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Effect of coinfections on neurocognitive functioning among people with clade C HIV infection in Zambia

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Abstract

Despite the fact that many coinfections in people with HIV (PWH) are treatable or suppressible, they may still impact neurocognitive (NC) functioning. Here, we aim to evaluate the presence of latent/treated coinfections and their association with NC functioning in a cohort of PWH in Zambia. We carried out a cross-sectional, nested study involving 151 PWH with viral suppression, and a normative sample of 324 adults without HIV. Plasma samples from PWH who underwent a comprehensive NC assessment were evaluated for the presence of treated/latent coinfections that are common in Zambia. Information about treated pulmonary tuberculosis (TB) was obtained from participants' clinical charts. Overall, PWH differed significantly from the HIV seronegatives on all neuropsychological domains except for fine motor control. ANOVA comparisons of all 3 HIV + groups' demographically corrected mean NC *T*-scores showed that the HIV + /TB + group had the poorest NC functioning in the following domains: executive functioning ($F = 4.23$, $p = 0.02$), working memory ($F = 5.05$, $p = 0.002$), verbal fluency ($F = 4.24$, $p = 0.006$), learning ($F = 11.26$, $p < 0.001$), delayed recall ($F = 4.56$, $p = 0.01$), and speed of information processing ($F = 5.16$, $p = 0.005$); this group also was substantially worse on the total battery (global mean *T*-scores; $F = 8.02$, $p < 0.001$). In conclusion, treated TB coinfection in PWH was associated with worse NC performance compared to both those with antibodies against other coinfections and without. PWH with antibodies for other coinfections (HIV + /CI +) showed somewhat better NC performance compared to those without (HIV + /CI −), which was not expected, although comparisons with the HIV + /CI + group are limited by its lack of specificity regarding type of coinfection being represented.

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Conflict of interest The authors declare no competing interests.

Keywords

HIV-associated neurocognitive disorders; HIV clade C; Coinfections in HIV; Neurocognition

Introduction

Sub-Saharan Africa, especially in its southern regions in which Zambia lies, has the world's highest prevalence of HIV and notably of the HIV-1 subtype C (Siddappa et al. 2006; Kabuba et al. 2016). The overall prevalence of HIV in Zambia stands at 11.3%, and this continues to be of great concern to the Millennium Development Goals at the international level (UNAIDS 2018).

Considerable progress has been made in the medical management of HIV infections in the last two decades, mainly due to the introduction of combination antiretroviral therapy (cART) (Ellis et al. 2011). As much as this has prolonged life and reduced severity of disease, there has been an increase in the population with chronic HIV infection living with associated neurocognitive (NC) disorders (Hong and Banks 2015). Although cART has reduced morbidity and mortality of HIV infection and led to a reduction in HIV-associated dementia (HAD) (Sacktor et al. 2007), the frequency of mild to moderate HIV-associated neurocognitive disorders (HAND) remains unchanged (Heaton et al. 2011.

In addition to HIV, several non-central nervous system (CNS) coinfections in PWH may be associated with NC complications (Rappaport and Volsky 2015). Latent toxoplasmosis, for example, has been linked to deficits in learning and memory (Hodkova et al. 2007; Wang et al. 2006). Cytomegalovirus (CMV) coinfection also is associated with neurocognitive decline in PWH (Letendre et al. 2018), and hepatitis B as well as syphillis infections can influence HIV disease outcomes including neurocognition (Marra 1992; Koliopoulos et al. 2009). In a study performed in Zambia, pulmonary tuberculosis was associated with worse neurocognitive performance in PWH (Hestad et al. 2019).

Importantly, most of the studies of the effects of HIV on the CNS have been done on the clade B viral strain, which is the predominant strain in Europe and the Americas. The need to investigate profiles regarding brain involvement and cognitive performance in clade C, which dominate the southern parts of Africa, is important because variations in neurovirulence have been associated with virus subtypes (Rao et al. 2013).

