Published in final edited form as:

New Dir Child Adolesc Dev. 2020 May ; 2020(171): 39–54. doi:10.1002/cad.20351.

Cognitive and language development at age 4–6 years in children HIV-exposed but uninfected compared to those HIV-unexposed and to children living with HIV

Rachel S. Gruver[a], **Sumaya Mall**[b], **Jane D. Kvalsvig**[c], **Justin R. Knox**[a], **Claude A. Mellins**[d], **Chris Desmond**[c], **Shuaib Kauchali**[b,c], **Stephen M. Arpadi**[a,e], **Myra Taylor**[c], **Leslie L. Davidson**[a,e]

[a]Department of Epidemiology, Columbia University Mailman School of Public Health, New York, NY, USA

[b]Division of Epidemiology and Biostatistics, School of Public Health, University of the Witwatersrand, Johannesburg, South Africa

[c]School of Nursing and Public Health, University of KwaZulu-Natal, Durban, South Africa

[d]HIV Center for Clinical and Behavioral Studies at Columbia University and New York State Psychiatric Institute, New York, NY, USA

[e]Department of Pediatrics, College of Physicians & Surgeons, Columbia University, New York, NY, USA

Abstract

Perinatal HIV infection is associated with delayed neurocognitive development, but less is known about children perinatally HIV-exposed but uninfected (CHEU). We compared cognitive and language outcomes in 4–6 year old CHEU versus children HIV-unexposed and uninfected (CHUU) and children living with HIV (CLHIV). We enrolled 1581 children (77% of the child population) in five communities in KwaZulu-Natal, South Africa. Children completed: Grover-Counter Scale of cognitive development, sub-scales of the Kaufman Assessment Battery for Children, Reynell Developmental Language Scales. HIV status of children and primary caregivers was determined by repeated rapid tests or report of prior testing. We conducted a cross-sectional multivariable linear regression on 922 dyads with complete data (257 CHEU, 627 CHUU, 38 CLHIV). On all outcome measures, CHEU and CHUU groups had comparable scores; CLHIV scored significantly lower. Emerging global progress towards elimination of vertical HIV transmission may not only reduce mortality, but also positively impact child development.

Keywords

HIV; pediatrics; cognition; child development; maternal-fetal infection transmission; South Africa

Corresponding Author: Rachel Gruver, Columbia University Mailman School of Public Health, Department of Epidemiology, 722 W 168th St. 16th floor, New York, NY, USA, 10032 rsg2139@cumc.columbia.edu.

INTRODUCTION

South Africa has the highest burden of HIV infection in the world (Kaiser Family Foundation, 2019), with 7.7 million individuals living with HIV (UNAIDS, 2019), including one in four women of childbearing age and an estimated 260,000 children (UNAIDS, 2019). Over the past decade, the scale-up of prevention of mother-to-child transmission of HIV (PMTCT) has decreased the vertical transmission rate to 0.9% (Republic of South Africa Department of Health, 2018), resulting in over 3.2 million children in South Africa who were perinatally exposed to HIV, but not infected (UNAIDS, 2018). It is known that children living with HIV (CLHIV) face significantly increased rates of mortality, morbidity, and neurocognitive and physical disabilities (Wachsler-Felder & Golden, 2002; Van Rie et al., 2007; Phillips et al., 2016). However, less is known about the health and developmental outcomes of children who are perinatally HIV-exposed but uninfected (CHEU). A number of recent studies have suggested that CHEU may be more likely to experience delay or disability in neurocognitive or language development compared to children who are HIV-unexposed and uninfected (CHUU) (McHenry et al., 2018; Wu et al., 2018; le Roux et al., 2018, 2019; Wedderburn et al., 2019; Mukherjee et al., 2019). However, conflicting evidence from methodologically similar studies indicates that developmental scores among CHEU do not differ from those of CHUU (McHenry et al., 2019; Springer et al., 2018, 2019; Boivin et al., 2018; Desmonde et al., 2016). Many of the studies to date have been limited by small sample size, differing recruitment and eligibility criteria for the CHEU, CHUU and CLHIV groups, and/or lack of adjustment for potentially confounding variables, such as household food insecurity or lower education. Recent systematic reviews have called for further studies to address this issue (McHenry et al., 2018; Desmonde et al., 2018).

For global and national health systems to support the optimal health of children in the future, especially in regions with high HIV prevalence, it will be essential to better understand the unique health and developmental trajectories of CHEU (Siberry, 2018). The objective of the current study is to assess the neurodevelopment of CHEU in a peri-rural community in KwaZulu-Natal, South Africa in relation to CHUU and CLHIV drawn from the same population-based sample, while accounting for a battery of potential confounding factors. This study compares cognitive and language developmental outcomes using multiple validated measures between CHEU, CHUU and CLHIV at ages 4–6 years in peri-urban communities in KwaZulu-Natal, South Africa, one of the regions most heavily impacted by HIV in the world (Kharsany et al., 2018).

