Neurocognitive function in youth living with HIV

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Abstract

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Background: Adolescents and youth who acquired HIV perinatally have increased risk for neurocognitive compromise. Evaluation of neurocognition is important to identify youth with HIV (YHIV) who may benefit from focused support.

Setting: A high volume HIV clinic within a tertiary facility in Nairobi, Kenya

Methods: Demographic and clinical characteristics of participants were collected and summarized using proportions for categorical and medians (interquartile range [IQR]) for continuous variables. Neurocognitive screening was performed using the *NeuroScreen* tool, a short, validated tablet-based application. Screening for depressive, anxiety symptoms, and behavioral problems was conducted using the Patient Health Questionnaire (PHQ-9), the Generalized Anxiety Disorders 7 questionnaire (GAD-7), and the Strengths and Difficulties Questionnaire, respectively. Neurocognitive test raw scores were summarized as means and z-scores. Total test scores were calculated as composite z-scores. Linear regression analysis was conducted to determine the correlates of neurocognitive performance. Analysis was adjusted for sex and level of education and stratified by gender.

Results: Among 149 participants, median age was 18 years, 53% were male and 79% were enrolled in school. Many YHIV (46%) had early-stage disease (WHO stage I/II) at HIV diagnosis and 23% had detectable viral load at last measurement. Male sex and education

were associated with significantly higher scores. Adjusted for sex and level of education, Adolescents with above average and average school grades had higher scores compared to those with below average grades (mean difference 4.68 [1.44,7.92]) p= 0.005 and 3.72 (0.71, 6.74) p=0.016, respectively. A trend towards higher scores for youth with WHO Stage I/II HIV disease at diagnosis was noted, though the correlation was not statistically significant (mean difference, 1.67 (95% CI -5.05, -0.05) p=0.114).

Conclusion: *Neuroscreen* testing was correlated with poorer school performance, suggesting that the test reflects functional performance. Sex differences may reflect social or educational differences. Non-severe HIV disease at diagnosis was associated with higher cognitive scores and underscores need for prompt diagnosis and treatment of pediatric/adolescent HIV.

Keywords: Adolescent, HIV, neurocognitive disorders, *NeuroScreen*

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Introduction

Youth in Sub-Saharan Africa (SSA) remain disproportionately affected by HIV and account for 88% of youth living with HIV globally (1). Neurocognitive impairment is an important consideration for children living with HIV as they age into young adulthood (2,3). Adolescents and youth who acquire HIV perinatally (YWH) are at risk of developing neurocognitive impairment compared to HIV negative age-matched adolescents (4). Successful transition to self-directed HIV care (5), and attainment of full academic and social potential requires optimal cognitive functioning.

Before wide availability of ART, > 50% of people living with HIV (PLHIV) experienced neurocognitive impairment (6,7). Higher (>60%) prevalence of neurocognitive impairment (NCI) occurred in YWH in the pre-ART era (8,9,10). However, NCI persists in the ART era, causing potential functional impairment. NCI prevalence of 46% and 60% has been reported in YWH in South Africa and Kenya respectively (2, 11). Most (69%) adolescents in the Kenyan study had initiated ART after 30 months of diagnosis. While the differences in prevalence may be explained by the characteristics of the populations sampled and the methods used to diagnose neurocognitive impairment, the overall occurrence remains high.

HIV infection preferentially affects fronto-striato-thalamo-cortical systems in the brain manifesting with deficits in the domains of executive functioning, memory, psychomotor speed, learning and fine motor skills (12,13) Executive function encompasses cognitive abilities that manage skills required for goal-directed behavior and self-regulation (14,15). Poor executive functioning in YWH can progressively worsen in perinatally infected youth on ART (16,8,3). Executive function matures during adolescence and dysfunction is more apparent during adolescence than in childhood. Poor executive functioning has negative consequences on medication adherence, academic achievement and adaptive behavior, each critical areas as adolescents transition into adult roles (17,18).

HIV enters the brain soon after infection leading to neuroinflammation, neuronal cell death and dysfunction (19). Replication of competent virus may persist in the brain even after ART is initiated, resulting in low level viral replication, inflammation and progressive neurodegeneration (19,20 21). Infants and children who acquired HIV perinatally are more vulnerable to the effects of HIV on the brain. Inflammation and viral replication occurs during a critical window for brain development and synapse formation; a critical period for motor and language development, and self-regulation. (22,23) .

Perinatally infected children often start ART late increasing the likelihood of adverse neurodevelopmental outcomes (23, 24). Targeting early ART initiation limits the pool of infected cells in the brain that persist (25). ART improves neurocognitive outcomes through viral suppression but may also lead to neurotoxicity exacerbating cognitive and psychiatric pathology (26, 27). Integrase inhibitors may result in less neurotoxicity and have been shown to be effective in reducing HIV-associated structural and functional brain changes when initiated very early after HIV infection (25). Lower CD4 nadir, previous history of advanced HIV, unsuppressed viral load and lower level of education are recognized risk factors for neurocognitive impairment in youth (6,7,12,28,29).

