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Quality of caregiving is positively associated with neurodevelopment during the first year of life among HIV-exposed uninfected children in Uganda

Itziar FAMILIAR[1], **Shalean M. COLLINS**[2], **Alla SIKORSKII**[3], **Horacio RUISENOR-ESCUDERO**[1], **Barnabas NATAMBA**[4], **Paul BANGIRANA**[5], **Elizabeth M. WIDEN**[6], **Daniel ACHIDRI**[5], **Harriet ACHOLA**[7], **Daniel ONEN**[7], **Michael BOIVIN**[1], and **Sera L. YOUNG**[2]

[1]Department of Psychiatry, Michigan State University, East Lansing MI, USA [2]Department of Anthropology, Northwestern University, Evanston, IL, USA [3]Department of Statistics and Probability, Michigan State University, East Lansing MI, USA [4]Department of Community Health and Behavioral Sciences, Makerere University School of Public Health, Kampala, Uganda [5]Department of Psychiatry, Makerere University College of Health Sciences, Kampala, Uganda [6]Department of Nutritional Sciences, University of Texas at Austin, Austin, TX, USA [7]Prenatal Nutrition and Psychosocial Health Outcomes (PRENAPS) Uganda. Kampala, Uganda

Abstract

Objective—We sought to evaluate if maternal characteristics and infant developmental milieu were predictive of early cognitive development in HIV-exposed uninfected (HEU) and un-exposed uninfected (HU) infants in Uganda.

Design—Longitudinal pregnancy study.

Corresponding author: Sera L. Young, PhD, 515 Clark Street Room 202, Department of Anthropology, Northwestern University, Evanston, IL, USA, sera.young@northwestern.edu, Phone: 847 467-2174.

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Author Contributions

Itziar Familiar– Responsible for secondary data analysis approach, wrote the first draft of the manuscript, and approved the manuscript as submitted.

Shalean M. Collins – Assisted with data collection, data management, data analysis, manuscript preparation, led the literature review, and critically read and approved the manuscript as submitted.

Alla Sikorskii – Responsible for all statistical analyses and tables and critically read and approved the manuscript as submitted.

Horacio Ruisenor-Escudero– Supported data analysis and participated in writing the manuscript, and critically read and approved the manuscript as submitted.

Barnabas Natamba – Helped to conceptualize the parent study, supervised data collection, and critically read and approved the manuscript as submitted.

Paul Bangirana – Offered analytic insight and critically read and approved the manuscript.

Elizabeth M. Widen – Proposed analyses pertaining to HAZ and critically read and approved the manuscript.

Daniel Achidri – Assisted with data collection and management and critically read the manuscript.

Harriet Achola –Performed infant cognitive development data collection and management and critically read the manuscript.

Daniel Onen –Performed infant cognitive development data collection and management and critically read the manuscript.

Michael Boivin– shared oversight of analysis plan, participated in the initial drafting and further revisions of manuscript, and approved the manuscript as submitted.

Sera L. Young-- (Corresponding author) Study PI, shared oversight over all phases of study design and implementation and analyses, wrote the first draft of the manuscript, and approved the manuscript as submitted.

Methods—Ugandan women (n=228) were enrolled into the Postnatal Nutrition and Psychosocial Health Outcomes (PostNAPS) study with a 2:1 HIV-uninfected:infected ratio. Maternal socio-demographic, perceived social support, and depressive symptomatology were assessed. Infant growth and neurocognitive development was assessed 6 and 12-months of age using Mullen Scales of Early Learning (MSEL). Caldwell Home Observation for Home Environment was used to gauge caregiving quality. Linear mixed effects models were built to examine the relationships between maternal and infant characteristics with infant MSEL scores by HIV exposure.

Results—Two MSEL measures were available for 215 mother-child dyads: 140 infants (65%) were HU, 57 (27%) were HIV-exposed and uninfected with mothers reporting ART (HEU-ART), and 18 (8%) were HIV-exposed, uninfected with mothers not reporting ART (HEU-nART). HEU had lower MSEL Composite (β=−3.94, p=0.03) and Gross Motor scores (β=−3.41, p=0.01) than HU. HOME total score was positively associated with MSEL Composite (β=0.81, p=0.01), Receptive Language (β=0.59, p=0.001), and Expressive Language (β=0.64, p=0.01) scores.

Conclusions—HIV exposure is associated with lower infant cognitive development scores. Increasing maternal quality of caregiving may be effective to improve early cognitive development.

Keywords

low-income country; child development; HIV; ART

Introduction

Each year, nearly 1 million HIV-exposed infants are born, but due to life-prolonging drugs and safe infant feeding practices, the rate of mother-to-child transmission (MTCT) is very low, such that most infants will be uninfected [1]. As such, public health interest has shifted to quality of life among HIV-exposed but uninfected (HEU) children [2].

Compared to their uninfected peers, HIV-infected children can present a wide range of neurological impairments including visual, language, motor and generalized cognitive deficits [3, 4]. In contrast, much less is known about the neurodevelopment of HEU children. Some have reported no evidence of neurodevelopmental delay [5, 6], while others have observed lower performance scores at 1 year of age [7] and small but significant reductions in neurodevelopmental outcomes [8]. The majority of these studies were carried out in high-income countries; with few studies about neurodevelopment conducted in low- and middle-income countries.