METHODS

Study population, setting and data collection

We conducted a cross-sectional analysis of data from the Asenze cohort study, a population-based study based in five resource-poor peri-urban communities in Kwa-Zulu Natal, South Africa. All children aged 4–6 years living in the study area were eligible to participate along with their primary caregiver. Using door-to-door recruitment, 88% of eligible families were enrolled; of those, 87% (n=1581 child-caregiver pairs) completed a clinical assessment visit in 2008–2010. At the assessment visit, experienced bilingual mid-level psychological assessors administered cognitive and language measures to children in their native language,

isiZulu, and rapid HIV testing was offered for children and caregivers. Children completed a comprehensive medical assessment. Caregivers provided demographic and health information about the participating child, caregiver and household. The present analysis uses data from this initial study visit. Detailed information on Asenze cohort study methods has been published previously (Ajayi et al., 2017a, 2017b; Knox et al., 2018; Uwedimo et al., 2014; Chhagan et al., 2011).

Our analysis included children whose birth mother was their primary caregiver (67%). We excluded those with a non-maternal primary caregiver since maternal HIV status was often not known reliably in those cases. Though maternal HIV status could be inferred for four- to six-year-old CLHIV, we also excluded the 20 CLHIV with a non-maternal primary caregiver in order to ensure comparability of the CHEU, CHUU and CLHIV groups. We also excluded any other children for whom HIV status was unavailable for either the child, mother, or both. The final sample included 922 mother-child pairs with complete HIV data. Informed consent was obtained from the caregiver for all child-caregiver pairs. This study was approved by the University of KwaZulu-Natal Biomedical Research Ethics Committee and the Columbia University Institutional Review Board.

Cognitive development measures

The Grover-Counter Scale of Cognitive Development (GCS) was used to assess child cognitive function. This measure was developed and validated for use in South Africa. Intended for children ages 3–10 years, it requires minimal verbal interaction, as it is designed to measure cognitive function even among children with expressive or receptive language impairment. Validation studies have confirmed construct validity of the GCS, finding that it is highly correlated with established screens for cognitive development (Grover & Sebate, 2000).

Subscales from the Kaufman Assessment Battery for Children, Second Edition (KABC-II) were used to measure specific aspects of cognitive function, including conceptual thinking, working memory (the Hand Movement test) and learning (the Atlantis subscale). The KABC-II is designed for children ages 3–18. It was chosen for its demonstrated reliability and cross-cultural functionality, including use in other African countries and pilot testing results of the isiZulu language version in South Africa (Kaufman & Kaufman, 2004; Ajayi et al. 2017a; Debeaudrap et al., 2018; Boivin et al., 2018, 2019).

The Reynell Developmental Language Scales (RDLS) Third Edition consists of two subscales measuring verbal comprehension and expressive language abilities in children ages 18 months to 7 years (Edwards et al., 1997). It has been widely used globally, including in low- and middle-income countries (Knox et al., 2018). It was translated into isiZulu for the Asenze study and back-translated to ensure correct interpretation.

On each cognitive development measure, children who were unable to undertake the assessment activities due to impairment were given a score of zero; those who were unable to complete the measure for other reasons, such as illness or behavioral issues (e.g., hyperactivity) were coded as missing for that scale.

HIV status

HIV status of children and primary caregivers was determined by rapid test (94% of children and 65% of mothers) or by caregiver report of prior testing. Testing was made voluntary for participants due to ethical considerations, such as individuals' emotional readiness to test, social stigma, and the feared risk of intimate partner violence for those testing positive. For participants who consented to HIV testing for themselves and/or their child, two rapid HIV tests were conducted for each individual. Those who tested newly positive, inconclusive or discordant on the rapid tests were referred for confirmatory testing and care. Those who neither tested nor reported HIV results, as well as those with inconclusive or discordant rapid test results, were classified as HIV status unknown and were excluded from this analysis.

Children were classified in the CLHIV group if both mother and child were living with HIV, CHEU if the mother was living with HIV but the child was not, and CHUU if neither the mother nor child was living with HIV. Of note, due to the cross-sectional nature of the study, we did not have complete data on the HIV status of mothers at the time of pregnancy. It is possible that some of the mothers of the CHEU group did not seroconvert until after the child was born, resulting in some CHUU being misclassified as CHEU. We conducted a sensitivity analysis (described in the analysis section) to address this issue.

Demographic and clinical variables

Caregiver questionnaires collected data on child and household sociodemographic information, including the child's sex, child's weight at birth, alcohol use during pregnancy with the child, whether the child was ever breastfed, whether the child ever attended crèche or preschool, and the total number of children (<18 years old) living in the household. Mothers previously diagnosed with HIV were asked if they had received ART during or after pregnancy with their child, and whether the child had ever received ART.

Mothers were asked to report their highest level of education completed and the education level of the child's father; these responses were dichotomized for analysis as completion of Grade 9 or higher compared to less than Grade 9. Household assets were assessed using questions from the South Africa Demographic and Health Surveys, and an asset index was then constructed using methods previously validated in India, Indonesia, Nepal and Pakistan (Filmer & Pritchett, 2001; Ajayi et al., 2017b). Scores across the full Asenze cohort were divided into thirds; the poorest third of households was denoted using a binary variable. Food insecurity was measured by asking "How many days in the last month has your family run out of food completely?" Any response greater than zero was coded as positive for household food insecurity on a binary variable.

