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Effect of HIV Subtype and Antiretroviral therapy on HIV-associated neurocognitive disorder (HAND) stage in Rakai, Uganda

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Abstract

Background—Combination antiretroviral therapy (ART) improves HIV-associated neurocognitive disorder (HAND) stage in the US where subtype B predominates, but the effect of ART and subtype on HAND stage in individuals in Uganda with subtypes D and A is largely unknown.

Setting—A community-based cohort of participants residing in Rakai, Uganda.

Methods—399 initially ART-naive HIV-seropositive (HIV+) individuals were followed over two years. Neurological, neuropsychological test and functional assessments were used to determine HAND stage. Frequency and predictors of HAND and HIV-associated dementia (HAD) were assessed at baseline and at follow-up after ART initiation in 312 HIV+ individuals. HIV subtype was determined from gag and env sequences.

Results—At two year follow-up, HAD frequency among HIV+ individuals on ART (n=312) decreased from 13% to 5% ($p<0.001$), but the overall frequency of HAND remained unchanged (56% to 51%). Subtype D was associated with higher rates of impaired cognition (global deficit score ≥ 0.5) compared to HIV+ individuals with subtype A (55% vs. 24%) ($p= 0.008$). Factors associated with HAD at baseline were older age, depression and plasma HIV viral load > 100,000 copies/mL. At follow-up, age and depression remained significantly associated with HAD.

Conclusion—HIV+ individuals on ART in rural Uganda had a significant decrease in the frequency of HAD, but HAND persists after two years on ART. The current guideline of immediate ART initiation after HIV diagnosis is likely to greatly reduce HAD in Sub-Saharan

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Africa. Further studies of the effect of HIV subtype and neurocognitive performance are warranted.

Keywords

HIV; dementia; cognitive impairment; global health

INTRODUCTION

HIV-associated neurocognitive disorder (HAND) represents a spectrum of neurocognitive impairment ranging from asymptomatic neurocognitive impairment (ANI) to minor neurocognitive disorder (MND) to HIV-associated dementia (HAD). HAND remains prevalent even in patients treated with effective antiretroviral therapy (ART) (1). Although half of the global HIV-infected (HIV+) population resides in Sub-Saharan Africa (SSA), most studies of HAND have been conducted in Western settings. However, several factors may differentially impact HAND in SSA compared to Western countries. HIV subtype A and D predominate in Uganda, whereas HIV subtype B is prevalent in the United States (US), and this difference may affect pathogenesis (2). Furthermore, research in SSA has mainly focused on urban centers, even though two-thirds of the SSA population is rural (in Uganda, this proportion is 84%), where there is less access to health care resources.

ART has improved cognition in HIV+ individuals in the US (3) and in urban Uganda (4), but the impact of ART on HAND stage has not been assessed in rural SSA. Furthermore, one urban study suggested that HIV subtype D was associated with higher rates of HAD than subtype A in advanced immunosuppression, but not in a population with less immunosuppression (5, 6).

The goals of this study were to evaluate: 1) the frequency of each HAND stage and factors associated with HAND among initially ART-naïve HIV+ individuals and at a visit two years after baseline after ART initiation in rural Uganda; 2) the impact of HIV subtype (D versus A) on the development of HAND and HAD among individuals with moderate and severe immunosuppression. Our hypotheses were that HIV+ individuals would have higher rates of cognitive impairment compared to HIV-seronegative (HIV-neg) individuals, and that HIV subtype D would be associated with an increased risk of HAD. This study represents the largest evaluation of the impact of HIV subtype and ART on HAND stage among HIV+ individuals in rural SSA.

METHODS

Study Participants.

Participants were drawn from local clinics and the Rakai Community Cohort Study, a cohort of participants residing in 40 communities in Rakai District, representative of rural Uganda. Enrollment occurred between July, 2013 and July, 2015. Eligible participants were ≥ 20 years old and either: (1) HIV-seropositive (HIV+) ART-naïve adults with advanced immunosuppression (CD4 ≤ 200 cells/μL); (2) HIV+ ART-naïve adults with moderate immunosuppression (CD4 350–500 cells/μL); and (3) HIV-neg adults age-, sex-, and

community-matched to the HIV+ participants. Exclusion criteria included severe systemic illness, inability to provide informed consent, physical disability preventing travel to the clinic, and plans to leave Rakai District.