The focus of the current study is to investigate treated or latent coinfections and their association with NC functioning, among PWH with clade C infection and suppressed HIV RNA levels in plasma. We hypothesized that PWH with a history of coinfections would have worse NC functioning compared to the group with no coinfections. A particular interest was to examine if virally suppressed PWH who also had a history of known pulmonary TB performed worse than other PWH, including those with other coinfections. The previously mentioned study of PWH in Zambia suggested that pulmonary TB may affect NC performance, but these coinfected participants were sicker, with high HIV RNA levels and more compromised immune systems than other participants in the study (Hestad et al. 2019).

Methods

Ethical consideration

Ethical approval to conduct the study was obtained from the University of Zambia Biomedical and Research Ethics Committee (UNZABREC-Ref. No. 007–07-12). To facilitate detection of antibodies for coinfections that are common in Zambia, permission to transfer plasma samples to the University of California San Diego was obtained from the Zambian Ministry of Health in the form of a material transfer agreement, and an import permit was obtained from the U.S. Immigration department and Customs Enforcement (ICE) agency.

Informed consent was obtained from each participant, and their identity remained anonymous. Additionally, they were at liberty to withdraw from the study at any point. A modest compensation for their transport and lunch was given.

Study design and participants

This was a nested cross-sectional study that included only virally suppressed PWH (151 out of 264 in the previously reported sample that also included those with detectable viral loads; Kabuba et al. 2016) and compared them to a recently obtained normative sample of 324 Zambian adults without HIV (Hestad et al. 2016). Participants were drawn from major urban clinics around Lusaka (i.e., Chipata, Matero referral, Kabwata, Kalingalinga, Matero main, and Chilenje). These sites were chosen because they are the main centers of HIV testing and management in Lusaka Province under the Lusaka District Health Management Board, a wing of Zambia's Ministry of Health.

All participants enrolled in this study had undetectable HIV RNA in plasma. Information on the current and nadir CD4 counts and the duration of ART as well as other accessible clinical characteristics was obtained from the participants' medical files and, when necessary, a one-on-one interview with the clinical staff. The current CD4 count was obtained by use of single platform flow cytometry using standard methods at the time of sample collection.

Individuals were excluded from participating in the study if they had a past history of neurological and psychiatric disorders such as epilepsy, head injury with loss of consciousness, coma with a known or unknown onset, schizophrenia, alcohol abuse, drug abuse, or detectable HIV viral load in their blood. Persons with physical disability that could interfere with performance on motor tests were also excluded.

Procedure

Blood samples from all PWH were assayed for the presence of antibodies against coinfections common in Zambia (Kapembwa et al. 2011); these included hepatitis B, cytomegalovirus, toxoplasmosis, hepatitis C, and *Treponema pallidum*. The participants were stratified into HIV-positive without coinfections (HIV + /CI −), HIV-positive with a history of pulmonary TB as coinfection (HIV + /TB +), and HIV-positive with other coinfections (HIV + /CI +). PWH with treated pulmonary TB were identified by review of

medical files to ascertain TB treatment at the TB clinic. The evidence was through a record of national TB and leprosy identity card, TB case number, TB treatment ID card, and Lusaka District Health office TB listing at a health center. Sputum was examined by the Ziehl–Neelsen stain for acid-fast bacilli with chest X-ray being the main supporting diagnostic tool. All participants were on continuous TB treatment and without acute symptoms such as fever, continuous coughing, malaise, weight loss, and severe anemia at the time of enrollment in this study. All data were anonymized before analyses were performed.

Immunoassays

With all PWH, we performed serologic assays for coinfections at the University of California, San Diego Center for AIDS Research Translational Virology Core. Evidence of coinfections in previously stored plasma samples (− 80 °C) was determined by the presence of IgG antibodies via ELISA. The following ELISA kits were used: HepB sAg ELISA Kit (OKCA0185), IgG TP ELISA Kit (human) (OKCA01986), IgG Toxo ELISA Kit (human) (OKCA00443), IgG HepC ELISA Kit (human) (OKCA00471), and IgG CMV ELISA Kit (human) (OKCA00059). Concentrations were measured in replicates for assay precision, according to manufactures' recommendations (AVIVA Systems Biology 2017).