Psychiatric co-morbidity is prevalent in YWH (30,31). Depressive and anxiety comorbidity may occur more commonly in PLHIV who have poor cognitive function (32, 33). The relationships between mental health disorders and cognitive impairment are difficult to disentangle because relationships between parenting and the social milieu in early childhood, socio-emotional and cognitive development are intertwined. (34). Regardless, the two should be considered comorbidities capable of worsening the quality of life and functional capability of adolescents with HIV.

Functional impairment consequent to cognitive dysfunction in adolescents makes it difficult for this group to adapt to challenges encountered in adulthood. Preparing YWH for transition to self-directed care by providing psychosocial support and developmentally appropriate health

services (2, 35) is critical. Poor academic achievement and school drop-out associated with cognitive impairment can affect the acquisition of skills needed for many aspects of adult life (17). Neurocognitive functioning in adolescents and YWH is under studied in the Sub-Saharan context. Further, simple screening tools adaptable to busy clinic settings are under-investigated. Tablet-based tools demonstrate high correlation with traditional paper-and-pencil neuropsychological test batteries and are promising options for screening and assessment (36,38,39). To address the gaps in use of rapid low-cost tools for assessment of cognition in YLH in the Kenyan context, we utilized the *NeuroScreen* tool, a recently validated, easy to administer, tablet/smartphone-based, highly automated screening tool.

Methods

Study design and population

The overall goal of this study was to describe neurocognitive functioning in YWH aged 13-24. This was a cross-sectional study.

Study Sites

Study participants were recruited from Kenyatta National Hospital (KNH) HIV clinic. KNH is a public tertiary referral hospital in Nairobi providing services to approximately 900 adolescents aged 10-24 years enrolled in the HIV clinic.

Population

YWH aged 13-24 attending the KNH HIV clinic and on ART were eligible for enrollment. Our lower limit for the age group was selected based on the lowest age the cognitive assessment tool was validated for. YWH with severe neuropsychiatric disease, previous serious head injury, a history of meningitis and acute illness were excluded.

Study procedures

Recruitment and enrollment

Adolescents were sampled by convenience during clinic days and screened to determine eligibility for study participation. Parents or caregivers of eligible adolescents under the age of 18 and youth over the age of 18 provided written informed consent. Oral assent was obtained from adolescents <18. Enrolment into the study followed consenting procedures.

Conceptual model

Potential factors associated with cognitive impairment were evaluated using a conceptual framework built as a Directed Acyclic Graph describing the relationship between clinical, environmental and behavioral factors with neurocognition (Figure 1). Based on this model, we evaluated the relationships between age, WHO clinical stage at ART start, viral load, age at start of ART, level of education, mental health comorbidity, learning difficulties and neurocognitive impairment.

Ethical approval

Approval to conduct research on human subjects was sought from the University of Nairobi/Kenyatta National Hospital Ethics and Research Committee (UoN/KNH ERC), and the University of Washington Institutional Review Board (UW IRB). Permission to conduct the study at the KNH HIV clinic was also sought from the clinic administration and the KNH Research and Programs department.

Data collection and analysis

Demographic, clinical and mental health data were collected and managed on REDCap, a secure password-protected platform sponsored by the University of Washington Institute of Translational Health science. Clinical data were abstracted from clinic electronic records and information on depressive and anxiety symptoms were collected using interviews administered to participants using the Patient Health Questionnaire (PHQ-9) and Generalized Anxiety Disorders 7-scale (GAD-7) questionnaire respectively. Depression and anxiety symptom severity was determined using the pre-set cut-off scores in each test. Neurocognitive testing was conducted using the *NeuroScreen* Tool (version 4.9.2), a tablet-based brief, highly

automated tool composed of 12 tests evaluating performance in the domains working memory, processing speed, verbal learning, verbal recall/memory, executive function and motor speed domains (38). The primary outcome was neurocognitive test performance among YWH aged 13-24. Demographic and clinical characteristics were summarized using proportions for categorical and medians (interquartile range [IQR]) for continuous variables. *NeuroScreen* raw scores were standardized as z-scores and then summed to a composite z-score per participant. Timed tests were reverse scored to enable interpretation of all tests in the same direction as has been done previously (38). Linear regression analysis was conducted to determine the relationship between the correlates of interest and neurocognitive test scores. The correlates analysis was adjusted for highest level of education and sex as test scores may be higher among YWH with higher levels of education attained and may be influenced by gender. Analysis was conducted using R version 2022.02.3 + 492.

