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Title: Postpartum maternal mental health is associated with cognitive development of HIV-exposed infants in Zimbabwe: a cross-sectional study

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Postpartum maternal mental health is associated with cognitive development of HIV-exposed infants in Zimbabwe: a cross-sectional study

Abstract

This study examines the cognitive profiles of infants born to HIV positive mothers in Zimbabwe.

Caregivers with HIV exposed infants delivered in 30 clinics in two areas of Zimbabwe were recruited to the study. Of the 574 study participants, 562 caregiver-infant dyads with a biological HIV+ve mother and infant aged 0-24 months were interviewed.

All infants were tested by a trained administrator for cognitive development on the Mullen Scales of Early Learning (MSEL). The Edinburgh Postnatal Depression Scale and Parental Stress Index-Short Form were completed by the mothers together with infant and caregiver socioeconomic characteristics. Linear regression models were used to relate cognitive development scores to maternal stress scores, maternal depression scores and infant HIV status adjusting for infant and caregiver characteristics, as well as socioeconomic factors.

Higher maternal depression scores were associated with lower overall infant cognitive scores (adjusted mean difference (aMD)=-0.28; CI 95%:-0.50 to -0.06; p=0.01) and in the expressive language (aMD=-0.14; CI 95%:-0.27 to -0.01; p=0.04), fine motor skills (aMD=-0.17; CI 95%: -0.33 to -0.01; p=0.03), gross motor (aMD=-0.22; CI 95%:-0.40 to -0.04; p=0.02), and visual reception (aMD=-0.22; CI 95%:-0.40 to -0.05; p=0.01) domains. Higher maternal stress was associated with poorer overall infant cognitive scores (aMD=-0.11; CI 95%:-0.20 to -0.02; p=0.02) and in the specific domains of expressive language (aMD=-0.07; CI 95%:-0.12 to -0.01; p=0.01), gross motor skills (aMD=-0.12; CI 95%:-0.18 to -0.05; p<0.01) and visual reception (aMD=-0.09; CI 95%:-0.16 to -0.02; p=0.02). Comparisons between the small number of HIV positive infants (n=16) and the HEU infants (n=381) showed the latter to have higher mean gross motor scores (50.3 vs. 40.6; p=0.01). There was no evidence of difference by HIV status in the other MSEL domains or overall mean cognitive scores.

Our findings demonstrate the association between maternal mood and stress levels and child cognitive functioning, particularly in expressive language and visual reception development. Although cross sectional data cannot shed light on the direction of this association, the study suggests that interventions to address maternal stress and depression symptoms may prove to be beneficial.

Word count: 337

Key words: Maternal mental health; Cognitive development; HIV infected and exposed infants; Mullen scales of early learning; Sub-Saharan Africa

Introduction

Although the burden of HIV/AIDS in children is steadily decreasing, an estimated 2.1 million (<15 years) children worldwide are living with HIV (UNAIDS, 2017). The majority (81%) of new paediatric HIV infections are recorded in children living in Africa (UNAIDS, 2015). There is substantial evidence documenting the negative impacts of HIV on child development outcomes, particularly cognitive development.

