

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

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

33 **Abstract**

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

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

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

44 Higher maternal depression scores were associated with lower overall infant cognitive scores
45 (adjusted mean difference (aMD)=-0.28; CI 95%:-0.50 to -0.06; p=0.01) and in the expressive
46 language (aMD=-0.14; CI 95%:-0.27 to -0.01; p=0.04), fine motor skills (aMD=-0.17; CI 95%: -
47 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
48 reception (aMD=-0.22; CI 95%:-0.40 to -0.05; p=0.01) domains. Higher maternal stress was
49 associated with poorer overall infant cognitive scores (aMD=-0.11; CI 95%:-0.20 to -0.02; p=0.02)
50 and in the specific domains of expressive language (aMD=-0.07; CI 95%:-0.12 to -0.01; p=0.01),
51 gross motor skills (aMD=-0.12; CI 95%:-0.18 to -0.05; p<0.01) and visual reception (aMD=-0.09;
52 CI 95%:-0.16 to -0.02; p=0.02). Comparisons between the small number of HIV positive infants
53 (n=16) and the HEU infants (n=381) showed the latter to have higher mean gross motor scores
54 (50.3 vs. 40.6; p=0.01). There was no evidence of difference by HIV status in the other MSEL
55 domains or overall mean cognitive scores.

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

61 *Word count: 337*

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

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Introduction

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

71 Multiple studies examining the effects of HIV infection and exposure (without becoming infected)
72 on children's cognitive development have described the risk of developmental delay and impairment
73 in both HIV infected and HIV-exposed uninfected infants (HEU) (Blanchette, Smith, Fernandes-
74 Penney, King, & Read, 2001; Gay et al., 1995; Hutchings & Potterton, 2013; Knight, Mellins,
75 Levenson, Arpadi, & Kairam, 2000) compared to healthy control infants (Van Rie, Mupuala, &
76 Dow, 2008), particularly in resource-limited settings (Le Doare, Bland, & Newell, 2012; Sherr,
77 Croome, Parra Castaneda, Bradshaw, & Herrero Romero, 2014; Smith et al., 2012). Furthermore,
78 perinatally-infected children face greater risk of neurological and neuropsychological deficits
79 compared to HEU infants. This may be due to direct effects of HIV on the central nervous system
80 and the brain structures involved in the regulation of emotion, behaviour, and cognition (Albright,
81 Soldan, & Gonzalez-Scarano, 2003; Blanchette et al., 2001; Epstein & Gelbard, 1999; Gay et al.,
82 1995; Revicki, Chan, & Gevirtz, 1998), exposure to treatment or other HIV related factors. HIV can
83 also impact the neurodevelopment of children indirectly through its negative influences on the
84 child's living environment (Van Rie et al., 2008), including poverty, food insufficiency, community
85 stigma and discrimination, caregiver unemployment, caregiver illness and bereavement (Lowick,
86 Sawry, & Meyers, 2012; L. Richter, 2004; L. M. Richter et al., 2009; Sherr et al., 2014; Walker et
87 al., 2007). The developmental outcomes of children affected by HIV are further influenced by other
88 factors, including the extent of early years stimulation, and maternal mental health (Grantham-
89 McGregor et al., 2007; Murphy, Marelich, Armistead, Herbeck, & Payne, 2010). Research suggests
90 that quality of caregiving provided to HIV positive and affected children plays a role in mitigating
91 these negative outcomes (Bass et al., 2016).

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

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

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

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

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Methods

117 *Study Design*

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

122 *Participants*

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

127 *Enrolment Procedures*

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

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

138 *Assessment Measures*

139 *i) Infant cognitive measure*

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

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

158 *ii) Maternal mental health measure*

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

161 Sagovsky, 1987) was administered to participating mothers. The EPDS comprises 10 questions
162 which generate scores ranging from 0-30. The literature provides a cut-off point (≥ 12) indicating
163 concerns for referral. These cut-off levels used in past research in similar settings found that this
164 threshold was effective in detecting woman with major, and minor depression with sensitivity of
165 80% (Gibson, McKenzie-McHarg, Shakespeare, Price, & Gray, 2009). The EPDS scores allow for a
166 categorisation into none or minimal (EPDS scores 0-6), mild (EPDS scores 7-13), moderate (EPDS
167 scores 14-19) and severe depression (EPDS scores 20-30) (McCabe-Beane, Segre, Perkhounkova,
168 Stuart, & O'Hara, 2016). The EPDS is not diagnostic.

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

175 *iii) Socioeconomic measure*

176 Hunger has consistently emerged to be a major concern among Sub-Saharan African populations
177 living with HIV (Murray et al., 2017), hence a subset of questions from the Household Food
178 Insecurity Access Scale (Coates, Swindale, & Bilinsky, 2007) were used to assess household food
179 security. These were used to categorise participants as living in: i) food secure (rarely worried about
180 food access or quality), ii) moderately food insecure (sometimes i.e. 3-10 times in the last month,
181 worried about food access or quality), or iii) severely food insecure households (≥ 1 household
182 member going to bed hungry or often worrying about food access or quality).

183 Other sociodemographic information such as: infant characteristics (age, gender, birth weight,
184 growth rate-obtained from child's health card), caregiver characteristics (age, marital status) and
185 socioeconomic factors (educational level, employment status, and number of adults living in the
186 household) were also collected.