It has been hypothesized that antenatal HIV-exposure itself (without infection) may compromise HEU children's cognitive development, for example, when maternal immune activation negatively affects the developing fetal brain [9, see Online Supplementary Material Table 1 for review]. However, there is potential for confounding by environmental factors frequently encountered in low-income settings and related to HIV disease in the mother. These include maternal psychological factors (e.g. depression) [10] or behavioral factors (e.g. compromised caregiving) [11], and socioeconomic factors. Indeed, data from low-income countries demonstrate that children born into poverty are more likely to

experience impairments in cognitive development [12, 13], particularly in sub-Saharan Africa [14, 15]. As such, maternal caregiving factors should be studied concomitantly with the effects of HIV-exposure, but few studies have.

An additional consideration for HEU children is that pre- and postnatal ART exposure (through breastfeeding) may impact infant neurodevelopment due to the association between nucleoside reverse transcriptase inhibitors (NRTI's) with mitochondrial toxicity [16]. Although most ART regimens given to prevent MTCT have demonstrated favorable safety profiles with little evidence for serious adverse events [7, 17], studies of the effects of in-utero exposure to ART on neurodevelopmental outcomes of HEU children have differed in methodologies and results [5, 6], such that data are inconclusive. As such, a better understanding of the impact of HIV and ART on HIV-exposed infants is needed in order to develop interventions that take into consideration the long-term health needs of this growing segment of the population.

Given the few studies and inconclusive evidence about neurodevelopment in HIV-exposed but uninfected infants (HU), we aimed to evaluate neurodevelopment in a sample of HEU and HU infants <12 months in northern Uganda and assess whether maternal HIV status, maternal ART status, and demographic and environmental characteristics, and infant growth were predictive of infant neurodevelopment. Specifically, we hypothesized that cognitive development would be worse in HEU infants in comparison to HU infants.

Methods

Setting

This is a secondary data analysis from the Prenatal Nutrition and Psychosocial Health Outcomes Study (PreNAPS, NCT02922829) and Postnatal Nutrition and Psychosocial Health Outcomes Study (PostNAPS, NCT02915429) conducted at the antenatal care clinic of Gulu Regional Referral Hospital (GRRH) in Gulu, northern Uganda. Together these studies comprised a longitudinal observational cohort designed to examine the relationships between food security, psychosocial health and nutritional status during pregnancy and postpartum in post-conflict northern Uganda.

Uganda is an appropriate setting in which to evaluate the impact of HIV exposure and ARVs on early infant neurodevelopment. For one, the prevalence of HIV among pregnant women in Uganda is high: 7.2% among pregnant women attending antenatal clinics. Second is the widespread and increasing coverage of ART. Approximately 72% of HIV-infected mothers received ART to prevent MTCT in 2012 [18], up from 13% in 2005 [19].

Subjects

Procedures of the parent studies have been described elsewhere [20, 21]. Briefly, women (n=403) were purposively sampled at the GRRH if they met the following eligibility criteria: gestational age between 10 and 26 weeks (assessed with last menstrual period), living within 30 km of GRRH, and a known HIV status. HIV-uninfected women were oversampled to obtain a ratio of 2 HIV-uninfected to 1 HIV-infected participant [22]. Mothers were enrolled and followed throughout pregnancy. All PreNAPS participants who delivered after May 9,

2013 were invited to participate in PostNAPS after delivery if the pregnancy resulted in a live singleton birth, and the mother visited the study clinic within 1 week of delivery (n=228). Dyads with at least one non-missing assessment were included in this analysis (n=215).

Data were collected between October 10, 2012 to January 19, 2015. All study instruments were translated by local research staff into Acholi and Langi, the two predominant languages. The questionnaires were then back-translated into English by the same team and discrepancies were resolved through discussion involving all the translators, the research assistants, and study staff.

Maternal assessments

Women's demographics were measured at the prenatal enrollment visit, and included age, marital status (married vs. unmarried), education, and employment. A household asset index modified from the Ugandan National Panel Survey 2009/2010 for households was derived using principal components analysis from self-report of household assets and included ownership of a home, other buildings, land, furniture, appliances, electronics, etc., where higher scores indicated greater wealth.

Maternal HIV status was determined prior to enrollment in PreNAPS at antenatal care clinics based on the Ugandan government's HIV counseling and testing guidelines [23]. ART regimen and adherence were self-reported. All HIV-infected women were initiated on ART and sulfamethoxazole-trimethoprim (Septrin©), consistent with national policy in Uganda. HIV-infected women who were not receiving HAART at the first antenatal care visit were given the first-line option B+: Tenofovir, Lamivudine, and Efavirenz (TDF/3TC/EFV). HIV-infected women receiving HAART were given several options for continuing treatment: 1) Duovir-N (Zidovodine, Lamivudine, Nevirapine (AZT/3TC/NVP)); 2) Duomune (Lamivudine, Tenofovir, 3TC/TDF) and Nevirapine; 3) Duomune and Efavirenz.

Home Observation for the Measurement of the Environment (HOME) was used to assess maternal quality and quantity of stimulating and supportive interactions as proxy of the infant developmental milieu at 12 months postpartum [24]. This measure has been validated previously in Uganda [25]. For this analysis, we used the Infant Toddler version, which includes 45 yes/no items. A total HOME score was generated by summing the number of 'yes' responses to each item, with higher scores indicating higher quality of care. The HOME inventory was administered at participant's household when the infant was 12 months of age.

Maternal depression at 6 months post-partum was assessed using the Center for Epidemiologic Studies Depression Scale (CES-D) [26]. The CES-D is a 20-item measure assessing depressive symptomatology during the past week in the general population, with higher scores indicating greater number of depressive symptoms, and a range of 0 to 60. The commonly used cutoff of 16 or greater [27] has been validated in this population [28] and was used to differentiate depressed from non-depressed individuals.