Multiple studies examining the effects of HIV infection and exposure (without becoming infected) on children's cognitive development have described the risk of developmental delay and impairment in both HIV infected and HIV-exposed uninfected infants (HEU) (Blanchette, Smith, Fernandes-Penney, King, & Read, 2001; Gay et al., 1995; Hutchings & Potterton, 2013; Knight, Mellins, Levenson, Arpadi, & Kairam, 2000) compared to healthy control infants (Van Rie, Mupuala, & Dow, 2008), particularly in resource-limited settings (Le Doare, Bland, & Newell, 2012; Sherr, Croome, Parra Castaneda, Bradshaw, & Herrero Romero, 2014; Smith et al., 2012). Furthermore, perinatally-infected children face greater risk of neurological and neuropsychological deficits compared to HEU infants. This may be due to direct effects of HIV on the central nervous system and the brain structures involved in the regulation of emotion, behaviour, and cognition (Albright, Soldan, & Gonzalez-Scarano, 2003; Blanchette et al., 2001; Epstein & Gelbard, 1999; Gay et al., 1995; Revicki, Chan, & Gevirtz, 1998), exposure to treatment or other HIV related factors. HIV can also impact the neurodevelopment of children indirectly through its negative influences on the child's living environment (Van Rie et al., 2008), including poverty, food insufficiency, community stigma and discrimination, caregiver unemployment, caregiver illness and bereavement (Lowick, Sawry, & Meyers, 2012; L. Richter, 2004; L. M. Richter et al., 2009; Sherr et al., 2014; Walker et al., 2007). The developmental outcomes of children affected by HIV are further influenced by other factors, including the extent of early years stimulation, and maternal mental health (Grantham-McGregor et al., 2007; Murphy, Marelich, Armistead, Herbeck, & Payne, 2010). Research suggests that quality of caregiving provided to HIV positive and affected children plays a role in mitigating these negative outcomes (Bass et al., 2016).

Current literature has established that maternal stress and anxiety are negatively associated with child developmental outcomes (Murphy et al., 2010; Murray et al., 2017) in the general population and affect a broad range of parenting skills, which are negatively associated with poorer parent-child communication, poorer and less consistent parenting discipline leading to child problem

behaviours (Murphy et al., 2010). Exposure to maternal depression in particular has a negative influence on child development in infancy and early childhood, and is associated with impaired cognitive performance leading to social, behavioural problems and compromised physical health (Black et al., 2007; Comaskey et al., 2017; Cummings & Davies, 1994; LeWinn et al., 2009). A South African study found that maternal depression was related to increased parenting stress and parent–child dysfunction which was again associated with children's behaviour and functioning (Allen et al., 2014).

Understanding the role of HIV and maternal mental health in child development is critical. A study has shown that living with HIV and caring for AIDS orphaned children increased the odds of clinically relevant anxiety symptoms among South African caregivers (Kuo, Cluver, Casale, & Lane, 2014). It is understandable that maternal stress is exacerbated when living with a chronic condition such as HIV, where caregiving duties and coping with psychological and medical demands of dealing with life-threatening condition are difficult (Murphy et al., 2010). However, there is a circular pattern observed between parenting stress and children dysfunctional behaviour, where parenting stress and children's behavioural problems exacerbate one another.

The relationship of maternal mental health and cognitive functioning of children needs further exploring, with a need for studies in other Sub-Saharan African countries. This study aimed to investigate cognitive differences in children infected and affected by HIV and the relationship between maternal stress and depression scores, and child cognitive performance in Zimbabwe.

Methods

Study Design

This is a cross-sectional analysis of baseline data collected as part of a cluster-randomized controlled trial (The Child Health Initiative for Developmental Outcomes [PACTR201701001387209]) prior to implementation of the intervention. Participants were recruited from catchment areas surrounding 30 clinics in 2 rural districts of Zimbabwe.

Participants

All mothers with confirmed HIV status during pregnancy were recruited to the trial, via the Exposed Infant Registers, held at clinics. For infants to be eligible for inclusion, they had to be singleton births, aged 0 to 24 months, and not suffering from other chronic illness (not including HIV).

Enrolment Procedures

Eligible participants were invited to attend an orientation meeting to learn about the trial. After orientation, eligible caregivers who provided verbal consent to enrol were booked for enrolment procedures and baseline assessments. At enrolment, a questionnaire was administered to participating caregivers by a trained interviewer with more sensitive information being collected using audio computer-assisted survey instrument (Langhaug et al., 2011).

Two trained nurses who were blind to the infant's HIV status carried out the developmental assessments using the Mullen Scales of Early Learning (MSEL). Data on the developmental assessment of the infants were collected and double-entered onto a specialized database by the research team. The developmental assessment procedures of the infants were video recorded and randomly selected sessions were reviewed to assess reliability and repeatability of assessments.

