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The effect of HIV infection and exposure on cognitive development in the first two years of life in Malawi.

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Abstract

OBJECTIVES—To assess longitudinal patterns and determinants of cognitive development in infants living with HIV, infants exposed to maternal HIV infection, and HIV-unexposed infants.

METHODS—Prospective, community-based cohort study of 555 Malawian infants aged 8 weeks to 24 months, using multivariable linear mixed-effects regression models with random intercepts to analyze repeated measures of cognitive function.

RESULTS—At 3 months of age, cognitive scores on the Bayley Scales of Infant Development (BSID 3rd edition) were lower in the 96 HIV-infected infants (mean=14.1 (SD:4.8)) compared to the 289 HIV-exposed (mean=16.5 (SD:3.7)) and the 170 unexposed infants (mean=17.5 (SD:3.3)).

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Contributors' Statement Page

Mr. Struyf carried out the statistical analyses and drafted the manuscript.

Prof. Van Rie conceptualized and designed the cohort study, supervised data collection, data management and data analysis, and reviewed and revised the manuscript.

Dr. Dube supervised all field activities, assisted in data management, and reviewed and revised the manuscript

Dr. Cromwell assisted in data management and data analysis, and reviewed and revised the manuscript

Dr. Sheahan designed data collection instruments, assisted in supervision of field activities, supervised data management, carried out analyses, and reviewed and revised the manuscript.

Prof. Heyderman coordinated and supervised data collection, and critically reviewed the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Over the first two years of life, the small deficit in cognitive development of infants living with HIV who survived and remained in care did not increase (mean score 52.9 among HIV-infected vs 55.6 among HIV unexposed). In multivariable analysis, malnutrition and a more advanced clinical infant HIV stage had a negative impact on cognition at age 3, while financial security, care by the biological mother, and ART for mother and child were associated with better cognitive status at this young age. The positive influence of maternal ART reversed with age.

CONCLUSIONS—Malawian infants exposed to HIV had a cognitive development that was similar to their unexposed peers in the first two years of life, while that of HIV infected infants lagged behind from the start. Early initiation of effective ART in all HIV infected mothers and infants, and prevention of infant malnutrition are important to safeguard cognitive development of children affected by HIV.

Keywords

cognitive development; HIV; AIDS; infants; Africa

1. Introduction

Every year, there are about 160,000 new Human Immunodeficiency Virus (HIV) infections in children. [(1)] More than 90% of these occur in the developing world, and almost all are due to perinatal Mother To Child Transmission (MTCT) or breastfeeding. [(2)] An important consequence of perinatal HIV infection is the impact on the development of the child's central nervous system (CNS). [(3–8)] The reported prevalence of delay in cognition, motor function, speech and language in perinatally HIV-infected children has varied from low (8%, high-income countries) to high (>60%, sub-Saharan Africa). Prevalence of neurodevelopmental delay increases with age and level of immunodeficiency, and was highest when access to antiretroviral treatment (ART) was still limited. [(4, 7–17)] The highest incidence rate of HIV-related CNS manifestations occurs in the first two years of life, with an estimated incidence of 9.9% in the first year of life, 4.2% in the second and less than 1% thereafter. [(18–21)] ART can improve neurologic outcomes,[(6, 15, 22, 23)] with treated children showing better recovery towards developmental milestones than their untreated counterparts. [(24)]

In 2008, the CHER study demonstrated that very early ART, initiated before 12 weeks of age, improves clinical and immunological outcomes compared to ART initiated after immunodeficiency develops. [(25)] Emerging evidence suggests there may be a benefit to cognitive development of very early ART initiation. [(25, 26)]

Apart from HIV infection itself, psychosocial and contextual factors such as poverty, limited family resources, malnutrition and stressful child rearing environments, impairment in overall functioning and increased hospitalization may all further impact the cognitive development of these infants. [(27–32)]

Even though more than 80% of young infants (age 0–2) living with HIV reside in sub-Saharan Africa, little is known about their cognitive development and its predictors, especially in the context of access to early infant diagnosis (using a DNA PCR assay) and

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early ART initiation (test and treat strategy). [33] To date, studies have focussed on older children and found that significant cognitive deficits were present among children at school age living with HIV, even when started on ART at an 'early' age (median =1.2 years). [15, 34]

We performed a longitudinal, prospective, observational study of perinatal HIV-infected infants, HIV-exposed uninfected infants, and HIV unexposed infants in Blantyre, Malawi, to describe their longitudinal patterns of cognitive development and to identify predictors of their cognitive development.