Results

Among 160 YWH recruited, 6 were excluded due to previous history of meningitis, 3 re-scheduled but did not return for assessment and 1 declined enrolment. In total, 150 YWH were enrolled, and complete demographic and clinical data were available for 149 participants. Three participants were excluded from analysis as 2 had incomplete test results and one had visual impairment precluding accurate test performance. Among the 146 YWH included in analysis, the median age of the participants was 18 (interquartile range [IQR], 15,21), 47% were female and the highest level of education for the majority (49%) of the adolescents was secondary school. Most (75%) YWH were enrolled in school. Median age of ART initiation was 10 years (IQR 5,14), 85% were on an Integrase strand inhibitor (INSTI) based regimen and 77% had undetectable viral load (VL) at last assessment, with 92% suppressed using a VL cut-off of <1000 c/ml **(**T**able 1**).

NeuroScreen test performance

The mean completion time on the *NeuroScreen* test was 25 seconds. Median completion times for trail making tests 1, 2 and 3 were 9, 20 and 12 seconds, respectively. The average number of finger taps on non-dominant hands and dominant hands were 243 and 213, respectively. Females had fewer finger taps dominant and non-dominant hands compared to males (p=0.003). Mean total number span forward and backward was 4 and 2, respectively out of a maximum total of 8 on each test. Mean completion time on the number speed test was 35 seconds. Participants were able to learn an average of 9 words on two trials out of a maximum possible 10 words and had a 5-minute delayed recall average of 3 words out of a maximum of 5 **(Table 2).**

Correlates of test performance

Age in years and total number of years of education were each associated with neurocognitive test performance (p=0.086 and p=0.002 respectively) (**Figure 2)**. On univariate analysis (**Table 3**), female adolescents had lower composite z-scores than males (mean difference 2.12 [-4.14, -0.09] p=0.04). YWH who had lower (1-8) years of education had almost 4 points lower composite z-scores (mean difference 3.74 [95% CI -6.48, -1.00], p=0.002) than those with higher years of education (>9 years). YWH with secondary (high school) and university level education had 3 and close to 5 points higher composite z-scores, respectively (mean differences 3.38 (95% CI 0.98, 5.78, p=0.006) and 4.83 (95% CI 1.71, 7.95, p=0.002) compared to those who whose highest level of education was primary school. Among adolescents who were still in school, those with difficulties completing assignments, difficulties understanding what they were taught and difficulties reading, had lower (mean differences 2.92(95% CI -5.80, -0.04, p= 0.047), 2.52(95% CI -5.00, -0.04, p=0.047) and 7.56 (95% CI -14.85, -0.26, p=0.043) composite z-scores respectively, than those who did not have learning difficulties. Adolescents with above average school performance during the preceding term

had higher (mean difference 3.60 (95% CI 0.07, 7.13, p= 0.046) composite z-scores compared to those who had below average (< Grade C) performance.

Adjusted for sex and highest level of education, adolescents with Early HIV (WHO stages I or II) at the time of HIV diagnosis had higher (mean difference 1.67 (-5.05, -0.05) p=0.114) composite z-scores compared to those with advanced (WHO stages III or IV) disease. This difference was not statistically significant though showed a trend towards better scores among those with early disease. Youth with difficulty understanding taught material and difficulties in math had lower composite z-scores compared to those who did not (mean difference 2.55 (95% CI -4.55, 0.03, p= 0.037) and 6.38 (95% CI -11.29, -1.47, p= 0.013). Youth with average and above average school performance at the last school term had higher composite z-scores compared to those with below average school grades (mean difference 5.31 (95% CI 1.93, 8.68, p= 0.002) and 4.09 (95% CI 1.44, 7.92, p=0.012), respectively. In sex stratified analyses, females with difficulty completing assignments and understanding what they were taught had lower composite z-scores p=0.003, while males who reported difficulties with math had lower composite z-scores (mean difference 7.95 (-15.12, -0.78) p=0.032) compared to those who did not. Multivariate analysis was not conducted due to multicollinearity.

Depression and anxiety symptoms and neurocognitive test performance

Depression and anxiety symptoms were present in 35% and 24% of the adolescents respectively. Most symptoms were of mild severity for both depression and anxiety. The proportion of males and females with depression symptoms was 30% and 27% respectively. Anxiety symptoms were reported in 20% and 27% of males and females respectively. No significant linear correlation was found between depression and anxiety symptoms and cognitive test scores.

Discussion

In this cohort of YWH, we found that *Neuroscreen* scores were associated with WHO stage at diagnosis, academic performance and reported academic understanding. Our findings provide important data to support prompt diagnosis and treatment of children with HIV and suggest that *Neuroscreen* may be a useful screening tool to detect neurocognitive impairment in clinics serving YWH.

We utilized the *NeuroScreen* tool, an automated, approximately 25-minute long screening test that is validated in the sub-Saharan region (39). The test was easy to administer as instructions provided are automated, less prone to different interpretation, and useable by non-specialized providers. The *NeuroScreen* tool has been used to assess neurocognition in adults with advanced HIV from the US, South African adults on ART and ART-experienced, virally suppressed youth from the US (38, 39,40). It is difficult to make comparisons between these populations and ours because of contextual and biological differences. Comparison with local norm populations will be critical for future studies.