For this analysis, we used women's perceived social support (SS) assessed at 6 months postpartum using a modified 10 item Duke-UNC Functional SS instrument [29]. Participants could respond "much less than I would like or never" (scored 1); "less than I would like" (2); and, "as much as I would like" (3) for each question. Scores were summed (range 10–30), such that higher scores reflect lower levels of SS, but for ease of interpretation, we inverted the individual items on the scale before administration such that high scores reflect higher levels of SS.

Infant assessments

The Mullen Scales of Early Learning (MSEL) was used to assess infants in the developmental domains of (1) visual reception, (2) gross motor skills, (3) fine motor skills, (4) receptive and (5) expressive language. Standardized t-scores were generated for each domain. Four scales (visual reception, fine motor, receptive language, and expressive language) are combined to yield the MSEL Composite score. The MSEL Composite score serves as a general measure of fluid intelligence thought to underlie cognitive ability in general [30]. The MSEL was selected because it was designed to be more adaptable to resource-constrained settings than the Bayley scales, which need a professional psychologist to administer in a valid manner due to its complexity. The MSEL has been validated and used across multiple African-based studies [4, 31, 32].

Infants were assessed for growth parameters; length was measured using a recumbent board and weight was assessed with an infant scale. Developmental outcomes were assessed at the study clinic at approximately 6 and 12 months of age by 2 study staff. Testers held Bachelor's degree in Psychology and Social Work and were trained by a Ugandan psychologist with expertise in infant neurocognitive assessment. All infants were breastfed and HIV negative (HIV status was determined using DBS for Early Diagnosis).

Statistical analyses

Distributions of the characteristics of women and children, including the scores for the MSEL, the HOME scale, measures of social support and depression, and demographic factors were summarized and compared by maternal HIV status using t- or chi-square tests. HIV exposure status was included in models as HU and HEU. Exploratory analyses to assess ART exposure used the same models with a 3-level categorical variable with levels HU, HEU-ART, and HEU-nART.

Linear mixed effects (LME) models were employed to analyze two repeated measures of child outcomes at 6 and 12-months after delivery: the MSEL Composite score and each of the 5 sub-scales separately (Gross Motor, Fine Motor, Expressive Language, Receptive Language, and Visual Reception). Each outcome was analyzed separately using LME approach with a common set of covariates based on our previous related research [33, 34]. These covariates included child sex, maternal age, education level, employment status, marital status, asset index, HIV and ART status, depression symptomatology, and social support. Child age corresponded with assessment time point, which is why age was omitted from models.

Least square (LS) or adjusted means with respect to the levels of this categorical variable were obtained from the LME models to reflect average differences over time among subgroups defined by HIV or ART exposure, separately. Because of potential collinearity, the effects of correlated predictors were explored by considering models with correlated variables removed one at a time.

The final models for each MSEL sub-scale included time of assessment, infant gender, HIV exposure, ART exposure, maternal age, SES, level of education and marital status, the HOME score, postnatal social support and depression as covariates. In an additional model, we also evaluated if the effect of the HOME score on child outcomes differed according to maternal HIV and ART status by including the interaction term between these variables, separately.

We explored potential mediating effects of height-for-age (HAZ) on the relationship between HIV and ARV exposure and child outcomes by adding HAZ as a covariate to the models described above All statistical tests were two-sided and p-values < 0.05 indicated statistical significance. All analyses were performed using SAS 9.4.

Power calculations

Given the available sample size for this analysis of 140 HU infants, 57 HEU-ART infants, and 18 HEU-nART (n=215), and the correlation coefficient of 0.29 between two repeated measures of the MSEL Composite scores, we conservatively evaluated the magnitude of differences that were detectable as statistically significant with power of 0.80 or greater in two-sided tests at 0.05 level of significance. The effect sizes, expressed as Cohen's *d*, (i.e. differences between adjusted means divided by the adjusted standard deviation) were as follows: 0.35 for the comparison of HU with HEU-ART; 0.62 for the comparison of HEU-ART versus HEU-nART, and 0.56 for the comparison of HU with HEU-nART. In other words, differences of the magnitude equal to the standard deviation times *d* were detectable as statistically significant.

Results

From the 215 dyads available for analyses, 140 women (65%) were HIV−, 57 (27%) were HIV+ and reported currently on ART, and 18 (8%) were HIV+ not taking ART. Overall, HIV+ women were more likely to be unmarried, less educated, and less employed when compared to the HIV− women in this sample (Table 1). There were no significant differences across the three groups in maternal age, social support or HOME scores. A sensitivity analysis revealed no significant differences between dyads with complete (n=215) and incomplete data (n=13) comparing characteristics summarized in Table 1 (data not shown).

On average, HU children had higher mean MSEL scores than HEU children at both 6 and 12-months of age for both sub-scales and composite scores (Table 2, Figure 1). Scores declined over time for both groups. HEU had lower HAZ scores at both 6 and 12 months.

In linear mixed effect models, HEU infants had lower Mullen Composite (least squares (LS) mean =103.10, standard error (SE) 1.84) and Gross Motor scores (LS mean 53.31, SE 1.39) than HU children (LS mean 107.04, SE 1.46 and LS mean 56.72, SE 1.11, respectively).

