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Sex Differences in Neuropsychological Performance as an Effect of Human Immunodeficiency Virus Infection:

A Pilot Study in Zambia, Africa

Knut A. Hestad, PhD[*,†,‡], **J. Anitha Menon, PhD**[§], **Mary Silalukey-Ngoma, MD**[‖], **Donald R. Franklin Jr, BS**[¶], **Mwiya L. Imasiku, PhD**[§], **Kalima Kalima, Med**[#], and **Robert K. Heaton, PhD**[¶]

[*]Department of Psychology, The Norwegian University of Science and Technology, Trondheim, Norway

[†]Department of Psychology, Lillehammer University College, Lillehammer, Norway

[‡]Center for Old Age Psychiatry Research, Innlandet Hospital Trust, Hamar, Norway

[§]Department of Psychology, University of Zambia, Lusaka, Zambia

[‖]Department of Paediatrics and Child Health, University Teaching Hospital, Lusaka, Zambia

[¶]HIV Neurobehavioral Research Center, University of California, San Diego, CA

[#]Department of Education, University of Zambia, Lusaka, Zambia.

Abstract

This study examined whether there are neuropsychological performance differences between human immunodeficiency virus–seropositive participants being followed at a University of Zambia clinic and demographically comparable seronegative controls being tested for infection in the same setting. All participants were administered a standardized neurocognitive test battery that has been found sensitive to HIV-associated Neurocognitive Disorder in the United States and internationally (e.g., in China, India, Romania, and Cameroon). The test battery was found to be applicable to a Zambian population. A clear HIV effect was seen with a medium to large overall effect size (Cohen $d = 0.74$). However, it was only the female seropositive participants who showed this HIV effect. HIV can result in neuropsychological deficits in Zambia, where clade C of the virus dominates. It is suggested that the HIV-infected women are more at risk of developing cognitive deficits than are men in this population, possibly because of sex-related social, financial, and healthcare disadvantages. However, further analyses are required regarding this conclusion because the finding was a result of an unplanned subanalysis.

Keywords

HIV; Zambia; clade C; neuropsychology; sex; post-CART; AIDS

It has been established that the human immunodeficiency virus (HIV) enters the central nervous system early after infection and eventually results in both structural and functional brain changes in about 30% to 50% of the cases (Shaw et al., 1985). Even in their milder

Send reprint requests to Knut A. Hestad, PhD, Center for Old Age Psychiatry Research, Innlandet Hospital Trust, 2312 Ottestad, Norway. Knut.Hestad@svt.ntnu.no. .

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forms, these changes may have significant effects on day-to-day functioning (Antinori et al., 2007). As the individual develops serious immunological decline and/or acquired immunodeficiency syndrome (AIDS)–defining clinical disorders, the risk of neuropsychological impairment becomes greater (Sirois and Hill, 1993). Heaton et al. (1995) demonstrated increased rates of impairment at each successive clinical stage of HIV infection. The most affected cognitive functions were attention, speed of information processing, and learning efficiency. Other abilities such as executive functions, working memory, and verbal fluency were frequently affected as well (Heaton et al., 1995). Today, it is quite clear that HIV-associated dementia and milder cognitive deficits related to HIV infection are two separate entities (Report of a Working Group of the American Academy of Neurology AIDS Task Force, 1991). After the introduction of Combination Antiretroviral Therapy (CART), there has been a decline in HIV dementia from around 20% to 5% (Sacktor, 2002). Nonetheless, there does not seem to be any reduction in milder cognitive impairments occurring in HIV-infected individuals, and, in fact, the prevalence of such disorders may be increasing as HIV-positive people are living longer because of modern antiretroviral therapy (Heaton et al., 2011).

In 2009, an estimated 14.3% of Zambia's 12.9-million population was infected with HIV, and Zambia is seventh among the countries most affected by this epidemic (National AIDS Council, 2010). The country's first reported AIDS diagnosis was in 1984, and this was followed by a rapid rise in estimates of HIV prevalence (Zambian Ministry of Health and Central Board of Health, 2005). Initially, the concentration of HIV and AIDS cases was noticed in urban areas, but it soon became clear that all parts of the country were affected (Central Statistical Office Zambia, 2003).

Neuropsychological studies of HIV-positive groups in sub-Saharan Africa have found inconsistent results. Previous work out of Lusaka, Zambia (Kvalsund et al., 2009) examined HIV-positive participants not on antiretroviral therapy using the Mini-Mental State Examination (Folstein et al., 1975), the HIV dementia scale (HDS) (Power et al., 1995), and Color Trials 1 (CT1; Maj et al., 1993) administered in local languages. This study has found evidence of cognitive impairment in 24 (50%) of the HIV-positive persons compared with none among HIV-negative persons, using 2 SD on the MMSE as a measurement of impairment. Eight of those 24 scored more than 2 SD below comparison means on the HDS and CT1.

Robertson et al. (2007) assessed 110 HIV-positive and 100 HIV-negative adults in Uganda. Of the infected participants, 44.5% had histories of antiviral treatment, and the total HIV-positive group did significantly worse on the neuropsychological (NP) test battery. Clifford et al. (2007) however, found deficits related to HIV only on the Finger Tapping Test. A possible explanation is that the HIV subtype that is most common in Ethiopia (clade C as in Zambia) may be less neurotropic than clades A and D, which dominate in Uganda, and clade B, which is most common in the United States and other Western countries. However, there is evidence of neuropsychological and electroencephalographic abnormalities being associated with clade C infection in India and South Africa, suggesting that individuals infected with clade C may be at risk of developing HIV-associated neurocognitive disorders, similar to individuals infected with other clades (Gupta et al., 2007; Joska et al., 2010; Yepthomi et al., 2006). Finally, using the same comprehensive test battery that was used in the current study, Kanmogne et al. (2010) found a significant HIV effect in a pilot study in Cameroon, where there is a considerable diversity of non–clade B HIV strains circulating.