YWH in our study reflect the all too common late-diagnosed perinatally infected population. In addition, some YWH in our study were old enough to pre-date guidelines for universal ART. Median age at ART start in our cohort was 10 years, older than other cohorts from South Africa, US and Netherlands in similar studies (4.2, 2.8 and 2.5 years respectively). Many YWH in our study (62.4%) had early disease (WHO stages I/ II) at diagnosis and did not initiate ART immediately or soon after diagnosis, placing them at higher risk for cognitive compromise later in life. We noted detectable viremia in 23% of the youth using a cut-off of < 50 RNA copies/ml. Viral non-suppression at a cut-off of <1000 RNA copies/ml was noted in 9% of the youth, lower than that reported in adolescent populations in Kenya (48,49). The differences are more likely attributable to clinic factors and likely, the recent roll-out of treatment optimization using dolutegravir-based regimens.

We found that female YWH had lower scores than males. Gender differences in cognitive test performance have been reported in HIV negative older populations in the opposite direction; with females having better scores in verbal learning and memory and lower advantage in spatial ability assessments (41,42). In a study of PLHIV, average age 23 years, males performed better in psychomotor domains (43). The sex differences we observed may be biologic or may reflect the relative disadvantage females in SSA face with access to education, comprehensive health services and higher rates of adversity.

Somewhat counterintuitively, we found a slight increase in test scores with each year higher age at ART initiation. This may reflect survival bias as ART was previously reserved for children who had immunosuppression or more advanced disease status. Children who initiated ART earlier may have had more advanced disease and had already experienced deleterious effects of HIV on the brain. The overall goal of early treatment is to suppress virus, prevent severe immune suppression (low CD4 nadir) and protect the brain and other organs from poor long-term outcomes. We found higher scores in YWH with WHO stages I/ II disease compared to those with stages III/IV, though the differences were not of statistical significance. Prior studies have shown that advanced HIV has also been strongly associated with cognitive impairment (33,44,45).

YWH who reported having learning difficulties had lower test scores compared to those who did not. Specifically, those who had difficulties understanding what they were taught at school and difficulties in math had lower scores. Higher scores were recorded among adolescents with above average school performance. Executive functioning influences academic performance and adaptive flexibility. Sirois at al evaluated the effects of executive disfunction on learning problems and found that difficulties in this domain increased the risk of school failure (17). In the study, advanced HIV in the past was associated specifically with difficulties in math, a similar finding from Woods et al among adolescents and youth with perinatally acquired HIV (17,33). Caregiver level of education is a crucial factor to evaluate when assessing impact of neurocognition among adolescents on learning for clearer interpretations

of associations. In this study we did not evaluate caregiver level of education. Sirois et al described better performance in math in children with HIV whose caregivers had a high school education. In our study, adolescents with primary-level education as their highest level of education had lower cognitive test scores compared to those with high school, and university level education, as we expected. Similarly, those with higher total number of years of education scored better than those with fewer years of education. These findings highlight the need for early detection (at school or clinic level) of learning difficulties so that targeted educational, psychosocial and clinical support can be provided to mitigate academic outcomes. Adolescent brains demonstrate good levels of neuroplasticity and given the opportunity to learn or re-learn, the adolescent brain can be "trained" to adapt and function appropriately (46). Despite having a disadvantageous start, YWH with cognitive impairment, especially milder forms, may still benefit from academic support and social adaptive training to enable them to transition successfully into adulthood.

Depression and anxiety symptoms were reported among 35% and 24% of our sample respectively, and neither were associated with neurocognitive test scores. This differs from a study in Ethiopia, which found twice as high neurocognitive impairment among YWH with co-occurring mental health morbidity (32). In our study, 4% and 1% of the youth had moderate and severe depression symptoms respectively while 6% and 1% had moderate and severe anxiety symptoms respectively (Table 6). Despite not finding an association between mental health and cognitive function in our study, screening for both is important and associations may be more likely to be detected in larger studies, perhaps with different measures.

Our study had several limitations. We did not evaluate HIV negative age-matched adolescents for comparison. Formal functional evaluation using validated tools, which could provide insight into implications of lower cognitive test scores on everyday functioning, was not conducted. However, evaluation of academic performance and learning difficulties in our study provide

useful insights into the possible effects of cognitive problems on the functional domain of academic performance.

Conclusions

Early diagnosis and treatment of HIV remain the key preventive measures for better cognitive outcomes. We demonstrated that a simple, scalable, low-cost tablet-based tool to screen for cognitive impairment could be used in a real-world clinic setting. Lower test scores correlated with female sex, self-reported learning difficulties and academic performance. Screening tools such as *Neuroscreen* could be useful in clinic or school settings to identify and refer YWH for additional support.

