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Impact of HIV and Antiretroviral Therapy on Neurocognitive Outcomes Among School Aged Children

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Abstract

Introduction—The impact of HIV infection and antiretroviral therapy (ART) on neurocognitive outcomes among children aged 7 to 14 years was assessed. We hypothesized that ART would ameliorate neurocognitive sequelae of HIV infection.

Methods—HIV-positive and negative mother-child pairs from the Rakai Community Cohort Study (RCCS) and ART clinics in Rakai, Uganda were followed prospectively over 4 years. Exposures were stratified as: Perinatally HIV Infected (PHIV), Perinatally HIV Exposed but Uninfected (PHEU), and HIV Unexposed and Uninfected (HUU). The Kaufman Assessment Battery for Children (KABC II) assessed sequential and simultaneous processing, learning, planning, knowledge, and Fluid Crystallized Index (FCI) for overall functioning. Multivariable generalized linear models estimated adjusted Prevalence Rate Ratios (adjPRR) by age.

Results—Of the 370 mother-child pairs, 55% were HUU, 7% were PHEU and 37.9% were PHIV. Among HIV infected children, longer duration of ART was associated with a significant improvement of sequential processing skills (adj.PRR 25–36 months: 0.55, 95% CI: 0.34–0.9; 37–48 months: 0.39, 95% CI 0.2–0.76; 49+ months 0.23, 95% CI: 0.1–0.54). Each additional year of schooling was associated with a 30–40% decrease of impairment for all neurocognitive measures assessed. Healthier children (higher age standardized height and weight), had improved sequential and simultaneous processing and overall FCI.

Conclusions—Sequential processing skills of working memory improved with prolonged ART and increased duration of schooling was associated with a reduction of neurocognitive impairment.

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Early initiation and sustained use of ARTs and longer schooling are needed to reduce neurocognitive impairment among HIV infected, school aged children.

Keywords

HIV; ARTs; Neurodevelopment; Schooling

Introduction

Despite the fact that over 90% of the 3.2 million children estimated to be living with HIV/AIDS resided in sub-Saharan Africa by the end of 2015¹, there is a paucity of data on the impact of HIV/AIDS on the neurodevelopment of school aged children in resource-poor settings. In addition to the health consequences, older children infected with or exposed to HIV are significantly more likely to drop out of school which has many significant long term consequences, including the neurocognitive development of children.² In addition, studies on African populations have shown that healthier children with better nutritional status as indicated by anthropometric assessments had better visual spatial processing and learning scores³⁻⁵. With the increasing availability of antiretroviral therapy (ART) and improvements in the survival of these children⁶, there is an urgent need to understand the consequences of HIV-infection in older children so as to better address the medical, neurocognitive, psychosocial and physical needs of children affected or infected with HIV in resource-poor settings.

Cognitive impairment as a result of disruption of the central nervous system (CNS) by the HIV virus has been recognized as one of the consequences of HIV infection in children and can manifest as either global or selective delays in neurodevelopment⁷. Studies have shown significant neurocognitive impairment in PHIV infants, including delays in cognitive and motor skills⁸⁻¹². Brahmbhatt, et al in a previous study of younger children aged 0 to 6 years in Rakai, Uganda found that HIV infected children had global deficits in all measures of neurodevelopment except gross motor skills, and perinatally HIV-exposed (PHEU) children suffered impairment in receptive language skills¹³. In addition, the study found that longer duration of ART was associated with significant improvements in fine motor, receptive and expressive language skills¹³, highlighting the benefits of early ART initiation on cognitive development in children as found in other studies in sub-Saharan Africa¹⁴. The study suggests that some of the neurologic damage due to HIV infection in infants or HIV exposure *in-utero* for infants who escape HIV infection, could potentially be reversed by ART. However, little is known about the neurologic manifestations of HIV infection in older PHIV and PHEU children, and whether neurologic damage in infancy could be reversed by ART exposure later in life. Studies on HIV and neurodevelopment in school aged children are limited and the findings are mixed with some studies reporting that PHIV children were functioning within the normal range for cognitive, motor and learning development¹⁵⁻¹⁷, whereas others found cognitive and learning impairment¹⁸, language and learning disorders¹⁹, as well as impairment of executive function and processing speed²⁰.