Study Procedures.

Each participant completed a sociodemographic and behavioral interview, depression screen (Center for Epidemiologic Studies Depression Scale (CES-D) (7), functional status assessments, and neuropsychological testing. A Ugandan medical officer trained for evaluation of neurological complications by two US neurologists (N.S, D.S.) performed a neuromedical evaluation including assessment of extrapyramidal signs, gait, strength, reflexes, and neuropathy signs (8). HIV+ participants also underwent CD4 count and plasma viral load, comprehensive metabolic panels, complete blood counts, and syphilis assays. HIV+ participants were also offered an optional lumbar puncture for cerebrospinal fluid (CSF) HIV viral load at each visit.

Standard protocol approvals, and patient consents, and access to HIV care and ART.

Written informed consent for the study was approved by the Western Institutional Review Board, the Research and Ethics Committee of the Uganda Virus Research Institute, and the Uganda National Council for Science and Technology and complied with the Helsinki Declaration as revised in 2000. All participants were offered free ART, based on Ugandan Ministry of Health ART initiation criteria between 2013 and 2015.

Neuropsychological Test Battery: The battery has been described previously (9). Neuropsychometricians were trained and supervised by Dr. Robertson, with ongoing quality assurance and site visits. Briefly, neuropsychological instruments administered to both HIV+ and HIV- patients were chosen for their cultural independence as well as their sensitivity for detecting HAD (10). The tests include assessments in the domains of Gross motor functioning (Timed Gait (11)), Fine motor functioning (Grooved pegboard, Finger tapping), Executive functioning (Color Trails 2), Speed of Processing (Color Trails 1, Symbol Digit Modalities Test), Verbal Learning/Memory (WHO-UCLA Auditory Verbal Learning Test), and Attention/Working Memory (Digit Span, Forward and Backward). The WHO-UCLA Auditory Verbal Learning Test is similar to the Rey Auditory Verbal Learning Test (12, 13). The tests measure both verbal learning and memory through a scored immediate and delayed recall of a 15 word list, with words used in the WHO-UCLA test chosen to be universally recognized objects independent of culture and language (14). Color Trails 1 and 2 test an individual's speed of processing and are designed as cross-cultural variants of the Trail Making tests (12, 14–16).

All tests had their content translated into Luganda, the predominant local language. (All participants were fluent in Luganda.) Z scores for each neuropsychological test were established by comparison with data from the 400 HIV- controls.

Functional assessments.

Functional assessment included the Bolton Functional assessment developed in Rakai, Uganda (17), the Patient's Assessment of Own Functioning Inventory (PAOFI) (18), the

Instrumental activities of Daily Living (IADL) assessment (19), and the Karnofsky functional status score (20). Functional impairment was defined as Karnofsky score < 80, Bolton score > 0 on any question, PAOFI score ≤ 4 on the functional status component or an IADL current performance abnormality compared to previous best performance.

Assessment of HAND stage and global cognitive impairment.

HAND stage was determined using the Frascati criteria (21). Specifically, ANI was defined as ≥ 1 SD abnormality (compared to the age and education stratified HIV-neg norms) on at least two unrelated neuropsychological tests and the absence of functional complaints. MND was defined as ≥ 1 SD abnormality on at least two unrelated neuropsychological tests and functional complaints. HAD was defined as ≥ 2 SD abnormality on at least 2 unrelated neuropsychological tests and functional impairment. If a subject had ≥ 14 SD abnormality total on the neuropsychological test battery, then a rating of HAD was assessed even in the absence of functional impairment. The global deficit scale (GDS) (22) was used to define a global cognitive score, dichotomized as impaired (GDS ≥ 0.5) or unimpaired (GDS < 0.5).

HIV subtyping.