Neurocognitive measures

All study participants were administered a comprehensive neurocognitive test battery that assessed seven neurocognitive domains that are known to be affected in HIV-associated neurocognitive disorders (HAND; Antinori et al. 2007). The battery of tests has been used in many international settings and found to be sensitive to HAND. Norms that were demographically corrected for age, education, sex, and rural/urban status were generated for the Zambian population, based upon the results of the 324 Zambian participants without HIV (Hestad et al. 2016; Kabuba et al. 2016a, b). The domains measured were (1) executive functioning, (2) verbal fluency, (3) learning, (4) delayed recall, (5) working memory/attention, (6) speed of information processing, and (7) complex motor functioning. The tests were administered by students in the Master of Science in Clinical Neuropsychology program at the University of Zambia, who had undergone training and certification by experienced staff from the University of California at San Diego.

Raw data obtained from scores on the neuropsychological tests were converted into demographically corrected standard scores (*T*-scores) based upon Zambian norms, as mentioned above. Prior to that, raw scores were converted to normalized scaled scores with a mean of 10 and a standard deviation (SD) of 3 and thereafter to the demographically corrected *T*-scores with a mean of 50 and an SD of 10. Seven domain scores were created based on means of scores on the component tests. Detailed procedures and results of the norming study on the 324 healthy adults are reported elsewhere (Hestad et al. 2016).

Deficit scores were used to classify the participants' presence and severity of impairment, in individual domains and globally (Blackstone et al. 2012). Deficit scores are the impairment ratings that are generated from demographically corrected *T*-scores on a 5-point scale from 0 (normal) to 5 (severely impaired). A deficit score of 0 (*T*-score ≥ 40) indicates normal performance (no impairment), whereas a deficit score of 1 (*T*-score of 35–39) indicates

mild impairment, a score of 2 (*T*-score of 30–34) indicates mild-to-moderate impairment, a score of 3 (*T*-score of 25–29) indicates moderate impairment, a score of 4 (*T*-score 20–24) indicates moderate-to-severe impairment, while a score of 5 (*T*-score < 20) indicates severe impairment. A participant is classified as impaired in an ability domain if they had an average deficit score of greater than 0.5 on a particular cognitive domain. Participants are rated as being globally impaired if they had a total average deficit score (global deficit score) of 0.5 or greater across the entire test battery (Blackstone et al. 2012; Carey et al. 2004; Jumare et al. 2017).

We used deficit scores, in addition to *T*-scores, as they give some additional information of neurocognitive impairment (vs. performance) per domain and globally. The GDS method of classifying global impairment reduces the likelihood of type-1 error in considering multiple test results and is consistent with the more clinical approach defined in the Frascati criteria for HAND (Antinori et al. 2007; Blackstone et al. 2012).

Statistical analysis

Data were analyzed using SPSS version 20. Independent *t*-tests were used to compare demographically corrected NP performance (continuous variables) on all 7 domains between all the PWH (HIV group) with undetectable viral load and the group of people without HIV. Thereafter, one-way ANOVAs between infection groups with post hoc effects were used to compare neurocognitive performance among the HIV + /CI − , HIV + /CI + groups, and the HIV + /TB + participants. Means of demographically corrected *T*-scores as well as deficit scores, overall and for the seven domains, were compared among the 3 groups. Current and nadir CD4 counts were also compared among the 3 HIV + groups. Multiple linear regression analysis was performed to determine if CD4 count (both nadir and current), and duration on cART, could be used to develop models that predict the outcome variables (all NC measures).

Results

Demographic and clinical characteristics

Participants were between 20 and 65 years of age, with a minimum of 5 years formal education, because at that level of education, they were able to read and understand test materials in English, because the neuropsychological tests were administered in English (the official language of the Zambian educational system).