In the present study, we examined the NP functioning of demographically comparable HIV-positive and HIV-negative individuals in Zambia using a comprehensive test battery that has

been successfully deployed in neuroAIDS research in the United States, Asia, Africa, and South America (Heaton et al., 2008, 2010; Kanmogne et al., 2010).

METHODS

Participants

The participants were recruited from the University of Zambia antiretroviral therapy clinic in consultation with the medical officer. They included 38 individuals who were found to be HIV-positive and 42 who were found to be HIV-negative. Inclusion criteria are a minimum of 8 years of education, age range of 20 to 40 years, no known risk of neurological impairment other than HIV infection, and no history of alcohol or drug abuse. Signed consent was obtained from all participants. All were fluent English speakers and had their schooling in English (the country's official language), although the typical Zambian speaks at least two of the local African languages as well (more than 70 tribal languages or dialects are spoken in the country). The participants were recruited and enrolled in the study on a consecutive basis. One prospective seropositive subject was excluded because of alcohol use a short time before the scheduled testing.

In the past, all HIV-positive Zambians with a CD4 count below 200 or a clinical diagnosis of AIDS were eligible for antiretroviral therapy. Currently, the cutoff for providing antiretroviral therapy is changed to a CD4 count below 350. CD4 count was obtained for all study participants, and plasma HIV viral load was obtained for the HIV-positive participants (limit of detection, 400 copies/ml or less). All participants were screened for malaria, and sexually transmitted infections other than HIV. Because the HIV-positive participants were followed by the clinic, it was possible to examine nadir (lowest ever) CD4 count and clinical diagnosis. A total of 7 of 37 seropositive cases in the present study had a current CD4 count below 200. However, 17 of 37 cases had nadir CD4 count below 200. Eighteen of the seropositive participants had AIDS based on the World Health Organization's (WHO) clinical staging at the time of testing. The 19 participants without the WHO AIDS criteria were typically on CART because of their previous experience of opportunistic infections (mostly bacterial), weight loss, pain in limbs, rash, or recurrent coughing.

The neuropsychological examiner was blinded to the HIV serostatus of the participants.

Measurements

Clinical Assessment—The neuromedical examination included a systematic review of medical and neurological histories, review of any current or past antiretroviral medications and their adverse effects, and a brief medical and neurological examination,

Neurobehavioral Evaluation—All neurobehavioral instruments were adapted from ongoing studies being conducted in the United States and several international sites (China, India, Brazil, Romania, Cameroon), coordinated by the University of California–San Diego HIV Neurobehavioral Research Center (Heaton et al., 2008, 2010; Kanmogne et al., 2010).

The neurocognitive assessment consisted of tests of the following ability domains: verbal fluency, abstraction/executive functions, attention/working memory, speed of information processing, learning, delayed recall, and motor function. The tests are well-known NP instruments and have been widely used in neurobehavioral studies of HIV/AIDS (Gupta et al., 2011; Heaton et al., 2004a, 2008, 2010; Kanmogne et al., 2010; Woods et al., 2004); see Table 2 for a listing of tests.

We also collected information regarding the severity of depressive symptoms using the Beck Depression Inventory–2nd Edition (BDI-II; Beck et al., 1996), a 21-item self-report scale,

with each item having four response options of graded severity. The time frame is the past 2 weeks. Scores of 0 to 13 signify “minimal” depressive symptoms; 14 to 19, mild; 20 to 28, moderate; and 29 to 63, severe symptom severity.

The Patient’s Assessment of Own Functioning Inventory (PAOFI), a self-report of cognitive difficulties experienced in everyday life, and an Instrumental Activities of Daily Living scale (IADL) were also administered (Heaton et al., 2004a).

Data Analysis and Management

Quantitative data were analyzed using SPSS for Windows, 16th version. The test results of all participants were transformed into comparable *Z*-scores based on the results from the HIV-negative group.

Ethical Consideration

Approval was obtained from the Biomedical Research Ethics Committee of the University of Zambia before the commencement of the research. The data from each participant were coded to ensure confidentiality, and identifying details were stored separate from the data.

RESULTS

The demographic characteristics of the participants, CD4 counts (current and nadir), and AIDS status using WHO criteria can be seen in Table 1.

There were no significant differences between groups on sex, age, or education. Overall, the mean current CD4 count of the HIV-positive group was higher than their nadir CD4 ($p = 0.000008$), showing an expected benefit of CART. All participants had undetectable viral loads (limit of detection, 400 copies/ml). Persons with AIDS were significantly older (mean, 31.5 years) than the HIV-infected non-AIDS participants (25.1 years). When the comparison was done among HIV-positive patients with AIDS, HIV-positive patients without AIDS, and seronegative control participants, there was an overall difference in age among the groups ($p = 0.04$ for a three-group comparison). However, the post hoc analysis showed no significant difference in age between participants with AIDS and the seronegative control (29 years) participants or between HIV patients without AIDS and control participants.