RNA extraction from serum was automated on QIAsymphony SP workstations with the QIAsymphony DSP Virus/ Pathogen Kit (Cat. No. 937036, 937055; Qiagen, Hilden, Germany), followed by one-step reverse transcription polymerase chain reaction (RT-PCR) as described previously (23). Amplification was assessed through gel electrophoresis on a fraction of samples, and samples were shipped to the Wellcome Trust Sanger Institute, Hinxton, United Kingdom. Next-generation sequencing was performed on Illumina MiSeq and HiSeq instruments in the DNA pipelines core facility (23). Only gene sequences with >75% of the genome determined were included in the analyses. Sequencing failure was higher in samples with lower viral loads and in the env and pol genes (24). HIV-1 subtyping was performed using the COMET-HIV-1 subtyping tool (25).

Data Analysis.

Demographic characteristics were compared between groups using t-tests for continuous variables, chi square tests for categorical variables with ≥10 participants in each category, and Fisher's exact tests for categorical variables with <10 participants per category. Demographic characteristics of ART experienced participants followed up at two years were compared to those not on ART. Other analyses of follow-up visits excluded ART-naïve participants. HAND stage frequencies were compared between groups using ANOVA analyses. Risk factors for HAD were initially assessed using univariate logistic regression analyses. All factors with p≤0.20 in univariate analyses were then evaluated in a multivariate logistic regression model. CSF HIV viral load was not included in the multivariate analysis because the sample size was smaller (n=198), and its inclusion would have resulted in a loss of power. Subtype results were analyzed in several ways. First, participants with subtype A and D in the gag gene were compared. Next, participants with subtype A and D in both the gag and env genes were compared. Also, participants with subtype A and D in the gag, env and pol regions were compared. In sensitivity analyses, we also compared any A vs any D irrespective of gene loci. Statistical analyses were completed using Stata/SE 14.2 (College Station, Texas).

RESULTS

Demographics

The demographic characteristics for the 399 HIV+ individuals and 400 HIV- individuals are shown in Table 1. Compared to HIV-neg participants, HIV+ individuals had less education [mean(SD) education = 5(3) years vs 6(4) years] (p=0.03), lower body mass index (BMI) [mean(SD) = 21.8(3.5) vs 23.2(3.9), p < 0.001)], higher rates of tobacco (16% vs 11%, p=0.03), narcotics use (3% vs 0.8%, p=0.02), and hypertension (1% vs. 3%) (p=0.04).

Follow-up of HIV+ subjects

333 of the 399 (83.3%) of baseline HIV+ individuals were seen at the two year follow-up visit. There were 18 deaths (4%), and 49 subjects (12%) were lost to follow up. Of those followed up, 94% (n=312) had initiated ART. The most common regimen consisted of tenofovir, emtricitabine, and efavirenz (78%). Compared to all HIV+ participants at baseline, participants at follow-up had higher CD4 counts, higher BMIs, and lower rates of depression at baseline (Table 1). There were no significant differences between participants on ART and those who were ART naïve at follow-up, other than CD4 count.

HAND stage and global cognitive score at baseline

At baseline, HIV+ individuals had a higher rate of cognitive impairment (HAND = 59%) and a higher GDS [Median [IQR] = 0.33 (0.08,0.67)] than HIV-neg individuals [cognitive impairment rate = 44%, [GDS Median [IQR] = 0.17 (0.0,0.42)] (p<0.001). In addition, HIV + individuals had a higher rate of dementia (15%) compared to HIV-neg individuals (4%, p<0.001) but not ANI or MND based on the HAND criteria, (see Table 2).

HAND stage and global cognitive score stratified by subtype

At baseline, subtyping results were available for 310 subjects in the gag region, 147 subjects in the env region, and 162 subjects in the pol region. Of these, 135 (43.5%) subjects had sequence data available for both the gag and env genes, and 67 (21.6%) had sequence data for all three genes. A-D recombinants were the most common subtype based on gag-env results (30%). Subtype D was slightly more common than subtype A in the gag-env analysis (D: n=35 (26%); A: n=29 (21%)). Subtype D was also more common than subtype A among patients with advanced immunosuppression, compared to those with moderate immunosuppression, in the gag-env analysis (D vs A in advanced immunosuppression: 68% vs 42%, p=0.04).