Table 3 shows coefficients in the LME models that reflect these differences, for example, beta=−3.94 represents the difference between a mean Mullen Composite score of 107.04 and 103.10 (p=0.03). Controlling for other explanatory variables in the model, HOME total score was associated with higher MSEL Composite (β=0.81, SE=0.31, p=0.01), Receptive Language (β=0.59, SE=0.18, p=0.001), and Expressive Language (β=0.64, SE=0.24, p=0.01) scores. The effects of the HOME score on child outcomes did not differ by maternal HIV status. Women reporting greater postnatal social support had infants with higher Visual Reception (β=0.25, SE=0.11, p=0.03) scores at 6- and 12-months.

In the exploratory analyses assessing impact of ART on neurodevelopment, HEU infants whose mothers were not receiving ART had lower Mullen Composite scores (LS mean 102.34, SE 2.96) compared to HEU-ART infants (Figure 1). Statistical significance was not reached (p=0.07) due to smaller size of no ART exposure relative to other groups. HU infants had the highest Mullen Composite score LS mean, followed by HEU-ART, and HEU-nART infants having the lowest LS mean. A similar pattern was observed with Expressive Language, Receptive Language, and Visual Reception scores.

In the mediation analysis where we evaluated whether further adjustment for child height influenced observed associations, we found that child HAZ was positively associated with all MSEL sub-scales, including the Mullen Composite score (β=2.22, SE=0.72, p=0.01, data not in tables). With adjustment for child HAZ, the Mullen Composite score LS mean differences observed among the 2 HIV exposure status groups were attenuated. Although HU infants continued to have the highest Mullen Composite score LS mean (LSMean=106.49, SE= 1.45) compared to HEU infants (LSMean=103.63, SE= 1.82), these differences were no longer statistically significant (p=0.11).

Discussion

We assessed the neurocognitive function of HEU infants at 6 and 12 months of age born to mothers of mixed HIV and ART adherence status using the Mullen Scales of Early Learning. As we had hypothesized, HEU infants in our sample had lower scores in neurodevelopment tests than their HU counterparts across several cognitive domains. Specifically, our results and others [35, see Online Supplementary Material Table 1 for review] show that HEU children have significantly more motor and language delay than HU infants. In non-related studies among Ugandan children, we have previously reported lower language development scores among HEU and HIV-infected samples of infants [33, 36], [4, 25]. Taken together with results from Thai and Cambodian samples reporting lower verbal IQ scores among HEU children [37], and a study in DR Congo reporting lower mean MSEL Composite score [38] these findings suggest that language production is a sensitive measure of neurocognitive development in HIV affected children.

In terms of HIV-exposed samples, children in our study presented with a similar range of neurodevelopment scores to other HEU samples of infants in Uganda [36] [4]. Findings presented here show that cognitive outcomes over time are lower than that seen in the United States or other high-income countries, which is why the standardized scores appear to decline over time for all groups. This is in itself an important finding that highlights the at-risk nature of HEU children and the need to continue to focus on identifying programs that not only provide incremental improvements to their cognitive development, but also positively shift their developmental trajectories.

Our exploratory results suggest that in-utero exposure to ART is not associated with altered development at 6 and 12 months of age. Given that current ART regimens include nucleoside analogues that can potentially cause mitochondrial toxicity, evaluating the impact on neurodevelopment is of relevance. Our findings are in line with previous studies of ART safety and tolerability during pregnancy [7] and neurodevelopmental outcomes among HEU children [8, 39]. Previous studies reporting no association between HIV exposure and neurodevelopment were primarily conducted in children from high-income countries [5] [6], suggesting that deficits in early infant neurodevelopment could be the result of a combination of environmental and social risk factors such as poverty, low socioeconomic status, low maternal education, and malnutrition, known or suspected to have adverse influence on developmental growth, especially in low-income settings [12]. For example, Alimenti and colleagues (2006) showed that the lower neurodevelopmental scores observed among HIV and ART-exposed infants, compared to HU infants, were attenuated after accounting for maternal substance abuse.

We found a positive association between child HAZ and all MSEL sub-scales, including the Mullen Composite score. Previous studies from Uganda [40] and Tanzania [41] have found that wasting and stunting were independently associated with poorer psychomotor and neurodevelopmental outcomes. Given Uganda's high prevalence of child undernutrition (estimated at 35% among children younger than 5 years) [42] and the high vulnerability to poor neurodevelopmental outcomes of undernourished infants affected by HIV, wasting and stunting should be considered as markers of children who might benefit from early neurodevelopment interventions coupled with nutritional support.

The HOME measurement [24] was designed to assess the quality and quantity of stimulation that a child is exposed to in their home environment as a proxy for quality of caregiving. In our sample, we observed a strong association between the HOME score and the MSEL Composite score (Table 3), such that children living in environments with more stimulation presented with a higher level of general neurocognitive development. Home environment has been associated with greater gains in cognitive and language in Italy [43]. The relevance of the home environment to the developmental milieu supports previous findings from an intervention in Uganda where participation in a year-long parenting skills training program increased the quality of the home environment (HOME score) and the child MSEL Receptive Language score [33]. Taken together, these results suggest that programs for HIV-affected children that are family oriented with a strong emphasis on parent-child relationships may support optimal child development.

Women in our study reporting higher levels of social support had infants with higher MSEL scores, also as in previous studies [44, 45]. Social support may improve self-esteem and sense of well-being by increasing available social and tangible resources [46]. A qualitative study in South Africa showed that informal social networks are an important resource for coping with financial and health adversities among HIV-infected individuals [47]. Collectively, these results highlight the importance of the social environment for child development and suggest that social support can be a valuable and potentially modifiable component of child-development interventions aimed toward at-risk children in LMICs. Understanding the type of post-partum support that is most helpful to mothers may be an effective strategy to bolster early cognitive development in this context.

