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Frequency and Predictors of HIV-related Cognitive Impairment in East Africa: The African Cohort Study (AFRICOS)

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Abstract

Background: Medication adherence is a critical issue in achieving viral suppression targets, particularly in resource-limited countries. As HIV-related cognitive impairment (CI) impacts adherence, we examined frequency and predictors of CI in the African Cohort Study.

Setting: Cross-sectional examination of enrollment data from PEPFAR supported clinic sites.

Methods: In a 30-minute cognitive assessment, CI was defined as −1SD on two tests or −2SD on one, as compared to 429 controls. We performed univariable and multivariable logistic and linear

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models examining clinical and demographic factors associated with CI and global neuropsychological performance (NP-6).

Results: 2472 HIV+ participants from Kenya (n=1503), Tanzania (n=469) and Uganda (n=500). The mean (SD) age was 39.7 (10.7) years and 1452 (59%) were female. The majority reported completing or partially completing primary school (n=1584, 64%). Mean (SD) current and nadir CD4 count were 463 (249) and 204 (221) cells/mm3, respectively; 1689 (68%) were on cART. 939 (38%) HIV+ versus 113 (26%) HIV- individuals showed CI (p<0.001). We found significant effects of literacy (OR: 0.3; 95% CI: 0.2–0.4; p<0.001) and WHO stage 4 (OR: 1.5; 95% CI: 1.0–2.q; p=0.046) on CI. Tanzanians (OR: 3.2; 95% CI: 2.4–4.3; p<0.001) and Kenyans (OR: 2.0; 95% CI: 1.6–2.6; p<0.001) had higher risk of CI compared to Ugandans. Results were relatively unchanged in predictive models of NP-6, with the only difference being an additional significant effect of current CD4 cell count (coeff: 0.0; 95% CI: 0.0–0.0; p=0.005).

Conclusion: Literacy, country, WHO stage and current CD4 cell count were associated with increased risk of cognitive dysfunction. Our findings help optimize care practices in Africa, illustrating the importance of strategies for early and effective viral-immunological control.

Keywords

HIV; HIV-associated neurocognitive disorders; neurologic disease; Africa; Eastern

INTRODUCTION

The HIV epidemic is a critical public health issue worldwide and is prominent in low and middle income countries (LMIC). The Joint United Nations Programs on HIV/AIDS (UNAIDS) estimates that approximately 36.9 million people were living with HIV in 2017, majority of whom from LMICs.[1] Eastern and southern Africa have the highest proportion of cases, with an overall prevalence of 7.4% and some countries with a prevalence rate that is above 20%.[1] Early combination antiretroviral therapy (cART) improves health of HIV-infected individuals and reduces HIV transmission.[2–4] In 2014, the UNAIDS established an ambitious, but achievable target, known as the 90-90-90 targets: by 2020, at least 90% of HIV-infected individuals will be diagnosed, at least 90% of those diagnosed will be receiving cART and at least 90% of those on treatment will be virally suppressed.[5] In 2015, the World Health Organization (WHO) recommended to begin cART as early as possible, regardless of CD4 cell count.[6] More recently, UNAIDS called for faster progress to reach 90-90-90 by 2020 and further updated the targets to 95-95-95 by 2030 in order to accelerate the end to the HIV epidemic.[7]

Despite a global consensus to “treat all” who are infected and an expansion of cART in LMICs, most sub-Saharan Africa regions remain significantly below the UNAIDS goal, emphasizing the need to implement effective policies to diagnose, treat and achieve good viral control in these patients.[8–10] These strategies will likely require careful attention to mental and cognitive health indices for achieving the third UNAIDS target given the adverse impact of HIV-associated neurocognitive disorders (HAND) on daily functioning including adherence to medication.[11,12] In one study, HIV-associated cognitive impairment was

associated with a 2.3 times greater risk of adherence failure, thus pointing to the clinical implications of HAND.[11]

cART is currently the only effective pharmacological treatment to prevent or halt HAND, which remains a considerable health concern for 30–50% of HIV-infected patients and remains frequent in chronic HIV even among virally suppressed individuals.[13–17] The reported prevalence of HAND among HIV-infected Africans varies widely ranging from 25% to 64%.[18–22] The discrepancy in cognitive impairment rates across studies is likely due to multiple factors including the use of cognitive screening tests versus comprehensive neuropsychological testing batteries to detect HAND and heterogeneous levels of disease severity. In LMICs, HAND diagnosis poses several challenges in primary care settings due to limited number of specialized personnel and suboptimal diagnostic tools.