Assessment Measures

i) Infant cognitive measure

The cognitive profiles of the participating infants were assessed using the MSEL. The MSEL is based on the theory that a child's intelligence is most accurately conceptualized as a network of interrelated but functionally distinct cognitive skills (Boivin, Nakasujja, Sikorskii, Opoka, & Giordani, 2016; Mullen, 1995). It is an individually administered comprehensive measure that assesses a child's abilities in visual, linguistic, and motor domains, and distinguishes between receptive and expressive processing for infants and preschool children from birth through 68 months. The five domains assessed here were gross motor skills, visual reception, fine motor skills, receptive language, and expressive language (Mullen, 1995). The MSEL was administered to all infants in the standardized format upon enrolment in the study. The infant's primary caregiver was sat in a chair behind the child if the child was able to sit at a chid sized testing table, or with the caregiver depending on age.

The test scores obtained by the children for each MSEL scale were transformed into an age-standardized T-score, using a US reference population as there is no local Zimbabwean reference population on this index. The standardized T-scores of four components - the fine motor, expressive language, receptive language, and visual perception scales were combined to produce the Early Learning Composite (ELC) score. Composite scores were used in this analysis to measure general cognitive functioning. Gross motor scale was not included in the ELC score and was used separately as an indicator concentrating on their motor skills (Akshoomoff, 2006; Mullen, 1995).

ii) Maternal mental health measure

The Edinburgh Postnatal Depression Scale (EPDS), a postpartum depression-screening questionnaire that has been validated for use in Zimbabwe (Chibanda et al., 2010; Cox, Holden, &

Sagovsky, 1987) was administered to participating mothers. The EPDS comprises 10 questions which generate scores ranging from 0-30. The literature provides a cut-off point (≥12) indicating concerns for referral. These cut-off levels used in past research in similar settings found that this threshold was effective in detecting woman with major, and minor depression with sensitivity of 80% (Gibson, McKenzie-McHarg, Shakespeare, Price, & Gray, 2009). The EPDS scores allow for a categorisation into none or minimal (EPDS scores 0-6), mild (EPDS scores 7-13), moderate (EPDS scores 14-19) and severe depression (EPDS scores 20-30) (McCabe-Beane, Segre, Perkhounkova, Stuart, & O'Hara, 2016). The EPDS is not diagnostic.

Parental Stress Index-Short Form (PSI-SF), a self-completed screening tool used for identifying different types of stress associated with parenting, was administered to caregivers (Abidin, 1995). This index comprises of 3 subscales: Parental Distress, Parent–Child Dysfunctional Interaction and Difficult Child. Child and Parent domains combine to form Total Stress Score. These are scored using the following 5-point scales: (strongly agree, agree, not sure, disagree, and strongly disagree) and generate scores ranging from 40-149.

iii) Socioeconomic measure

Hunger has consistently emerged to be a major concern among Sub-Saharan African populations living with HIV (Murray et al., 2017), hence a subset of questions from the Household Food Insecurity Access Scale (Coates, Swindale, & Bilinsky, 2007) were used to assess household food security. These were used to categorise participants as living in: i) food secure (rarely worried about food access or quality), ii) moderately food insecure (sometimes i.e. 3–10 times in the last month, worried about food access or quality), or iii) severely food insecure households (≥1 household member going to bed hungry or often worrying about food access or quality).
Other sociodemographic information such as: infant characteristics (age, gender, birth weight, growth rate-obtained from child's health card), caregiver characteristics (age, marital status) and socioeconomic factors (educational level, employment status, and number of adults living in the household) were also collected.