Mean (SD) neuropsychological raw scores of the total HIV-positive and HIV-negative groups, and mean *Z*-scores for the HIV-positive (based upon the HIV-negative group data) can be seen in Table 2. In addition, ability domain and total battery summary *Z*-scores were computed as average scores on the component tests, and effect sizes (Cohen *d*) were based on group differences in *Z*-scores. As can be seen from this table, the differences between HIV seronegative and seropositive participants are mainly in the areas of speed of information processing (large effect), verbal fluency and executive function (both medium effects), and verbal episodic memory (small to medium effect). The HIV-positive group did not show any significant disadvantage on tests of complex motor skills, visual episodic memory, or working memory. A global mean *Z*-score was calculated with the group comparison showing a *p*-value of 0.004 and an HIV effect size of 0.74 (medium to large).

There were no significant differences in the test results between AIDS and non-AIDS seropositive participants when a post hoc analysis was done. After further exploration of the neurocognitive data, it was clearly seen that the difference between HIV-positive and HIV-negative cohorts was primarily caused by HIV-seropositive women. Demographics, along with nadir and current CD4 count, are presented in Table 3. There was a strong effect of HIV in the two female groups (Table 4), but no significant difference was seen between

HIV-positive and HIV-negative men. There was no significant difference in summary score between AIDS and non-AIDS seropositive women. In the male group, there was large variation in test results, where the HIV-positive men actually had somewhat better results in many of the tests. Data are presented as *Z*-scores.

Students from the Master's degree program in clinical neuropsychology at the University of Zambia collected data on the same neuropsychological test battery from 324 healthy (HIV-negative) Zambian adults between 20 and 60 years old. Subject recruitment was done using targeted stratification regarding age, sex, education level, and rural versus urban place of living as a basis for developing demographically corrected norms (T-scores). Detailed reporting of this project is beyond the scope of the current paper but will be presented in forthcoming publications. Briefly, the test raw scores were converted to normally distributed scaled scores (mean, 10; SD, 3) based on the results of a census-matched subgroup of the controls; afterward, regression techniques were used with the total sample to convert scaled scores to demographically corrected T-scores (Heaton et al., 2004b). These T-scores are normally distributed and have a mean of 50 and an SD of 10 in the standardization sample; they reflect how well or poorly a participant did on the tests, compared with normal expectations for a healthy Zambian adult with the same demographic characteristics. T-scores on all individual tests, and domain and total composites were computed in the current study to further explore the generalizability of the above results that are based on our relatively small group of "at-risk" seronegative controls. Global mean T-scores (based on the norms derived from the 324 healthy Zambians) of our study groups of seronegative men, seropositive men, seronegative women, and seropositive women were compared using analysis of variance, with a post hoc Bonferroni correction that showed that seropositive women scored significantly below the three other groups (Mean T-score for the HIV seropositive women, 44.0; SD, 6.5; $df = 3$; $F = 10.91$; $p = 0.000005$). No significant differences were seen among the three other groups (mean T-score for HIV-seronegative women, 53.7; SD, 5.1; mean T-score for HIV-seropositive men, 49.1; SD, 6.1; HIV-seronegative men, 50.8; SD, 5.6). The apparent interaction between HIV serostatus and sex ($F = 6.94$, $p = 0.01$) cannot be explained on the basis of disease severity because there was no difference in the occurrence of AIDS in women and men.

There was a tendency for higher scores in HIV-infected women relative to noninfected women on the Beck Depression Scale–II, with a mean score of 16.5 (SD, 11.1) relative to 11.0 (SD, 5.9; $F = 4.58$, $p = 0.04$), indicating more depressive symptoms among female HIV-positive persons. For the men, the results were more equal, with 13.1 *vs*. 13.4 in the respective serostatus groups.

On the PAOFI, there were more complaints in the female groups regardless of HIV infection, relative to the men (mean, 6.1; SD, 5.1 *vs*. 3.7; SD, 4.4; $p = 0.026$).

We performed bivariate correlations between a global mean T-score (controlled for demographics) and IADL, PAOFI, and BDI-II. There was a significant correlation between the global T-score and BDI-II ($r = -0.34$, $p = 0.002$) but not between the global T-score and the other scales. Therefore, an analysis of covariance, with the global mean T-score as the dependent variable, HIV-positive versus HIV-negative (only in the female group) as the fixed factor, and BDI-II as the covariate variable was run. The main effect of HIV was still significant ($F = 21.2$, $p = 0.00004$) even after controlling for depressive symptoms.

DISCUSSION

Similar to findings in the United States and in other parts of the world, the Zambian HIV-infected group in this study had worse neuropsychological performance than the matched

seronegative group, with an overall effect size that was medium to large. The HIV-positive participants performed especially poorly on the tests related to Processing Speed (large effect size), although medium effect sizes also were observed for Verbal Fluency, Executive Function, and Verbal Episodic Memory.