To identify stunted growth, children's height-for-age was calculated; scores more than two standard deviations below the WHO Child Growth Standards median were defined as stunting on a binary variable (WHO, 2006). Results from the hearing exam indicating impairment in one or both ears were coded as positive for hearing impairment.

Statistical analysis

To compare developmental outcomes between CHEU, CHUU and CLHIV groups, we used simple linear regression models to compare the groups' mean scores (GCS total, RDLS subscales and total, and KABC-II subscales), followed by multivariable linear regression models adjusting for confounding variables.

Potential confounders were identified from the literature and included breastfeeding, preschool attendance, maternal ART during pregnancy or perinatally, child ART, maternal alcohol use during pregnancy, poverty, food insecurity, and parental education level (McHenry et al., 2018; Ajayi et al., 2017a, 2017b). To select confounding variables for inclusion in the final models, we used bivariable analyses (t-tests or Wilcoxon rank-sum tests for categorical variables, and Spearman's correlation for continuous variables) of each potential confounder by HIV exposure group and by each outcome variable; covariates associated ($p<0.10$) with both HIV exposure and the selected outcome variable were tested in the multivariable model using a forward selection approach. Variables that resulted in more than a 10% change in the beta coefficient for the HIV exposure-developmental outcome relationship when included in the model, as compared to the simple regression, were retained; the final adjusted models included preschool attendance (all outcomes) and household food insecurity (Kaufman Hand Movement and RLDS Expressive Language only). For maternal ART, we assessed the bivariable association between this potential confounder and each outcome variable within the CHEU and CLHIV groups individually. We also assessed the association of child ART with developmental outcomes within the CLHIV group.

In sensitivity analyses to assess the impact of potential misclassification of CHUU into the CHEU group, we reclassified various proportions of the highest-scoring CHEU (the top 4%, 5% and 10% in the CHEU group on each outcome measure; a highly conservative assumption since only top scorers were reclassified) into the CHUU group, and then repeated the multivariable analyses. To assess potential bias due to the exclusion of caregiver-child dyads with a non-maternal primary caregiver or lack of HIV status data, we compared the excluded group to the mother-child dyads included in the analysis on key demographic variables using chi-squared tests and t-tests.

RESULTS

Participant characteristics

The Asenze cohort study assessed 1581 children. We excluded 545 children (35%) whose primary caregiver was not their biological mother, and an additional 110 (7%) due to incomplete data on the mother or child's HIV status. We also removed four children with HIV whose mothers did not have HIV from the analysis, since this indicated some irregularity in either the mode of transmission or validity of the data. After these exclusions, 922 mother-child pairs (58%) remained for analysis: 257 in the CHEU group, 627 in the CHUU group, and 38 in the CLHIV group.

Table 1 shows child- and household-level characteristics of study participants. Children were approximately 5 years old on average at the time of participation, and 51% were female.

Groups were roughly comparable on child weight at birth (mean 2988 grams), number of children per household (mean 3.7), and percent of parents with 9th grade education or higher (64% of mothers and 59% of fathers).

Children in the CLHIV group exhibited a number of disadvantages compared to CHEU: A higher proportion (45%) had stunted growth compared to the CHEU and CHUU groups (14 and 12%, respectively; $p<0.01$), and a higher proportion (24%) had hearing impairment, although the latter trend did not reach statistical significance (Table 1). A lower proportion of CLHIV had ever attended preschool compared to the other two groups, and a greater percentage of the CLHIV group lived in a household experiencing food insecurity (neither comparison was statistically significant). In contrast, a lower proportion of CLHIV were in the poorest third of Asenze cohort households compared to CHEU and CHUU. However, a significantly higher proportion of mothers of CHEU (9%) reported drinking alcohol during their pregnancy, compared to 4% of mothers of CHUU and 3% of the mothers of CLHIV.

The proportion of children who were ever breastfed was 74% in the CHEU group, 92% in the CHUU group, and 87% in the CLHIV group and ($p<0.001$). Comparing the CLHIV to the CHEU group, significantly more mothers of the CLHIV group reported receiving antiretroviral therapy (ART) during pregnancy and/or delivery (47% vs. 34%, $p=0.01$). Among the 26 CLHIV whose status was known prior to study participation, 54% (n=14) had ever received ART, 31% (n=8) had not, and data were unavailable for the remaining 15% (n=4).

Child-caregiver dyads who were excluded from this analysis were equivalent to the included dyads on child age, sex, stunted growth, hearing impairment, preschool attendance, food insecurity, father's education level, and maternal use of ART during pregnancy (which suggests similar rates of maternal HIV across these groups). Excluded dyads had a lower mean child birthweight, lower rate of breastfeeding, higher rate of maternal alcohol use during pregnancy, and a higher mean number of children in the household, compared to those included in the analysis. However, the excluded dyads were also less likely to be in the poorest third of the Asenze cohort, and reported higher levels of maternal education.