Growing evidence documents the adverse effect of HAND on factors such as medication adherence, quality of life and everyday functioning.[11,12,23,24] Cognitively impaired HIV-infected individuals also have higher rates of unemployment, particularly when executive functioning and memory are involved.[12,24] These same cognitive areas along with attention and psychomotor speed are directly linked to disruption of fronto-subcortical circuits.[25–27] Given the substantial burden of HIV infection in these regions and the deleterious effects of HAND on everyday functioning including medication adherence, identifying and addressing potential risk factors in these regions cannot be overlooked in an effort to achieve UNAIDS targets.

Several risk factors for HAND have been described including low nadir CD4 cell count, older age, substance abuse, lower educational achievement, hepatitis C (HCV) coinfection, cerebrovascular disease risk factors, sleep disorders and psychiatric comorbidities.[26,28] However, these findings are based largely on studies conducted in industrialized countries and less evidence is currently available on prevalence and risk factors of HAND in lower resource settings. An enhanced understanding of factors that lead to the best clinical outcomes will optimize care practices in these countries. In the present study, we investigated frequency and predictors of cognitive impairment in a large African cohort (AFRICOS). We hypothesized that both HIV and non-HIV factors may contribute to worse cognitive functioning in people with HIV.

METHODS

Study Cohort

The African Cohort Study (AFRICOS) is a longitudinal study enrolling 3000 HIV-infected and 600 HIV-uninfected individuals at Public Health facilities supported through the US Military HIV Research Program (MHRP) by the President's Emergency Plan for AIDS Relief (PEPFAR) in Kenya, Tanzania, Uganda, and Nigeria.[29,30] Its objective is to assess the impact of clinical practices, biological factors and socio-behavioral issues on HIV infection and disease progression in African settings with aims of informing practice and policy. Individuals were eligible if they were at least 18 years or older, consented to data and specimen collection, and receipt of HIV care in a clinic associated with PEPFAR. Exclusion criteria were limited to any condition that, in the opinion of the study investigators, would

interfere with study conduct in order to achieve a representative sample. Our study included all the program sites except the Nigerian ones, given notable differences in educational attainment and test performance in Nigeria compared to the other African countries.[30]

All participants provided written informed consent. The study was approved by institutional review boards of the Walter Reed Army Institute of Research, Makerere University School of Public Health, Kenya Medical Research Institute, Tanzania National Institute of Medical Research, and Nigerian Ministry of Defense.

Data Collection

Demographic and clinical predictors—At study entry, participants received a medical history and physical examination, a broad demographic and behavior questionnaire and underwent laboratory and other clinical assessments consistent with routine clinical HIV care at the study site or specific to the study aims. For the purpose of this study, among all the data collected, we investigated available variables known to be associated with cognitive functioning including age, literacy, sex, current and nadir CD4 cell count, plasma HIV RNA, duration of HIV infection, WHO stage, being on cART, duration of cART, undetectable viral load (HIV RNA < 200 copies/ml) and depression. Since in a prior work we identified statistically significant differences in neuropsychological performance across countries, we also included country as one of the main predictors.[30]