Limitations

Results should be interpreted in light of study limitations. We recognize that in this secondary analysis the sample size might not have been adequate to capture all potentially practically meaningful differences of approximately 1/3 to 1/2 of the standard deviation, however many of the differences corresponded to larger effect sizes and were detected as statistically significant. The clinical significance of these findings remains to be determined. Additionally, we relied on self-report of ART and adherence, which might have been prone to recall errors.

Conclusions

Despite study limitations, results presented here contribute to the limited literature on HIV− and ART exposed children and its relation with cognitive development in the first year of life. Although findings are reassuring, examination of the effects of HIV and ART exposure on child cognitive development beyond 1 year are warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Sugandhi N, Rodrigues J, Kim M, Ahmed S, Amzel A, … Tolle M. Children, HIV Exposed Infants: Rethinking care for a lifelong condition. AIDS (London, England). 2013; 27(2):S187.
2. Evans C, Jones CE, Prendergast AJ. HIV-exposed, uninfected infants: new global challenges in the era of paediatric HIV elimination. The Lancet Infectious Diseases. 2016; 16(6):e92–e107. [PubMed: 27049574]
3. Sherr L, Mueller J, Varrall R. A systematic review of cognitive development and child human immunodeficiency virus infection. Psychology, health & medicine. 2009; 14(4):387–404.

4. Brahmbhatt H, Boivin M, Ssempijja V, Kigozi G, Kagaayi J, Serwadda D, Gray RH. Neurodevelopmental benefits of Anti-Retroviral Therapy in Ugandan children 0–6 Years of age with HIV. Journal of acquired immune deficiency syndromes. 1999; 67(3):316. 2014.
5. Le Doaré K, Bland R, Newell M-L. Neurodevelopment in children born to HIV-infected mothers by infection and treatment status. Pediatrics. 2012 peds. 2012–0405.
6. Williams PL, Marino M, Malee K, Brogly S, Hughes MD, Mofenson LM. Neurodevelopment and in utero antiretroviral exposure of HIV-exposed uninfected infants. Pediatrics. 2010 peds. 2009–1112.
7. Van Dyke RB, Chadwick EG, Hazra R, Williams PL, Seage GR 3rd. The PHACS SMARTT Study: Assessment of the Safety of In Utero Exposure to Antiretroviral Drugs. Front Immunol. 2016; 7:199. [PubMed: 27242802]
8. Kerr SJ, Puthanakit T, Vibol U, Aurpibul L, Vonthanak S, … Kosalaraksa P, Valcour V. Neurodevelopmental outcomes in HIV-exposed-uninfected children versus those not exposed to HIV. AIDS Care. 2014; 26(11):1327–35. [PubMed: 24878112]
9. Sirois PA, Huo Y, Williams PL, Malee K, Garvie PA, Kammerer B, … Nozyce ML. Safety of perinatal exposure to antiretroviral medications: developmental outcomes in infants. Pediatr Infect Dis J. 2013; 32(6):648–55. [PubMed: 23340561]
10. Surkan PJ, Kennedy CE, Hurley KM, Black MM. Maternal depression and early childhood growth in developing countries: systematic review and meta-analysis. Bull World Health Organ. 2011; 89(8):608–15. [PubMed: 21836759]
11. Cooper PJ, Tomlinson M, Swartz L, Woolgar M, Murray L, Molteno C. Post-partum depression and the mother-infant relationship in a South African peri-urban settlement. The British Journal of Psychiatry. 1999; 175(6):554–558. [PubMed: 10789353]
12. Grantham-McGregor S, Cheung YB, Cueto S, Glewwe P, Richter L, Strupp B. and International Child Development Steering, G. Developmental potential in the first 5 years for children in developing countries. Lancet. 2007; 369(9555):60–70. [PubMed: 17208643]
13. Walker SP, Wachs TD, Grantham-McGregor S, Black MM, Nelson CA, Huffman SL, … Richter L. Inequality in early childhood: risk and protective factors for early child development. Lancet. 2011; 378(9799):1325–38. [PubMed: 21944375]
14. Escueta M, Whetten K, Ostermann J, O'Donnell K. Positive Outcomes for Orphans Research T. Adverse childhood experiences, psychosocial well-being and cognitive development among orphans and abandoned children in five low income countries. BMC Int Health Hum Rights. 2014; 14:6. [PubMed: 24606949]
15. Sigman M, Neumann C, Jansen AA, Bwibo N. Cognitive abilities of Kenyan children in relation to nutrition, family characteristics, and education. Child Dev. 1989; 60(6):1463–74. [PubMed: 2515042]
16. Foster C, Lyall H. HIV and mitochondrial toxicity in children. J Antimicrob Chemother. 2008; 61(1):8–12. [PubMed: 17999978]
17. Williams PL, Hazra R, Van Dyke RB, Yildirim C, Crain MJ, Seage GR 3rd, … Rich K. Antiretroviral exposure during pregnancy and adverse outcomes in HIV-exposed uninfected infants and children using a trigger-based design. Aids. 2016; 30(1):133–44. [PubMed: 26731758]
18. UNAIDS. HIV and AIDS Uganda Country Progress Report. 2013. [cited 2015 04/20/2015]; Available from: http://www.unaids.org/sites/default/files/country/documents/UGA_narrative_report_2014.pdf
19. WHO. 2008 Report on the global AIDS epidemic. 2008. [cited 2016 05/13/16]; Available from: http://www.unaids.org/en/KnowledgeCentre/HIVData/GlobalReport/2008/2008_Global_report.asp (2008)
20. Natamba BK, Achan J, Arbach A, Oyok TO, Ghosh S, Mehta S, … Young SL. Reliability and validity of the center for epidemiologic studies-depression scale in screening for depression among HIV-infected and -uninfected pregnant women attending antenatal services in northern Uganda: a cross-sectional study. BMC Psychiatry. 2014; 14:303. [PubMed: 25416286]
21. Widen EM, Collins SM, Khan H, Biribawa C, Acidri D, Achoko W, … Young SL. Food insecurity, but not HIV-infection status, is associated with adverse changes in body composition during lactation in Ugandan women of mixed HIV status. The American Journal of Clinical Nutrition. 2017 ajcn142513.