2. Methods

2.1. Study Setting and Participants

A total of 555 infants, of which 96 perinatally HIV-infected, 289 HIV-exposed and 170 non-exposed, were enrolled at two health clinics in Blantyre, Malawi, from January 2008 till June 2011. Pregnant women living with and without HIV were identified through the Department of Health PMTCT program in Blantyre (funded by UNICEF), which provided HIV counseling and testing of all pregnant women and nevirapine for PMTCT to women living with HIV and their newborns. Other PMTCT regimens and universal treatment were not yet available during the study period. [2] All infants born to mothers living with HIV were offered participation in an early infant HIV testing program at age 6 weeks, provided by the study as this was not yet standard of care. All infants living with HIV were referred for care and treatment to the closest pediatric ART center. [35]

Infants born to a mother living with HIV were classified as HIV infected if infection was demonstrated by a positive HIV DNA PCR test on dried blood spot and confirmed by a second HIV DNA or a quantitative HIV RNA viral load test. Infants born to a mother living with HIV were classified as HIV exposed uninfected if the absence of HIV infection was demonstrated by a negative PCR test for HIV at enrollment *and* all follow-up visits. Infants were considered HIV unexposed if born to a mother with documented HIV negative status at the time of antenatal visit and the infant tested negative on a rapid HIV antibody test performed after age 18 months. All HIV-infected infants and all HIV-exposed uninfected infants were invited for study participation. To ensure recruitment of a random sample of HIV unexposed infants over a similar recruitment period, we invited one in 8 HIV exposed infants.

2.2. Data collection

At enrollment, clinical and anthropometric data on the infant, and socioeconomic and health status of the mother/caregiver was collected on a standardized form. Socioeconomic status was estimated by inquiring about food security, financial security, housing and education level of the caregiver. Presence of malnutrition and stunting was interpreted according to the WHO definitions.[36] An infant was considered malnourished or stunted when a weight for age Z-score was below 2 SD of the reference mean.

The Bayley Scales of Infant Development, 3rd edition, (BSID-III) were used to assess the cognitive development of all children at age 10 to 14 weeks, and at months 6, 9, 12, 15, 18 and 24. These scales have been validated for the use in Malawian children. [37] All tests were

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administered by study staff (medical officers, pediatricians and nurses) trained in the use of the BSID-III. Because the scoring system employed by the Bayley results in a rate of change over age that is not necessarily constant, raw test scores were used in the analysis to assess the developmental trajectories and the influence of potential predictors on those trajectories.

2.3. Data Analysis

To analyze the repeated measures of cognitive function during the first two years of life, analyses were conducted using a multivariable linear mixed-effects regression model with random intercepts (PROC MIXED procedure, SAS 9.3), fitted by maximum-likelihood methods. [38] The analysis included all infants with one or more assessments of cognitive development and coped with missing values via correct specification of the likelihood function. We assumed that data was missing at random, i.e. the probability of missingness of data, conditional on all observed outcomes, was unrelated to unobserved concurrent outcomes. Missing outcomes (10 % of all outcome data) were imputed using a multiple imputation technique. An iterative algorithm was used for full maximum likelihood estimation of the fixed and random portions of the models.

The functional, linear form of the models was checked at both levels, and visual inspection of the residual distributions revealed the tenability of the normality assumptions. The homoscedasticity assumption was checked by plotting raw residuals against predictors at the respective levels of the models.

Three models were developed by stepwise inclusion of *a priori* determined covariates. A covariate was retained in the model if it had a significant effect on the initial cognitive score or cognitive growth rate, or if the fit statistics (Deviance, AIC, BIC and R^2) of the model improved after inclusion of the variable, in order to increase the precision of the fixed effects estimates. Time-varying predictors were not retained because the model fit did not improve when including them into the random effects of the models. An unstructured error covariance structure fitted the data best.

HIV-exposed infants who seroconverted during follow-up (n=21/289), were censored from the analysis on the date the first HIV-positive DNA PCR test was collected.