Subtype D was associated with a worse global cognitive score with 55% of HIV+ individuals with subtype D having a GDS score ≥ 0.5 compared to 24% of HIV+ individuals with subtype A (p=0.008) (Table 3). This result was more pronounced in the moderate immunosuppression group where 64% of HIV+ individuals with subtype D had an abnormal GDS compared to 25% of HIV+ individuals with subtype A (p=0.04).

There was no difference in the presence of HAND comparing subtype results from the gag gene alone, the gag-env genes, or the gag-env-pol genes (Table 3). However, more participants with subtype D had symptomatic HAND (*i.e.,* MND or HAD) compared to

participants with subtype A (gag-env: 63% vs 39%, p=0.06; gag-env-pol: 77% vs 45%, p=0.11), although this was not statistically significant. The same trend was seen when results were stratified by immune status and was more pronounced in the moderate immunosuppression group, though none of these analyses reached significance. In the moderate immunosuppression group, there was a trend for more participants with subtype D to have symptomatic HAND (*i.e.,* MND or HAD) compared to participants with subtype A (gag-env: 72% vs 39% (n= 32), p=0.09), whereas in the advanced immunosuppression group, there was less of a difference (gag-env: 57% vs 40% (n= 31), p=0.46).

Associations between patient characteristics and HIV-associated dementia at baseline

Associations between patient characteristics and HAD among HIV+ individuals at baseline are shown in Table 4. In univariate analyses, HIV+ participants had increased odds of HAD with each additional year of age (odds ratio (OR) 1.03, p=0.049), CD4 cell count < 200 cells/μL (OR 1.89, p=0.03), depression symptoms (OR 3.49, p<0.001), higher aspartate aminotransferase (AST) levels (1.01, p=0.03), and a plasma viral load > 100,000 copies/mL (OR 2.32, p=0.003). Alcohol use in the past month was associated with decreased odds of HAD (OR 0.52, p=0.02). However, in multivariate analyses, only age (OR 1.04, p=0.04), depression symptoms (OR 2.77, p=0.001), and plasma viral load >100,000 copies/μL (OR 2.26, p=0.02) were significantly associated with increased HAD risk. In the subset of participants who consented to and underwent lumbar puncture (n=198), CSF viral load > 100,000 copies/mL was also associated with risk of HAD (OR 3.23, p=0.049) in univariate analyses.

HAND stage and global cognitive scores at follow-up

HAND stage frequencies for the 312 HIV+ individuals on ART at the two-year follow-up are compared to their pre-ART baseline in Table 2. The rate of HAD among these ART experienced participants decreased from 13% at baseline to 5% at the two year follow-up (p<0.001). There were 7 cases of incident HAD at follow up. The overall rate of HAND did not change (56% at baseline to 51% at the two-year follow-up. The rate of ANI increased from 7% to 13%, while the prevalence of MND remained relatively unchanged (35% to 33%) compared to baseline. Among HIV+ individuals initiating ART, HAND stage improved in 32%, remained unchanged in 51%, and worsened in 17%. The GDS among HIV+ individuals seen at both baseline and follow-up decreased from GDS median (IQR) = 0.25 (0.08,0.65) to GDS median (IQR) = 0.24(0.08,0.5), (p= 0.001).

HAND stage at follow-up stratified by subtype

There was no difference in HAND stage, GDS, or the proportion of participants with improved or worsened HAND stage, when stratified by subtype at the follow-up visit (data not shown). However, sample sizes were small.