187 *Statistical Analysis*

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

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

196 ***i) Maternal stress and mood and cognitive development of infants***

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

202 ***ii) HIV status and cognitive development of infants***

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

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

212 ***Ethical Approval***

213 The trial has been approved by the Medical Research Council of Zimbabwe (MRCZ/A/1943),
214 University College London (6789/002) and the London School of Hygiene and Tropical Medicine
215 (9912).

216 **Results**

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

222 ***Maternal stress and mood***

223 Infant and caregiver characteristics are summarized in Table 1. The mean age of infants was 11.9
224 (SD 6.5) months, and 51% were girls. The mean age of mothers was 32 years (SD 6.3). Over half
225 (54%) of mothers had completed secondary school level education and 37% were in paid
226 employment. Most households (91%) had 1-3 resident adults, and two in five (40%) households
227 suffered from food insecurity i.e. members worried about food access or at least one family member
228 went to bed hungry. The mean maternal depression score on the EPDS scale was 11.5 (SD 6.5).
229 When using the EPDS cut-off scores for mild, moderate and severe depression, over half (64%) of
230 mothers experienced mild or moderate depression, with 10% categorised as having severe
231 depression. The mean maternal stress score on the PSI SF scale was 84.8 (SD 16.3).

232 Results from multivariate models suggest that maternal stress and depression scores were associated
233 with the infants' cognitive scores. Higher maternal EPDS depression scores were associated with
234 lower infant cognitive scores in the early learning composite score (adjusted mean difference
235 (aMD)= -0.28; CI 95%: -0.50 to -0.06; p=0.01) and all domains; expressive language (aMD=-0.14;
236 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),
237 gross motor (aMD=-0.22; CI 95%: -0.40 to -0.04; p=0.02), visual reception (aMD=-0.22; CI 95%: -
238 0.40 to -0.05; p=0.01), and weakly associated with receptive language (aMD=-0.15; CI 95%: -0.30
239 to 0.01; p=0.07) (Table 2). Infant's age, and caregiver's employment status, were found to
240 negatively influence the relationship between maternal depression scores and MSEL scores.

241 Similarly, maternal stress scores were associated with infant cognitive scores (Table 3). Higher
242 stress scores were associated with poorer infant scores in the early learning composite score
243 (aMD=-0.11; CI 95%: -0.20 to -0.02; p=0.02) and in expressive language (aMD=-0.07; CI 95%: -
244 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
245 reception (aMD=-0.09; CI 95%: -0.16 to -0.02; p=0.02), and weakly associated with receptive
246 language (aMD=-0.06; CI 95%: -0.13 to 0.00; p=0.06). Infant's age, growth rate, and examiner to
247 administer MSEL were found to be confounders in the relationship between maternal stress scores
248 (PSI-SF total stress) and MSEL scores.

249 *Infant HIV Status*

250 From a total of 397, there were 16 HIV positive infants and 381 HEU infants. HIV status was not
251 associated with infant's age at enrolment, gender, or birth weight (Table 4). However, the mothers
252 of HEU infants were slightly older than HIV positive infants mothers (32 vs. 29; p=0.05). Mothers
253 caring for HIV positive infants reported higher mean stress scores compared to the HEU group
254 (95.8 vs. 85.0; p=0.01).

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

259 **Discussion**

260 Our study shows a high level of stress and depressed mood scores among HIV+ve mothers.
261 Although the EPDS scale used was not diagnostic, the general literature cut-off points indicate that
262 10% of mothers had scores in the severe range, while over half of the sample had scores falling in
263 the mild to moderate range. Stress levels were also notably high.

264 Our study strongly suggests that higher maternal stress and depression symptoms are associated
265 with poorer infant cognitive performance in an HIV affected sample. Maternal stress was also found
266 to be higher in the group caring for HIV positive infants. Of note we did not find a relationship
267 between HIV status of the infants and cognitive development – but the analysis was confined to the
268 16 HIV positive infants.

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

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

288 performances between HIV infected and HEU children (Van Rie et al., 2008; Whitehead, Potterton,
289 & Coovadia, 2014), we were unable to detect a difference in the overall cognitive scores between
290 the two groups. This could be due to the very small sample size of HIV infected infants, the fact
291 that both groups of infants lived in an HIV endemic population affected by the multifaceted
292 ramifications of HIV, or early diagnosis and early initiation on treatment (Weber et al., 2017), as all
293 16 HIV positive children in this study were initiated on ART at 0 and 1 month old.

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

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

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

321 for child development (Tomlinson et al., 2015; Tomlinson, Rotheram-Borus, Scheffler, & le Roux,
322 2017). It seems from our data that maternal factors are equally important in Zimbabwe.

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324 *Word count: 3,034*

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333 **Disclosure statement**

334 The authors declare that they have no competing interests.

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500

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 <i>-Severity ranges of Edinburgh Postnatal Depression Scales, n</i>		

(%)		
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

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

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

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

506 *+There was 1 inaccurate record for the variable “Number of adults living in the same household” which*
507 *was excluded from the table.*

508

509 *Table 2: Summary of association of maternal mental health (using EPDS) with child cognitive*
510 *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

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

513

514 *Table 3: Summary of association of maternal stress (using the PSI-SF total stress score) with child*
515 *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

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

519

520 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

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

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

524

525

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*
	Mean	SD	Mean	SD		
Mullen Scales (T-scores)						
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.*