Sample sizes for the HIV-infected, HIV-exposed and unexposed groups were determined *a priori* using data from a pilot study in the Democratic Republic of the Congo.[4] Assuming a 14% mother-to-child transmission rate of HIV by age 6 weeks, a vertical transmission rate of 5% between age 6 weeks and 6 months, loss of follow up rates of 15% among HIV unexposed infants, 10% among HIV exposed uninfected infants and 5% among HIV infected infants, the intended sample size to achieve 80% power was 130 HIV-infected, 150 HIV exposed uninfected, and 150 unexposed infants.

All statistical analyses were performed using SAS software, Version 9.3 (SAS Institute Inc., Cary, NC, USA).

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2.4. Ethics approval

The study was approved by the University Of Malawi College Of Medicine Research Ethics Committee, the University of North Carolina Institutional Review Board and the University of Antwerp Ethics Committee. Parents or guardians of all participants provided written informed consent before study enrollment.

3. Results

3.1. Study population

A total of 555 infants (96 HIV-infected, 289 HIV-exposed uninfected and 170 HIV unexposed) were enrolled at a median age of 11.5 weeks (range 8–78 weeks) (table 1). Half (51%) of the infants was female, 13.9 % were malnourished and 43.5% stunted during follow-up. Malnutrition and stunting were more frequent in infants living with HIV (22.3% and 50.4%) and HIV-exposed uninfected infants (15.2% and 46.0%) compared to HIV-unexposed infants (8.5% and 36.5%). Most infants (96.4%) were cared for by their biological mother. The educational status of the mothers was low, with 48.6% of the mothers living with HIV and 36.1% of HIV negative mothers not attending formal education beyond primary school. Socio-economic status of the infants' households was poor, independent of HIV exposure/infection status. Overall, 60.7% of caregivers reported financial insecurity, 91.7% did not have access to a flush toilet, and 99% lived in a house with a grass (16.5%) or iron sheet roof (82.5%). During the two-year follow-up period, hospitalization rate was low (3%), even among HIV infected children (4.6%). HIV-infected and HIV-exposed uninfected children were more likely to die (21.9% and 9.3% resp.) compared to and HIV unexposed children (3.5%). HIV-exposed and unexposed children died at an older age (median age at death resp. 36 and 34 weeks) than HIV-infected children (median age at death 18.5 weeks).

3.2. Cognitive development in the first two years of life

Cognitive scores at 15 weeks of age were significantly lower in HIV-infected infants (mean=14.1) compared to HIV-exposed (mean=16.5) and unexposed infants (mean=17.5), but the difference was lower than the 5 difference points which is considered clinically relevant. Furthermore, population variability in cognitive scores within each group was moderate (SD of 4.8, 3.7, and 3.3 for HIV infected, HIV exposed uninfected and HIV unexposed groups, respectively), resulting in differences between the groups that were not statistically significant from age 10 months onwards (table 2, figure 1).

Figure 1 depicts the mean trajectories of cognitive development in the first two years of life for the three groups. The small deficit in cognitive development did not increase among children living with HIV who survived and remained in care until age 2. The trajectories of an HIV-exposed uninfected child and an HIV unexposed child were similar from age 15 weeks to age 2 years.

3.3. Factors associated with impaired cognitive development

The cognitive scores of infants living with HIV at age 3 months were negatively associated with infant malnutrition (table 3). The difference in population average initial cognitive score between malnourished and non-malnourished HIV-infected infants was −3.48 (95%CI

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−5.12 to −1.84), meaning that, on average, a malnourished child would have a 3.48 points lower cognitive score than a child who is not suffering from malnutrition at age 3 months, if all other variables in the model are kept the same. A more advanced clinical HIV stage of a child also had a negative effect on cognition (on average −1.16 points per stage (95%CI: −1.95 to −0.37)).

Initial cognitive development scores of infants living with HIV were positively associated with maternal ART (+3.48, 95%CI: 0.59 to 6.38), but this effect reversed into a negative influence over time (−7.10 annually, 95%CI: −11.08 to −3.12). A 3-month old HIV-infected infant whose mother is on ART at that time would thus have a 3.48 point higher cognitive score compared to an infant whose mother is not on ART, but on average, over the first two years of life, would lose 7.10 points per year in comparison with an infant whose mother is not on ART, if all other variables in the model would have the same value in both infants. Initial cognitive development scores of infants living with HIV were also positively associated with ART in the infant (+2.76, 95%CI: 0.41 to 5.12) and with financial security (+1.15, 95%CI: 0.50 to 1.79). There was no association between maternal ART and infant cognitive development in HIV-exposed uninfected infants.