Statistical Analysis

Infant and caregiver characteristics as well as socioeconomic factors were described using mean and standard deviations (SD) for continuous variables, and frequency percentages for categorical variables. Only biological mothers (i.e. excluding other type of caregivers) were included in this analysis. The MSEL scores were reported using mean, SD, and adjusted mean differences (95% CI). Prior to data analysis, score distributions on all dependent measures were examined to test the assumptions of normality and homogeneity of variance. In addition, data were

adjusted for clustering by clinic. All analyses were performed using STATA v.14.1 (StataCorp LP, College Station, Texas, USA).

i) Maternal stress and mood and cognitive development of infants

Linear regression models were fitted to relate MSEL scores to exposure variables maternal stress (using PSI-SF), and mental health (using EPDS) respectively. EPDS and PSI-SF total stress scores were tested against the MSEL scales both univariably and adjusting for confounders. HIV status was included in the models a priori. Results were reported using mean EPDS scores, mean total stress scores, SD, unadjusted and adjusted mean differences.

ii) HIV status and cognitive development of infants

For this analysis infants with unknown HIV status were excluded. Infant HIV status was established by caregiver report and/or clinic records at enrolment or baseline assessment. HEU infants were defined as having confirmed HIV negative status but born to an HIV infected biological mother. Student's t-test and Pearson's chi square were used to test for differences in selected demographic infant and caregiver characteristics by HIV status.

Univariate models were used to assess the relationship between MSEL scores and the infant's HIV status, and multivariate regression was then used adjusting for potential confounders - i.e. variables that were associated with both the outcome and the exposure ($p<0.2$). Infant's age and gender were included in the models a priori.

Ethical Approval

The trial has been approved by the Medical Research Council of Zimbabwe (MRCZ/A/1943), University College London (6789/002) and the London School of Hygiene and Tropical Medicine (9912).

Results

Of the 671 eligible caregiver-infant dyads invited to participate in the trial, 574 (86%) agreed to do so. The caregivers sample included 562 (98%) biological mothers and 12 (2%) other caregivers-mainly grandmothers. Data from the biological mothers only were included for analysis. For the HIV status and infant cognitive development models, infants with unknown HIV status were further excluded (n=165), leaving a total of 397 dyads.

Maternal stress and mood

Infant and caregiver characteristics are summarized in Table 1. The mean age of infants was 11.9 (SD 6.5) months, and 51% were girls. The mean age of mothers was 32 years (SD 6.3). Over half (54%) of mothers had completed secondary school level education and 37% were in paid employment. Most households (91%) had 1-3 resident adults, and two in five (40%) households suffered from food insecurity i.e. members worried about food access or at least one family member went to bed hungry. The mean maternal depression score on the EPDS scale was 11.5 (SD 6.5). When using the EPDS cut-off scores for mild, moderate and severe depression, over half (64%) of mothers experienced mild or moderate depression, with 10% categorised as having severe depression. The mean maternal stress score on the PSI SF scale was 84.8 (SD 16.3).

Results from multivariate models suggest that maternal stress and depression scores were associated with the infants' cognitive scores. Higher maternal EPDS depression scores were associated with lower infant cognitive scores in the early learning composite score (adjusted mean difference (aMD)= -0.28; CI 95%: -0.50 to -0.06; p=0.01) and all domains; expressive language (aMD=-0.14; CI 95%: -0.27 to -0.01; p=0.04), fine motor skills (aMD=-0.17; CI 95%: -0.33 to -0.01; p=0.03), gross motor (aMD=-0.22; CI 95%: -0.40 to -0.04; p=0.02), visual reception (aMD=-0.22; CI 95%: -0.40 to -0.05; p=0.01), and weakly associated with receptive language (aMD=-0.15; CI 95%: -0.30 to 0.01; p=0.07) (Table 2). Infant's age, and caregiver's employment status, were found to negatively influence the relationship between maternal depression scores and MSEL scores.

Similarly, maternal stress scores were associated with infant cognitive scores (Table 3). Higher stress scores were associated with poorer infant scores in the early learning composite score (aMD=-0.11; CI 95%: -0.20 to -0.02; p=0.02) and in expressive language (aMD=-0.07; CI 95%: -0.12 to -0.01; p=0.01), gross motor skills (aMD=-0.12; CI 95%: -0.18 to -0.05; p<0.01), visual reception (aMD=-0.09; CI 95%: -0.16 to -0.02; p=0.02), and weakly associated with receptive language (aMD=-0.06; CI 95%: -0.13 to 0.00; p=0.06). Infant's age, growth rate, and examiner to administer MSEL were found to be confounders in the relationship between maternal stress scores (PSI-SF total stress) and MSEL scores.