Table 1: Participant characteristics

	N	All N= 149 Median (IQR)/N (%)
Demographic characteristics		
Age 13-15 16-19 20-24	149	18(15, 21) 57(38) 42(28) 50(34)
Female	149	70 (47)
Total number of years in school	149	11 (8,12)
Level of education Primary Secondary College/vocational University	149	 39 (26) 73 (49) 13 (9) 24 (16)
Clinic type Adolescent Other	149	 95 (64) 54(36)
Schooling		
Currently in school	149	111(75)
Participants reporting any learning difficulties	111	44(40)
Trouble completing school assignments	100	22(22)
Difficulties with reading	35	5 (14)
Difficulties with math	36	25(69)
Difficulties with writing	36	5(14)
Difficulties understanding taught material	109	35(32)
Difficulties in concentration	36	13(36)
Other learning difficulties	36	3(8.3)
School performance in the past year Above average (Grade A) Good (Grade B) Average (Grade C) Poor (Below Grade C)	109	 3 (3) 34 (31) 55 (51) 17 (16)
Clinical characteristics		
Age at initiation of ART	149	10(5,14)
Current ART regimen PI based INSTI based Other	149	 5(3) 126(85) 18(12)
Previous first line ART regimen PI based INSTI based NNRTI based	131	 30(23) 9(7) 92(70)
Duration on ART in years	132	10(9,10)
WHO stage at diagnosis Stage I Stage II Stage III Stage IV	148	 62 (42) 30 (21) 45 (30) 11 (7)
Last clinic WHO stage Stage I Stage II Stage III Stage IV	148	 147(99) 0 (0) 1 (1) 0(0.0)
Log $_{10}$ Peak Viral load	145	2.4 (0, 4.187)
Current Viral load (copies/ml) Detectable Undetectable (<50 c/ml) Suppressed <1000 c/ml)	143	 33(23) 110(77) 131 (92)

ART adherence Good	142	 141 (99)
Depression symptoms None Mild Moderate Severe	149	 106 (71) 36(24) 6 (4) 1(1)
Anxiety symptoms Minimal Mild Moderate Severe	91	 70(77) 15(16) 5(6) 1(1)

Table 2: *NeuroScreen* overall performance: All participants

Test N=147	**Mean score SD**	**Median score**	**Mean (SD) Male**	**Mean (SD) Female**	**p-value**
Trail making test 1*	13.44(15.89)	9.03 (7.14,12.44)	11.83 (10.10)	15.21 (20.39)	0.198
Trail making test 2*	30.69(24.01)	20.42 (15.15,39.22)	27.69 (23.94)	34 (23.82)	0.112
Trail making test 3*	16.39(14.29)	12.34 (8.78, 17.95)	15.45 (15.79)	17.39 (12.47)	0.416
Finger tap (dominant hand)	242.95 (44.22)	243 (224.00, 270.00)	253.25 (44.60)	231.61 (41.19)	**0.003**
Finger tap (non-dominant hand)	212.83 (38.11)	207 (189.00, 239.00)	221.52 (41.26)	203.27 (31.94)	**0.003**
Visual discrimination 1	13.52 (4.35)	13 (10.00, 16.00)	13.58 (4.92)	13.46 (3.64)	0.860
Visual discrimination 2	30.95 (6.51)	30 (27.00, 35.00)	31.42 (6.46)	30.43 (6.56)	0.360
Number speed*	34.83 (11.30)	33.03 (26.15, 40.46)	33.86 (10.27)	35.90 (12.33)	0.277
Number span forward	3.52 (1.05)	4 (3.00, 4.00)	3.58 (1.06)	3.44 (1.04)	0.416
Number span backward	2.20 (0.95)	2 (2.00, 3.00)	2.22 (0.88)	2.17 (1.02)	0.754
Verbal learning total score	9.14 (1.12)	9 (9.00, 10.00)	9.14 (1.14)	9.14 (1.09)	1.000
Verbal learning (delayed recall)	3.44 (1.43)	4 (3.00, 5.00)	3.43 (1.54)	3.44 (3.31)	0.952

*score = time in seconds.