At age 3 months, care by the biological mother was positively associated with cognitive development scores in infants living with HIV (+4.17, 95%CI: 0.99 to 7.34), HIV-exposed uninfected (+9.70, 95%CI: 7.15 to 12.25) and unexposed infants (+5.83, 95%CI: 3.40 to 8.25). This effect declined with age among HIV-exposed uninfected (−11.08, 95%CI: −14.66 to −7.50) and HIV unexposed infants (−8.66, 95%CI: −14.20 to −3.11). Stunting had a negative effect over time in the HIV-exposed uninfected (−2.28, 95%CI: −3.19 to −1.36) and HIV unexposed infants (−2.57, 95%CI: −3.63 to −1.50).

Note that the magnitude of the effect estimates cannot be compared across groups, because of the fact that they are conditional on all the other variables in the models.

4. Discussion

In this prospective cohort study, Malawian infants living with HIV diagnosed through an early infant diagnosis program and referred for early ART initiation had a small, clinically insignificant, cognitive deficit, with a 2.4 point lower mean cognitive score on the BSID-III at age 3 months compared to HIV-exposed uninfected and a 3.4 lower BSID-III score compared to HIV-unexposed infants. This small, but biologically relevant deficit (more than 1 SD below the mean of the HIV-unexposed infants)[39] did not increase in the first 2 years of life among the children who survived and remained in HIV care. We also did not observe a difference in cognitive development between HIV exposed uninfected and HIV unexposed infants at age 3 months nor during the first two years of life.

Studies on development of HIV infected infants on ART in resource poor settings at a very young age are scarce. While several studies have shown that infants reached their developmental gross and fine motor outcome milestones at a later age than their healthy peers [24,40], cognitive outcomes at this young age have not yet been reported. Studies in infants and children have shown a developmental “catch up”, but mainly when ART was

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initiated in older symptomatic children who were not yet severely immunosuppressed. [14,41] Older children may also perform better as a result of a "survival effect," as those infants with less aggressive disease are more likely to survive. [4]

In our cohort of Malawian infants living with HIV, maternal ART was associated with better cognitive development at a very young age. We were unable to identify other studies assessing the effect of maternal ART on the cognitive status of perinatally infected infants. We hypothesize this effect is due to an absolute reduction in the perinatal exposure of the infant to the virus, as maternal ART lowers the viral load during pregnancy and the perinatal period. This finding, as well as the finding that HIV-exposed but uninfected infants perform similar to unexposed infants, strengthen the call for universal option B+ for PMTCT, test-and-treat for all women living with HIV, and safer conception programs to prevent horizontal HIV transmission during the earliest stages of pregnancy.[42–50]

In contrast to the positive effect at age 3 months, the effect of maternal ART reversed with age. While this finding may be counter-intuitive, we believe it could, at least in part, be explained by the fact that in our cohort mothers were only eligible for ART when they had developed severe immunodeficiency (CD4 count < 250 cells/mm3). (51) The impaired health status of mothers on ART compared to that of mothers not yet eligible for ART could result in decreased capability of parenting. [52, 53] This hypothesis is supported by the fact that care by the biological mother was another factor positively associated with cognitive development at a very young age in infants living with HIV. Similarly, the positive effect of care by the biological mother may be explained by the fact that mothers living with HIV who were able to care for and nurture their infants themselves were healthier compared to those mothers who could not take on the role of primary caregiver. This effect should disappear in a setting where universal ART is implemented.

Malnutrition negatively impacted cognitive development in infants living with HIV at age 3 months. Malnutrition has been associated with both structural and functional pathology of the brain in HIV uninfected infants, which can lead to a wide range of cognitive deficits, especially during the first months of life. [54, 55]

In our cohort, early initiation of infant ART did benefit the initial cognitive level but not afterwards. Because of the observational study design, the absence of an effect of ART on cognitive development in our cohort cannot be interpreted as the absence of a causal effect of ART on cognitive development. Even though all infants were to be started on ART 'upon diagnosis', the infrastructure for early infant diagnosis of HIV, with transport of dried blood spots for HIV DNA PCR at a centralized laboratory and the requirement to confirm a possible infant HIV infection resulted in a delay in ART initiation, with an average age of ART initiation of 30.3 weeks and 19.8% of infants dying prior to initiating any ART. In the sickest children, ART was initiated prior to confirmation of HIV status, which may have resulted in confounding by indication.