Cognitive and language outcomes

In both unadjusted and adjusted analyses (Table 2), mean scores in the CHEU and CHUU groups were equivalent on all cognitive measures. Children in the CHEU group had higher average scores on every cognitive outcome measure compared to the CLHIV group. In adjusted analyses, the CHEU group had significantly higher average scores on the Kaufman Hand Movement working memory test (CHEU mean 4.6 vs. CLHIV mean 3.8, $p=0.03$), the GCS (CHEU mean 24.3 vs. CLHIV mean 17.7, $p=0.03$), the RLDS verbal comprehension (CHEU mean 59.2 vs. CLHIV mean 55.5, $p=0.01$) and RLDS total score (CHEU mean 106.5 vs. CLHIV mean 101.3, $p=0.02$), but not the Kaufman Atlantis, Kaufman conceptual thinking tests, or the RLDS expressive language scale.

Within both the CHEU and CLHIV groups, bivariable analyses showed no association between maternal PMTCT and any outcome. Similarly, within the CLHIV group, we observed no association between child ART and any outcome. However, interpretation of

these findings in the CLHIV group is limited by small cell counts. Data on the timing and duration of child ART were not available.

Sensitivity analysis

In sensitivity analyses to assess the potential impact of misclassification of CHUU as CHEU, we explored an extreme though unlikely situation, in which those misclassified as CHEU were the highest-scoring in the CHEU group on each measure. This is a scenario in which misclassification would produce maximum bias. When CHEU in the top 4% of CHEU group scores on each outcome were moved into the CHUU group and analyses were repeated, the CHEU-CHUU comparison remained non-significant on all outcome measures. With all CHEU in the top 10% reclassified to CHUU, we found a statistically significant difference between the CHEU and CHUU groups on the GCS and the three KABC-II subscales, but RDLS findings still remained non-significant.

DISCUSSION

In a population-based sample of children in a high HIV-prevalence setting, we found that CHEU scores were not significantly different from those of CHUU on any measure of cognitive development at ages 4–6 in children whose caregivers are their biological mothers. CHEU were also significantly less likely than CLHIV to experience cognitive and language delay. This suggests that peri- and neonatal exposure to maternal HIV infection did not significantly delay children's neurocognitive and language development in this population.

Our results align with those of several previous studies in sub-Saharan Africa (Boivin et al., 2018; Chaudhury et al., 2017), Asia (Jahanshad et al., 2015), and the US (Sirois et al., 2016; Nichols et al., 2016; Rice et al., 2013). However, the current literature on cognitive development in CHEU contains disparate results. Some studies have identified cognitive and language delay in CHEU groups relative to CHUU (le Roux et al., 2018; Wu et al., 2018; McHenry et al., 2018) and to population norms (Rice et al., 2013, 2018).

One possible explanation for some of these conflicting results is the age at which outcomes are measured. Many of the studies that have found differences between CHEU and CHUU, particularly for language outcomes, have focused on children younger than four years (Wederburn et. al, 2019, le Roux et al., 2019, Desmonde et al., 2018; McHenry et al., 2018), suggesting the possibility that cognitive delays observed in very young CHEU may improve with age. Our findings of no cognitive delay in 4–6-year-old CHEU are consistent with this explanation.

Previous studies have suggested exposure to maternal ART during pregnancy as a biological mechanism that may account for at least some of the poorer outcomes previously observed in CHEU compared to CHUU children (Chaudhury et al., 2017). Thus, varying rates of ART usage and specific drug agents in different populations are another potential explanation for mixed findings in the literature. In fact, a recently published study of RCT data from Malawi and Uganda by Boivin et al. (2019) even suggests that mothers being maintained on triple ART pre- and post-partum may be protective for CHEU development, while less intensive treatment regimens result in poorer outcomes. However, in our study, in which only early

therapies (primarily Neviripine alone) were available to participants, we still observed no differences in development between the CHEU and CHUU groups. Furthermore, maternal ART was not significantly associated with any developmental outcomes within the CHEU group, nor did it appear to be associated with these outcomes within the CLHIV group. The lack of observed association may have been due to the small number of women receiving ART perinatally at the time cohort children were born (2002–2006). It is also possible we did not see an association because effects differ by dose, timing, or duration of ART medication. We did not have detailed data on ART usage, so we were unable to explore heterogeneity of this exposure.

Finally, in the present study, all participants were enrolled from a single population-based sample using identical criteria and recruitment methods, which allowed us to compare CHEU and CHUU groups that were equivalent on most measured sociodemographic variables. In most prior studies, CHEU and CHUU were drawn from different source populations. Our finding that CHEU did not differ from CHUU in their cognitive and language abilities at ages 4–6 may simply reflect sufficient similarity of comparison groups on key social, economic, and environmental factors that affect cognitive development.