A potentially important finding in the present study is that greater cognitive deficits were seen in female relative to the male seropositive participants. In fact, there were actually no signs of neuropsychological deficits among the Zambian seropositive men, either in relation to the "at risk" clinic controls or the larger Zambian neuropsychological standardization sample. The natural questions would then be whether, and, more importantly, why, Zambian women are more at risk of HIV-associated cognitive deficits than men? Although our sex-by-serostatus groups are relatively small, the interaction effect on neurocognitive outcome was quite significant. In earlier studies in Western countries, some authors have suggested that women have a poorer neurological outcomes than men (Morlat et al., 1992; Robertson et al., 1996), whereas others have found no such sex difference (Bouwman et al., 1998; Marder et al., 1995). Robertson et al. (2004) designed a prospective study to follow a US cohort to look for sex differences in neuropsychological functions over time in HIV-infected subjects. They found no evidence of differential declines regarding neuropsychological functioning in women and men. Similar inconsistent findings have been reported concerning sex differences in clinical symptoms not involving the central nervous system (Farzadegan et al., 1998; Moore et al., 2003; Napravnik et al., 2002; Robertson et al., 2004). Overall, therefore, available data regarding sex differences in HIV effects remain inconclusive, even though most studies that have seen a sex effect have reported poorer disease-related outcomes in women.

Informal observations of Zambian healthcare providers also suggest that women in that country may be at more at risk of developing HIV-related cognitive deficits than their male counterparts. In the national capital, Lusaka, more women than men are seen with HIV-related mental difficulties at the psychiatric clinic at the University Teaching Hospitals (personal communication/anecdotal information from Drs. Paul and Banda, psychiatrists at University Teaching Hospital). In the last 2 years, they have had 12 cases of HIV-related mental disturbances, and all of them were women. Typically, these women are referred to the clinic with low CD4 count, confusion, agitation, marked self-neglect, and poor prognosis.

The situation related to sex can also be seen in the proportion of women relative to men who are HIV-positive in the sub-Saharan countries, which appears to have greatly increased during the last 3 decades (Erb-Leoncavallo et al., 2004). Bah (2005) suggests that sex inequality, the subordination of women, and what she calls "predatory behavior" (by men) are major contributors of the epidemic. The result is that there is a larger number of women compared with men with HIV and AIDS and, also, that women contract the virus at a younger age than men. The social situation of women may also have consequences for their adherence to medication. Even when treatment is free, there are obstacles related to other costs involved, like transport to the clinic and the fact that time at the clinic takes them away from work and caregiver duties within the family (Esplen, 2007). It also might be that poverty, which is a widespread condition in Zambia with an unemployment rate of about 70%, puts women more at risk of HIV-related disorders because of the lack of adequate food intake because the husband (and children) has a priority before the wife. Furthermore, it is known that women living with HIV and AIDS in this part of the world may face greater discrimination because of social values surrounding the importance of female purity, and this may affect access to a range of information, treatments, and support (Esplen, 2007). In the present study, it could be seen that HIV-positive women had a trend for higher scores on the Beck Depression Scale, indicating more affective disturbances among HIV-positive

women than in the other three groups examined. The Beck Depression Scale has not been validated in Zambia, and to our knowledge, it is the first time that the scale has been used in any study in Zambia, but this is a face valid scale that worked well in our population. Depression (in general, even without HIV) can also be related to immunological change (Hestad et al., 2009).

It could be that HIV clade C, which dominates in Zambia, may give a somewhat different cognitive profile than other clades of HIV, although preliminary studies in India and South Africa have suggested that individuals infected with clade C may be at similar risk of developing HIV-associated neurocognitive disorders as individuals infected with other clades (Gupta et al., 2007; Joska et al., 2010; Yepthomi et al., 2006). Only one of these studies related to clade C has looked at sex differences. That study, performed in South Africa, actually found a trend, for men rather than women, and evidence of “HIV dementia” (none of the subjects in the present study were demented), although this difference did not achieve statistical significance (Joska et al., 2010).

When it comes to specific NP deficits, the present pilot study suggests minimal effects of HIV for visual learning (especially the brief visuospatial memory test-revised), which, in the United States and elsewhere, has been found to be quite sensitive to HIV effects (Heaton et al., 2008, 2010). In addition, the lack of difference on the Grooved Pegboard is different from what that has been seen elsewhere. For instance, in a study by Hestad et al. (1992), it was the Grooved Pegboard that showed the strongest correlation with brain atrophy in a large group of HIV-positive participants in Baltimore, MD. However, after the introduction of CART, it has been seen that motor difficulties in the HIV-positive population has been reduced (Heaton et al., 2011). Significant motor difficulties seen in HIV-1 infection have been reported to be associated with subcortical AIDS dementia, although such severe neurobehavioral disorders have become less common as a result of better medication (Sacktor et al., 2006).

There are some limitations to the present study. The neuropsychological examiner was “blinded” to HIV status in as much as that was possible. However, there, sometimes, are outward signs of HIV infection or CART usage, and a savvy evaluator cannot help but notice these. The sex-specific findings were not an expected finding and were a result of an unplanned subanalysis. The findings require confirmation through further research and, at present, must be looked upon as preliminary. In addition, the group of people enrolled in the study was not representative of the general population of Zambia. They were much more educated. The instruments and assessments used in this study might not be appropriate for a less educated population of Zambians.

In conclusion, the findings of the present study suggest that there is a clear HIV effect seen on neuropsychological functioning in Zambia. However, more research is needed to better understand the HIV × sex interaction effect that was observed here. In addition to using larger male and female subject samples, future neuroAIDS research in Zambia should systematically collect potentially relevant information about any sex differences in access to health care and other (*e.g.*, financial, nutritional) resources, medication adherence, HIV disease history, and possible comorbid conditions (*e.g.*, malaria, sexually transmitted diseases, and psychiatric difficulties such as history of major depression and posttraumatic stress disorders).