Cognitive outcomes—Participants underwent a 30-minute neuropsychological testing battery assessing attention [WHO auditory verbal learning test (AVLT) trial 1]; learning (AVLT sum of trials 1–5); memory (AVLT delayed recall); psychomotor speed (Trails A); verbal fluency (action fluency) and manual dexterity (Grooved Pegboard). Testers were trained on all neuropsychological tests, certified and re-certified every 6 months to assure consistent testing across all sites. Comparative data were acquired from 429 HIV-uninfected individuals who also sought care at the same clinics and stratified to four levels of age and two levels of education (Supplemental Table 1). Individual z-scores were then calculated based on the collected comparative data.[30] A composite global score was also derived by averaging the individual z-scores (NP-6). Cognitive impairment was defined as at least −1 standard deviation (SD) below the mean on two measures or −2 SD below the age and education matched mean from the local comparative data on at least one test.[30] Depression symptoms were evaluated using the 20-item Center for Epidemiologic Studies Depression (CES-D) scale.[31] A cut-off of 16 on this scale was used to indicate clinically significant depression.[32]

Statistical Analysis—We employed one-way analysis of variance for continuous variables and chi-squared test for categorical variables to compare demographic, clinical and cognitive factors across countries. All the independent variables investigated in our analyses had less than 2% missing data (see Table 1).[33] We used log10-transformed values of plasma HIV RNA in all analyses. Cognitive functioning was analyzed as a dichotomous (i.e., presence of cognitive impairment) as well as continuous variable (i.e., NP-6).

We selected the best set of predictor variables by employing univariable regression models to investigate associations between each predictor with the outcome. Factors with a p-value

<0.20 in the univariable analyses were entered into the multivariable logistic and linear models to identify significant predictors of cognitive impairment and NP-6, respectively. Since undetectable viral load (HIV RNA <200 copies/ml) and plasma HIV RNA were found to be strongly correlated (i.e., Pearson correlation coefficient ≥0.70), only the latter was included in the multivariable linear model.[34] Secondary sets of logistic regression models were conducted to investigate factors associated with cognitive impairment (1) within each country, (2) among viral suppressed individuals, and (3) among literate participants. Significance level was set at p<0.05. Analyses were conducted using STATA 15 (STATA: Release 15, College Station, Texas, USA: StataCorp).

RESULTS

Study Participants

We enrolled 2472 HIV-infected participants between January 2013 and November 2017 from Kenya (n=1503), Tanzania (n=469) and Uganda (n=500). Participants had a mean (SD) age of 39.7 (10.7) years and 1452 (59%) were female. All but 10% were literate (n=2215; 90% literate) and the majority reported completing or partially completing primary school (n=1584, 64%). The mean (SD) current and nadir CD4 cell count was 424 (264) and 204 (221) cells/mm^3, respectively and 1689 (68%) were on cART at the time of enrollment (Table 1). Among those on treatment, 1310 (79%) had HIV RNA less than 200 copies/ml.

The HIV-uninfected group comprised 429 individuals from Kenya (n=267), Tanzania (n=63) and Uganda (n=99). They had a mean (SD) age of 37.4 (10.4) years, 246 (57%) were female and all but 7% were literate (n=399; 93% literate; Supplemental Table 1).

Cognitive impairment was common in this cohort of HIV-infected individuals, with 939 individuals (38%) meeting our definition of impairment compared to 113 (26%) in the control group (p<0.001). The rate of impairment was not significantly different between treated versus untreated participants (n=640, 37.9% versus n=299, 38.3%; p=0.834) or between aviremic versus viremic participants (n=496, 36.4% versus n=420, 39.7%; p=0.100). As expected, we found differences across countries with participants from Tanzania showing the highest cognitive impairment rate (n=242, 52%), followed by those in Kenya (n=553, 37%) and Uganda (n=144, 29%; p<0.001; Table 1). The mean (SD) NP-6 was −0.2 (0.6); participants from Tanzania performed worst compared to the other countries [−0.4 (0.7); p<0.001; Table 1]. The most affected cognitive areas were speed of information processing [−0.3 (1.1)] and manual dexterity [−0.3 (1.1)] followed by verbal fluency [−0.2 (1.0); Figure 1].