The mean ages for the control group of uninfected people and total group with HIV were 38.5 years (SD 12.80) and 41.03 years (SD 8.68), respectively (group difference; $p = 0.027$). The mean level of education for the group without HIV was 11.02 years (SD 2.58) and 10.03 years (SD 2.11) for PWH (group difference; $p \leq 0.001$). The overall percentage of females for the entire HIV sample was 55.7%. Importantly, these demographic differences on the NC outcomes were controlled by use of the published, demographically corrected NC test norms (Hestad et al. 2016). The most common coinfections detected in the non-TB (HIV + /CI +) group were hepatitis B ($n = 59$) and *Treponema pallidum* ($n = 43$). Some participants ($n = 3$) had multiple antibodies for other coinfections. This necessitated the stratifications and

analysis of the sample of these separate coinfections. However, this did not pose additional effects on the results of the global deficit scores and rates of global impairment that were found. All participants with tuberculosis were included in the HIV + /TB + group regardless of other coinfections. The HIV + /TB + group had a very high prevalence of detectable cytomegalovirus (CMV) antibodies (n = 17 of 18), and a high number also had detectable hepatitis B antibodies (n = 9). For analyses, the participants were stratified into HIV + /CI − (n = 47), HIV + /CI + (n = 86), and HIV + /TB + (n = 18).

Table 1 shows that the virally suppressed PWH differed significantly from the HIV seronegatives on the overall battery and on all NC domains except for fine motor control. PWH evidenced a higher overall impairment rate than the HIV negative group on the global deficit score (37.1% vs. 18.9%; X^2 (1,N = 457) = 14.83, $p < 0.001$), as well as on all domain deficit scores except that for fine motor control.

Demographic and clinical characteristics of the HIV + subgroups are shown in Table 2. The HIV + /CI − and HIV + /CI + groups are not significantly different on any of these characteristics. The HIV + /TB + group was younger and had fewer years of education than the HIV + /CI + group, but these group differences in age and education should be viewed in the context of our use of NC outcomes that are demographically corrected. However, the HIV + /TB + group also had a much shorter duration of ART exposure than both other groups. Duration of ART exposure was not related to global neurocognitive outcomes.

Table 3 details NC comparisons of mean T-scores in each domain and globally between the three HIV + subgroups. Overall p values with their respective F statistics showed highly statistically significant differences in subgroup performance on the overall test battery (global mean T-score) and on 6 of the 7 domains (all except complex motor skills).

Post hoc analyses of the overall results revealed that the HIV + /TB + group performed worse than the HIV + /CI + subgroup on the global mean T-score ($p \leq 0.001$) and on 6 of the 7 NC domains: executive functioning ($p = 0.02$), working memory ($p = 0.002$), verbal fluency ($p = 0.006$), learning ($p < 0.001$), recall ($p = 0.01$), and speed of information processing ($p = 0.005$); the HIV + /TB + subgroup also performed worse than the HIV + /CI − subgroup on tests of working memory ($p = 0.01$) and delayed recall ($p = 0.01$). Unexpectedly, the HIV + /CI + subgroup performed better than the subgroup without coinfections (HIV + /CI −) on the overall NC battery (global mean T-score, $p = 0.01$), executive functioning ($p = 0.02$), learning T-score ($p = 0.001$), delayed recall ($p = 0.03$), and speed of information processing ($p = 0.03$).

Table 4 reports group differences in neurocognitive impairment, using domain and global deficit scores. The overall p values show significant differences among the three groups regarding prevalence of impairment in all the domains except motor skills. Post hoc comparisons revealed that the HIV + /CI + group performed significantly better on executive function ($p = 0.02$), learning ($p = 0.006$), delayed recall ($p = 0.01$), and the global deficit score (0.05) than the HIV + /CI − group. The HIV + /TB + group evidenced more impairment than the HIV + /CI + group on tests of executive function ($p = 0.03$), working memory ($p < 0.001$), verbal fluency ($p = 0.03$), learning ($p < 0.001$), speed of information

processing ($p = 0.002$), and the overall battery (GDS; $p \leq 0.001$). The HIV + /TB + group also had more impairment than the HIV + /CI − group on tests that measure working memory (< 0.001) and speed of information processing ($p = 0.02$), as well as on the global deficit score ($p = 0.03$).