Associations between patient characteristics and HIV-associated dementia at follow-up

Among HIV+ participants on ART at two-year follow-up, patient characteristics associated with HAD are described in Table 5. In univariate analyses, increased odds of HAD were associated with depression symptoms (OR 9.75, p < 0.001), CD4 cell count < 200 cells/μL

(OR 3.70, p=0.02), plasma viral load > 100,000 copies/mL, and lower fasting glucose (OR 0.95, p=0.04). However, in the multivariate analyses, only increasing years of age (OR 1.10, p=0.01) and depression symptoms (OR 14.6, p<0.001) were significant. Among the participants who underwent lumbar puncture, a CSF viral load > 10,000 copies/mL was associated with HAD [17% (n = 1 of 6) of participants with CSF viral load > 10,000 copies/mL met criteria, whereas 3% (n = 3 of 90) of participants with CSF viral load < 10,000 copies/mL had HAD, (p =0.04)].

DISCUSSION

Our results suggest that HIV+ individuals in rural Uganda show significant improvement in HAD after two years of ART compared to their pre-ART status. There was no decrease in the frequency of MND, and ANI frequency increased, likely due to HIV+ individuals with HAD at baseline who changed to ANI and MND at follow-up.

Even though HAND stage improved in 24% of HIV+ individuals, HAND stage was unchanged in 57% of individuals who were more likely to have ANI and MND. This suggests that persistent cognitive impairment related to HIV may have occurred prior to initiation of ART *(i.e.,* legacy effect) or that confounding factors may have contributed to the cognitive impairment in individuals with milder HAND stage. Rural Ugandans are largely free of the confounding factors for cognitive impairment common in the US such as use of narcotics, cocaine and methamphetamine, hepatitis C co-infection, and cerebrovascular disease risk factors, *e.g.,* hypertension, diabetes (26, 27). Lower educational levels in rural Uganda could account for increased neurocognitive impairment, but the use of local comparison participants for normative score derivation addresses this issue.

Older age and depression were independently associated with HAD at both baseline and follow-up. Plasma viral load was independently associated with HAD at baseline but was not significant in multivariate analyses at follow-up following ART initiation. These findings are in keeping with other studies (28–32) that showed HAD risk increased substantially with increasing age and suggest that HAD will remain a global problem as HIV+ populations survive to older ages worldwide. The increased risk of HAD associated with depressive symptoms has been previously reported (33) and may be due to higher plasma immune activation (34). CSF HIV viral load was associated with HAD risk at both baseline and follow-up suggesting that ongoing central nervous system viral replication may contribute to HAND pathogenesis, and that the brain may constitute a reservoir for HIV which is an important target in future viral eradication strategies (1). Higher levels of AST were significantly associated with baseline HAD risk in univariate but not multivariate analyses. Liver function has primarily been evaluated with HAND in the context of hepatitis C co-infection, but hepatitis C is uncommon in Rakai (26).

Subtype D was associated with worse global cognition (GDS ≥ 0.5) compared to subtype A. However, viral clade was not associated with HAND or HAD, although there was a trend toward higher rates of symptomatic HAND among those with subtype D infection compared to subtype A. These results contrast prior work in Kampala, Uganda where subtype D infection was associated with higher rates of HAD amongst patients with advanced

immunosuppression (5) and is somewhat similar to a follow up study in which patients with less severe immunosuppression did not exhibit higher rates of HAD with subtype D compared to subtype A infection (6). The finding that the trend was observed in the subgroup of participants with moderate immunosuppression suggests that the difference is not due to higher rates of more advanced disease in subtype D infection alone. No difference in HAND stage by subtype was observed at the follow-up visit when participants were on ART. Of note, in a prior study among a pediatric HIV+ cohort in Uganda, subtype A infection was associated with higher rates of neurocognitive impairment than subtype D infection before participants initiated ART, but not after ART initiation (35, 36). Taken together, these results suggest that any additional risk conferred by particular HIV subtypes may be negated with initiation of ART.

This report is the first study to describe improvement in HIV+ individuals with a well-defined HAND stage, detailed neuropsychological testing and functional assessment in rural SSA. A further strength of this study are the data on 400 HIV-neg individuals, age, education, and gender matched to the HIV+ participants, which provide one of the largest databases of normative data in rural SSA. Another strength is the use of a detailed series of functional assessments necessary for accurate HAND staging.