Demographic and Clinical Predictors of Cognitive Functioning

The univariable logistic regressions identified literacy, sex, age, country, depression, WHO stage, current and nadir CD4 cell count and plasma HIV RNA as the best predictors of cognitive impairment (p<0.20; Table 2). The multivariable regression model confirmed a statistically significant effect of literacy (OR: 0.3; 95% CI: 0.2–0.4; p<0.001) and WHO stage 4 (OR: 1.5; 95% CI: 1.0–2.1; p=0.046; Table 2). Furthermore, those from Tanzania

(OR: 3.2; 95% CI: 2.4–4.3; p<0.001) and Kenya (OR: 2.0; 95% CI: 1.6–2.6; p<0.001) had higher risk of showing cognitive impairment compared to participants from Uganda.

Results were relatively unchanged in predictive models of NP-6. The univariable linear regression models identified the same factors as the logistic regressions but sex, in addition to being on cART (p<0.20; Table 3). The findings of the multivariable linear model were similar to those predicting cognitive impairment, with the only difference being an additional significant effect of current CD4 cell count (unstandardized coeff: 0.0; 95% CI: 0.0–0.0; p=0.005; Table 3).

Evaluating factors associated with cognitive impairment within each country did not substantially change the overall findings with significant effects of literacy in all countries [(Kenya: OR: 0.3; 95% CI: 0.2–0.5; p<0.001); (Tanzania: OR: 0.2; 95% CI: 0.1–0.4; p<0.001); Uganda (OR: 0.3; 95% CI: 0.2–0.5; p<0.001)], WHO stage 4 (OR: 2.3; 95% CI: 1.4–3.9; p=0.001) and plasma HIV RNA (OR: 1.1; 95% CI: 1.0–1.1; p=0.041) in Kenya. Restricting the logistic analysis to literate participants, we found a significant increased risk for cognitive impairment with Kenya (OR: 1.9; 95% CI: 1.5–2.6; p<0.001), Tanzania (OR: 2.9; 95% CI: 2.1–4.0; p<0.001), WHO stage 4 (OR: 1.5; 95% CI: 1.0–2.3; p=0.036) and plasma HIV RNA (OR: 1.1; 95% CI: 1.0–1.1; p=0.033). Lastly, in the sensitivity analysis limited to virally suppressed participants (i.e. plasma HIV RNA <200 copies/ml), we found a significant association between cognitive impairment with literacy (OR: 0.3; 95% CI: 0.2–0.4; p<0.001), WHO stage 4 (OR: 1.8; 95% CI: 1.1–3.0; p=0.020), Kenya (OR: 2.1; 95% CI: 1.4–3.1; p<0.001) and Tanzania (OR: 3.4; 95% CI: 2.1–5.5; p<0.001).

DISCUSSION

In this large sample of HIV-infected individuals from Kenya, Tanzania and Uganda, we found that literacy, higher levels of plasma HIV RNA, current CD4 cell count and higher WHO stage are associated with increased risk of cognitive dysfunction. Tanzanian and Kenyan participants were more likely to show cognitive impairment compared to Ugandans. Our findings provide further evidence that HIV-related cognitive impairment is frequent in this population of patients and correlates with demographic and clinical determinants.

The advent of cART has transformed HIV to a chronic disease with life expectancy approaching population norms for patients compliant with medications in both low and high income countries.[35–38] Yet, even with effective treatment and viral control, individuals living with HIV are at risk for developing non-AIDS conditions including cognitive disorders.[36] Given the known impact of HAND on everyday functioning and medication adherence, close attention to mental health issues will be important to achieving the UNAIDS targets.

In our study the frequency of cognitive impairment was similar between treated and untreated participants. By using the UNAIDS definition of viral suppression as viral loads less than 1000 copies/ml, 85% of those on treatment were virally suppressed in our study, close to the 90% goal.[5] Effective cART does not seem to consistently protect against mild HAND; although the degree to which cognitive impairment occurred before treatment and incompletely remediated is not clear.[28,39] Some suggested that antiretroviral therapies with

poor distribution into the central nervous system (CNS) are associated with worse neuropsychological performance.[40] However, evidence linking lower CNS penetrating effectiveness (CPE) to impaired cognitive functioning have been mixed.[17,41,42] For instance, one study conducted in South Africa found that cART preserved or improved cognitive functioning in HIV-infected individuals after 1 year, regardless of the regimen's CPE.[43] Additionally, until very recently national guidelines allowed that the majority of HIV-infected patients be started on treatment only when their CD4 count was below 200 cells/ml, thus leading to a longer overall exposure to the neurological effects of HIV. Our findings provide further evidence that severe immunosuppression and history of AIDS-defining illnesses represent risk factors for developing HIV-associated cognitive impairment.[44]