The KABC-II²¹ measures neuropsychological outcomes in school-aged children and its structural validity in Uganda has been used to document neurocognitive deficits in PHIV

ARV-naïve Ugandan children²², especially those with HIV subtype A²³, and to document the neurocognitive profile of PHIV Ugandan children undergoing computer-based cognitive rehabilitation²⁴. The KABC-II is presently being used in a longitudinal study of the neurocognitive differences among PHIV, PHEU, and HUU children at six study sites in 4 sub-Saharan African countries (Uganda, Malawi, Zimbabwe, South Africa) participating in the Maternal, Pediatric, Adolescent AIDS Clinical Trials (IMPAACT) Network. Thus far, they found poorer neurocognitive performance among PHIV children on different ART regimens compared with PHEU and HUU children across all study sites²⁵. The purpose of the present study is to compare the neurocognitive ability of PHIV, PHEU, and HUU children in Rakai District, Uganda. We also evaluated the association between time on ART and subsequent KABC-II performance in PHIV children.

There has been no study to our knowledge assessing the effect of HIV infection and ART in school-aged children in a rural, resource-poor setting, which is where the majority of infected children in sub-Saharan Africa reside. With the increasing availability of ART, it is critical we fill this gap in our knowledge and understanding of the consequences of HIV infection on neurodevelopmental outcomes in school-aged children as well as the potential impact of ART and other interventions.

Patients and Methods

Mothers and children irrespective of their HIV status were recruited from September 2007 to April 2011 from the Rakai Community Cohort Study (RCCS), the Nevirapine prevention of Mother to Child HIV Transmission (NVP-PMTCT) study (a nested study where HIV positive mothers from RCCS received ART for PMTCT) and ART clinics in the Rakai communities by the Rakai Health Science Program (RHSP) where free ART funded by PEPFAR was provided to eligible HIV-positive adults and children. The PMTCT programs implemented in Rakai, Uganda in 2004 and scaled up widely were quite successful, particularly among RCCS participants and hence we recruited HIV infected children from the ART clinics in Rakai. Irrespective of where the child was recruited from, these programs overlap in the same population and the same setting. Rakai Health Science Program was the sole provider for ART treatment in this population at the time, so we linked to the ART treatment datasets and established ART initiation and treatment information for the children using an RHSP study-wide unique ID that links between study cohort and health services. Our sampling for this study was done based on a convenience sampling. As detailed in other studies in Rakai, Uganda^{26,27}, the setting is rural and the population is fairly homogenous with all participants in our study, irrespective of where they were recruited from (RCCS cohort or ART clinics), residing in the Rakai communities. The eligibility criteria were known HIV status for mother and child, and written informed consent from the parent and assent from all children over 8 year of age as per the Ugandan National guidelines²⁸. Details of the RCCS cohort and NVP-PMTCT study are provided elsewhere^{29,30}.

Maternal HIV status was based on two separate EIAs (Vironestika, Organon Teknika and Welcozyme) with Western blot confirmation (HIV-1 Western Blot, Bio-Metriux-Vitek) of EIA discordant samples and of new seroconverters. HIV infection in infants was detected by RNA-RT PCR using Roche Amplicor 1.5 assays (Branchberg, NJ). ART information was

collected during the KABC-II assessments done on the child. The HIV positive children recruited from the ART clinics, provided information on when ART was initiated as well as how long the child has been on ARTs and all this information was easily linked to the child's neurocognitive outcomes. All measurements that remained unchanged such as gender were recorded at baseline whereas height, weight and age were recorded at each assessment.