Furthermore, at the time of the study, nevirapine was the only drug available for prevention of mother to child transmission, and the combination of nevirapine, lamivudine and stavudine was the only available antiretroviral drug regimen, initially as split adult tablets

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and later as pediatric syrup. Under these conditions, resistance to the prescribed ART's (NNRTI+NRTI) in our cohort was high, with 63.9% of infants tested after 1 year of life (n=36) having documented mutations associated with resistance of the virus (table 4). Consequently, while children were on ART, many may not have received effective ART and thus not have been virally suppressed. The importance of viral suppression on neurodevelopment was demonstrated in one study, where young HIV-infected infants with viral suppression on ART were found to have better motor development better than those without suppression on ART. [24]

The only factors associated with cognitive development of HIV-exposed and unexposed infants were stunting, which was detrimental to cognitive development in the first two years of life, and care by the biological mother, which was beneficial for the cognitive status at age 3 months but negatively associated with cognitive development after age 3 months. This is in contrast to other studies in older infants and children in the US, which have found that care by the mother, including maternal education level, is important for cognitive development, in combination with the availability of sufficient household resources and an adequate level of nutrition. [33, 56, 57]

Important strengths of the study include the longitudinal cohort design with careful assessment of HIV status at very young age *and* throughout the first two years of life, the multiple measurements of cognitive development using a validated and widely used BSID instrument, and the inclusion of both HIV exposed and HIV unexposed infants from the same communities as controls. Some limitations should however be noted when interpreting the results. First, due to a well-functioning prevention of mother to child program, only 96 out of the intended 130 perinatally infected infants were recruited. Furthermore, due to a combination of loss-to follow-up and a high level of mortality, the sample size of infants living with HIV was relatively small, especially after the first year of life. The use of a linear mixed-effects regression model however allowed us to use all available data, even if an infant only contributed a single visit. A disadvantage of this type of analysis is the requirement to use the raw Bayley scores that change systematically over time. Because this method was not used in other studies, this limited our ability to compare results with prior studies. Second, given the continued improvements made in the global policies regarding prevention of mother to child transmission and infant ART, our findings may underestimate what can be achieved under current program conditions.

A final limitation is the fact that HIV prevention and treatment policies have changed since the observations included in the analysis. We believe that our findings are still important and relevant. First, even though our sample of children living with HIV was smaller than intended, it is still the largest study of neurodevelopment of infants age 0 to 2 years living with HIV. Second, the observation that we could not find important differences in cognitive development under suboptimal circumstances suggests that it is highly unlikely these would be observed under current, vastly improved PMTCT and ART programs. Third, the observation that the cognitive development of HIV exposed uninfected children is not different from HIV unexposed infants is important as this is a growing and highly vulnerable population in sub-Saharan Africa which is likely to persist for decades to come. [42]

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5. Conclusion

In the context of early infant diagnosis and early initiation of ART, infants living with HIV had a small but biologically relevant cognitive deficit at age 3 months. This deficit did not increase among infants who survived and remained in HIV care in the first two years of life. Infants exposed to HIV who remained uninfected had similar cognition in the first two years of life as HIV unexposed children. Furthermore, the higher mortality observed in infants living with HIV also strengthens the call for effective ART in all pregnant women, safer conception care for all HIV affected couples, very early ART for infants living with HIV, and prevention of malnutrition and stunting.