Besides HIV-related determinants, patient-related factors such as education and age have been linked to cognitive functioning in HIV.[39,45] Our results document a significant effect of literacy on cognitive impairment, after controlling for clinical variables. Growing evidence show that cognitive reserve is neuroprotective in HIV-infected patients at risk for cognitive decline.[46,47] In one study symptomatic HIV-infected individuals evidenced lower reserve scores (i.e. combination of years of education, premorbid intelligence and occupational attainment) compared to asymptomatic and cognitively normal participants, suggesting that lower reserve might contribute to functional impairment.[48] In African settings, the finding of low education as an independent risk factor for HIV-related cognitive impairment has been reported in several studies conducted in Nigeria, South Africa, Botswana and Cameroon among others.[45,49–51] Other studies noted that reading ability is a better predictor of cognitive performance than years of education in individuals with disadvantaged socio-economic backgrounds.[52,53] Importantly, low literacy levels or low educational attainment are also associated with faster age-related cognitive and functional decline and higher dementia rates in the general HIV-uninfected population, thus emphasizing the need to monitor of patients at higher risk of cognitive impairment.[53,54]

The HIV epidemic has affected all sectors of society, making it not only a major public health concern, but also a socio-economic and development problem. The burden of HIV and AIDS on nations' economies and depletion of human capital, particularly in the sectors of health, education and agriculture, constrains growth and productivity.[55] Despite the high prevalence of mental health illness and neurocognitive deficits in people living with HIV in LMICs, HIV clinics generally lack policies related to mental health services and staff are not trained on mental health screening or basic treatment.[56,57] Many HIV clinics in LMICs are designed to provide acute care and are less capable to effectively treat and support all patients needing chronic care.[36,58] Often understaffed, there is minimal time for comprehensive patient visits that may be needed to capture the milder, yet common forms of HAND. Identifying the current prevalence of HIV-associated cognitive impairment in these regions might positively impact accessibility to cART and integrated HIV-mental health services. At the same time, determining correlates of cognitive impairment in the setting of HIV might help with the early detection of individuals at higher risk of cognitive decline. Our results may have relevant implications for the optimal management of HIV-infected patients in Africa.

This study has several limitations. Although our study included a large cohort of HIV-infected Africans, the findings may not be generalized to individuals treated in regions other than Kenya, Uganda and Tanzania. Differences in neuropsychological functioning between males and females should also be acknowledged. Investigating whether the described associations were similar between male and female participants revealed a significant effect of literacy and country in both groups, while WHO stage 4 showed a trend towards significance in women and was no longer statistically associated with cognitive impairment in men. While the composite global score estimates overall cognitive performance, it is notable that three of the individual scores that make up this average come from the AVLT, meaning that performance on this task may have disproportionately influenced the global score. A strength to our point estimates is that our comparative data were acquired by seronegative individuals with similar demographic and socio-economic characteristics and recruited at the same program sites. While the norms were not computed by country due to power issues, the effect of using all the country data combined rather than calculating norms within each country (if sample sizes permitted) was not statistically significant. This demographic matching allows us to more clearly isolate HIV effects. However, some of these HIV-uninfected individuals might have had confounding factors such as head injuries and alcohol use or other factors that are known to adversely affect cognition. In prior work a thorough investigation of these factors revealed minimal impact on cognitive outcomes, hence these individuals were included in the analyses.[30] In the control group 26% of the individuals showed an abnormal performance on neuropsychological testing. Variability in neuropsychological performance is expected in healthy controls, pointing to each individual's relative cognitive strengths and weaknesses rather than the presence of brain dysfunction and providing a reference point to understand the difference between variation and impairment in any patient group.[59,60] Lastly, in order to track long term outcomes, 254 out of the 2472 participants were selected from previous research studies rather than in a fashion representative of the general clinic population. Sensitivity analyses excluding those 254 individuals produced similar results.