The Kaufman Assessment Battery for Children, 2nd edition (KABC-II) was used to measure processing and cognitive abilities in the children aged 7 years to 14 years. The KABC-II is appropriate for children aged 3 to 18 years and assesses abilities measured by the original KABC³¹ (Sequential and Simltaneous Processing ability), and Planning and Learning. A clinical psychologist trained nurses and midwives who conducted the neuropsychological assessments. Quality control was maintained by random assessment of children by the study coordinator. Short breaks, drinks, and snacks were provided to the child and caregiver every 30 to 45 minutes. The KABC-II tests were done at baseline and then every 6 months up to 30 months of follow up. All HIV+ children recruited from ART clinics were recruited based on ART clinic visit and consent was given by parent and assent from the child if over 8 years of age to additional assessments done for that child.

The KABC-II assesses cognitive abilities in five main domains³⁰: 1) Sequential Processing is a measure of short-term memory and includes "Number Recall" (the child repeats a series of numbers in the same sequence as the examiner said them), "Word Order" (the child touches a series of objects in the same order as the examiner said their names), and "Hand Movements" (child copies examiner's precise sequence of hand movements), 2) Simultaneous Processing is a measure of visual processing and includes "Rover" (child moves a toy dog to a bone on a board by trying to find the quickest path), "Triangles" (child assembles colourful plastic shapes to match a model shown on an easel or constructed by examiner), "Block Counting" (child counts the exact number of blocks in various pictures of stacks of blocks), "Gestalt Closure" (child mentally "fills in the gaps" in a partially completed drawing), "Face Recognition" (child looks at photographs of 1 or 2 faces and then selects the correct face or faces, shown in a different pose, from a group photograph), "Conceptual Thinking" (child views a set of 4 or 5 pictures and identifies the one picture that does not belong with the others), 3) Planning which tests for fluid reasoning and includes "Story Completion" (child fills out missing picture in a row of pictures that tell a story), and "Pattern Reasoning" (child completes a stimulus from 4 to 6 options to form a logical pattern), 4) Learning tests for long-term storage and retrieval and includes "Atlantis" (examiner teaches the child nonsense names for pictures of fish, plants and shells. The child demonstrates learning by pointing to each picture (out of a group of pictures) when it is named), "Rebus" (examiner teaches the child a word or concept associated with a particular drawing (rebus), and the child then reads allowed phrases and sentences composed of these rebuses), "Atlantis Delayed" (the child demonstrates delayed recall of paired associations learned about 15 to 25 minutes earlier during Atlantis), "Rebus Delayed" (child demonstrates delayed recall of paired associations learned about 15 to 25 minutes earlier during Rebus), and 5) Knowledge which tests for crystallized ability and includes "Verbal Knowledge" (child selects from an array of six pictures the one that illustrates the meaning of a vocabulary word), "Riddles" (examiner says several characteristics of a verbal concept, and child points to it or names it), and "Expressive Vocabulary" (the child says the names of

a pictured object). Participants with limited speech were administered the nonverbal portion of the KABC-II. The KABC-II also yields a composite global scale index, the Fluid Crystallised Index (FCI) which provides an overall level of executive functioning.

Statistical Methods

For the analyses with the five KABC-II global domains (sequential processing, learning, planning and knowledge), as well as for the FCI and non-verbal index (NVI) composites, the standardized scores were used computed from the KABC-II manual (American-based norms). Although the standardized scores are already adjusted for age, age was still controlled for in the regression analyses because at-risk children in the African context can be at an increasing disadvantage in comparison to American norms for the KABC-II as they progress through middle childhood. Standardized scores are necessary to compute the FCI and NVI composite indices.