We performed an additional post hoc analyses related to CMV since the prevalence was very high in the HIV + TB + group. The question asked was if those with antibodies against CMV in the HIV + /CI + group performed at the same level as those without such antibodies on the NC tests. No significant differences were found on global mean *T*-score ($p = 0.07$). The trend was actually for a better (normal) performance by participants with CMV detected antibodies (mean score = 50.5 (SD = 5.7) vs. 47.2 (SD = 3.6)). On the domain of learning, those with CMV antibodies also were normal and significantly better than those without such antibodies ($p < 0.04$, mean *T*-score 50.6 (SD = 8.1) vs. 44.9 (SD = 7.9)). Also, the only participant without CMV in the HIV + /TB + group performed far below the mean global T-score than those with such antibodies (data not shown).

Discussion

Suppressive cART has considerably improved the outcome of HIV medical management. However, despite viral suppression, HIV-associated neurocognitive disorders persist in the cART era. In addition to HIV itself, several coinfections in PWH might be associated with NC complications. Several studies of these coinfections (mostly individually) and their CNS effects have been carried out in the setting of the clade B subtype of the virus. However, relatively little has been done on NC outcomes with the clade C viral subtype.

Our results show that the Zambian PWH on suppressive cART differed significantly from the HIV seronegatives on all neuropsychological domains except for fine motor control; this was reported previously with a significantly larger group of Zambian PWH, but this included many participants who had detectable HIV viral loads. Motor skills have been reported to be improved in the cART era (Heaton et al. 2011; Kabuba et al. 2016). The overall inferior NC performance of the virally suppressed PWH compared to the group without HIV was clearly seen with the large difference in the overall battery's global mean *T*-score between the two groups, and also in the GDS measure of global impairment.

We hypothesized that the presence of antibodies for previous or latent coinfections like pulmonary TB, hepatitis B, and syphilis, which is represented by the groups we referred to as HIV + /TB + and HIV + /CI + , respectively, would show worse neurocognitive performance than the HIV + CI − group. This hypothesis was partly supported, in that those with a combination of HIV and TB performed worse than the HIV + /CI − group overall, and on the domains of working memory, delayed recall, and speed of information processing (Tables 3 and 4). Furthermore, the HIV + /TB + group showed worse functioning than the HIV + /CI + group overall, and in executive function, working memory, verbal fluency, learning, delayed recall, and speed of information processing. The biggest differences seen in cognitive performance were between the HIV + /TB + and the HIV + /CI + groups.

We have seen earlier that participants with pulmonary TB show inferior scores relative to other PWH (Hestad et al. 2019). However, in Hestad et al. the HIV + /TB + coinfected group had more immunosuppression with lower CD4 count and more virus in their blood compared to those without pulmonary TB. These variables were controlled for in the present study, but the HIV + /TB + participants still had worse performance and a larger percentage of globally impaired participants (44%) compared to the other HIV + participants (32%). Our participants were treated, symptom-free patients regarding their pulmonary TB infection. Any residual symptoms of TB therefore are probably not a major driver of cognitive impairment. We suggest that clinical status before treatment may have contributed to the cognitive impairment, though we do not have any systematic data regarding severity of the disease before treatment. Therefore we are unable to assess possible associations with current cognitive functioning. Additionally, our participants had no other CNS disease symptoms, because the presence of overt CNS disease symptoms was in itself an exclusion criterion in our study.