22. Fabiani M, Nattabi B, Pierotti C, Ciantia F, Opio AA, Musinguzi J, … Declich S. HIV-1 prevalence and factors associated with infection in the conflict-affected region of North Uganda. Confl Health. 2007; 1:3. [PubMed: 17411455]
23. Health, UMo. National Implementation guidelines for HIV Counselling and Testing in Uganda. Kampala: 2010.
24. Caldwell, B., Bradley, R. Home Observation for Measurement of the Environment Administration Manual. Family and Human Dynamics Research Institute, Arizona State University; Tempe, Arizona: 2003.
25. Bangirana P, John CC, Idro R, Opoka RO, Byarugaba J, Jurek AM, Boivin MJ. Socioeconomic predictors of cognition in Ugandan children: implications for community interventions. PLoS One. 2009; 4(11):e7898. [PubMed: 19936066]
26. Radloff LS. The CES-D Scale: a self-report depression scale for research in the general population. Applied Psychological Measurement. 1977; 1(3):285–401.
27. Craig TJ, Van Natta PA. Current medication use and symptoms of depression in a general population. The American Journal of Psychiatry. 1978; 135(9):1036–1039. [PubMed: 29500]
28. Natamba BK, Achan J, Arbach A, Oyok TO, Ghosh S, Mehta S, … Young SL. Reliability and validity of the center for epidemiologic studies-depression scale in screening for depression among HIV-infected and -uninfected pregnant women attending antenatal services in northern Uganda: a cross-sectional study. BMC Psychiatry. 2014:14. [PubMed: 24443820]
29. Broadhead WE, Gehlbach SH, de Gruy FV, Kaplan BH. The Duke-UNC Functional Social Support Questionnaire. Measurement of social support in family medicine patients. Medical care. 1988; 26(7):709–723. [PubMed: 3393031]
30. Mullen, E. Mullen Scales of Early Learning: AGS edition. American Guidance Service; Minneapolis, MH: 1995. Mullen Scales of Early Learning.
31. Koura GK, Boivin MJ, Davidson LL, Ouédraogo S, Zoumenou R, Alao MJ, … Bodeau-Livinec F. Usefulness of child development assessments for low-resource settings in francophone Africa. Journal of developmental and behavioral pediatrics: JDBP. 2013; 34(7)
32. Boivin MJ, Bangirana P, Nakasujja N, Page CF, Shohet C, Givon D, … Klein PS. A year-long caregiver training program to improve neurocognition in preschool Ugandan HIV-exposed children. Journal of developmental and behavioral pediatrics: JDBP. 2013; 34(4):269. [PubMed: 23535340]
33. Bass JK, Nakasujja N, Familiar-Lopez I, Sikorskii A, Murray SM, Opoka R, … Boivin MJ. Association of caregiver quality of care with neurocognitive outcomes in HIV-affected children aged 2–5 years in Uganda. AIDS Care. 2016; 28(Suppl 1):76–83. [PubMed: 26888568]
34. Familiar I, Nakasujja N, Bass J, Sikorskii A, Murray SM, Ruisenor-Escudero H, … Boivin MJ. Caregivers' depressive symptoms and parent-report of child executive function among young children in Uganda. Learning and individual differences. 2016; 46:17–24. [PubMed: 27175052]
35. Van Rie A, Mupuala A, Dow A. Impact of the HIV/AIDS Epidemic on the Neurodevelopment of Preschool-Aged Children in Kinshasa, Democratic Republic of the Congo. Pediatrics. 2008; 122(1):e123–8. [PubMed: 18595957]
36. Boivin MJ, Bangirana P, Nakasujja N, Page CF, Shohet C, Givon D, … Klein PS. A year-long caregiver training program improves cognition in preschool Ugandan children with human immunodeficiency virus. J Pediatr. 2013; 163(5):1409–16. e1–5. [PubMed: 23958115]
37. Kerr SJ, Puthanakit T, Vibol U, Aurpibul L, Vonthanak S, Kosalaraksa P, … Luesomboon W. Neurodevelopmental outcomes in HIV-exposed-uninfected children versus those not exposed to HIV. AIDS care. 2014; 26(11):1327–1335. [PubMed: 24878112]
38. Van Rie A, Dow A, Mupuala A, Stewart P. Neurodevelopmental trajectory of HIV-infected children accessing care in Kinshasa, Democratic Republic of Congo. Journal of acquired immune deficiency syndromes. 1999; 52(5):636. 2009.
39. Alimenti A, Forbes JC, Oberlander TF, Money DM, Grunau RE, Papsdorf MP, … Burdge DR. A prospective controlled study of neurodevelopment in HIV-uninfected children exposed to combination antiretroviral drugs in pregnancy. Pediatrics. 2006; 118(4):e1139–45. [PubMed: 16940166]