Strengths and Limitations

To our knowledge, this is the first population-based cohort study to compare the neurodevelopment of CHEU, CHUU and CLHIV in a high HIV-prevalence setting. Most prior studies have recruited participants from medical facilities, an approach that is not likely to result in a study that is representative of the full population in the area of interest. Furthermore, some studies have used different criteria and source populations for the enrollment of different HIV exposure status groups; in most of these cases, the CLHIV children were clinical trial participants. In contrast, the mother-child pairs in the Asenze study were enrolled from a single population using identical criteria and methods across all HIV exposure status groups. An additional strength is the use of a full cognitive assessment battery that allowed us to assess development based on both measures developed and validated locally (the GCS) and a global measure widely used in sub-Saharan Africa (the KABC-II). These measures were also based in two different theoretical approaches to child development, those of Piaget (Grover & Sebate, 2000) and Vygotsky (Kaufman & Kaufman, 1997).

A limitation of this study is the lack of more rigorous HIV exposure data at the time of pregnancy. It is likely that some of the women in the study contracted HIV *after* their child was born, resulting in children being misclassified as CHEU when they should have been in the CHUU group. If the children who were truly exposed scored lower on average than the truly unexposed children and such misclassification did occur, CHEU group scores would be inflated and appear closer to the CHUU group scores, resulting in bias towards a null finding for the CHEU-CHUU comparison. Sensitivity analyses indicated that our findings were reasonably robust to misclassification, even under extremely conservative assumptions.

Additionally, we relied on self-reported HIV status data from participants who declined testing but provided HIV status information on study surveys. Some false negative responses may have occurred due to concerns around privacy and stigma; however, participants were

given the option to decline the question. If such misclassification did occur, the CHEU-CHUU and CHEU-CLHIV comparisons could have been biased towards null findings. Future studies should obtain clinical data on HIV status whenever possible, though in population-based studies such as this one, it is generally necessary to allow participants to opt out of testing for ethical reasons.

Another limitation is that a substantial proportion of the original 1581 children in the study could not be included in this analysis, either because the child's primary caregiver was not the child's biological mother, or because HIV status data was unavailable for child, mother, or both. Both scenarios may be more likely among children who are exposed to or living with HIV. However, there is no reason to believe that either would be independently associated with the child's cognitive outcomes. Additionally, an analysis comparing the included and excluded dyads showed that although excluded children had lower average birthweight and were less likely to be breastfed, they were equivalent to the included children on key variables, including age and sex, stunted growth, hearing impairment, and preschool attendance. We would thus not expect this limitation to significantly bias our findings.

Implications

We found that CHEU had equivalent cognitive and language outcomes to CHUU children at ages 4–6, in contrast to CLHIV who had significant developmental delays. The observation that CHEU did not appear to be at higher risk is promising. It indicates that the emerging success of PMTCT programs in high HIV prevalence areas may positively impact child development, in addition to reducing other HIV-related morbidities and mortality. There is a need for future epidemiologic research that includes longitudinal assessment of perinatal HIV exposure status and later child developmental outcomes.

Acknowledgements:

We thank all the Asenze study participants and their families, as well as the study staff. Research reported in this publication was supported by the National Institute on Drug Abuse under award number R01-DA023697 and by the Fogarty International Center, National Institutes of Health, and the Office of Behavioral and Social Sciences Research, Office of Disease Prevention of the National Institutes of Health, under award number R01-TW011228. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

References

Ajayi OR, Matthews G, Taylor M, Kvalsvig J, Davidson LL, Kauchali S, et al. (2017). Factors associated with the health and cognition of 6-year-old to 8-year-old children in KwaZulu-Natal, South Africa. Trop Med Int Health, 22(5), 631–637. doi: 10.1111/tmi.12866 [PubMed: 28278357]

Ajayi OR, Matthews GB, Taylor M, Kvalsvig JD, Davidson L, Kauchali S, et al. (2017). Structural Equation Modeling of the Effects of Family, Preschool, and Stunting on the Cognitive Development of School Children. Front Nutr, 4, 17. doi: 10.3389/fnut.2017.00017 [PubMed: 28555186]

Boivin MJ, Barlow-Mosha L, Chernoff M, Laughton B, Zimmer B, Joyce C et al. (2018). Neuropsychological performance in African children with HIV enrolled in a multi-site anti-retroviral clinical trial. AIDS, 32(2), 189–204. doi: 10.1097/QAD.0000000000001683 [PubMed: 29112069]

Boivin MJ, Maliwichi-Senganimalunje L, Ogwang LW, Kawalazira R, Sikorskii A, Familiar-Lopez I, et al. (2019). Neurodevelopmental effects of ante-partum and post-partum antiretroviral exposure in

HIV-exposed and uninfected children versus HIV-unexposed and uninfected children in Uganda and Malawi: a prospective cohort study. Lancet HIV, 6(8), e518–e530. doi: 10.1016/S2352-3018(19)30083-9 [PubMed: 31122797]

Chaudhury S, Williams PL, Mayondi GK, Leidner J, Holding P, Tepper V et al. (2017). Neurodevelopment of HIV-Exposed and HIV-Unexposed Uninfected Children at 24 Months. Pediatrics, 140(4), e20170988. doi: 10.1542/peds.2017-0988 [PubMed: 28912368]