Demographic characteristics were summarized by the mother and child's HIV status and chi squared statistics were used to assess differences between children born to HIV infected mothers and the control children born to HIV-negative mothers. All KABC-II cognitive scores were age standardized using KABC-II age-standardization software. Z-scores were calculated using the mean KABC-II cognitive score standardized by the child's age. Nutrition was assessed by comparing weight and height for age and obtaining a standardized z-score. A 15% cut-off of each age standardized z-score was used to create a dichotomous disability score for each of the five KABC-II cognitive assessments as well as the FCI index. The 15% cut-off z-score value was determined among the HUU children as the average upper bound for the 5th lowest bin in a 5-bin clustering for each age-standardized cognitive score. Generalized linear models accounting for repeated study visit assessment measurements per child were used to estimate Prevalence Rate Ratios (PRR) of all five KABC-II tests as well as the FCI and non-verbal indexes. The PRR were estimated as the ratio of the of the prevalence rate average of disability at each assessment study visit. We assumed a poisson distribution of the disability events and the robust variance estimation was used to compute 95% confidence intervals. We conducted a baseline neurodevelopment measurements and then repeated the measurements every 6 monthly thereafter. So the prevalence rate ratios reported are the averages from the repeated measures for the duration of the study. Adjusted PRR were obtained after controlling for age, gender, education, age standardized height and weight. All analyses were stratified by the following exposure groups: 1) PHIV, 2) PHEU, and 3) HUU.

A sub-analyses was conducted for all HIV-positive children to assess the impact of ART initiation and ART duration on the PRR of neurodevelopment scores, adjusting for age, gender, education, age standardized height and weight. All analyses were determined a priori and were performed using the statistical analysis software STATA version 10 (StataCorp LP, College Station, TX, USA).

The study was approved by IRBs from the Johns Hopkins Bloomberg School of Public Health and the Scientific and Ethics Committee of the Uganda Virus Research Institute.

RESULTS

370 mother and child pairs aged 7 to 14 years were enrolled of whom 204 (55.1%) were HIV-uninfected mothers and children (HUU), 26 (7.0%) were PHEU and 140 (37.9%) were PHIV. The PHEU group was smaller than expected due to challenges with recruiting uninfected children born to HIV-positive mothers.

As summarized in Table 1, median children's age was significantly higher among the HUU compared to the PHIV and PHEU groups (11 years compared with 8). There were no significant difference in child's gender by HIV serostatus of the mother-child pairs. Weight for age and height for age z-scores were significantly lower among PHIV compared with the HUU children. Perinally HIV infected children were significantly more likely to have none or pre-primary schooling only. A higher proportion of HUU children completed higher levels of schooling, whereas the proportion reporting high education levels was significantly lower and similar among children born to HIV positive mothers, irrespective of the HIV status of the child (HUU-49.5%, PHEU15.4%, PHIV, 18.6%, $p<0.001$). A significantly higher proportion of PHIV children had an impairment in simultaneous processing, learning and knowledge skills compared with PHUU and PHEU children at baseline.

As shown in Table 2, there were no significant differences in the neurocognitive measures between PHIV and HUU children (all reference groups indicated in the tables). Neurodevelopment scores were similar in males and females and when assessing nutritional outcomes by anthropometric measurements, we found that with each increase in age standardized height, there was a significant decrease in impairment of the overall FCI scores and with each increase in age standardized weight, there was a significant decrease in impairment of sequential and simultaneous processing scores. However, the risk of a neurocognitive impairment was significantly higher with each year of age, and significantly lower by each additional year of schooling.

As summarized in Table 3, among the 140 PHIV children, 58 (41.4%) had initiated ART; 47 initiated at baseline, 5 initiated ART by visit 2, 3 initiated ART by the third visit, 2 initiated by the fourth visit and 1 initiated by fifth visit. ART initiation was associated with a significant higher risks of impairment in sequential processing (adj.PRR=1.6, CI: 1.14–2.26), learning (adj.PRR=1.5, CI: 1.07–2.1), and FCI (adj.PRR=1.63, CI: 1.09–2.44) abilities. At ART initiation, boys were less likely than girls to have impairment in simultaneous processing (adj.PRR=0.59, CI: 0.41–0.85), knowledge (adj.PRR=0.65, CI: 0.47–0.89) and non-verbal index scores (adj.PRR=0.62, CI: 0.45–0.86). For all neurodevelopment assessments, each additional year of schooling was associated with a significant decrease in the risk of an impairment for the PHIV children. A significant decrease in impairment of simultaneous processing and overall FCI were also seen with each increase in age standardized height scores.