Infant HIV Status

From a total of 397, there were 16 HIV positive infants and 381 HEU infants. HIV status was not associated with infant's age at enrolment, gender, or birth weight (Table 4). However, the mothers of HEU infants were slightly older than HIV positive infants mothers (32 vs. 29; p=0.05). Mothers caring for HIV positive infants reported higher mean stress scores compared to the HEU group (95.8 vs. 85.0; p=0.01).

Results of the cognitive function analyses by HIV status are shown in Table 5. Infant's HIV status was associated with gross motor scores, with the HEU infants having higher mean gross motor T-scores compared to HIV positive infants (50.3 vs. 40.6; p=0.01). There was no evidence of a significant difference by HIV status in the other MSEL domains and overall score.

Discussion

Our study shows a high level of stress and depressed mood scores among HIV+ve mothers. Although the EPDS scale used was not diagnostic, the general literature cut-off points indicate that 10% of mothers had scores in the severe range, while over half of the sample had scores falling in the mild to moderate range. Stress levels were also notably high.

Our study strongly suggests that higher maternal stress and depression symptoms are associated with poorer infant cognitive performance in an HIV affected sample. Maternal stress was also found to be higher in the group caring for HIV positive infants. Of note we did not find a relationship between HIV status of the infants and cognitive development – but the analysis was confined to the 16 HIV positive infants.

Contrary to findings from a Ugandan study where caregivers' depression scores were related only to the measure of child behaviour and not to the performance-based measures of cognition (Familiar et al., 2016), our results show that the expressive language and visual reception cognitive domains in particular were consistently affected by both maternal stress and depression symptoms. However, a study examining maternal depression and caregiving during the first year of life in England, suggested that maternal depression was associated with poorer caregiving of children and that the poorer caregiving was subsequently associated with poorer language development , through an indirect pathway (Stein et al., 2008). In the presence of chronic infection such as HIV, home environment and external stressors could contribute to explaining our findings of how maternal depression scores and child cognitive performance are linked. Previous studies show depression or stress among HIV positive mothers (Murphy et al., 2010) to be high when caring for HIV infected children (Murray et al., 2017) as well as being associated with negative child development outcomes (Black et al., 2007; Comaskey et al., 2017; Cummings & Davies, 1994). It is possible that the association could be explained by both directions – the mood and stress affecting child development, or child development delays affecting maternal mood and stress.

Some of our findings were consistent with other studies which describe infants who are HIV infected experiencing an increased risk of developmental delays in the gross motor domain compared to HEU children (Hutchings & Potterton, 2013; Knight et al., 2000; Tahan, Bruck, Burger, & Cruz, 2006). Although available research suggests differences in the cognitive

performances between HIV infected and HEU children (Van Rie et al., 2008; Whitehead, Potterton, & Coovadia, 2014), we were unable to detect a difference in the overall cognitive scores between the two groups. This could be due to the very small sample size of HIV infected infants, the fact that both groups of infants lived in an HIV endemic population affected by the multifaceted ramifications of HIV, or early diagnosis and early initiation on treatment (Weber et al., 2017), as all 16 HIV positive children in this study were initiated on ART at 0 and 1 month old.

Our study had a large sample size which was representative of the study population. It also utilises assessment tools previously validated in Africa, such as the MSEL and EPDS. Nevertheless, there were a number of limitations. The cross-sectional nature of our data limited our ability to fully understand the developmental differences of the two groups over time. We were underpowered to detect a difference between HIV positive and HEU infants due to the small number of HIV positives, increasing the risk of chance effects. The Mullen scales use a US reference group which is not ideal given the setting of the study in Zimbabwe. Ideally locally validated scales and reference groups would be preferable. However the Mullen scales has been used to good effect in other studies of cognitive performance in Africa (Boivin et al., 2016; Mireku et al., 2016; Ruiseñor-Escudero et al., 2016) and is effective in independently measuring infants cognition rather than relying on caregiver reporting. Mental health outcome was assessed using a screening tool (EPDS) and only gave an indication of depressive symptoms rather than a clinical diagnosis of depression in mothers.

