparous *N* (%)	5 (15.5)	7 (25.9)	0.33
Planned pregnancy *N* (%)	6 (18.8)	11 (42.3)	0.04
Gestation in weeks at first antenatal visit – mean (SD)	21.9 (6.8)	21.4 (6.8)	0.81
Tobacco use during pregnancy *N* (%)	4 (12.5)	1 (3.7)	0.21
Alcohol use in pregnancy *N* (%)	8 (25.0)	4 (14.8)	0.33
Maternal CD4 percentile at birth – mean (SD) (*N*)	28.4 (8.2) ($N = 29$)	38.8 (8.0) ($N = 27$)	<0.01
Infant gender, male *N* (%)	19 (59.4)	13 (48.2)	0.39
Gestation at delivery in weeks – mean (SD)	38.7 (1.5)	39.0 (1.6)	0.49
Late preterm (36–37 weeks) *N* (%)	2 (6.2)	2 (7.4)	
Low birth weight < 2500 g *N* (%)	3 (9.4)	1 (3.7)	0.38
Birth weight (g) – mean (SD)	3048 (380)	3096 (445)	0.65
Birth length (cm) – mean (SD)	48.8 (3.2)	48.5 (4.0)	0.78
Breastfeeding duration in months – mean (SD)	5.5 (4.7)	13.7 (8.8)	<0.01
Breastfeeding at age 2 weeks *N* (%)	13 (40.6)	27 (100)	<0.01
Still breastfeeding at 6 months *N* (%)	3 (9.3)	18 (66.7)	<0.01
Type of Housing *N* (%)		$N = 26$*	
Formal Housing	16 (50)	15 (59.2)	0.56
Informal Housing	16 (50)	11 (42.7)	
Subsequent pregnancy *N* (%)	6 (19)	4 (14.8)	0.74
Maternal employment *N* (%)	15 (46.9)	11 (40.8)	0.64
Regular contact with father (*N*)	12 (37.5%)**	13 (48%)***	0.24

MIHS = Mother Infant Health Study; SD = standard deviation.
*One value missing; **two fathers demised; ***one father demised.

Table 2. Sociodemographic and anthropometric characteristics of HIV-exposed uninfected and HIV-unexposed children at 2–3 years of age in the MIHS cohort.

Characteristic	HIV-exposed uninfected $N = 32$	HIV-unexposed $N = 27$	P value
Age at assessment in months – mean (SD)	36 (2.6)	35 (2.6)	0.15
Gender (male) *N* (%)	19 (59.4)	13 (48.2)	0.39
Currently living with mother *N* (%)	32 (100.0)	26 (96.3)	0.46
Temporary change in primary caregiver *N* (%)	6 (18.8)	3 (11.1)	0.49
Daycare attendance *N* (%)	8 (25.0)	14 (51.8)	0.64
Head circumference-for-age z-score – mean (SD)	0.39 (1.38)	0.07 (0.87)	0.31
Weight-for-age z-score – mean (SD)	0.36* (0.87)	0.09 (0.69)	0.19
Height-for-age z- score – mean (SD)	−0.90 (0.85)	−0.83 (0.95)	0.77
Weight-for-height z-score – mean (SD)	1.26* (0.98)	0.77 (0.77)	0.04

MIHS = Mother Infant Health Study SD = standard deviation.
Missing Data *One participant value missing.

Table 3. Neurodevelopmental outcomes of HIV-exposed uninfected (HEU) and HIV-unexposed uninfected (HU) children according to the Bayley Scales of Infant and Toddler Development 3rd edition (BSID) and the Strengths and Difficulties Questionnaire pre-school version (SDQ).