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REFERENCES

Antinori A, Arendt G, Becker JT, Brew BJ, Byrd DA, Cherner M, Clifford DB, Cinque P, Epstein LG, Goodkin K, Gisslen M, Grant I, Heaton RK, Joseph J, Marder K, Marra CM, McArthur JC, Nunn M, Price RW, Pulliam L, Robertson KR, Sacktor N, Valcour V, Wojna VE. Updated research nosology for HIV-associated neurocognitive disorders. Neurology. 2007; 69:1789–99. [PubMed: 17914061]

Bah, I. Gender inequality and HIV/AIDS in Zambia -A study of the links between gender inequality and women's vulnerability to HIV/AIDS [Master's thesis]. Department of Political Science; Södertörns Högskola: 2005.

Beck, AT.; Steer, RA.; Brown, GK. Beck Depression Inventory. 2nd ed. Pearson psychCorp; San Antonio, TX: 1996.

Bouwman FH, Skolasky RL, Hes D, Selnes OA, Glass JD, Nance-Sproson TE, Royal W, Dal Pan GJ, McArthur JC. Variable progression of HIV-associated dementia. Neurology. 1998; 50:1814–1820. [PubMed: 9633733]

Central Statistical Office, Lusaka, Zambia. Zambia Demographic and Health Survey 2001-2002. Central Statistical Office; Lusaka, Zambia: 2003.

Clifford DB, Mitike MT, Mekonnen Y, Zhang J, Zenebe G, Melaku Z, Zewde A, Gessesse N, Wolday D, Messele T, Teshome M, Evans S. Neurological evaluation of untreated human immunodeficiency virus infected adults in Ethiopia. J Neurovirol. 2007; 13:67–72. [PubMed: 17454450]

Erb-Leoncavallo, A.; Holmes, G.; Jacobs, G.; Urdang, S.; Vanek, J.; Zarb, M. A Joint Report by UNAIDS / UNFPA / UNIFEM. Women and HIV/AIDS: Confronting the crisis. UNAIDS, UNFPA and UNIFEM; Geneva and New York: 2004.

Esplen, E. Women and girls living with HIV/AIDS: Overview and annotated bibliography report prepared at the request of Irish Aid by BRIDGE in collaboration with the International Community of Women Living with HIV and AIDS (ICW). 2007. BRIDGE (development—gender), Bibliography No. 18

Farzadegan H, Hoover DR, Astemborski J, Lyles CM, Margolick JB, Markham RB, Quinn TC, Vlahov D. Sex differences in HIV-1 viral load and progression to AIDS. Lancet. 1998; 352:1510–1514. [PubMed: 9820299]

Folstein MF, Folstein SE, McHugh PR. 'Mini-mental state.' A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975; 12:189–198. [PubMed: 1202204]

Gupta JD, Satishchandra P, Gopukumar K, Wilkie F, Waldrop-Valverde D, Ellis R, Ownby R, Subbakrishna DK, Desai A, Kamat A, Ravi V, Rao BS, Satish KS, Kumar M. Neuropsychological deficits in human immunodeficiency virus type 1 clade C-seropositive adults from South India. J Neurovirol. 2007; 13:195–202. [PubMed: 17613709]

Gupta S, Vaida F, Riggs K, Jin H, Grant I, Cysique L, Shi C, Yu X, Wu Z, Heaton RK, HIV Neurobehavioral Research Center (HNRC) Group. Neuropsychological performance in mainland China: The effect of urban/rural residence and self-reported daily academic skill use. J Int Neuropsychol Soc. 2011; 17:163–173. [PubMed: 21083967]

Heaton RK, Clifford DB, Franklin DR Jr, Woods SP, Ake C, Vaida F, Ellis RJ, Letendre SL, Marcotte TD, Atkinson JH, Rivera-Mindt M, Vigil OR, Taylor MJ, Collier AC, Marra CM, Gelman BB, McArthur JC, Morgello S, Simpson DM, McCutchan JA, Abramson I, Gamst A, Fennema-Notestine C, Jernigan TL, Wong J, Grant I, CHARTER Group. HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER Study. Neurology. 2010; 75:2087–2096. [PubMed: 21135382]

Heaton RK, Cysique LA, Jin H, Shi C, Yu X, Letendre S, Franklin DR Jr, Ake C, Vigil O, Atkinson JH, Marcotte TD, Grant I, Wu Z, HNRC group. Neurobehavioral effects of HIV infection among former plasma donors in rural China. J Neurovirol. 2008; 14:536–549. [PubMed: 18991068]

Heaton R, Franklin D, Ellis R, McCutchan JA, Letendre SL, Leblanc S, Corkran SH, Duarte NA, Clifford DB, Woods SP, Collier AC, Marra CM, Morgello S, Mindt MR, Taylor MJ, Marcotte TD,

Atkinson JH, Wolfson T, Gelman BB, McArthur JC, Simpson DM, Abramson I, Gamst A, Fennema-Notestine C, Jernigan TL, Wong J, Grant I, CHARTER Group; HNRC Group. HIV-associated neurocognitive disorders before and during the era of combination antiretroviral therapy: differences in rates, nature, and predictors. J Neurovirol. 2011; 17:3–16. [PubMed: 21174240]

Heaton RK, Grant I, Butters N, White DA, Kirson D, Atkinson JH, McCutchan JA, Taylor MJ, Kelly MD, Ellis RJ, Wolfson T, Velin R, Marcotte TM, Hesselink JR, Jernigan TL, Chandler J, Wallace M, Abramson I, THE HNRC GROUP. The HNRC 500-Neuropsychology of HIV infection at different disease stages. J Int Neuropsychol Soc. 1995; 1:231–251. [PubMed: 9375218]

Heaton RK, Marcotte Mindt MR, Sadek J, Moore DJ, Bentley H, McCutchan JA, Reicks C, Grant I, HNRC Group. The impact of HIV-associated neuropsychological impairment on everyday functioning. J Int Neuropsychol Soc. 2004a; 10:317–331. [PubMed: 15147590]

Heaton, RK.; Miller, SW.; Taylor, MJ.; Grant, I. Revised comprehensive norms for an expanded Halstead–Reitan Battery: Demographically adjusted neuropsychological norms for African American and Caucasian adults. Psychological Assessment Resources, Inc.; Odessa, FL: 2004b.