Table 3: Correlates of neurocognitive test performance

Variable	Unadjusted linear regression		Adjusted linear regression	
	Coefficient (95% CI)	p-value	Coefficient (95% CI)	p-value
Age	0.25 (-0.04, 0.54)	0.086	-0.32 (-0.77, 0.14)	0.174
Age group				
13-15	-1.65 (-4.05, 0.75)	0.176	2.44 (-1.11, 5.98)	0.177
16-19	0.48 (-2.12, 3.07)	0.718	1.50 (-1.30, 4.30)	0.291
20-24	Reference			
Female	-2.12 (-4.14, -0.09)	**0.040**		
Total number of years of education	0.57 (0.22, 0.91)	**0.002**	0.47 (-0.25, 1.19)	0.198
Total number of years in school				
1-8 years	-3.74 (-6.48, -1.00)	**0.008**	-2.93 (-8.26, 2.40)	0.279
9-12 years	-0.49 (-2.95, 1.98)	0.697	-3.71 (-8.00, 0.57)	0.089
>12 years	Reference			
Highest level of education				
Primary	-4.83 (-7.96, -1.71)	**0.003**		
Secondary	-1.45 (-4.29, 1.39)	0.315		
Technical	-2.70 (-6.85, 1.44)	0.200		
University	Reference			
Age at ART initiation	0.18 (0.00, 0.36)	**0.049**	0.00 (-0.23, 0.23)	0.998
Duration on ART	0.04 (-0.39, 0.47)	0.843	0.07(-0.35, 0.49)	0.739
Previous ART regimen				
PI-based	-0.67 (-5.47, 4.13)	0.783	1.55 (-3.33, 6.42)	0.532
NNRTI-based	0.90 (-3.52, 5.31)	0.688	0.63 (-3.59, 4.84)	0.687
INSTI-based	Reference			
WHO stage at diagnosis				
Early (Stages I and II) - Advanced (Stages III and IV)	0.90 (-1.21 3.02) Reference	0.40	1.67 (-5.05, -0.05)	0.114
Viral load				
Detectable	1.16 (-1.35, 3.66)	0.363	1.20 (-1.21, 3.61)	0.326
Undetectable	Reference			
Log10 Peak viral load	0.54(0.22, 1.32)	0.175	0.62 (0.26, 1.45)	0.264
CD4 nadir				
Difficulty completing assignments	-2.92 (-5.80, -0.04)	**0.047**	-1.84 (-4.64, 0.95)	0.193
Difficulty understanding taught material	-2.52 (-5.00, -0.04)	**0.047**	-2.55 (-4.55, 0.03)	**0.037**
Difficulty reading	-7.56 (-14.85, -0.26)	**0.043**	-1.72(-10.13, 6.69)	0.679
Difficulty writing	-2.05 (-9.67, 5.57)	0.587	-2.19 (-9.02, 4.65)	0.518
Difficulty concentrating	-0.41 (-5.45, 4.63)	0.870	-0.37 (-4.99, 4.25)	0.871
Difficulty with math	-4.95 (-9.90, -0.01)	0.050	-6.38 (-11.29, -1.47)	**0.013**
School performance				
Above average	3.60 (0.07, 7.13)	0.046	5.31 (1.93, 8.68)	**0.002**
Average	2.96 (-0.38, 6.30)	0.081	4.09 (1.44, 7.92)	**0.012**
Below Average (reference)				
Hearing	-2.28 (-5.55, 1.00)	0.171	-2.45 (-5.75, 0.78)	0.134
Sight	1.78 (-0.59, 4.15)	0.139	2.06 (-0.20, 4.32)	0.074
Depressive symptoms	-0.00 (-2.25, 2.25)	0.999	-0.61 (-2.79, 1.56)	0.577
Depressive symptoms				
None	Reference		Reference	
Mild	-0.04 (-2.46, 2.38)	0.973	-0.40 (-2.72, 1.92)	0.734
Moderate	0.64 (-4.61, 5.89)	0.810	-0.88 (-5.96, 4.19)	0.732
Moderate - severe	-2.38 (-14.95, 10.18)	0.708	0.21 (-11.88, 12.29)	0.973
Anxiety symptoms	0.20 (-3.00, 3.39)	0.903	-0.13 (-3.31, 3.05)	0.934
Anxiety symptoms				

None	Reference		Reference	
Mild	0.37 (-3.32, 4.06)	0.844	0.15 (-3.60, 3.90)	0.937
Moderate	0.50 (-5.50, 6.50)	0.869	0.57 (-5.39, 6.53)	0.848
Severe	-3.86 (-16.90, 9.19)	0.558	-3.19 (-16.21, 9.83)	0.627