40. Ruisenor-Escudero H, Familiar-Lopez I, Sikorskii A, Jambulingam N, Nakasujja N, Opoka R, … Boivin M. Nutritional and Immunological Correlates of Memory and Neurocognitive Development Among HIV-Infected Children Living in Kayunga, Uganda. J Acquir Immune Defic Syndr. 2016; 71(5):522–9. [PubMed: 26605506]

41. McDonald CM, Manji KP, Kupka R, Bellinger DC, Spiegelman D, Kisenge R, … Duggan CP. Stunting and wasting are associated with poorer psychomotor and mental development in HIV-exposed Tanzanian infants. J Nutr. 2013; 143(2):204–14. [PubMed: 23256148]

42. UNICEF. Uganda: Maternal, Newborn and Child Survival. WHO, UNICEF; Basel, Switzerland: 2010.

43. Ronfani L, Vecchi Brumatti L, Mariuz M, Tognin V, Bin M, Ferluga V, … Barbone F. The Complex Interaction between Home Environment, Socioeconomic Status, Maternal IQ and Early Child Neurocognitive Development: A Multivariate Analysis of Data Collected in a Newborn Cohort Study. PLoS One. 2015; 10(5):e0127052. [PubMed: 25996934]

44. Sohr-Preston SL, Scaramella LV. Implications of timing of maternal depressive symptoms for early cognitive and language development. Clin Child Fam Psychol Rev. 2006; 9(1):65–83. [PubMed: 16817009]

45. McManus BM, Poehlmann J. Maternal depression and perceived social support as predictors of cognitive function trajectories during the first 3 years of life for preterm infants in Wisconsin. Child Care Health Dev. 2012; 38(3):425–34. [PubMed: 21651608]

46. Husain N, Bevc I, Husain M, Chaudhry IB, Atif N, Rahman A. Prevalence and social correlates of postnatal depression in a low income country. Arch Womens Ment Health. 2006; 9(4):197–202. [PubMed: 16633740]

47. Casale M. ‘I am living a peaceful life with my grandchildren. Nothing else.‘Stories of adversity and ‘resilience’ of older women caring for children in the context of HIV/AIDS and other stressors. Ageing and Society. 2011; 31(08):1265–1288.

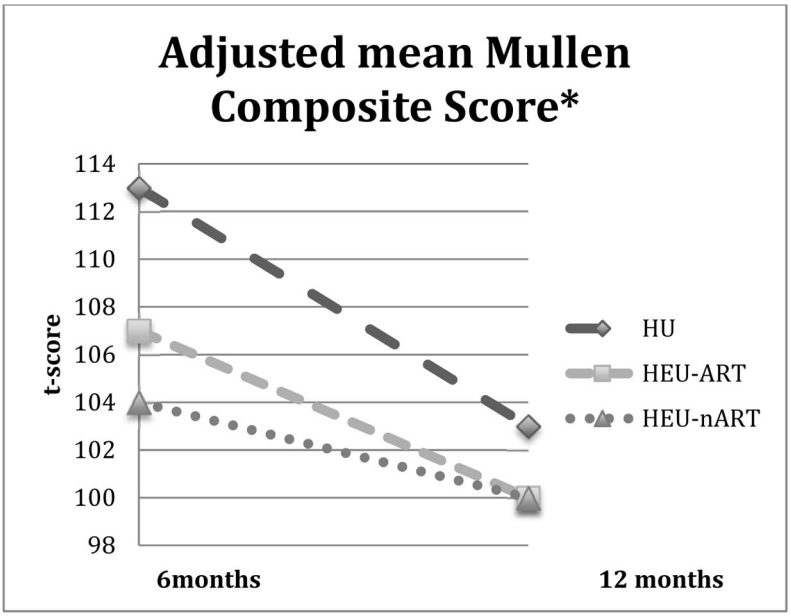

Figure 1.

Adjusted mean Mullen Composite Score among children over time by maternal HIV and ART status.

*Adjusted for child age, sex, and maternal education, marital status, HOME, SES, social support and depression score.

Table 1

Maternal characteristics of PostNAPS study participants at 6 months postpartum, by HIV status (n=215).

	HIV− n=140	HIV+ n= 75	Total n=215	p-value*
Receiving ART	-	57 (72)	57 (72)	-
Marital status, n (%)				0.10
Married	127 (91)	62 (82)	199 (86)	
Unmarried	13 (9)	13 (18)	29 (13)	
Education, n (%)				0.01
Primary	73 (49)	49 (62)	122 (53)	
Secondary	51 (34)	28 (35)	79 (34)	
Technical/University	25 (17)	2 (2)	27 (13)	
Employment, n (%)				0.32
Unemployed	70 (47)	38 (48)	108 (47)	
Farmer	20 (13)	18 (23)	38 (17)	
Trader/shopkeeper	18 (12)	8 (10)	26 (11)	
Formal employment	14 (9)	4 (5)	18 (8)	
Other	27 (18)	11 (14)	38 (17)	
Age, years: mean (SD)	24.6 (4.9)	25.3 (5.2)	24.9 (5)	0.32
Asset index, mean (SD)	5 (1.6)	4 (1.6)	4.4 (1.6)	<0.01
Depressive symptomatology**, n (%)	65 (46)	28 (37)	93 (43)	<0.01
Postnatal perceived social support, mean (SD)	21 (5.5)	20 (5.9)	20.5 (5.7)	0.20
HOME score***, mean (SD)	3.1 (1.4)	2.8 (1.4)	3.1 (1.4)	0.12

*P-value for the difference between HIV negative and HIV positive women;

SD=standard deviation

**Center for Epidemiologic Studies Depression Scale

***Assessed at 12-months postpartum

Table 2

Demographic characteristics and standardized (t-scores) of Mullen Scales of Early Learning scores among Ugandan infants at 6 and 12-months of age, by HIV-exposure status (n=215).