We controlled for CMV, which was very prevalent in the HIV + /TB + participants. It was found that 95% of the HIV + /TB + group had antibodies for CMV, and none among the HIV + /CI − , as compared to only 9.41% in the HIV + /CI + participants. In a prior study of adults infected with HIV clade B, higher anti-CMV IgG levels in participants with CMV coinfection were associated with worse neurocognitive outcomes, but only in those who were on suppressive ART (Letendre et al. 2018). In the current study, presence of antibodies against CMV in HIV clade C coinfection did not confer an increased risk for impaired cognition, although we did not relate cognition to IgG levels. On the contrary, those with a history of CMV coinfection actually had tendency for better performance.

We examined other clinical parameters such as CD4 count that might help explain this finding, but no statistically significant difference was found among the 3 groups. However, it was found that the HIV + /TB + group had been on cART the shortest time (mean of 20.5 months) while the HIV + /CI + group had a longer duration with a mean of over 60 months, and this was statistically significant ($p < 0.001$).

The HIV + /TB + was younger and had less education compared to the other two groups of PWH. To address this issue, we transformed raw scores on the tests to demographically correct *T*-scores to control for effects of age, education, and sex. Additionally, we did not find any association between the global mean *T*-scores with age and education within the overall HIV + sample and the HIV + groups.

Contrary to our expectations, the HIV + /CI + group had better NC results than the HIV + /CI − group. Can it be that some of the previous infections in the HIV + /CI + group may have had a protective direct or indirect influence in HIV infection or its treatment? We cannot answer this question from our study, but it is conceivable that coinfection with hepatitis B and syphilis may have been the driving factor to seek medical attention early in some cases and as a consequence may have resulted in HIV seropositivity discovered and treated earlier without symptoms of sickness; hence, the sample that had been screened and treated for hepatitis B and syphilis may have had the benefit of an earlier HIV management. Consistent with that possibility is that the HIV + /CI + group had the longest duration of

ART exposure, even though this difference was not statistically significant relative to the HIV + /CI − group. Additionally, however, we cannot rule out the possibility that some sampling bias exists here, which we did not manage to identify or control for. It could, for instance, be that those who had more severe sickness related to hepatitis B at an earlier stage were not those who showed up for our study. Some patients may die from hepatitis B; others may develop chronic liver complications.

This study is novel in that we measured the neurocognitive effects of well-treated PWH subtype C, along with possible effects of other prevalent coinfections in Zambia. Other strengths of the study include (1) consideration of clinical parameters available that revealed information relevant to different aspects of HIV management, (2) the use of demographically corrected NC norms, which are specific for the Zambian population, and (3) lab assays were carried out in well equipped and internationally accredited laboratories at University of California, San Diego.

Limitations of the study include that (1) it lacked neuroimaging to identify possible structural brain alterations that have been linked to worse performance on neurocognitive tests (Kallianpur et al. 2020); (2) we did not have data on the duration of HIV disease before treatment, which may increase risk for neurocognitive decline (Chan et al. 2016), or timing of the HIV infections in relation to coinfections; (3) we did not have serotesting for non-HIV infection antibodies in the HIV-normative comparison group and were unable to consider HIV − /CI + status in our group comparisons; and (4) we did not have biomarkers of systemic inflammation to compare across groups, which may have helped explain the group differences in neurocognitive findings. Finally, a limitation in our study is that we did not have a reference group of people with TB only. Therefore, we cannot assess whether TB alone or together with HIV created the additional cognitive deficits seen in the HIV + TB + group, compared to the HIV-only group. However, a study of multidrug-resistant tuberculosis patients in South Africa found that TB patients had significant neurocognitive impairment and even more-so together with HIV infection (Ramlall et al. 2020).

In conclusion, treated TB coinfection in PWH despite being viral load suppressed was associated with worse NC performance compared to those with antibodies against other coinfections and those with no antibodies for other coinfections. PWH with antibodies for other coinfections showed somewhat better NC performance compared to those in the HIV + /CI − group, which was not expected, although comparisons with the HIV + /CI + group are limited by its lack of specificity regarding type of coinfection being represented.