As shown in Table 4, longer duration on ART was associated with a significant decrease in impairment of sequential processing skills (25–36 months: adj.PRR=0.55, CI: 0.34–0.9; 37–48 months: adj.PRR=0.39, CI: 0.2–0.76; 49+ months: adj.PRR=0.23, CI: 0.1–0.54) but there was no significant effect of ART duration on the other neurodevelopment measures. For

PHIV children on ARTs, each year increase in age was associated with a significant increase in impairment of sequential processing (adj.PRR=1.46, CI: 1.11–1.94) and planning skills (adj.PRR=1.82, CI: 1.14–2.91). Age at ART initiation did not significantly affect any of the neurologic measures. Males were significantly less likely to have an impairment in knowledge skills (adj.PRR=0.55, CI: 0.32–0.95) or non-verbal index (adj.PRR=0.49, CI: 0.29–0.82) than girls. The only measure that was significantly associated with an improvement of all neurocognitive outcomes assessed was education; each additional year of schooling was associated with a significant decrease in impairment for all neurodevelopment measures: sequential processing, adj.PRR=0.69, CI:0.58–0.82; simultaneous processing, adj.PRR=0.65, CI:0.54–0.78; learning, adj.PRR=0.65, CI:0.57–0.74; planning, adj.PRR =0.78, CI:0.65–0.94; knowledge, adj.PRR=0.65, CI:0.54–0.77; FCI, adj.PRR=0.62, CI:0.52–0.75; non-verbal index, adj.PRR =0.63, CI:0.52–0.76. Each increase in age standardized height was associated with a significant decrease in impairment in simultaneous processing (adj.PRR=0.78, CI: 0.64–0.94) and FCI index (adj.PRR=0.64, CI: 0.46–0.89) and each increment in age standardized weight was associated with a significant decrease in impairment of sequential processing skills (adj.PRR=0.71, CI: 0.53–0.94).

DISCUSSION

The goal of our paper was to examine neurocognitive performance among perinatally HIV infected (PHIV) compared with HIV exposed (PHEU) and HIV uninfected (HUU) school aged children. At baseline, PHIV children had lower simultaneous processing, learning, and composite non-verbal cognitive performance measures than the other groups. A significantly higher proportion of PHIV children had impaired knowledge skills, compared to HUU or PHEU children. Among PHIV children, longer duration on ART was associated with significantly better performance in sequential processing skills, but had no effect on other KABC-II measures. Among HIV-positive children, each additional year of schooling was associated with a 30 to 40% decrease in neurologic impairment. Early initiation and sustained use of ARTs and continued schooling of HIV infected children should be a priority.

The adverse effect of HIV infection on school attainment has been well documented in Uganda^{3,31} and supports our findings. A study in Ugandan children aged 5–12 years found that an increase in years of schooling was associated with improved memory, attention and special learning scores.³ A World Bank study estimated that HIV/AIDS may reduce the enrolment of children in school by 14 to 22% as a result of increased mortality, and school drop out.³² At baseline, a higher proportion of PHIV children did not go to school or complete primary school and a significantly lower proportion completed primary or secondary schools. This trend is unfortunate, since educational attainment consistently demonstrated a neurocognitive benefit for children in our study; the benefit of increased schooling was seen consistently among PHIV children by ART initiation as well as by ART duration.

Among PHIV children, duration on ART was associated with a decrease risk of impairment in sequential processing skills. HAART lowers the incidence of HIV-related encephalopathy³³ and reduces the number of HIV-infected cells entering the CNS³⁴. A

retrospective cohort study found improvements in neurocognitive outcomes in HIV-infected children on HAART, although a significant proportion continued to experience neurocognitive delay³⁵, while other studies have found no improvement in cognitive function³⁶, short-term memory or fine motor skills after 48 months on HAART³⁷. A study in the Netherlands found that higher CD4 levels at HAART initiation and longer duration on treatment were associated with better working memory and attention control²⁰. Previous studies have noted that these cognitive ability domains are especially vulnerable to the neurodevelopmental effects of HIV disease, even when children are clinically stable^{22,23,38,39}. Neurologic impairment was found in HIV infected children with higher CD4 counts; Ruel et al²², found significant motor and cognitive deficits in PHIV ART-naïve Ugandan school aged children with CD4 cell counts of >350 cells/mm³ and CD4 percentages $>15\%$.