Chhagan MK, Kauchali S, Arpadi SM, Craib MH, Bah F, Stein Z, et al. (2011). Failure to test children of HIV-infected mothers in South Africa: implications for HIV testing strategies for preschool children. Trop Med Int Health, 16(12), 1490–1494. doi:10.1111/j.1365-3156.2011.02872.x [PubMed: 21883725]

Desmonde S, Goetghebuer T, Thorne C & Leroy V (2016). Health and survival of HIV perinatally exposed but uninfected children born to HIV-infected mothers. Curr Opin HIV AIDS, 11(5), 465–476. doi: 10.1097/COH.0000000000000300 [PubMed: 27716731]

Edwards S, Fletcher P, Garman M, Hughes A, Letts C & Sinka I (1997). Reynell Developmental Language Scales III – The University of Reading Edition. GL Assessments.

Filmer D & Pritchett LH (2001). Estimating wealth effects without expenditure data–or tears: an application to educational enrollments in states of India. Demography, 38(1), 115–132. doi: 10.2307/3088292 [PubMed: 11227840]

Grover VM & Sebate KM (2000). Revised manual for the Grover-Counter Scale of Cognitive development. Human Sciences Research Council.

Jahanshad N, Couture M, Prasitsuebsai W, Nir TM, Aurpibul M, Thompson PM, et al. (2015). Brain Imaging and Neurodevelopment in HIV-uninfected Thai Children Born to HIV-infected Mothers. Pediatr Infect Dis J, 34, e211–e216. doi: 10.1097/INF.0000000000000774 [PubMed: 26090574]

Kaiser Family Foundation. (2019, 9 19). Fact Sheet: The Global HIV/AIDS Epidemic. Kaiser Family Foundation https://www.kff.org/global-health-policy/fact-sheet/the-global-hivaids-epidemic/

Kaufman AS & Kaufman NL (2004). Kaufman Test of Educational Achievement Comprehensive Form, Second Edition American Guidance Service.

Kharsany AB, Cawood C, Khanyile D, Lewis L, Grobler A, Puren A, et al. (2018). Community-based HIV prevalence in KwaZulu-Natal, South Africa: results of a cross-sectional household survey. The Lancet HIV, 5(8), e427–e437. doi: 10.1016/S2352-3018(18)30104-8 [PubMed: 30021700]

Knox J, Arpadi SM, Kauchali S, Craib M, Kvalsvig JD, Taylor M, et al. (2018). Screening for developmental disabilities in HIV positive and HIV negative children in South Africa: Results from the Asenze Study. PLoS ONE, 13(7), e0199860. doi: 10.1371/journal.pone.0199860 [PubMed: 29969474]

le Roux SM, Donald KA, Brittain K, Phillips TK, Zerbe A, Nguyen KK, et al. (2018). Neurodevelopment of breastfed HIV-exposed uninfected and HIV-unexposed children in South Africa. AIDS, 32(13), 1781–1791. doi: 10.1097/QAD.0000000000001872 [PubMed: 29794831]

le Roux SM, Donald KA, Kroon M, Phillips TK, Lesosky M, Esterhuyse L, et al. (2019). HIV Viremia During Pregnancy and Neurodevelopment of HIV-Exposed Uninfected Children in the Context of Universal Antiretroviral Therapy and Breastfeeding: A Prospective Study. Pediatr Infect Dis J., 38(1), 70–75. doi: 10.1097/INF.0000000000002193 [PubMed: 30234792]

McHenry MS, McActeer CI, Oyungu E, McDonald BC, Bosma CB, Mpofu PB, et al. (2018). Neurodevelopment in Young Children Born to HIV-Infected Mothers: A Meta-Analysis. Pediatrics, 141(2), e20172888. doi: 10.1542/peds.2017-2888 [PubMed: 29374109]

Mukherjee SB, Devamare S, Seth A & Sapra S (2019). Development, Cognition, Adaptive Function and Maladaptive Behavior in HIV-infected and HIV-exposed Uninfected Children Aged 2–9 Years. Indian Pediatr, 56(11), 933–937. doi: 10.1007/s13312-019-1650-z [PubMed: 31441434]

Nichols SL, Chernoff MC, Malee KM, Sirois PA, Woods SP, Williams PL, et al. (2016a). Executive Functioning in Children and Adolescents with Perinatal HIV Infection and Perinatal HIV Exposure. J Pediatr Infect Dis Soc, 5(1), S15–S23. doi: 10.1093/jpids/piw049

Nichols SL, Chernoff MC, Malee KM, Sirois PA, Williams PL, Figueroa V, et al. (2016b). Learning and Memory in Children and Adolescents with Perinatal HIV Infection and Perinatal HIV Exposure. Pediatr Infect Dis J, 35(6), 649–654. doi:10.1097/INF.0000000000001131 [PubMed: 26967812]

Phillips N, Amos T, Kuo C, Hoare J, Ipser J, Thomas KGF, et al. (2016). HIV-Associated Cognitive Impairment in Perinatally Infected Children: A Meta-analysis. Pediatrics, 138(5), e20160893. doi: 10.1542/peds.2016-0893 [PubMed: 27940772]

Republic of South Africa Department of Health. (2018, 10 1). Annual report 2017/18. South African Government https://www.gov.za/documents/department-health-annual-report-20172018-1-oct-2018-0000.