Data Availability

The data analyzed in this study was subjected to the Zambian laws and Regulations. Since there was no acceptance from participants to deliver data to a third party, availability of the data is restricted. Questions regarding data availability can be directed to the first author.

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Table 1

Neurocognitive comparisons between PWH with undetectable viral load versus HIV-seronegative participants

	HIV + (*n* = 151) mean *T*-scores and SD	**HIV − (*n* = 324) mean *T*-scores[a] and SD**	***p* value between HIV + and HIV −; *T*-scores**	**HIV + mean deficit scores and SD**	**HIV − mean deficit scores and SD**	***p* value between HIV + and HIV− ;DDS/GDS**
Executive functioning	46.90 (6.62)	49.84 (6.29)	< **0.001**	0.38 (0.51)	0.24 (0.37)	**0.005**
Fluency	47.28 (7.63)	49.57 (6.96)	**0.002**	0.45 (0.62)	0.26 (0.42)	**0.001**
Working memory	47.28 (7.63)	49.78 (7.52)	< **0.001**	0.54 (0.76)	0.24 (0.52)	< **0.001**
Learning	44.22 (8.15)	50.00(7,72)	< **0.001**	0.45 (0.67)	0.23 (0.44)	< **0.001**
Motor	52.57 (10.87)	49.88 (9.21)	**0.007**	0.23 (0.61)	0.23 (0.55)	0.883
Recall	45.01 (8.08)	50.02 (7.83)	< **0.001**	0.41 (0.69)	0.26 (0.49)	**0.022**
Speed of information processing	47.14 (7.23)	49.74 (7.04)	< **0.001**	0.39 (0.51)	0.26 (0.41)	**0.011**
Global	47.19 (5.62)	49.77 (5.15)	< **0.001**	0.40 (0.38)	0.25 (0.27)	< **0.001**

Bolded values represent statistically significant *p* values

DDS Domain Deficit Scores, *GDS* Global Deficit Score

[a]Based on Zambian normative data

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Table 2

Demographic and disease characteristics of the three HIV + subgroups: only HIV + (HIV + /CI −), together with tuberculosis (HIV + /TB +), and together with other coinfections than tuberculosis (HIV + /CI +)

Demographics and clinical characteristics	**HIV + /CI − mean (SD) *n* = 47**	**HIV + /CI + mean (SD) *n* = 86**	***p* value between HIV +/CI − and HIV + /CI +**	**HIV + /TB + mean (SD) *n* = 18**	***p* value between HIV + /CI + and HIV + /TB +**	***p* value between HIV + /CI − and HIV + /TB +**
Age	40.3 (9.11)	42.5 (8.20)	0.154	36.0 (7.98)	**0.004**	0.069
Education	9.98 (2.08)	10.27 (1.89)	0.443	9.06 (2.88)	**0.026**	0.113
Female	68.1%	64.7%	0.848	55.6%	0.592	0.393
Current CD4	538.8 (197.2)	545.6 (315.3)	0.890	420.2 (156.7)	0.073	0.112
Nadir CD4	227.63 (142.95)	189.47 (130.82)	0.172	198.70 (137.07)	0.842	0.549
Duration on cART (months)	52.2 (29.7)	60.8 (30.7)	0.249	20.0 (27.5)	< **0.001**	**0.003**

Bolded values represent statistically significant *p* values

cART Combined Antiretroviral Therapy

HTV + /CI − represents PWH without other coinfections; *HIV + /CI +* represents PWH with other coinfections apart from pulmonary tuberculosis, *HIV + /TB +* represents PWH with pulmonary tuberculosis

Table 3

Neurocognitive domains with mean *T*-scores, ANOVAs, and post hoc analyses using least significant difference across the three HIV + subgroups: only HIV + (HIV + /CI −), HIV + together with tuberculosis (HIV + /TB +), and HIV + together with coinfections other than tuberculosis (HIV + /CI +)