The study has several limitations. While HIV+ participants who were dead or lost to follow-up were more likely to have HAD than those who returned for their follow-up visit, the rate of HAD still decreased amongst those with HAD at baseline who returned for follow-up. Also, Luganda is generally spoken widely in the Rakai district region. However, other disparities related to ethnicity could have impacted neuropsychological test performance. Neuroimaging also was not available to rule out a history of brain opportunistic infections or other prior structural lesions such as stroke. However, in evaluating neurocognitive change over time, HIV+ individuals were compared to their baseline performance so that improved performance was likely due to the effects of ART on HIV-associated cognitive impairment rather than confounding conditions for cognitive impairment.

We found an association between HIV subtype and overall global cognition but did not find a significant association between HIV subtype and HAND. Our sample sizes for these analyses were smaller than anticipated due to higher rates of recombinant genotypes. In our prior studies in Kampala, Uganda, (5, 6) 70%−80% of participants were identified as either having subtype A or D infection based on gag and env gene subtyping. In this study, only 46% of participants in the gag-env analysis and 40% in the gag-env-pol analysis had subtype A or D infection. This may be due to increasingly sensitive genotyping methods, which are more likely to identify recombinants than prior methods. More sensitive analytic methods to determine whether specific epitopes of particular subtypes are associated with higher rates of symptomatic HAND or HAD, even in individuals with recombinant subtype infections, may also be useful.

Since low CD4 count and higher plasma viral loads were risk factors for HAND at baseline, our results suggest that the current WHO guideline to initiate ART immediately upon HIV diagnosis will reduce HAD prevalence in SSA. Higher CSF viral loads were a risk factor for HAD at both the baseline and follow-up visits highlighting the need for future studies to

examine the roles of CSF escape and potential CNS compartmentalization in HAND and its response to treatment. A future study with larger sample size may be useful to definitively answer the question of whether subtype D is associated with higher rates of more severe HAND stages. Further studies are also needed to evaluate HAND and the long-term response to ART as the HIV+ population ages and develops increased rates of age-associated conditions leading to cognitive impairment such as vascular dementia or Alzheimer's disease.

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Table 1.

Demographic characteristics and global cognitive scores of baseline and follow-up cohorts.

	BASELINE COHORT			HIV+ Only: BASELINE VS FOLLOW-UP			HIV+ only: FOLLOW-UP		
	HIV+ (n=399)	**HIV- (n=400)**	**p**	**Baseline Cohort (n=399)**	**Follow-Up Cohort (n=333)**	**p**	**On ART (n=312)**	**Not on ART (n=21)**	**p**
Male Sex [n (%)]	211 (53%)	210 (52%)	0.91	211 (53%)	170 (51%)	0.62	158 (51%)	12 (57%)	0.56
Age (years) [mean (SD)]	35 (8)	35 (8)	0.9	**35 (8)**	**37 (9)**	**0.002**	37 (8)	36 (10)	0.46
Right Handed [n (%)]	370 (93%)	364 (91%)	0.37	370 (93%)	308 (92%)	0.32	288 (92%)	20 (95%)	0.62
Education (years) [mean (SD)]	**5 (3)**	**6 (4)**	**0.03**	5 (3)	6 (3)	0.22	6 (3)	6 (4)	1
Currently Married [n (%)]	**250 (63%)**	**315 (79%)**	**< 0.001**	250 (63%)	213 (64%)	0.72	198 (63%)	15 (71%)	0.46
CD4 count [mean (SD)]	----	----	----	**257 (171)**	**403 (198)**	**< 0.001**	**412 (195)**	**282 (200)**	**0.004**
BMI [mean (SD)]	**21.8 (3.5)**	**23.2 (3.9)**	**< 0.001**	**21.8 (3.5)**	**22.8 (3.5)**	**< 0.001**	23 (4)	22 (2)	0.39
Underweight [n (%)]	**51 (13%)**	**29 (7%)**	**0.009**	**51 (13%)**	**17 (5%)**	**< 0.001**	16 (5%)	1 (5%)	1
Overweight/Obese [n (%)]	**52 (13%)**	**98 (24%)**	**< 0.001**	**52 (13%)**	**65 (20%)**	**0.02**	62 (20%)	3 (14%)	0.78
Depression (CESD ≥ 16) [n (%)]	**96 (24%)**	**44 (11%)**	**< 0.001**	**96 (24%)**	**28 (8%)**	**< 0.001**	25 (8%)	3 (14%)	0.4
Diabetes [n (%)]	0 (0%)	3 (0.75%)	0.08	0 (0%)	0 (0%)	---	0 (0%)	0 (0%)	---
Hypertension [n (%)]	**4 (1%)**	**12 (3%)**	**0.04**	4 (1%)	1 (0.3%)	0.25	1 (0.3%)	0 (0%)	1
TB [n (%)]	0 (0%)	0 (0%)	1	**0 (0%)**	**4 (1%)**	**0.03**	4 (1%)	0 (0%)	1
Tobacco use [n (%)]	**63 (16%)**	**42 (11%)**	**0.03**	63 (16%)	38 (11%)	0.09	37 (12%)	1 (5%)	0.49
Narcotics use [n (%)]	**12 (3%)**	**3 (0.75%)**	**0.02**	**12 (3%)**	**3 (1%)**	**0.04**	3 (1%)	0 (0%)	1
Alcohol use in past month [n (%)]	194 (49%)	186 (46%)	0.55	194 (49%)	144 (43%)	0.15	135 (43%)	9 (43%)	1
Global Deficit Score (GDS) [median (IQR)]	**0.33 (0.08, 0.67)**	**0.17(0,.0, 0.42)**	**<0.001**	0.25 (0.08, 0.5)	0.17 (0, 0.45)	0.44	**0.25 (0.08,0.63)**	**0.24 (0.08, 0.5)**	**<0.001**