Several studies have demonstrated the impact of HIV infection on childhood neurocognitive impairment^{8,13,40}. Studies with Congolese children reported that PHEU children did better neurocognitively than the PHIV group, but significantly poorer than the HUU children^{11,41}. This suggests that it is important to disentangle the effects of compromised caregiving due to maternal HIV status and illness, from the direct effects of HIV infection in the child³⁸. Similar to other studies that found that poor nutritional status as measured by anthropometric indicators was associated with poor developmental outcomes³⁻⁵, our study also found that increases in both age standardized weight and height resulted in significant improvements of sequential and simultaneous processing skills as well as overall executive functioning (FCI scores), highlighting the importance of programs providing nutritional support to families affected by HIV infection.

We had hypothesized that continued use of ARTs would reverse some of the neurologic impairment from HIV infection. However, it would appear that the potential neurologic impairment due to HIV is more readily modifiable if ART is initiated early in infancy as shown by our previous study in children less than 6 years of age¹³. Laughton and colleagues documented similar neurodevelopmental benefits with earlier sustained ART intervention in South Africa⁴². The older children in our study initiated ARTs following WHO guidelines⁴³ and were born before the policy was changed to universal treatment for all HIV positive infants. Approximately 41% of HIV-positive children in our study had initiated ARTs. We found an increased risk of impaired sequential processing, learning, and overall functioning scores, but since ART was initiated in sicker children, the impact on neurocognitive outcomes may be an indicator of more advanced HIV. We found that longer duration on ART modified neurologic damage in younger children¹³, but among older children in this study, the reduction in the risk of impairment was only seen in sequential processing skills.

Koekkoek and others have concluded that ART alone is not sufficient to reverse the neurodevelopmental consequences of pediatric HIV infection^{20,44} and ART may even contribute to neuromotor decline⁴⁴. In American children, studies found that only 1 of 13 neuropsychological measures significantly improved. They concluded that “treatment strategies for children with HIV disease need to be re-evaluated so that they consider restoration of neuropsychological functioning in addition to lowering the viral load”³⁷.

Early initiation of ART is critical among HIV infected children, however interventions that optimize cognitive development are urgently needed. A randomized study in South Africa found that a home stimulation intervention given to the caregiver significantly improved cognitive and motor development in young children with HIV⁴⁵. Interventions need to focus on the comprehensive needs of children which include the physical, nutritional, educational, mental, and neurocognitive needs of children infected and exposed to HIV infection.

There were limitations in our study. Despite repeated attempts, we were unable to follow all children who initiated ART for the full duration of follow up. In addition, the HEU group was too small to provide adequate statistical power and hence findings for this group should be interpreted with caution. Also, for school-aged children, the environment is expected to have a significant impact on development, but in our study, we lacked data on caregivers, members of the household or the environment. Although the Rakai population has been shown to be quite homogenous, extrapolation of these findings to other rural African settings should be done with caution.

CONCLUSIONS

In conclusion, even though neurocognitive impairment in Ugandan HIV-infected children can be mitigated with early ART, good medical and nutritional support, mild to moderate cognitive disorders may still persist, despite complete viral suppression. We propose that educational, neurocognitive rehabilitative, and behavioral interventions are needed to fully address the needs of school-age children living with HIV.