Despite the limitations, the study demonstrates the potential importance of maternal mood and stress levels in infant language and visual perception development within an HIV affected population. Introducing a comprehensive intervention, which incorporates elements of parental stress and depression reduction, as well as adequate child stimulation, may address this. Further studies exploring the drivers of maternal stress and depression symptoms could also prove to be insightful for future research.

With the roll out of B+ strategies in pregnancy the level of HIV infection in infants will dramatically decrease. However, the group of HEU children will increase. Treatment may affect health outcomes for caregivers, but the strains of an HIV diagnosis may still be high and may influence the quality of child care and stimulation. Our data clearly indicates that mothers are recording high levels of stress and low mood and these are associated with cognitive development in young infants. Interventions to routinely identify and modify such burdens are clearly needed. These would be of benefit directly to the HIV positive mothers, and in turn may affect child development outcomes. Studies in South Africa aimed at maternal depression have shown benefits

for child development (Tomlinson et al., 2015; Tomlinson, Rotheram-Borus, Scheffler, & le Roux, 2017). It seems from our data that maternal factors are equally important in Zimbabwe.

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Disclosure statement

The authors declare that they have no competing interests.

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List of tables

501 *Table 1: Baseline characteristics of study sample*

Characteristics	**Total Sample (n=562)**	
Infant		
Age (Months), mean (SD)	11.9	6.5
Gender, n (%)		
Female	287	51.1
Male	275	48.9
Birth weight (Kilograms)**~**, mean (SD)	3.0	0.5
Growth rate~, n (%)		
Normal	262	47.1
Moderately underweight	273	49.1
Severely underweight	21	3.8
Caregiver		
Age (Years), mean (SD)	31.5	6.3
Education level (Completed secondary school and above), n (%)	301	53.6
Marital status ~ ^, n (%)		
Married	447	79.7
Divorced/separated	74	13.2
Widowed	27	4.8
Never been married	13	2.3
Employment status (Yes-employed), n (%)	206	36.7
Number of adults living in the same household $^{+}$**,** n (%)		
1-3 adults	502	90.5
4-6 adults	50	9.0
7-9 adults	3	0.5
Household food security, n (%)		
Little to no hunger	335	59.6
Moderate to severe hunger	227	40.4
Maternal depression scores (EPDS), mean (range), SD	11.5 (0-30)	6.5
Maternal depression scores *-Severity ranges of Edinburgh Postnatal Depression Scales,* n		

(%)		
None or minimal depression score	143	25.4
Mild depression score	190	33.8
Moderate depression score	171	30.4
Severe depression score	58	10.3
Maternal total stress scores (PSI-SF), mean (range), SD	84.8 (49-149)	16.3

Abbreviations: PSI-SF, Parental Stress Index-Short Form | SD, Standard Deviation

~ Missing data: Growth rate variable had 6 missing records |Birth weight variable had 2 missing records | marital status variable had 1 missing record

^ Marital status variable was recoded to married/not married during analysis

+There was 1 inaccurate record for the variable "Number of adults living in the same household" which was excluded from the table.

Table 2: Summary of association of maternal mental health (using EPDS) with child cognitive outcomes

Mullen Scales (T-scores)	**Unadjusted mean difference (95% CI)**	**Adjusted mean difference (95% CI)**	**P value***
Expressive Language	-0.16 (-0.30 to -0.03)	-0.14 (-0.27 to -0.01)	0.04
Fine Motor	-0.14 (-0.28 to -0.00)	-0.17 (-0.33 to -0.01)	0.03
Gross Motor	-0.06 (0.20 to 0.07)	-0.22 (-0.40 to -0.04)	0.02
Receptive Language	-0.13 (-0.27 to 0.01)	-0.15 (-0.30 to 0.01)	0.07
Visual Reception	-0.14 (-0.29 to 0.01)	-0.22 (-0.40 to -0.05)	0.01
Early Learning Composite Score	-0.25 (-0.46 to -0.04)	-0.28 (-0.50 to -0.06)	0.01