Hestad K, Aukrust P, Tønseth S, Reitan SK. Depression has a strong relationship with alterations in the immune, endocrine and neural system. Curr Psychiatry Rev. 2009; 5:287–297.

Hestad, K.; McArthur, JH.; Dal Pan, GJ.; Selnes, OA.; Nance-Sproson, TE.; Aylward, TE.; Mathews, VP.; McArthur, JC. Neuroscience of HIV infection, basic and clinical frontiers. Amsterdam, the Netherlands: Jul 14–17. 1992 Regional atrophy in HIV-1 infection: Association with specific neuropsychological test performance. 1992

Joska JA, Fincham DS, Stein DJ, Paul RH, Seedat S. Clinical correlates of HIV-associated neurocognitive disorders in SouthAfrica. AIDS Behav. 2010; 14:371–378. [PubMed: 19326205]

Kanmogne GD, Kuate CT, Cysique LA, Fonsah JY, Eta S, Doh R, Njamnshi DM, Nchindap E, Franklin DR Jr, Ellis RJ, McCutchan JA, Binam F, Mbanya D, Heaton RK, Njamnshi AK. HIV-associated neurocognitive disorders in sub-Saharan Africa: A pilot study in Cameroon. BMC Neurol. 2010; 10:60. [PubMed: 20626870]

Kvalsund MP, Haworth A, Murman DL, Velie E, Birbeck GL. Closing gaps in antiretroviral therapy access: Human immunodeficiency virus-associated dementia screening instruments for non-physician healthcare workers. Am J Trop Med Hyg. 2009; 80:1054–1059. [PubMed: 19478275]

Maj M, D'Elia L, Satz P, Janssen R, Zaudig M, Uchiyama C, Starace F, Galderisi S, Chervinsky A, World Health Organization; Division of Mental Health/Global Programme on AIDS. Evaluation of two new neuropsychological tests designed to minimize cultural bias in the assessment of HIV-1 seropositive persons: AWHO study. Arch Clin Neuropsychol. 1993; 8:123–135. [PubMed: 14589670]

Marder K, Liu X, Stern Y, Malouf R, Dooneief G, Bell K, Todak G, Joseph M, Sorrell S, el Sadr W, Williams JBW, Eberhardt A, Stein Z, Gorman J. Risk of human immunodeficiency virus type 1-related neurologic disease in a cohort of intravenous drug users. Arch Neurol. 1995; 52:1174–1182. [PubMed: 7492292]

Moore AL, Kirk O, Johnson AM, Katlama C, Blaxhult A, Dietrich M, Colebunders R, Chiesi A, Lungren JD, Phillips AN, EuroSIDA group. Virologic, immunologic and clinical response to highly active antiretroviral therapy: The gender issue revisited. J Acquir Immune Defic Syndr. 2003; 32:452–461. [PubMed: 12640206]

Morlat P, Parneix P, Douard D, Lacoste D, Dupon M, Chêne G, Pellegrin JL, Ragnaud JM, Dabis F. Women and HIV infection: A cohort study of 483 HIV-infected women in Bordeaux, France, 1985–1991. AIDS. 1992; 6:1187–1193. [PubMed: 1466851]

Napravnik S, Poole C, Thomas JC, Eron JJ Jr. Gender difference in HIV RNA levels: a meta-analysis of published studies. J Acquir Immune Defic Syndr. 2002; 31:11–19. [PubMed: 12352145]

National AIDS Council. Zambia Country Progress Report—monitoring the Declaration of Commitment on HIV and AIDS and the Universal Access. 2010. Biennial Report, March 31st

Power C, Selnes OA, Grim JA, McArthur JC. HIV Dementia Scale: A rapid screening test. J Acquir Immune Defic Syndr Hum Retrovirol. 1995; 8:273–278. [PubMed: 7859139]

Report of a Working Group of the American Academy of Neurology AIDS Task Force. Nomenclature and research case definitions for neurologic manifestations of human immunodeficiency virus-type

1 (HIV-1) infection. Report of a Working Group of the American Academy of Neurology AIDS Task Force. Neurology. 1991; 4:778–785.

Robertson K, Kapoor C, Robertson WT, Fiscus S, Ford S, Hall CD. No gender differences in the progression of nervous system disease in HIV infection. J Acquir Immune Defic Syndr. 2004; 36:817–822. [PubMed: 15213565]

Robertson KR, Nakasujja N, Wong M, Musisi S, Katabira E, Parsons TD, Ronald A, Sacktor N. Pattern of neuropsychological performance among HIV positive patients in Uganda. BMC Neurol. 2007; 7:8. [PubMed: 17411437]

Robertson K, Wilkins J, Messenheimer J, Robertson W, Hall C. Gender differences in HIV neurological progression: A preliminary study. J NeuroAIDS. 1996; 1:166.