Ability domain	HIV + / CI − mean *T*-scores (SD) *n* = 47	HIV + / CI + mean *T*-scores (SD) *n* = 86	*p* value HIV + / CI − and HIV + /CI +	HIV + / TB + mean *T*-scores (SD) *n* = 18	*p* value HIV + / CI + and HIV + /TB +	*p* value HIV + / CI − and HIV + /TB +	*F* stat	Overall *p* value
Executive function	45.16 (6.14)	47.86 (6.71)	**0.02**	44.05 (5.73)	**0.02**	0.54	4.23	**0.016**
Working memory	44.88 (6.78)	45.90 (8.44)	0.49	39.21 (9.68)	**0.002**	**0.01**	5.05	**0.008**
Fluency	45.93 (7.89)	48.01 (7.42)	0.13	42.58 (7.18)	**0.006**	0.11	4.24	**0.016**
Learning	42.23 (8.06)	46.91 (7.46)	**0.001**	36.66 (8.41)	< **0.001**	0.10	11.26	< **0.001**
Recall	43.99 (8.34)	47.12 (7.55)	**0.03**	42.21(5.35)	**0.01**	**0.01**	4.56	**0.012**
Motor	50.94 (10.37)	53.47 (11.10)	0.20	51.20 (10.84)	0.42	0.93	0.96	0.387
Speed of information processing	45.33 (6.68)	48.14 (7.36)	**0.03**	42.81 (7.91)	**0.005**	0.21	5.16	**0.007**
Global mean *T*	45.49 (5.41)	48.13 (5.54)	**0.01**	42.98 (5.90)	< **0.001**	0.11	8.02	< **0.001**

Bolded values represent statistically significant *p* values

HIV + /CI − represents PWH without other coinfections; *HIV + /CI +* represents PWH with other coinfections apart from pulmonary tuberculosis; *HIV + /TB +* represents PWH with pulmonary tuberculosis

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Table 4

Neurocognitive global and domain deficit score (DDS) ANOVAs and post hoc analyses using least significant difference across the three HIV + subgroups: only HIV + (HIV + /CI −), HIV together with tuberculosis (HIV + /TB +), and HIV with coinfections other than tuberculosis (HIV + /CI +)

Ability domain	HIV + / CI − mean DDS (SD) *n* = 47	HIV + / CI + mean DDS (SD) *n* = 86	*p* value HIV + / CI − and HIV + /CI +	HIV + / TB + mean DDS (SD) *n* = 18	*p* value HIV + / CI + and HIV + /TB +	*p* value HIV + / CI − and HIV + /TB +	*F* stat	Overall *p* value
Executive function	0.51 (0.50)	0.30 (0.50)	**0.02**	0.58 (0.51)	**0.03**	0.61	4.02	**0.02**
Working memory	0.54 (0.71)	0.54 (0.79)	1.00	1.39 (1.17)	< **0.001**	< **0.001**	8.40	< **0.001**
Verbal fluency	0.54 (0.67)	0.40 (0.58)	0.24	0.77 (0.95)	**0.03**	0.20	2.63	0.076
Learning	0.70 (0.81)	0.32 (0.53)	**0.006**	1.08 (1.34)	< **0.001**	0.07	9.33	< **0.001**
Delayed recall	0.62 (0.76)	0.30 (0.62)	**0.01**	0.58 (0.60)	0.10	0.85	3.92	**0.03**
Motor	0.23 (0.58)	0.22 (0.63)	0.91	0.22 (0.60)	0.99	0.94	0.007	0.99
Speed of information processing	0.45 (0.50)	0.36 (0.52)	0.37	0.82 (0.89)	**0.002**	**0.02**	4.93	**0.008**
Global deficit score	0.50 (0.39)	0.35 (0.37)	0.05	0.772 (0.73)	< **0.001**	**0.03**	7.37	**0.001**

Bolded values represent statistically significant *p* values

HIV + /CI − represents PWH without other coinfections; *HIV + /CI +* represents PWH with other coinfections apart from pulmonary tuberculosis; *HIV + /TB +* represents PWH with pulmonary tuberculosis

DDS domain deficit scores