Rice ML, Zeldow B, Siberry GK, Purswani M, Malee K, Hoffman HJ, et al. (2013). Evaluation of risk for late language emergence after in utero antiretroviral drug exposure in HIV-exposed uninfected infants. Pediatr Infect Dis J, 32(10), e406–413. doi: 10.1097/INF.0b013e31829b80ee [PubMed: 24067563]

Rice ML, Russell JS, Frederick T, Purswani M, Williams PL, Siberry GK, et al. (2018). Risk for Speech and Language Impairments in Preschool Age HIV-exposed Uninfected Children with In Utero Combination Antiretroviral Exposure. Pediatr Infect Dis J, 37(7), 678–685. doi: 10.1097/INF.0000000000001875 [PubMed: 29278615]

Siberry G (2018). Commentary: Beyond Prevention of Vertical HIV Transmission—Improving Outcomes of HIV-Uninfected Infants Born to Mothers with HIV Infection. Pediatr Infect Dis J, 37(3), 245. doi: 10.1097/INF.0000000000001854

Sirois PA, Chernoff MC, Malee KM, Garvie PA, Harris LL, Williams PL, et al. (2016). Associations of Memory and Executive Functioning with Academic and Adaptive Functioning Among Youth with Perinatal HIV Exposure and or Infection. J Pediatr Infect Dis Soc, 5(suppl 1), S24–S32. doi: 10.1093/jpids/piw046

Springer PE, Slogrove AL, Laughton B, Bettinger JA, Saunders HH, Molteno CD, et al. (2018). Neurodevelopmental outcome of HIV-exposed but uninfected infants in the Mother and Infants Health Study, Cape Town, South Africa. Trop Med Int Health, 23(1), 69–78. doi: 10.1111/tmi.13006 [PubMed: 29131457]

Springer PE, Slogrove AL, Kidd M, Kalk E, Bettinger JA, Esser MM, et al. (2019). Neurodevelopmental and behavioural outcomes of HIV-exposed uninfected and HIV-unexposed children at 2–3 years of age in Cape Town, South Africa. AIDS Care, 7, 1–9. doi: 10.1080/09540121.2019.1637506

UNAIDS. (2019). Country Factsheet: South Africa 2018. UNAIDS.org https://www.unaids.org/en/regionscountries/countries/southafrica

UNAIDS. (2018). New HIV infections averted due to PMTCT. AIDSinfo https://www.AIDSinfo.unaids.org

Uwemedimo OT, Arpadi SM, Chhagan MK, Kauchali S, Craib MH, Bah F, et al. (2014). Compliance with referrals for non-acute child health conditions: evidence from the longitudinal ASENZE study in KwaZulu Natal, South Africa. BMC Health Serv Res, 14, 242. doi: 10.1186/1472-6963-14-242 [PubMed: 24888212]

Van Rie A, Harrington PR, Dow A & Robertson K (2007). Neurologic and neurodevelopmental manifestations of pediatric HIV/AIDS: a global perspective. Eur J Paediatr Neurol, 11(1), 1–9. doi: 10.1016/j.ejpn.2006.10.006 [PubMed: 17137813]

Wachsler-Felder JL & Golden CJ (2002). Neuropsychological consequences of HIV in children: a review of current literature. Clin Psychol Rev, 22(3), 443–464. doi: 10.1016/s0272-7358(01)00108-8 [PubMed: 17201193]

Wedderburn CJ, Yeung S, Rehman AM, Stadler JAM, Nhapi RT, Barnett W, et al. (2019). Neurodevelopment of HIV-exposed uninfected children in South Africa: outcomes from an observational birth cohort study. Lancet Child Adolesc Health, 3(11), 803–813. doi: 10.1016/S2352-4642(19)30250-0 [PubMed: 31515160]

WHO Multicentre Growth Reference Study Group. (2006). WHO Child Growth Standards: length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age. World Health Organization https://www.who.int/childgrowth/standards/technical_report/en/

Wu J, Li J, Li Y, Loo KK, Yang H, Wang Q, et al. (2018). Neurodevelopmental outcomes in young children born to HIV-positive mothers in rural Yunnan, China. Pediatr Int, 60(7), 618–625. doi: 10.1111/ped.13584 [PubMed: 29663621]

Table 1.