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Table 1

Basic demographic information by maternal and child HIV Status

ALL CHILDREN	HUU Group N=204	PHEU Group N=26	PHIV Group N=140	P-Value
Age, years				
Median	11	8	8	<0.001
Mean	10.9	8.8	8.6	<0.001
Gender				
Males	47.2%	53.9 %	46.6%	0.791
Females	52.8%	46.1%	53.4%	
WAZ (mean)	−1.35	−1.48	−1.66	<0.001
HAZ (mean)	−1.75	−1.48	−2.25	0.0118
School year reported				
No school - Pre primary	1.5%	11.5%	27.1%	<0.001
Primary 1–4	49.0%	73.1%	54.3%	
Primary 5 - Secondary 2	49.5%	15.4%	18.6%	
Neurocognitive Disability*				
Sequential	20.0 %	23.1 %	22.1 %	0.871
Simultaneous	21.1 %	26.9 %	33.6 %	0.035
Learning	20.1 %	30.8 %	31.4 %	0.047
Planning	20.6 %	7.7 %	13.6 %	0.105
Knowledge	16.2 %	26.9 %	40.7 %	<0.001
Fluid-Crystallized Index (FCI)	17.2 %	15.4 %	22.1 %	<0.455
Non-verbal Index (NVI)	17.7 %	44.0 %	34.3 %	<0.001

* A 15% cut-off based on the HIV uninfected and unexposed (HUU) children was used to create a dichotomous disability score

Table 2

Neurocognitive Disability Comparing HUU and PHIV children at Baseline
HUU=204 Children
PHIV=140 Children

Characteristics	Sequential PRR* (95% CI)	Simultaneous PRR* (95% CI)	Learning PRR* (95% CI)	Planning PRR* (95% CI)	Knowledge PRR* (95% CI)	FCI PRR* (95% CI)	Non-verbal Index PRR* (95% CI)
Children HIV Status							
<i>HIV Negative Controls</i>	Ref	Ref	Ref	Ref	Ref	Ref	Ref
HIV Infected children	0.77[0.45–1.33]	0.8[0.51–1.26]	1.11[0.71–1.74]	1.38[0.8–2.37]	0.94[0.57–1.54]	0.68[0.39–1.18]	0.91[0.55–1.53]
Current Age (years)	1.38[1.2–1.58]	1.23[1.11–1.37]	1.32[1.18–1.48]	1.97[1.69–2.3]	1.01[0.87–1.17]	1.47[1.31–1.65]	1.15[1.02–1.3]
Gender							
<i>Female</i>	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Male	0.79[0.52–1.2]	0.66[0.47–0.93]	1.18[0.83–1.68]	1.03[0.67–1.58]	0.92[0.66–1.28]	0.79[0.53–1.18]	0.84[0.59–1.2]
Child Education (school years)	0.62[0.54–0.71]	0.64[0.58–0.72]	0.66[0.59–0.75]	0.72[0.63–0.82]	0.64[0.56–0.73]	0.56[0.5–0.63]	0.62[0.55–0.71]
Age standardized Height	0.94[0.79–1.13]	0.89[0.79–1.01]	0.9[0.8–1.03]	1.02[0.88–1.18]	0.91[0.81–1.02]	0.77[0.69–0.87]	0.98[0.86–1.1]
Age standardized weight	0.8[0.6–1.08]	0.82[0.68–0.98]	1[0.88–1.15]	0.89[0.69–1.15]	0.97[0.86–1.11]	0.96[0.83–1.11]	0.96[0.84–1.11]

Table 3

Neurocognitive Disability among PHIV Children by ART Initiation

Characteristics	Sequential PRR* (95% CI)	Simultaneous PRR* (95% CI)	Learning PRR* (95% CI)	Planning PRR* (95% CI)	Knowledge PRR* (95% CI)	FCI PRR* (95% CI)	Non-verbal Index PRR* (95% CI)
ART treatment status							
<i>Not on ART</i>	Ref	Ref	Ref	Ref	Ref	Ref	Ref
ON ART	1.6[1.14–2.26]	1.01[0.74–1.39]	1.5[1.07–2.1]	0.78[0.52–1.17]	1.07[0.82–1.39]	1.63[1.09–2.44]	0.96[0.73–1.25]
Current Age (years)	1.15[1.02–1.31]	1.15[1.02–1.29]	1.14[1–1.29]	1.68[1.49–1.89]	0.99[0.87–1.13]	1.2[1.06–1.35]	0.97[0.87–1.09]
Gender							
<i>Female</i>	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Male	0.92[0.61–1.39]	0.59[0.41–0.85]	1.3[0.93–1.83]	1.05[0.72–1.52]	0.65[0.47–0.89]	0.88[0.57–1.36]	0.62[0.45–0.86]
Child Education (school years)	0.76[0.67–0.86]	0.68[0.62–0.75]	0.65[0.59–0.72]	0.69[0.62–0.78]	0.68[0.61–0.76]	0.66[0.59–0.75]	0.69[0.63–0.75]
Age standardized Height	1.03[0.92–1.14]	0.84[0.75–0.95]	0.96[0.82–1.13]	0.95[0.82–1.1]	0.93[0.84–1.02]	0.83[0.71–0.98]	1.01[0.92–1.11]
Age standardized Height	0.76[0.56–1.01]	1[0.83–1.22]	1.01[0.76–1.34]	0.93[0.71–1.2]	0.94[0.79–1.12]	0.91[0.68–1.23]	0.89[0.74–1.07]
Study visit	0.98[0.89–1.08]	0.96[0.86–1.06]	1.01[0.89–1.15]	1.01[0.89–1.14]	0.97[0.87–1.08]	1.01[0.91–1.13]	1.07[0.96–1.2]