	6-months			12-months		
	HEU (n=79)	**HU (n=149)**	**p-value***	**HEU (n=79)**	**HU (n=149)**	**p-value***
Male infants, n (%)	46 (58)	82 (55)	0.66	46 (58)	82 (55)	0.66
WAZ, Mean, (SD)	−0.02 (1.30)	−0.08 (1.09)	0.71	−0.48 (1.26)	−0.38 (.96)	0.50
HAZ, Mean, (SD)	−0.77 (1.20)	−0.30 (1.02)	**<0.01**	−1.30 (1.40)	−.70 (1.02)	**<0.01**
MSEL, Mean, (SD)						
Gross Motor Mean, (SD)	54.67 (13.40)	59.00 (10.79)	**0.01**	51.80 (11.70)	52.56 (11.69)	0.64
Fine Motor Mean, (SD)	49.96 (11.25)	54.33 (11.41)	**0.01**	53.87 (12.15)	54.35 (12.87)	0.82
Visual Reception Mean, (SD)	54.52 (13.65)	59.64 (12.19)	**0.01**	52.86 (9.09)	52.93 (8.92)	0.95
Receptive Language Mean, (SD)	57.23 (10.55)	58.28 (9.89)	0.46	45.30 (7.75)	46.00 (7.02)	0.32
Expressive Language Mean, (SD)	50.24 (11.92)	53.02 (11.39)	0.09	48.00 (12.23)	50.84 (10.94)	0.06
Composite score	105.99 (15.53)	112.99 (15.72)	**<0.01**	99.93 (15.72)	102.80 (15.34)	**<0.01**

WAZ= weight for age z-score, HAZ= height for age z-score, HU= HIV-unexposed uninfected, HEU= HIV-exposed uninfected infants

*P-value for the difference between HEU and HU groups

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Table 3

Linear mixed effects models of child neurodevelopment outcomes with maternal predictors: coefficients, their significance and 95% confidence intervals (CIs).

	Mullen Composite		**Gross Motor**		**Fine Motor**		**Expressive Language**		**Receptive Language**		**Visual Reception**	
	Coef.	**CI 95%, p-value**	**Coef.**	**CI 95%, p-value**	**Coef.**	**CI 95%, p-value**	**Coef.**	**CI 95%, p-value**	**Coef.**	**CI 95%, p-value**	**Coef.**	**CI 95%, p-value**
Maternal age	0.01	−0.31, 0.34 p=0.93	−0.01	−0.26, 0.24 p=0.93	0.06	−0.19, 0.31 p=0.61	−0.01	−0.27, 0.24 p=.90	0.03	−0.16, 0.21 p=0.77	0.01	−0.23, 0.24 p=0.94
Asset index	0.09	−1.00, 1.18 p=0.86	0.18	−0.64, 1.00 p=.66	0.37	−0.47, 1.20 p=0.39	−0.12	−0.95, 0.71 p=.77	−0.47	−1.09, 0.14 p=0.13	0.27	−0.51, 1.05 p=0.49
HIV positive (v. HIV negative)	−3.94	−7.42, −0.47, **p=0.03**	−3.41	−6.04, −0.78 **p=0.01**	−2.21	−4.87, 0.45 p=0.10	−2.53	−5.17, 0.12 p=0.06	0.80	−2.75, 1.17 p=0.42	−1.76	−4.26, 0.73 p=0.16
Education												
None/primary	0.69	−4.68, 6.05 p=0.80	1.22	−2.84, 5.28 p=0.55	0.80	−3.31, 4.91 p=0.70	0.59	−3.50, 4.67 p=0.78	1.43	−1.61, 4.48 p=0.35	−1.22	−5.07, 2.64 p=0.53
Secondary	1.92	−3.48, 7.31 p=0.48	2.79 p=0.18	−1.29, 6.87	0.87	−3.25, 5.01 p=0.67	1.94	−2.16, 6.04 p=0.35	2.30	−0.76, 5.36 p=0.14	−0.12	−3.99, 3.77 p=0.95
College/university (ref.)	0	-									-	
Married (v. unmarried)	0.63	−4.43, 5.70 p=0.80	−2.47	−6.30, 1.36 p=0.20	−0.69	−4.57, 3.20 p=0.73	0.17	−3.69, 4.03 p=0.93	−0.37	−3.25, 2.51 p=0.80	0.26	−3.38, 3.90 p=0.89
Social support	0.29	−0.02, 0.60 p=0.06	−0.03	−0.26, 0.21 p=0.82	0.03	−0.20, 0.27 p=0.79	0.05	−0.18, 0.29 p=0.65	0.06	−0.11, 0.24 p=0.46	0.25	0.03, 0.47 **p=0.03**
Depressive symptomatology (>16)	−2.49	−5.86, 0.88 p=0.15	0.79	−1.76, 3.33 p=0.54	−0.89	−3.48, 1.68 p=0.49	−0.00	−2.57, 2.57 p=0.99	0.10	−1.81, 2.02 p=0.91	−3.06	−5.48, −0.64 **p=0.01**
HOME score	0.81	0.20, 1.43 **p=0.01**	0.41	−0.06, 0.87 p=0.09	0.37	−0.10, 0.84 p=0.12	0.64	0.16, 1.10 **p=0.01**	0.59	0.24, 0.94 **p=0.00**	0.12	−0.32, 0.56 p=0.58

*Models were adjusted for child sex