Ongoing longitudinal data collection will enable future examination of cognitive trajectories over time and the factors possibly leading to cognitive decline in this population of patients. This will become even more relevant in view of an aging HIV-population, which requires the management of comorbidities including conditions typically associated with aging. The research community will therefore be challenged to identify or develop behavioral interventions to prevent or treat neurocognitive disorders that can be integrated into the current health care models.

To conclude, in a large cohort of HIV-infected individuals from Eastern Africa we found that good viro-immunological control and literacy are protective factors against HIV-associated cognitive impairment, which remains frequent in these regions and is associated with poor cART adherence.[24] Identifying factors that lead to the best clinical outcomes might help implement optimal and effective care practices in these regions, particularly as the HIV-infected African population ages and cART access increases across the continent.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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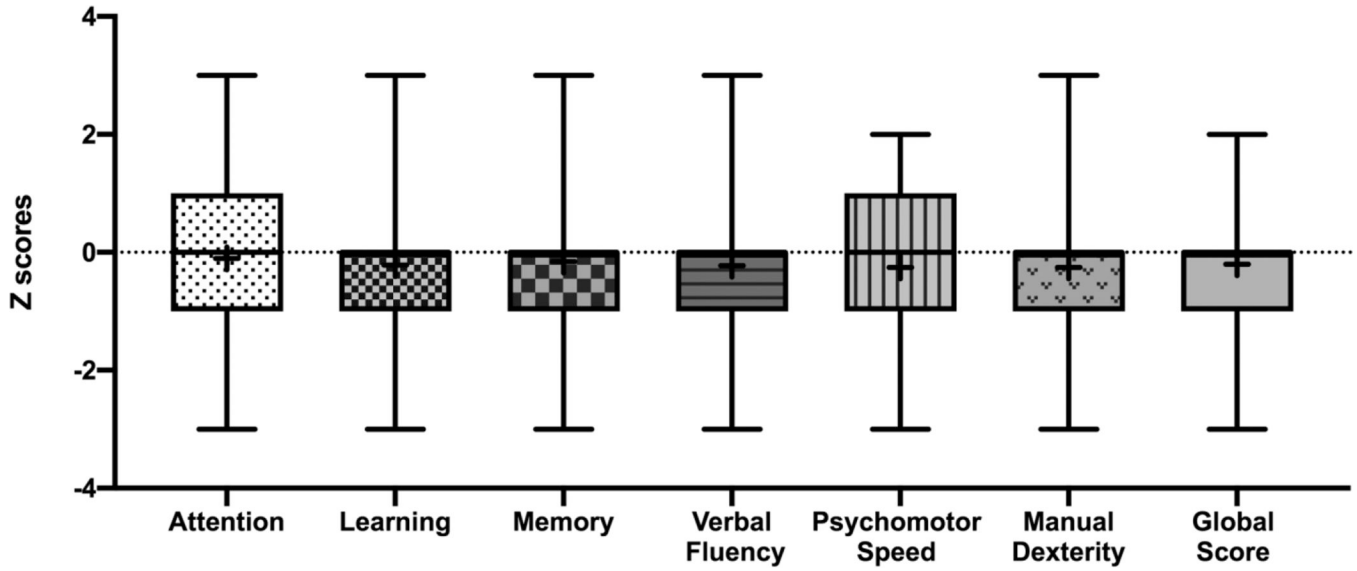

Figure 1. Neuropsychological performance across cognitive measures

Boxplots show z scores for the six cognitive scores and the global score. Plus symbols within each box indicate mean values.