Table 4

Impact of ART treatment Duration on Neurocognitive Impairment among PHIV Children

Characteristics	Sequential PRR* (95% CI)	Simultaneous PRR* (95% CI)	Learning PRR* (95% CI)	Planning PRR* (95% CI)	Knowledge PRR* (95% CI)	FCI PRR* (95% CI)	Non-verbal Index PRR* (95% CI)
Duration of ART treatment							
0–24	Ref	Ref	Ref	Ref	Ref	Ref	Ref
25–36	0.55[0.34–0.9]	1.01[0.64–1.6]	1.08[0.67–1.76]	0.86[0.48–1.53]	0.7[0.44–1.11]	0.92[0.54–1.56]	0.85[0.62–1.18]
37–48	0.39[0.2–0.76]	0.65[0.3–1.41]	0.84[0.4–1.73]	0.59[0.23–1.54]	0.68[0.35–1.3]	0.57[0.23–1.44]	0.62[0.33–1.18]
49+	0.23[0.1–0.54]	0.37[0.1–1.38]	0.62[0.22–1.72]	0.29[0.06–1.43]	0.63[0.23–1.76]	0.3[0.08–1.1]	1.08[0.48–2.44]
Current Age (years)	1.46[1.11–1.94]	1.05[0.74–1.49]	1.31[0.96–1.77]	1.82[1.14–2.91]	1.06[0.75–1.51]	1.23[0.87–1.74]	0.78[0.61–1]
Age at ART Initiation (years)	0.8[0.63–1.02]	1.02[0.75–1.38]	0.9[0.69–1.17]	0.83[0.56–1.24]	0.88[0.66–1.18]	0.89[0.65–1.22]	1.16[0.87–1.53]
Gender							
<i>Female</i>	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Male	0.83[0.47–1.47]	0.61[0.37–1.01]	1.12[0.75–1.67]	1.06[0.54–2.07]	0.55[0.32–0.95]	0.87[0.53–1.43]	0.49[0.29–0.82]
Child Education (school years)	0.69[0.58–0.82]	0.65[0.54–0.78]	0.65[0.57–0.74]	0.78[0.65–0.94]	0.65[0.54–0.77]	0.62[0.52–0.75]	0.63[0.52–0.76]
Age standardized height	1.15[0.96–1.38]	0.78[0.64–0.94]	0.96[0.66–1.39]	0.72[0.48–1.09]	0.94[0.81–1.1]	0.64[0.46–0.89]	1.14[0.91–1.43]
Age standardized weight	0.71[0.53–0.94]	1.23[0.93–1.61]	1.08[0.68–1.71]	1.16[0.63–2.16]	0.89[0.7–1.13]	1.45[0.92–2.26]	0.87[0.68–1.12]
Study visit	1.07[0.93–1.23]	1.08[0.91–1.29]	1.03[0.9–1.19]	1.14[0.9–1.45]	1.05[0.9–1.23]	1.22[1.05–1.43]	1.31[1.13–1.5]