Demographic, social and clinical characteristics of participating children by HIV exposure group

Characteristic	HIV exposure group			Total	Missing (n)	p-value†
	Children HIV-exposed and uninfected (CHEU)	Children HIV-unexposed and uninfected (CHUU)	Children living with HIV (CLHIV)			
Total children in sample, n (%)	**257 (28%)**	**627 (68%)**	**38 (4%)**	**922 (100%)**	--	--
Age at assessment, mean (SD)	5.0 (0.6)	4.9 (0.6)	5.0 (0.7)	**5.0 (0.6)**	0	0.66
Female sex, n (%)	132 (51%)	322 (51%)	19 (50%)	**473 (51%)**	0	0.99
Birthweight (kilograms), mean (SD)	3.0 (0.6)	3.0 (0.6)	2.9 (0.5)	**3.0 (0.6)**	96	0.53
Ever breastfed, n (%)	189 (74%)	578 (92%)	33 (87%)	**800 (87%)**	3	*<0.01***
Stunted growth, n (%)	35 (14%)	76 (12%)	17 (45%)	**128 (14%)**	111	*<0.01***
Weight-for-age z-score, mean (SD)	−0.12 (0.96)	−0.16 (0.95)	−.73 (0.95)	**−0.15 (0.96)**	13	*<0.01***
Hearing impairment, n (%)	38 (15%)	70 (11%)	9 (24%)	**117 (13%)**	28	0.06*
Ever attended preschool, n (%)	152 (59%)	381 (61%)	17 (45%)	**550 (60%)**	3	0.13
In poorest 1/3 of Asenze cohort households, n (%)	107 (42%)	225 (36%)	10 (26%)	**342 (37%)**	7	0.12
Household food insecure, n (%)	49 (19%)	147 (23%)	11 (29%)	**207 (22%)**	42	0.19
# of children (age<18) in household, mean (SD)	3.7 (2.2)	3.7 (1.9)	3.7 (1.9)	**3.7 (2.1)**	28	0.75
Mother completed Grade 9 or higher, n (%)	162 (63%)	404 (64%)	24 (63%)	**590 (64%)**	57	0.84
Father completed Grade 9 or higher, n (%)	144 (56%)	376 (60%)	20 (53%)	**540 (60%)**	174	0.65
Maternal alcohol use during pregnancy, n%	24 (9%)	27 (4%)	1 (3%)	**105 (6%)**	102	*<0.01***
Mother received antiretroviral therapy (ART) during pregnancy, n (%)	87 (34%)	N/A	18 (47%)	**105 (11%)**	141	*0.01*‡**

† Chi-square or Fisher's exact test (categorical variables) or ANOVA (continuous variables)

‡ Test compared CLHIV and CHEU groups only

* Difference approaching statistical significance, p<0.10

** Statistically significant difference, p<0.05

Table 2.

Unadjusted and adjusted mean cognitive and language scores by HIV exposure group

Scale	Total mean	Mean (95% CI), by HIV exposure group						Pairwise comparison of adjusted means, p-values	
		Children HIV-exposed and uninfected (CHEU)		Children HIV-unexposed and uninfected (CHUU)		Children living with HIV (CLHIV)		CHEU vs. CHUU	CHEU vs. CLHIV
		Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted		
Kaufman Atlantis	30.3	30.7 (29.1–32.4)	30.6 (30.3–31.0)	30.3 (29.2–31.4)	30.2 (30.0–30.5)	26.7 (23.0–30.3)	26.4 (25.5–27.4)	p=0.60	p=0.16
Kaufman Hand Movement †	4.5	4.6 (4.3–4.8)	4.6 (4.6–4.7)	4.5 (4.3–4.7)	4.5 (4.4–4.5)	3.6 (3.1–4.1)	3.8 (3.7–4.0)	p=0.25	p=0.03 *
Kaufman Conceptual Thinking	5.0	5.1 (4.6–5.6)	5.1 (5.0–5.2)	5.0 (4.7–5.3)	5.0 (4.9–5.0)	3.9 (2.9–4.9)	3.8 (3.6–4.1)	p=0.66	p=0.11
Grover-Counter scale (GCS)	24.4	24.5 (22.9–26.2)	24.3 (23.7–24.9)	24.8 (23.7–26.0)	24.6 (24.3–25.0)	17.9 (14.3–21.5)	17.7 (16.1–19.2)	p=0.89	p=0.03 *
Reynell Expressive Language †	47.1	47.3 (46.8–47.8)	47.4 (47.2–47.5)	47.1 (46.7–47.6)	47.1 (47.0–47.2)	45.7 (43.3–48.0)	45.9 (45.5–46.3)	p=0.40	p=0.16
Reynell Verbal Comprehension	59.0	59.3 (58.5–60.1)	59.2 (59.0–59.5)	59.2 (58.6–59.7)	59.1 (59.0–59.3)	55.7 (52.6–58.8)	55.5 (54.9–56.1)	p=0.66	p=0.01 *
Reynell total score	106.2	106.6 (105.5–107.7)	106.5 (106.2–107.0)	106.3 (105.5–107.1)	106.3 (106.0–106.5)	101.6 (97.2–106.1)	101.30 (100.3–102.3)	p=0.57	p=0.01 *

All models were adjusted for child preschool attendance.

† Adjusted model also includes food insecurity.

* statistically significant pairwise difference ($p<0.05$)