Assessment	HIV exposed uninfected ($N = 32$)	HIV unexposed ($N = 27$)	P value	Cohen's D effect size (CI)
BSID Domain Composite scores-mean (SD)				
Cognitive	87.5 (5.2)	88.5 (7.2)	0.61	0.16 (−0.36, 0.68)
Motor	93.9 (7.9)	94.5* (7.8)	0.73	0.08 (−0.45, 0.61)
Language	89.9 (6.6)	90.5 (8.0)	0.82	0.09 (−0.44, 0.61)
Scaled scores-mean (SD)				
Fine Motor	9.4 (1.7)	9.4 (1.6)	0.90	0.04 (−0.48, 0.57)
Gross Motor	8.6 (1.7)	8.6* (1.3)	0.73	0.06 (−0.47, 0.59)
Receptive Language	8.1 (1.4)	8.2 (1.5)	0.97	0.06 (−0.46, 0.59)
Expressive Language	8.4 (1.3)	8.5 (1.5)	0.65	0.1 (−0.42, 0.63)
SDQ scores-mean(SD)				
Total difficulties	13.4 (5.0)	15.8 (5.3)	0.05	0.47 (−0.07, 1.00)
Externalising problems	8.4 (3.7)	10.4 (4.0)	0.04	0.51 (−0.02, 1.04)
Internalising problems	5.1 (2.9)	5.4 (2.7)	0.49	0.14 (−0.39, 0.66)
Conduct problems	3.2 (1.8)	4.3 (2.3)	0.02	0.54 (0.01, 1.07)
Hyperactivity	5.2 (2.6)	6.1 (2.6)	0.20	0.35 (−0.18, 0.88)
Emotional problems	3.5 (1.8)	3.0 (2.0)	0.26	0.27 (−0.26, 0.80)
Peer problems	2.0 (1.4)	2.0 (1.6)	0.99	0.05 (−0.57, 0.48)
Prosocial behaviour	7.2 (1.7)	7.0 (2.2)	0.54	0.09 (−0.62, 0.43)

BSID Bayley Scales of Infant and Toddler Development- Third edition CI Confidence interval SD Standard deviation SDQ Strengths and difficulties questionnaire (pre-school version).
*=one value missing.

remained significantly higher in the HU participants while externalising difficulties showed a trend towards significance in HU children (Cohen's $d = 0.51$, $p = 0.05$). When applying British SDQ cut-off scores, there were twelve children (20.3%), (six HEU and six HU), with "very high" TDS, eleven children (18.6%), (two HEU and nine HU) with "very high" conduct scores

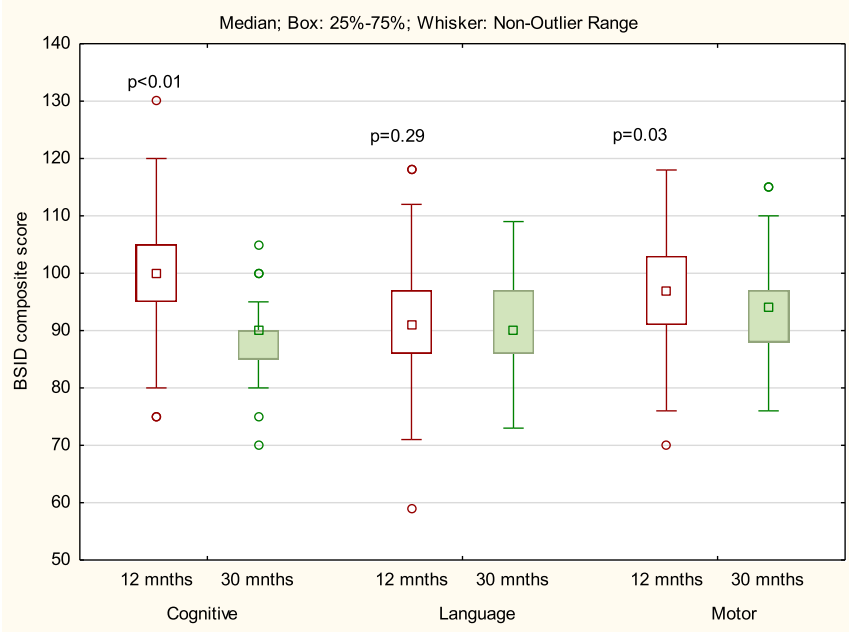

Figure 1. Comparison of Bayley composite scores of MIHS cohort at 12 months ($n = 96$) and 30 months ($n = 59$) visits. *Fifty three children had assessments at both 12 and 30 month visits.

and thirteen (22%), (six HEU and seven HU) with "very high" hyperactivity scores.