** Regression analysis was carried out relating MSEL scales and maternal depression. The models were adjusted for tested confounders (infant age, HIV status and caregiver's employment status).*

Table 3: Summary of association of maternal stress (using the PSI-SF total stress score) with child cognitive outcomes

Mullen Scales (T-scores)	**Unadjusted mean difference (95% CI)**	**Adjusted mean difference (95% CI)**	**P value***
Expressive Language	-0.12 (-0.17 to -0.07)	-0.07 (-0.12 to -0.01)	0.01

Fine Motor	-0.06 (-0.12 to -0.01)	-0.02 (-0.08 to 0.05)	0.58
Gross Motor	-0.08 (-0.13 to -0.02)	-0.12 (-0.18 to -0.05)	<0.01
Receptive Language	-0.09 (-0.14 to -0.03)	-0.06 (-0.13 to 0.00)	0.06
Visual Reception	-0.11 (-0.18 to -0.05)	-0.09 (-0.16 to -0.02)	0.02
Early Learning Composite Score	-0.19 (-0.27 to -0.10)	-0.11 (-0.20 to -0.02)	0.02

** Regression analysis was carried out relating MSEL scales and maternal stress. The models were adjusted for tested confounders (infant age, HIV status, growth rate, and examiner conducting the Mullen assessments).*

Table 4: Selected Infant and caregiver characteristics by HIV status

Characteristics	**HIV Positive infants (n=16)**		**HEU infants (n =381)**		**Total Sample (n=397)**		**P Values**
Infant							
Age (Months), mean (SD)	14.6	5.5	14.1	5.5	14.1	5.5	0.71
Gender, n (%)							0.71
Female	9	56.3	196	51.4	205	51.6	
Male	7	43.8	185	48.6	192	48.4	
Birth weight (Kilograms), mean (SD)	2.8	0.7	3.0	0.5	3.0	0.5	0.19
Caregiver							
Age (Years) *, mean (SD)	29.1	6.0	32.1	6.1	32.0	6.1	0.05
Maternal depression scores (EPDS), mean (range), SD	12.2 (0-30)	7.9	11.6 (0-30)	6.4	11.6 (0-30)	6.5	0.72
Maternal total stress scores (PSI-SF)*, mean (range), SD	95.8 (40-142)	22.0	85.0 (40-142)	15.9	85.4 (40-142)	16.3	0.01

Abbreviations: HEU, HIV-Exposed Uninfected |PSI-SF, Parental Stress Index-Short Form | SD, Standard Deviation.

*Variables with p <0.05 were considered to be statistically significant results.

526 *Table 5: Mullen T-scores of the HIV positive and HIV-exposed uninfected infants*

	HIV Positive infants (n=16)		**HEU infants (n=381)**		**Adjusted Mean difference (95% CI)**	**P value***
Mullen Scales (*T*-scores)	**Mean**	**SD**	**Mean**	**SD**		
Expressive Language	51.3	13.8	51.2	10.4	-1.92 (-6.69 to 2.83)	0.43
Fine Motor	51.2	13.4	49.8	11.7	-2.27 (-8.09 to 3.54)	0.44
Gross Motor	40.6	14.7	50.3	11.2	8.02 (1.93 to 14.11)	0.01
Receptive Language	48.4	13.2	46.2	11.7	-0.51 (-6.19 to 5.17)	0.86
Visual Reception	50.9	16.0	52.0	13.1	1.62 (-4.76 to 8.01)	0.62
Early Learning Composite Score	101.3	22.8	100.0	18.4	-1.18 (-9.14 to 6.79)	0.77

527 **Regression analysis was carried out relating MSEL scales and HIV status. Models were adjusted for*
528 *infant's age, gender, growth rate and mother's age.*