Table 2.

Stage of neurocognitive impairment (1) at baseline by HIV status and (2) at baseline and follow-up in HIV+ participants who initiated ART prior to their two-year follow-up visit.

	By HIV Status			HIV+ only: Pre- and Post-ART		
	HIV+ (n=399)	**HIV- (n=400)**	**p**	**Baseline (n=312)**	**Follow-Up (n=312)**	**p**
Normal	164 (41%)	225 (56%)	**< 0.001**	130 (44%)	141 (49%)	**< 0.001**
ANI	24 (6%)	22 (6%)		20 (7%)	39 (13%)	
MND	152 (38%)	135 (34%)		103 (35%)	97 (33%)	
Dementia	**60 (15%)**	**18 (4%)**		**39 (13%)**	**15 (5%)**	

Abbreviations:

ANI: asymptomatic neurocognitive impairment; MND: mild neurocognitive disorder

Table 3.

Baseline Global Deficit Score (GDS) and HAND Stage by HIV Subtype A vs D.

Baseline Global Deficit Score HAND stage compared between participants with (1) Gag-Env subtype A and D and (2) Gag-Env-Pol subtype A and D.

GAG-ENV ANALYSIS				GAG-ENV-POL ANALYSIS			
	A (n=34)	**D (n=38)**	**p**		**A (n=12)**	**D (n=3)**	**p**
GDS Normal (<0.5)	**26 (76%)**	**17 (45%)**	**0.008**		8 (67%)	1 (33%)	0.52
GDS Abnormal (≥0.5)	**8 (24%)**	**21 (55%)**			4 (33%)	2 (67%)	
Baseline HAND Stage	(n=28)	(n=35)		Baseline HAND Stage	(n=11)	(n=13)	
Normal	14 (50%)	10 (29%)	0.27	Normal	5 (45%)	3 (23%)	0.4
ANI	3 (11%)	3 (9%)		ANI	1 (9%)	0 (0%)	
MND	8 (29%)	18 (51%)		MND	4 (36%)	7 (54%)	
HAD	3 (11%)	4 (11%)		HAD	1 (9%)	3 (23%)	
Symptomatic vs. Asymptomatic HAND				Symptomatic vs. Asymptomatic HAND			
Normal/ANI	17 (61%)	13 (37%)	0.06	Normal/ANI	6 (55%)	3 (23%)	0.11
MND/HAD	11 (39%)	22 (63%)		MND/HAD	5 (45%)	10 (77%)	

Abbreviations: Global Deficit Score (GDS); ANI: asymptomatic neurocognitive impairment; MND: mild neurocognitive disorder; HAD: HIV-associated dementia; HAND: HIV-associated neurocognitive disorder

Table 4.