Adjusted for sex and level of education

Table 4: Correlates of neurocognitive test performance in males

Variable	Unadjusted linear regression		Adjusted linear regression	
	Coefficient (95% CI)	p-value	Coefficient (95% CI)	p-value
Age	0.21 (-0.18, 0.59)	0.283	-0.36 (-1.02, 0.30)	0.2797
Age group 13-15 16-19 20-24	 -1.64 (-4.89, 1.61) 0.50 (-3.20, 4.20) Reference	 0.319 0.790	 2.18 (--2.95, 7.31) 1.09 (-2.98, 5.16)	 0.400 0.595
Total number of years of education	0.59 (0.07, 1.10)	**0.0273**	0.78 (-0.45, 2.00)	0.209
Highest level of education Primary Secondary Technical University	 -4.526 (-9.31, 0.26) -1.003 (-5.47, 3.46) -2.980 (-9.36, 3.40) Reference	 0.064 0.656 0.355		
Age at ART initiation	0.12 (-0.13, 0.37)	0.357	-0.17 (-0.54, 0.20)	0.361
Duration on ART	-0.17 (-0.85, 0.51)	0.619	-0.00 (--0.70, 0.69)	0.993
Previous ART regimen PI-based NNRTI-based INSTI-based	 -2.03 (-9.22, 5.16) -0.10 (-6.81, 6.62) Reference	 0.575 0.977	 1.58 (-6.44, 9.61) -1.67 (-5.50, 8.50)	 0.694 0.670
WHO stage at diagnosis Early (Stages I and II) - Ref Advanced (Stages III and IV)	 1.29 (-0.65, 3.23) -0.46 (-3.32, 2.39)	 0.191 0.748	 -1.01 (-3.88, 1.87) -0.91 (-3.75, 1.93)	 0.488 0.526
Viral load Detectable Undetectable	 2.31 (-0.96, 5.57) Reference	 0.164	 1.70 (-1.60, 4.50)	 0.307
Difficulty completing assignments	-0.67 (-4.65, 3.30)	0.734	0.76 (-3.09, 4.61)	0.692
Difficulty understanding taught material	-1.42 (-4.88, 2.05)	0.417	-0.94 (-4.32, 2.43)	0.577
Difficulty reading	-5.16 (-20.95, 10.62)	0.499	-1.28 (-16.96, 14.39)	0.863
Difficulty writing	-6.65 (-15.50, 2.30)	0.132	-5.01 (-13.71, 3.69)	0.239
Difficulty concentrating	-1.11 (-7.87, 5.64)	0.733	-0.67 (-7.43, 6.10)	0.837
Difficulty with math	-5.48 (-12.32, 1.36)	0.110	-7.95 (-15.12, -0.78)	**0.032**
School performance Above average Average Below Average (reference)	 2.36 (-2.45, 7.16) 2.21 (-2.45, 7.16)	 0.329 0.335	 4.30 (-0.53, 9.12) 3.15 (-1.38, 7.68)	 0.079 0.169
Hearing	-2.11 (-6.72, 2.50)	0.365	-2.51 (-7.15, 2.14)	0.285
Sight	0.71 (-2.70, 4.12)	0.679	0.63 (-2.73, 3.99)	0.710
Depressive symptoms	-0.48 (-3.53, 2.57)	0.756	-0.64 (-3.66, 2.39)	0.676
Anxiety symptoms	-1.49 (-6.29, 3.32)	0.535	-1.57 (-6.46, 3.31)	0.519

*Adjusted for level of education

Table 5: Correlates cognitive test performance in females

Variable	Unadjusted linear regression		Adjusted linear regression	
	Coefficient (95% CI)	p-value	Coefficient (95% CI)	p-value
Age	0.30 (-0.13, 0.73)	0.174	-0.30 (-0.98, 0.38)	0.386
Age group 13-15 16-19 20-24	 -1.74 (-5.31,1.84) 0.78 (-2.91, 4.47)	 0.336 0.673	 3.05 (-2.23, 8.32) 2.19 (-2.03, 6.41)	 0.253 0.303
Total number of years of education	0.58 (0.12, 1.05)	**0.015**	0.27 (-0.67, 1.21)	0.567
Highest level of education Primary Secondary Technical University	 -5.80 (-10.06, -1.56) -2.60 (-6.37, 1.17) -2.68 (-8.17, 2.82) Reference	 **0.008** 0.174 0.334		
Age at ART initiation	0.26 (0.01, 0.52)	**0.049**	0.01 (-0.18, 0.43)	0.409
Duration on ART	0.15 (-0.39, 0.70)	0.575	0.15 (-0.39, 0.70)	0.574
Previous ART regimen PI-based NNRTI-based INSTI-based	 0.07 (-6.34, 6.48) 1.41 (-4.39, 7.21) Reference	 0.983 0.628	 1.64 (-4.93, 8.21) 0.23 (-5.71, 6.16)	 0.619 0.939
WHO stage at diagnosis Early (Stages I and II) - Ref Advanced (Stages III and IV)	 -0.39 (-2.14, 1.36) -2.39 (-5.59, 0.81)	 0.658 0.140	 2.08 (-1.02, 5.17) -2.66 (-5.91, 0.59)	 0.185 0.107
Viral load Detectable	 -0.78 (-4.65, 3.10)	 0.691	 -0.29 (-4.15, 3.57)	 0.883
Difficulty completing assignments	-6.04 (-10.18, -1.89)	0.005	-5.01 (-9.14, -0.87)	**0.019**
Difficulty understanding taught material	-4.22 (-7.78, -0.66)	0.021	-4.42 (-8.04, -0.80)	**0.018**
Difficulty reading	-7.03 (-15.44, 1.38)	0.094	-1.92 (-19.04, 15.20)	0.808
Difficulty writing	7.35 (-7.08, 21.77)	0.291	6.45 (-7.61, 20.52)	0.331
Difficulty concentrating	-1.39 (-9.86, 7.08)	0.729	-1.47 (-9.83, 6.90)	0.704
Difficulty with math	-4.65 (-12.12, 2.83)	0.203		
School performance Above average Average Below Average (reference)	 5.66 (0.35, 10.97) 4.70 (-0.32, 9.72)	 0.037 0.066	 6.84 (1.66, 12.03) 5.61 (0.74, 10.47)	 **0.011** **0.024**
Hearing	-2.33 (-6.98, 2.32)	0.321	-2.43 (-7.27, 2.42)	0.320
Sight	3.10 (-0.17, 6.37)	0.062	3.48 (0.32, 6.64)	0.031
Depressive symptoms	0.34 (-3.01, 3.69)	0.840	-0.66 (-3.98, 2.67)	0.694
Anxiety symptoms	1.93 (-2.42, 6.29)	0.376	1.05 (-3.36, 5.47)	0.632