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Abbreviations:

AIC	Akaike Information Criterion
AIDS	Acquired Immune Deficiency Syndrome
ART	Antiretroviral Therapy
BIC	Bayesian Information Criterion
BSID-III	Bayley Scales of Infant and toddler Development, 3rd edition
CNS	Central Nervous System
DNA	Deoxyribonucleic Acid
LOCF	Last Observation Carried Forward
MTCT	Mother to Child Transmission (of HIV)
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
PCR	Polymerase Chain Reaction
PMTCT	Prevention of Mother to Child Transmission (of HIV)
RNA	Ribonucleic Acid
SD	Standard Deviation
WHO	World Health Organization
−2LL	Deviance Statistic

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Highlights

- Infants living with HIV had a small cognitive deficit at age 3 months
- This deficit did not increase, if they were effectively treated
- Cognition of HIV-exposed uninfected children was similar to that of the unexposed
- Early initiation of effective ART in both mothers and infants is essential
- Malnutrition has a negative impact on early cognition in HIV infected children

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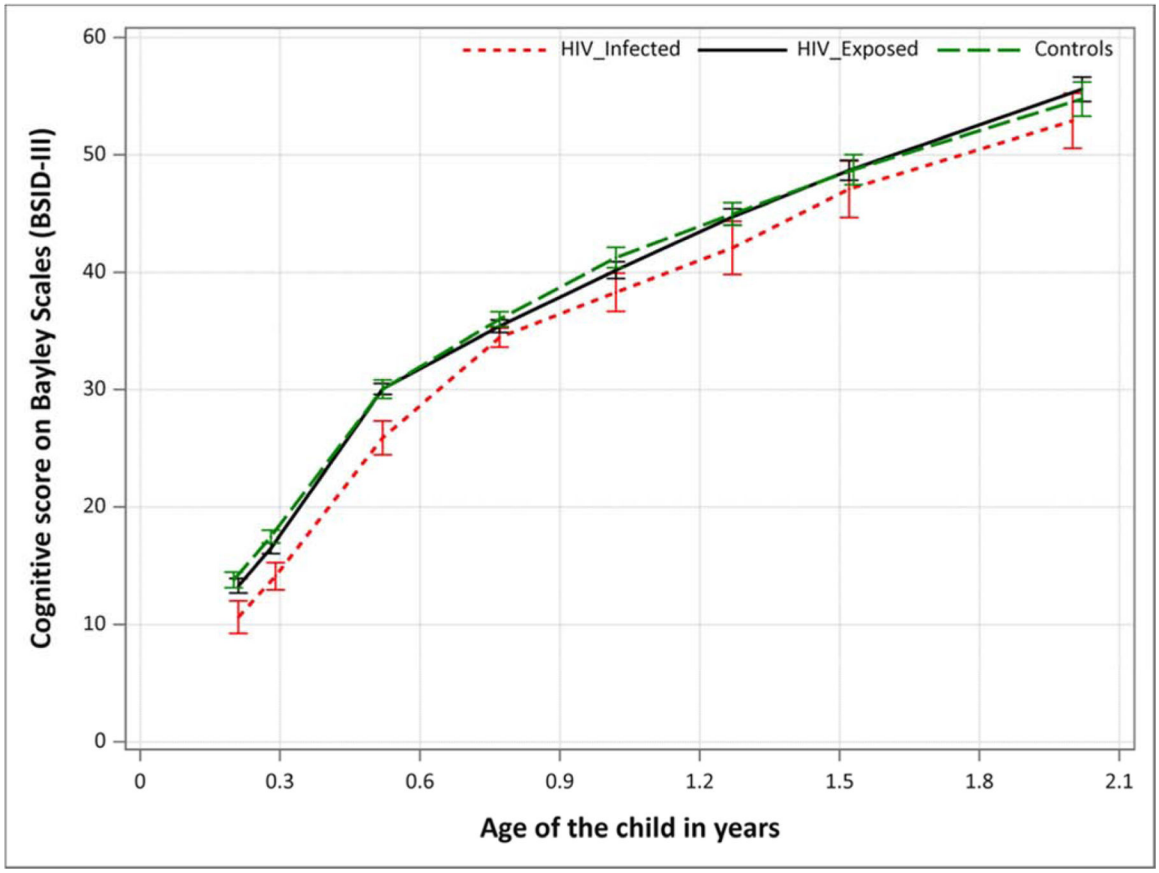

Figure 1:

Mean cognitive trajectories of HIV-infected, HIV-Exposed and unexposed children, including 95% confidence intervals

(Use of color in printed version is not necessary)

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Table 1:

Characteristics of 555 children, stratified by HIV infection and exposure status (N, % unless noted).