Associations between patient characteristics at baseline and HIV-Associated Dementia (HAD).

Univariate and multivariate logistic regression analyses of predictors of HAD among HIV+ participants at their baseline visit.

	UNIVARIATE ANALYSES		MULTIVARIATE ANALYSIS	
	OR (95% CI)	**p**	**OR (95% CI)**	**p**
Age (years)	**1.03 (1.00, 1.06)**	**0.049**	**1.04 (1.00, 1.07)**	**0.04**
Female Sex	1.45 (0.84, 2.52)	0.19	1.66 (0.87, 3.17)	0.12
Education (years)	0.97 (0.90, 1.06)	0.55	---	---
Alcohol use in the past month	**0.52 (0.29, 0.92)**	**0.02**	0.61 (0.32, 1.16)	0.13
Depression (CES-D Score ≥ 16)	**3.49 (1.97, 6.18)**	**< 0.001**	**2.77 (1.52, 5.06)**	**0.001**
CD4 Count < 200 cells/μL	**1.89 (1.07, 3.33)**	**0.03**	1.29 (0.62, 2.67)	0.49
Plasma HIV viral load >100,000 copies/mL	**2.32 (1.33, 4.04)**	**0.003**	**2.26 (1.16, 4.42)**	**0.02**
CSF HIV viral load > 100,000 copies/mL *	**3.23 (1.00, 10.4)**	**0.049**	---	---
Fasting glucose (mg/dL)	1.00 (0.98, 1.02)	0.79	---	---
AST (units/L)	**1.01 (1.00, 1.02)**	**0.03**	1.01 (1.00, 1.02)	0.11
ALT (units/L)	1.01 (1.00, 1.03)	0.1	1.00 (0.99, 1.02)	0.59
History of syphilis (TPHA positive)	0.58 (0.22, 1.5)	0.26	---	---

* CSF HIV viral load not included in the multivariate analysis due to small sample size.

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Table 5.

Associations between patient characteristics and HIV-Associated Dementia (HAD) at follow-up.

Univariate and multivariate logistic regression analyses of predictors of HAD among HIV+ participants on ART at their two-year follow-up visit.

	UNIVARIATE ANALYSES		MULTIVARIATE ANALYSES	
	OR (95% CI)	**p**	**OR (95% CI)**	**p**
Age (years)	1.05 (1.00, 1.11)	0.07	**1.10 (1.02, 1.18)**	**0.01**
Female Sex	0.67 (0.23, 1.93)	0.46	---	---
Education (years)	0.97 (0.83, 1.14)	0.75	---	---
Alcohol use in the past month	0.87 (0.30, 2.50)	0.79	---	---
Depression (CES-D Score ≥ 16)	**9.75 (3.14, 30.3)**	**< 0.001**	**14.6 (3.9, 54.3)**	**< 0.001**
CD4 Count < 200 cells/μL	**3.70 (1.20, 11.4)**	**0.02**	2.90 (0.74, 11.5)	0.13
Plasma HIV viral load >100,000 copies/mL	**8.86 (1.57, 50.06)**	**0.01**	3.55 (0.43, 29.1)	0.24
Fasting glucose (mg/dL)	**0.95 (0.91, 1.00)**	**0.04**	0.95 (0.90, 1.00)	0.06
AST (units/L)	1.01 (0.98, 1.03)	0.55	---	---
ALT (units/L)	1.01 (0.98, 1.04)	0.66	---	---
History of syphilis (TPHA positive)	0.26 (0.04, 2.02)	0.2	0.19 (0.02, 1.72)	0.14