Table 1.
Demographic and clinical characteristics of study participants

Analysis of variance and chi-squared performed for comparisons when appropriate

Characteristics	All HIV+ N (%)	Kenya	Tanzania	Uganda	P-value
N	2472	1503	469	500	
Age, mean (SD; range)	40 (11;18–76)	40 (10;19–76)	40 (12;19–73)	38 (10;18–70)	**0.004**
Sex, female	1452 (59%)	868 (58%)	283 (60%)	301 (60%)	0.463
Education					
• Primary or less	1584 (64%)	895 (60%)	327 (70%)	362 (72%)	**<0.001**
• Secondary or above	887 (36%)	607 (40%)	142 (30%)	138 (28%)	
Literacy	2215 (90%)	1420 (95%)	420 (90%)	375 (75%)	**<0.001**
Employed	871 (35%)	334 (22%)	75 (16%)	462 (92%)	**<0.001**
CES-D score, mean (SD)	10 (9)	10 (7)	10 (11)	10 (10)	0.060
Alcohol consumption	438 (18%)	181 (12%)	140 (30%)	(23%)	**<0.001**
Substance use	71 (3%)	52 (3%)	16 (35%)	3 (1%)	**0.003**
Tuberculosis	82 (3%)	56 (4%)	13 (3%)	13 (3%)	0.364
Syphilis *	112 (5%)	69 (5%)	27 (8%)	16 (3%)	**0.012**
Hepatitis C *	28 (1%)	18 (1%)	0	10 (2%)	**<0.001**
On cART	1689 (68%)	1181 (79%)	313 (67%)	195 (39%)	**<0.001**
cART regimens					
• NRTI/NNRTI	1584 (94%)	1106 (70%)	287 (18%)	191 (12%)	**0.018**
• NRTI/PI	100 (6%)	76 (76%)	20 (20%)	4 (4%)	
• Others	5 (0.3%)	2 (40%)	3 (60%)	0	
Years on cART, mean (SD) *	4 (3)	4 (3)	4 (4)	3 (2)	**<0.001**
Years of HIV infection *	4 (4)	4 (4)	4 (4)	3 (4)	**<0.001**
Undetectable viral load *					
• < 200 copies/ml	1363 (56%)	999 (68%)	190 (42%)	174 (35%)	**<0.001**
• < 1000 copies/ml	1501 (62%)	1.077 (73%)	235 (52%)	189 (39%)	**<0.001**
Current CD4 count, mean (SD) *	424 (264)	440 (262)	359 (255)	436 (270)	**<0.001**
Nadir CD4 count, mean (SD) *	204 (221)	207 (205)	127 (176)	265 (278)	**<0.001**
Log10 plasma HIV RNA, mean (SD) *	2 (2)	2 (2)	3 (2)	3 (2)	**<0.001**
WHO stage					
• Stage 1	610 (25%)	339 (23%)	118 (25%)	153 (31%)	**<0.001**
• Stage 2	784 (32%)	515 (34%)	115 (25%)	154 (31%)	
• Stage 3	915 (37%)	567 (38%)	179 (38%)	169 (34%)	
• Stage 4	163 (7%)	82 (5%)	57 (12%)	24 (5%)	
Composite global score, mean (SD)	−0.2 (0.6)	−0.2 (0.6)	−0.4 (0.7)	−0.1 (0.5)	**<0.001**
Cognitive impairment	939 (38%)	553 (37%)	242 (52%)	144 (29%)	**<0.001**

Abbreviations: CES-D: Center for Epidemiological Studies Depression Scale; cART: combination antiretroviral therapy; WHO: World Health Organization.

*Observations with missing values: n=144 for syphilis; n=117 for hepatitis C; n=30 for current CD4 cell count; n=2 for nadir CD4 cell count; n=47 for log10 and undetectable HIV RNA; n=22 for years of HIV infection and n=774 for years on cART.

Note: bold p-value denote statistical significance at the $p<0.05$.

Table 2.