Sacktor N. The epidemiology of human immunodeficiency virus-associated neurological disease in the era of highly active antiretroviral therapy. J Neurovirol. 2002; 8:115–121. [PubMed: 12491162]

Sacktor N, Nakasujja N, Skolasky R, Robertson K, Wong M, Musisi S, Ronald A, Katabira E. Antiretroviral therapy improves cognitive impairment in HIV+ individuals in sub-Saharan Africa. Neurology. 2006; 67:311–314. [PubMed: 16864825]

Shaw GM, Harper ME, Hahn BH, Epstein LG, Gajdusek DC, Price RW, Navia BA, Petito CK, O'Hara CJ, Groopman JE, Chor E-S, Oleske JM, Wong-Staal F, Gallo RC. HIV-III infection in brains of children and adults with AIDS encephalopathy. Science. 1985; 227:177–182. [PubMed: 2981429]

Sirois P, Hill S. Developmental change associated with human immunodeficiency virus infection in school-age children with haemophilia. Dev Neuropsychol. 1993; 9:177–197.

Strauss, E.; Sherman, EMS.; Spreen, O. A compendium of Neuropsychological Tests. Administration Norms and commentary. Oxford University Press; New York: 2006.

Woods SP, Rippeth JD, Frol AB, Levy JK, Ryan E, Soukup VM, Hinkin CH, Lazzaretto D, Cherner M, Marcotte TD, Gelman BB, Morgello S, Singer EJ, Grant I, Heaton RK. Interrater reliability of clinical ratings and neurocognitive diagnoses in HIV. J Clin Exp Neuropsychol. 2004; 26:759–778. [PubMed: 15370374]

Yepthomi T, Paul R, Vallabhaneni S, Kumarasamy N, Tate DF, Solomon S, Flanigan T. Neurocognitive consequences of HIV in southern India: A preliminary study of clade C virus. J Int Neuropsychol Soc. 2006; 12:424–430. [PubMed: 16903135]

Zambian Ministry of Health and Central Board of Health. HIV/AIDS in Zambia: Background, projections, impacts and interventions. Zambian Ministry of Health and Central Board of Health; Lusaka, Zambia: 2005.

TABLE 1

Demographic Characteristics of the Study Groups

	HIV− (*n* = 42)	HIV+ (*n* = 37)
Age	28.9 ± 7.7	28.3 ± 7.4
Education	11.0 ± 2.3	11.0 ± 2.3
Sex	18 men, 24 women	16 men, 8 with AIDS; 21 women, 10 with AIDS
HIV disease characteristics		
% AIDS	–	40.5%
Current CD4	812.52 (191.9)	351.19 (191.7)
Nadir CD4	–	221.19 (151.7)

HIV indicates human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome.

TABLE 2

NP Test Battery Raw Scores and *Z*-Scores in the HIV+ Group

Ability Domain/NP Tests (Reference)	Raw Scores, Mean (SD), HIV−; HIV+	HIV+ *Z*-Scores	*p*	Cohen's *d*
Verbal fluency				
Letter fluency	34.2 (11.5); 29.2 (12.8)	−0.44 ± 1.12	0.068	0.4109
Animal fluency	14.9 (3.1); 13.3 (4.7)	−0.53 ± 1.49	0.064	0.4019
Action fluency	13.8 (4.8); 10.7 (4.8)	−0.64 ± 1.00	0.006	0.6458
Summary score		**−0.54 ± 1.08**	**0.017**	**0.5481**
Executive functions				
Category test	65.3 (35.5); 84.1 (33.2)	−0.52 ± 0.93	0.02	0.5470
WCST-64 total errors	12.7 (9.3); 14.3 (10.4)	−0.17 ± 1.11	0.47	0.1622
Color trails II	114.7 (47.6); 133. 4 (49.5)	−0.39 ± 1.04	0.093	0.3769
Summary score		**−0.40 ± 0.79**	**0.026**	**0.5391**
Speed of information processing				
TMT-A	48.2 (18.1); 63.1 (22.2)	−0.81 ± 1.22	0.002	0.7357
WAIS-III digit symbol	60.4 (18.2); 47.5 (15.6)	−0.71 ± 0.86	0.001	0.7611
WAIS-III symbol search	22.6 (7.7); 18.1 (8.2)	−0.59 ± 1.08	0.014	0.5658
Stroop Color-Word	84.5 (17.1); 75.6 (17.0)	−0.51 ± 1.00	0.028	0.5220
Stroop Color	64.18 (12.6); 56.4 (11.5)	−0.62 ± .0.91	0.007	0.6450
Stroop Color incongruence	37.5 (11.8); 33.5 (7.5)	−0.34 ± 0.64	0.092	0.4046
Color Trails I	53.9 (22.3); 68.1 (31.4)	−0.64 ± 1.04	0.022	0.5214
Summary score		**−0.37 ± 0.52**	**0.001**	**0.8284**
Verbal episodic memory				
HVLT-R learning	22.93 (4.71); 21.51 (5.1)	−0.30 ± 1.08	0.203	0.2893
HVLT-R delayed recall	8.5 (2.1); 7.3 (2.3)	−0.62 ± 1.08	0.009	0.5449
Summary verbal episodic memory		**−0.46 ± 1.03**	**0.042**	**0.4658**
Visual episodic memory				
BVMT-R learning	21.2 (6.9); 21.2 (8.2)	−0.00 ± 1.19	0.999	0.0000
BVMT-R delayed recall	8.6 (2.5); 8.6 (3.2)	−0.00 ± 1.27	0.974	0.0000
Summary visual episodic memory		**−0.00 ± 1.20**	**0.986**	**0.0051**
Working memory				
PASAT 50	24.3 (10.67); 22.0 (12.8)	−0.21 ± 1.21	0.395	0.1952
WMS-III spatial span	14.7 (3.5); 13.2 (4.8)	−0.42 ± 1.34	0.115	0.3571
Summary working memory		**−0.31 ± 1.12**	**0.173**	**0.3100**
Motor function				
Grooved Pegboard DH	78.9 (29.2); 82.2 (23.7)	−0.11 ± 0.81	0.580	0.1240
Grooved Pegboard NDH	90.2 (29.7); 95.7 (24.0)	−0.18 ± 0.61	0.371	0.2037
Summary motor function		**−0.15 ± 0.79**	**0.46**	**0.1681**
Mean *Z*-score		**−0.45 ± 0.76**	**0.004**	**0.7431**