Stunted children (two HEU and four HU) had lower BSID motor scores (mean 88.0, SD 6.8) than those with normal height (93.8, SD 7.6; $p = 0.05$) and a trend towards lower fine motor scores (8.3 (SD 1.0) versus 9.5 (SD 1.6); $p = 0.08$). Stunting was also associated with higher SDQ TDS (17.8, SD 1.3) versus that of non-stunted children (14.1, SD 5.4; $p < 0.01$).

Higher level of maternal education was significantly associated with improved motor (Pearson's $r = 0.4$, $p < 0.01$), less strongly with cognitive ($r = 0.25$, $p = 0.06$) but not language domains ($r = 0.15$, $p = 0.27$). Antenatal alcohol and tobacco exposure were not associated with poorer outcome on the BSID or SDQ in either group. Mothers who had experienced depressive symptomatology at 12 months postpartum (CES-D. > 15) did not report higher child SDQ scores ($p = 0.18$) and this did not differ by group. Breastfeeding did not confer an advantage on behavioural outcomes in either group.

Serial BSID assessments of children tested at twelve months and 30–42 months ($n = 53$) showed significant decline in cognitive scores ($p < 0.001$) with similar decreases in HEU and HU groups (Figure 1). There was a statistical but not clinically significant decline in motor scores for the combined cohort ($p = 0.03$). Cognitive scores increased in only three (5.6%) HEU children at the second assessment, language scores increased in eight (27.5%) HEU and six (25%) HU children, and motor scores increased in ten HEU (34%) and six (25%) HU children.

Neither low placental weight nor pathological lesions (acute and chronic chorioamnionitis, chronic villitis, placental insufficiency and subacute fetal hypoxia) were associated with poorer neurodevelopmental or behavioural outcomes; a finding that persisted when stratified by HIV-exposure status.

Discussion

We demonstrated similar outcomes for low-risk HEU and HU children on the BSID. No child in our cohort had severe developmental delay, however this may be attributed to excluding all infants with preterm or perinatal complications. The high proportion of HEU children with macrocephaly observed at age 12 months was sustained at age 30–42 months (Springer et al., 2018). The neurodevelopmental findings are in keeping with observations from recent studies conducted in Zambia and Botswana (Chaudhury et al., 2017; Ngoma et al., 2014). Our HEU cohort resembled that from Botswana in terms of maternal ARV regimen and low rate of breastfeeding. In contrast, a multicentre study of older Thai and Cambodian children found slightly lower verbal, full scale IQ and Binet Bead memory scores in HEU children although the clinical significance of this finding was uncertain (Kerr et al., 2014).

This cohort had a lower prevalence of stunting than the national average of 27% (Said-Mohamed, Micklesfield, Pettifor, & Norris, 2015). Four of the six stunted children (three HU and one HEU) were breastfed for a

duration of four to six months while the other two HEU infants received formula feeds. Other potential causes for short stature were not investigated. However stunting was associated with lower BSID motor scores similar to other African studies; and was more prevalent in the HU group (Casale, Desmond, & Richter, 2014; McDonald et al., 2013).

Socioeconomic disadvantage leading to lack of educational opportunities is an independent risk factor for poor performance on neurodevelopmental assessments and may have accounted for the "low average" BSID composite scores of the cohort (Burchinal, Roberts, Hooper, & Zeisel, 2000), potentially overriding or masking the effects of other factors. Interpretation of the significance of these generally low-average scores is limited, by the lack of validated South African BSID norms for two to three year olds. A Malawian study argued that US BSID norms cannot be applied to categorise neurodevelopmental delay in other cultural contexts where child-rearing practices differ (Cromwell et al., 2014). This underlines the importance of comparing HEU with HU participants from a similar background, in the absence of local norms, as in our cohort.