Results of the logistic regression models predicting cognitive impairment

	Univariable Analysis		Multivariable Analysis	
	Odds ratio* [95% CI]	**P-value**	**Odds ratio* [95% CI]**	**P-value**
Age	1.00 [1.00, 1.01]	0.113	1.00 [1.00, 1.01]	0.260
Literacy	0.37 [0.28, 0.48]	<0.001	0.31 [0.23, 0.41]	<0.001
Female sex	1.19 [1.01, 1.41]	0.039	1.17 [0.96, 1.40]	0.102
Country				
• *Kenya*	1.44 [1.15, 1.79]	0.001	2.00 [1.55, 2.58]	<0.001
• *Tanzania*	2.64 [2.02, 3.44]	<0.001	3.21 [2.39, 4.31]	<0.001
CES-D score	1.01 [1.00, 1.02]	0.060	1.01 [1.00, 1.02]	0.200
Duration of HIV infection	0.99 [0.97, 1.02]	0.566		
WHO stage				
• *Stage 2*	0.97 [0.78, 1.21]	0.818	0.96 [0.76, 1.21]	0.721
• *Stage 3*	1.01 [0.82, 1.25]	0.905	0.99 [0.79, 1.26]	0.963
• *Stage 4*	1.62 [1.14, 2.29]	0.007	1.47 [1.01, 2.14]	0.046
Current CD4 cell count	1.00 [1.00, 1.00]	0.068	1.00 [1.00, 1.00]	0.405
Nadir CD4 cell count	1.00 [1.00, 1.00]	0.035	1.00 [1.00, 1.00]	0.980
Being on cART	0.98 [0.82, 1.17]	0.834		
Duration of cART	1.01 [0.98, 1.04]	0.568		
Log10 HIV RNA	1.03 [0.99, 1.07]	0.111	1.04 [0.99, 1.09]	0.101
Plasma HIV RNA <200 copies/ml	1.15 [0.97, 1.36]	0.100		

Abbreviations: CI: Confidence Intervals; CES-D: Center for Epidemiological Studies Depression Scale; WHO: World Health Organization.

*Unstandardized effect.

Note: all factors with p-value <0.20 in univariable analyses were included into the multivariable model except for undetectable viral load (i.e., plasma HIV RNA <200 copies/ml) that was omitted due to collinearity with plasma HIV RNA.

Table 3.

Results of the linear regression models predicting global neuropsychological score

	Univariable Analysis		Multivariable Analysis	
	Coeff* [95% CI]	**P-value**	**Coeff* [95% CI]**	**P-value**
Age	−0.00 [−0.01, −0.00]	0.006	−0.00 [−0.00, 0.00]	0.440
Literacy	0.32 [0.24, 0.40]	<0.001	0.39 [0.31, 0.47]	<0.001
Female sex	0.01 [−0.05, 0.05]	0.838		
Country				
• *Kenya*	−0.16 [−0.22, −0.09]	<0.001	−0.23 [−0.29, −0.16]	<0.001
• *Tanzania*	−0.34 [−0.41, −0.26]	<0.001	−0.36 [−0.44, −0.28]	<0.001
CES-D score	−0.00 [−0.01, −0.00]	0.036	−0.00 [−0.00, 0.00]	0.097
Duration of HIV infection	−0.00 [−0.01, 0.01]	0.948		
WHO stage				
• *Stage 2*	−0.01 [−0.07, 0.06]	0.825	0.01 [−0.06, 0.08]	0.745
• *Stage 3*	−0.09 [−0.15, −0.03]	0.006	−0.06 [−0.13, 0.00]	0.066
• *Stage 4*	−0.21 [−0.32, −0.10]	<0.001	−0.15 [−0.26, −0.04]	0.009
Current CD4 cell count	0.00 [0.00, 0.00]	<0.001	0.00 [0.00, 0.00]	0.005
Nadir CD4 cell count	0.00 [0.00, 0.00]	<0.001	0.00 [−0.00, 0.00]	0.836
Being on cART	−0.05 [−0.10, 0.00]	0.062	0.00 [−0.06, 0.06]	0.946
Duration of cART	0.00 [−0.01, 0.01]	0.539		
Log10 HIV RNA	−0.00 [−0.02, 0.01]	0.588		
Plasma HIV RNA <200 copies/ml	−0.01 [−0.06, 0.04]	0.773		

Abbreviations: CI: Confidence Intervals; CES-D: Center for Epidemiological Studies Depression Scale; WHO: World Health Organization.

*Unstandardized effect.

Note: all factors with p-value <0.20 in univariable analyses were included into the multivariable model.