See Heaton et al. (2008, 2010) and Strauss et al. (2006) for test references.

BVMT-R indicates brief visuospatial memory test-revised; DH, dominant hand; HIV, human immunodeficiency virus; HVLT-R, Hopkins verbal learning test-revised; NDH, non dominant hand; NP, neuropsychological; PASAT 50, paced auditory serial addition test 50; TMT-A, trail making test part A; WAIS-III, Wechsler adult intelligence scale-III; WCST, Wisconsin card sorting test; WMS-III, Wechsler memory scale-III.

TABLE 3

Demographic Characteristics for Each Sex Per HIV Study Group

	Women		Men		
	HIV−	**HIV+**	**HIV−**	**HIV+**	***p***
Age	27.88 (7.9)	27.52 (6.7)	30.39 (7.5)	29.38 (8.3)	NS
Education	11.00 (2.1)	10.38 (2.3)	11.00 (2.6)	11.75 (2.6)	NS
Beck depression	11.00 (5.9)	16.52 (11.1)	13.12 (9.8)	13.38 (7.3)	NS
Nadir CD4		238.38 (173.4)		198.62 (119.0)	NS
Current CD4[a]	829.30 (208.9)	368.71 (203.6)	789.82 (169.8)	328.19 (178.6)	<0.0000001

[a]There was no significant difference in the score between HIV+ men and women in current CD4.

HIV indicates human immunodeficiency virus; NS, not significant.

TABLE 4

Differences Between HIV-Positive and HIV-Negative Women and Between HIV-Positive and HIV-Negative Men Based on *Z*-Scores With Effect Size (Cohen's *d*)

	Women			Men		
	HIV+	**HIV−**	**Cohen's *d***	**HIV+**	**HIV−**	**Cohen's *d***
Letter fluency	−0.9673	−0.0256	−0.95**	0.2493	0.0351	0.22
Animal fluency	−1.1487	0.0697	−0.94**	0.2776	−0.0912	0.36
Action fluency	−0.9486	0.1552	−1.20 ****	−0.2381	−0.2060	−0.31
Digit symbol	−0.9852	0.1996	−1.42 *****	−0.3440	−0.2656	−0.08
Symbol search	−1.0076	0.2031	−1.30*****	−0.0336	−0.2704	0.23
Trails A	−1.3375	0.1838	−1.38*****	−0.1302	−0.2523	0.13
Color trails 1	−0.9648	0.2371	−1.02***	−0.2085	−0.3158	0.09
Stroop Word	−0.6928	0.2501	−0.88*	−0.2858	−0.3758	0.11
Stroop Color	−0.9212	0.3921	−1.43*****	−0.2096	−0.5314	0.39
Stroop Color-Word	−0.5289	0.2977	−1.00**	−0.1025	−0.4282	0.44
PASAT 50	−0.6905	0.2773	−1.05**	0.4106	−0.3537	0.66
Spatial span	−0.7960	0.0730	−0.79	0.0730	−0.0986	0.14
Category test	−0.8237	0.0515	−0.94*	−0.1378	−0.0741	−0.06
WCST-64	−0.3301	0.0066	−0.28	0.0412	−0.0086	0.06
Color trails 2	−0.7736	0.2756	−0.93*****	0.1393	−0.3675	0.50
BVMT Learning	−0.3517	0.2561	−0.56	0.4613	−0.3413	0.80
BVMT Delay	−0.3463	0.2241	−0.46	0.4377	−0.2962	0.80
HVLT Learning	−0.6924	0.0679	−0.74	0.2138	−0.0912	0.32
HVLT Delay	−0.9969	0.0898	−0.97*	−0.1287	−0.1155	−0.02
Pegs Dominant	−0.0530	0.1441	−0.47	−0.1964	0.1922	−0.30
Pegs Nondominant	−0.0909	0.1630	−0.57	−0.3112	−0.2177	−0.07

* $p < 0.01$.

** $p < 0.005$.

*** $p < 0.001$.

**** $p < 0.0005$.

***** $p < 0.0001$.

BVMT-R indicates brief visuospatial memory test-revised; HIV, human immunodeficiency virus; HVLT-R, Hopkins verbal learning test-revised; PASAT, paced auditory serial addition test; WCST, Wisconsin card sorting test.