Ballot et al reported declining BSID language scores between 9 and 19 months and low average cognitive scores in South African infants from a lower socioeconomic group. (Ballot et al., 2017). Our cohort's language quotients although similarly low, did not decrease over time, however there was a significant decline in their cognitive scores. This may partly be attributed to certain test items. Colour discrimination is an essential knowledge requirement of the BSID cognitive scales at 30 months, and tasks involving identification and naming of colours depend on early childhood education (Bonnier, 2008). Book-reading has also been associated with improved cognitive and language outcomes in young children (Raikes et al., 2006). Since only eight (13.5%) mothers read to their child more than once a week, it is unsurprising that we did not see this effect of book-reading. Early childhood education and book-reading are both areas that policymakers could target to improve cognitive outcomes in young children.

Mothers of HEU children reported fewer behavioural difficulties than the HU group. Reasons for this were unclear. Mothers with HIV are in a care system that may also give them access to psychosocial support which could indirectly assist parenting and coping strategies. Similar findings were described in a Thai cohort although differences did not reach statistical significance (Sanmaneechai, Puthanakit, Louthrenoo, & Sirisanthana, 2005) while Kerr found no difference in behavioural outcome in older Thai and Cambodian HEU and HU children (mean age 7.3 years) (Kerr et al., 2014). Smith reported poorer adaptive and socialisation skills in young HEU children, but suggested that cultural differences might be a confounding factor (Smith et al., 2017). We did not fully explore risk and protective factors; our cohort generally had high SDQ externalising behaviour scores possibly related to family stressors and socioeconomic adversity (Holtz et al., 2015; Hunt & Tomlinson, 2018).

Amongst other factors, breastfeeding can improve neurodevelopment although the lack of a dose-response effect suggests additional confounders (McCrory & Murray, 2013). This advantage was not evident in our cohort, but given that breastfeeding was not universally recommended to HIV positive mothers during our study, we were not fully able to interrogate this (Zunza et al., 2018). Furthermore, there was no association between placental pathology and neurodevelopmental delay as found previously (Hodyl et al., 2017). Likewise depressive symptomatology at 12 months postpartum was not associated with poorer behavioural outcome at 3 years. However, maternal mental health should be evaluated at multiple antenatal and postnatal time-points to determine duration and severity of depression (Rotheram-Fuller et al., 2018).

Strengths of the study included contemporaneous HEU and HU participant groups, which partially adjusted for confounders and enabled between-group comparisons. All children lived with their biological mothers and caregiver consistency was similar in both groups.

Limitations included small sample size with lower statistical power. Attrition was high throughout the MIHS study. There were similar numbers of HEU and HU in the non-retained group; the lower infant birth weight of participants tested at 2–3 years of age compared with the non-retained group was not clinically significant. Previous studies have reported high attrition in young HEU participants due to mothers returning to employment (Sidze et al., 2015; Williams et al., 2008), but our participants were lost to follow up, so the reason for attrition is not known. We did not investigate other aspects of the home environment (e.g., quality of caregiving) that have also been shown to improve early neurodevelopmental outcome (Bass et al., 2016) and SDQ scores reflected only the mothers' perceptions. Finally, interpretation of results of assessments without contextually relevant and validated tools can be challenging in different cultural environments.

In conclusion, the developmental and behavioural outcome of pre-school HEU children was equivalent to that of a well-matched HU control group from a similar socio-economic background while HEU children were reported to exhibit fewer conduct problems. Thus in

this cohort of term HEU children born to women with low-risk pregnancies and without advanced maternal HIV disease, HIV-exposure did not confer additional risk. Stunting was nevertheless associated with increased behavioural problems, regardless of HIV exposure.

Future recommendations include additional developmental surveillance for both HEU and HU children living in impoverished circumstances (Bonnier, 2008; Slogrove et al., 2018). Recent initiatives such as the "First 1000 days Campaign" involving partnership between the Western Cape Social Development and Health departments could provide caregiver education, counselling and support to optimise children's cognitive and emotional development as suggested by the WHO Nurturing Care Framework (Western Cape Government Department of Health, 2017) (WHO, 2018).

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