*Adjusted for level of education

Table 6: Depression and anxiety symptoms by severity in males and females

	Males N= 79	Females	P value
Depression	N= 79	N=70	
None	55(70)	51(73)	0.666
Mild	20(25)	16(23)	0.728
Moderate	4(5)	2(3)	0.497
Severe	0(0)	1(1)	0.290
Anxiety	N= 46	N=45	
None	37(80)	33(73)	0.427
Mild	6(13)	9(20)	0.377
Moderate	3(7)	2(5)	0.668
Severe	0(0)	1(2)	0.315

Figure 1: Directed Acyclic Graph Correlates of Cognitive Impairment

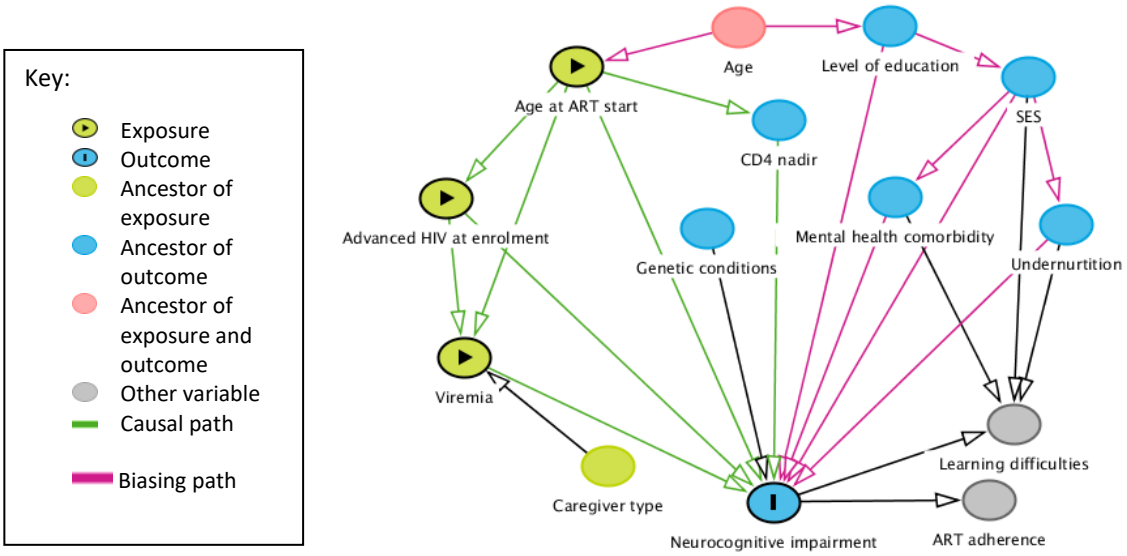
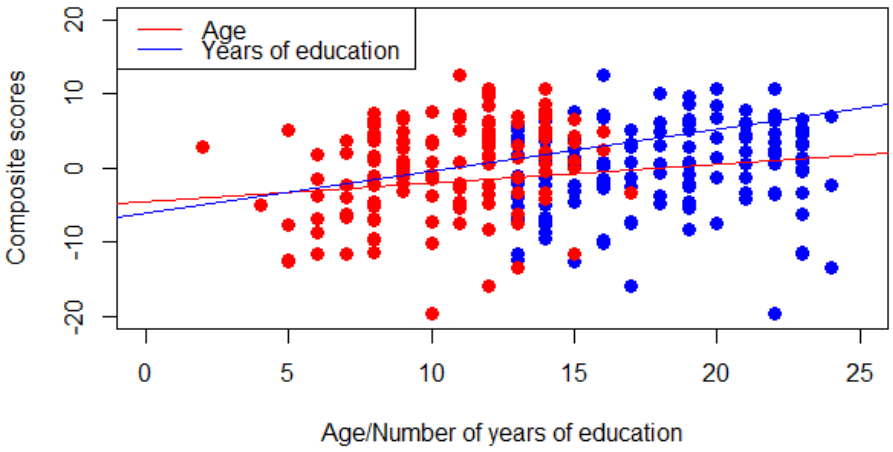


Figure 2: Age, years of education and neurocognitive test performance



Age p=0.860

No. years of education p=0.002

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