Characteristic		HIV-Infected (N=96)	HIV- Exposed (N=289)	HIV unexposed (N=170)	Total (N=555)
Age at enrollment (weeks, median+IQR[1])		13.7 (4.7)	12.0 (4.1)	10.8 (2.0)	11.6 (4.0)
Gender	Male	37 (39%)	144 (50%)	89 (52%)	271 (49%)
	Female	59 (61%)	145 (50%)	81 (48%)	285 (51%)
Malnutrition (WAZ[2] < −2SD) during 2 year follow-up (mean % + 95% Confidence Interval)		22.3% (18.1% – 26.5%)	15.2% (13.5% – 16.9%)	8.5% (6.7% – 10.2%)	13.9% (12.7% – 15.2%)
Stunting (HAZ[3] < −2SD) during 2 year follow-up (mean % + 95% Confidence Interval)		50.4% (45.3% – 55.5%)	46.0% (43.6% – 48.4%)	36.5% (33.4% – 39.5%)	43.5% (41.7% – 45.3%)
Mortality during 2 year follow-up		21 (21.9%)	27 (9.3%)	6 (3.5%)	54 (9.7%)
Age at death (weeks, median+IQR[1])		18 (11)	36 (38)	34 (14)	27.5 (25)
Caregiver relationship	Biological mother	88 (91.7%)	280 (96.9%)	164 (96.5%)	532 (95.8%)
	Other	8 (8.3%)	9 (3.1%)	6 (3.5%)	23 (4.2%)
Socioeconomic characteristics					
Financial insecurity[4]	None of the time	8 (9.5%)	33 (12.7%)	12 (8.5%)	53 (10.9%)
	Some of the time	39 (46.9%)	123 (47.3%)	80 (56.7%)	242 (49.8%)
	Most of the time	8 (9.5%)	41 (15.8%)	20 (14.2%)	69 (14.2%)
	All of the time	29 (34.5%)	63 (24.2%)	29 (20.6%)	121 (25.1%)
Food insecurity[5]	All of the time	5 (5.9%)	9 (3.4%)	2 (1.4%)	16 (3.3%)
	Most of the time	4 (4.8%)	11 (4.2%)	9 (6.4%)	24 (4.9%)
	Some of the time	23 (27.4%)	86 (32.7%)	43 (30.5%)	152 (31.1%)
	None of the time	52 (61.9%)	157 (59.7%)	87 (61.7%)	296 (60.7%)
Material of the roof	Grass/other	15 (17.9%)	37 (14.1%)	29 (20.3%)	81 (16.5%)
	Iron sheets	68 (80.9%)	222 (84.4%)	114 (79.7%)	404 (82.5%)
	Tiles	1 (1.2%)	4 (1.5%)	0 (0.0%)	5 (1.0%)
Toilet facilities	No toilet	0 (0.0%)	1 (0.4%)	0 (0.0%)	1 (0.2%)
	Pit or bucket	82 (97.6%)	236 (89.1%)	132 (92.3%)	451 (91.5%)
	Outdoor flush toilet	0 (0.0%)	4 (1.5%)	0 (0.0%)	4 (0.8%)
	Indoor flush toilet	2 (2.4%)	24 (9.1%)	11 (7.7%)	37 (7.5%)
Maternal education level	None	8 (9.5%)	24 (9.0%)	4 (2.8%)	6 (7.3%)
	Some primary school	31 (36.9%)	89 (33.5%)	39 (27.1%)	160 (32.3%)
	Completed primary school	12 (14.3%)	23 (8.6%)	9 (6.2%)	44 (8.9%)
	Some secondary school	19 (22.6%)	64 (24.1%)	60 (41.7%)	143 (28.9%)
	Completed secondary school or higher education	14 (16.7%)	66 (24.8%)	32 (22.2%)	112 (22.6%)
Number of siblings living with the child (mean+SD)		1.69 (1.20)	1.93 (1.43)	1.64 (1.42)	1.82 (1.42)
Nevirapine in infant (PMTCT)		71 (74.1%)	261 (90.3%)	NA	NA
ART in mother		16 (18.8%)	83 (29.5%)	NA	NA
ART in infant	at 15 weeks	4 (4.2%)	NA	NA	NA
	at 2 years	24 (92.3%)	NA	NA	NA

[1] IQR= Inter Quartile Range (75th percentile– 25th percentile);

[2] WAZ= Weight for Age Z-score (WHO);

[3] HAZ= Height for Age Z-score (WHO); SD= Standard deviation;

[4] Financial insecurity= Answering the question: “In the past week, how often did you have enough money to meet your needs?”;

[5] Food insecurity=Answering the question: “In the past week, how often were you hungry because you did not have enough food?”

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Table 2:

Mean cognitive levels (raw Bayley scores) and 95% confidence intervals at 15 weeks and at 2 years, by subgroup

		HIV-infected children (N=96)	HIV-exposed children (N=289)	Control children (N=170)
Cognitive score at 15 weeks	Mean (SD[1])	14.11 (4.8)	16.50 (3.7)	17.49 (3.3)
	95% confidence interval	12.92 – 15.30	16.04 – 16.97	16.94 – 18.04
Cognitive score at 2 years	Mean (SD[1])	52.91 (6.9)	55.61 (6.8)	54.78 (7.4)
	95% confidence interval	50.47 – 55.34	54.56 – 56.66	53.30 – 56.25

[1] SD = Standard Deviation

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Table 3:

Results of fitting the linear mixed-effects models to the data, by subgroup.

		Model A: HIV-Infected n=96	Model B: HIV-Exposed n=289	Model C: Controls n=170
Fixed effects				
Initial Status (at 3 months)	Intercept	13.57 ** *(8.80 15.52)*	12.16 *** *(10.61 19.52)*	17.98 *** *(15.64 20.32)*
	Caregiver=mother	4.16 * *(0.99 7.34)*	9.70 *** *(7.15 12.25)*	5.83 *** *(3.40 8.25)*
	ART(child)	2.76 * *(0.41 5.12)*		
	ART(mother)	3.48 * *(0.59 6.38)*		
	PMTCT (infant)	0.76 *(−0.77 2.29)*	0.20 *(−0.97 1.38)*	
	Clinical stage child	−1.16 ** *(−1.95 −0.37)*		
	Malnutrition	−3.48 *** *(−5.12 −1.84)*	−0.61 *(−1.60 0.37)*	−0.55 *(−2.09 0.99)*
	Financial insecurity	1.15 ** *(0.50 1.79)*	−0.04 *(−0.42 0.34)*	
	Number of siblings		0.12 *(−0.13 0.37)*	
	Material roof		0.65 *(−0.28 1.57)*	
Rate of change	Intercept (Time)	25.21 *** *(21.27 29.16)*	32.77 *** *(28.48 37.07)*	29.93 *** *(24.39 35.47)*
	ART (mother) *TIME	−7.10 ** *(−11.08 −3.12)*	no sign. effect [a]	
	ART (infant) *TIME	no sign. effect [a]		
	Stunting *TIME		−2.28 *** *(−3.19 −1.36)*	−2.57 *** *(−3.63 −1.50)*
	caregiver=mother *TIME		−11.08 *** *(−14.66 −7.50)*	−8.65 ** *(−14.20 −3.11)*
	Toilet facilities *TIME		0.23 *(−0.65 1.11)*	
Variance components				
	Residual variance (σ^2_e)	26.30 ***	27.75 ***	28.85 ***
	Initial status (σ^2_0)	0	0	0
	Covariance (σ_{01})	−8.23 **	−1.49	−0.42
	Rate of change (σ^2_1)	23.14 **	6.49 **	7.17 *
Fit statistics				
	−2LL [b]	1455.9	6523.4	4821.1
	AIC	1483.9	6551.4	4839.1
	BIC	1515.4	6599.0	4866.5
	Adjusted R^2	0.80	0.81	0.78

* p<.05;

** p<.01;

*** p<.001 95% Confidence Intervals in brackets.

Note: SAS Proc Mixed, Full ML.

[a] Predictors ART(infant)*Time and ART(Mother)*Time were removed from the model, because they did not improve model fit;

[b] −2LL = Deviance statistic;

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Table 4:

Resistance rates to NRTI's and to NNRTI's after 1 year of life in HIV-infected children

	Resistance to NNRTI's n/N, (%)	Resistance to NRTI's n/N, (%)
Tested samples from HIV-infected children after 1 year of life (n=36)	23/36 (63.9%)	12/36 (33.3%)

NNRTI: Non-Nucleoside Reverse Transcriptase Inhibitor

NRTI : Nucleoside Reverse Transcriptase Inhibitor