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ORIGINAL ARTICLE

Interaction Effects between HIV and Aging on Selective Neurocognitive Impairment

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Abstract HIV infection and aging are each associated with neurocognitive impairment (NCI). This study examined the combined effects of HIV infection and aging on NCI. We performed a cross-sectional survey among 345 HIV-infected and 345 HIV-uninfected participants aged at least 40 years. The International HIV Dementia Scale (IHDS) and Chinese version of Mini-mental State Examination (MMSE) were administered to screen for NCI. HIV-infected individuals had higher prevalence of NCI than uninfected individuals (46.7% vs 15.1% for IHDS using cut-off of ≤ 10; 17.1% vs 2.6% for MMSE). Significant main effects of HIV and age were observed on IHDS and MMSE composite scores and all domains except for HIV on attention and calculation. Significant interaction effects between HIV and age were observed on motor speed, orientation, registration and recall, and mainly attributed to the inferior performance of HIV-infected patients aged over 60 years. Among HIV-infected individuals, in multivariable logistic models, older age, depressive symptoms and history of nevirapine treatment were associated with NCI using both IHDS and MMSE, whereas lower education current smoker and current CD4 ≥ 800 cells/μL were associated only with NCI using IHDS, and hypertension was associated only with NCI using MMSE. Findings suggest that HIV and older age may confer interactive effects on cognitive function in several domains with older HIV-infected adults experiencing greater NCI, which requires further longitudinal investigation. Furthermore, HIV early diagnosis and treatment may prevent or reverse NCI, but extra attention should be given to adverse effects including metabolic changes associated with long-term treatment.

Keywords HIV · Older age · Accelerated aging · Neurocognitive impairment · CD4 count · China

Introduction

People living with HIV often experience neurocognitive impairment (NCI), referred to as HIV-associated neurocognitive disorders (HAND) (Heaton et al. 2010). Combination antiretroviral therapy (cART) has led to significant reduction in severe forms of HAND. Yet, mild to moderate forms of HAND are still highly prevalent and may even have increased (Cysique et al. 2004; Heaton et al. 2010; Sacktor et al. 2016; Tozzi et al. 2007), partly due to the aging of HIV population. Globally, an estimated 3.6 million people older than 50 years are living with HIV including 2.9 million in low- and middle-income countries, and the number continues to increase in all regions (United Nations Programme on HIV/AIDS 2013). The other possible reasons for sustained prevalence of HAND include irreversible HIV-related brain injury and neurotoxicity of specific antiretroviral drugs (ARVs) (Ciccarelli et al. 2011; Heaton et al. 2010).

It is also suggested that HIV may accelerate cognitive aging which is possibly caused by direct damage from the virus as well as indirectly through increased risk of other

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comorbidities such as cardiovascular diseases or chronic immune activation, and thereby facilitates the early expression of age-related cognitive disorders (Cohen et al. 2015; Hellmuth et al. 2014; Imp et al. 2017; McCutchan et al. 2012; Wright et al. 2010). However, studies on the synergistic (interaction) effects of HIV and aging on neurocognitive performance showed mixed results. Most neuropsychological studies found the main effects of aging and HIV on cognitive abilities but didn't identify the interaction effect (Ciccarelli et al. 2012; Valcour et al. 2011). Only a limited number of neuropsychological studies identified interaction effect of HIV and aging on verbal memory (Scott et al. 2011; Seider et al. 2014) but several neuroimaging studies found the interaction effects between HIV and aging in selected brain structures (Chang et al. 2013; Cysique et al. 2013; Kuhn et al. 2017; Pfefferbaum et al. 2014). It has to be noted that most of the neuropsychological studies either included no well-matched HIV-uninfected individuals for comparison or included only a small number of HIV-infected cases over 60 (Ciccarelli et al. 2012; Scott et al. 2011; Seider et al. 2014; Valcour et al. 2011), which may limit the ability to fully evaluate the interaction effect.

Thereby, this cross-sectional study was undertaken to determine if there is an interaction effect between HIV infection and aging on neurocognitive performance. HIV-infected individuals aged over 40 years and age-, gender-, education-matched HIV-negative individuals were recruited to participate in the study in China. Factors that might contribute to the high prevalence of NCI in HIV-infected adults were also explored.

Methods

Participants and Procedures

This study was conducted in Taizhou prefecture of Zhejiang province, China, as described elsewhere (Ding et al. 2017). HIV-infected individuals in Taizhou registered with the Chinese National Information System for AIDS Prevention and Control (CNISAPC) were consecutively enrolled in this special survey between June 2014 and May 2015, and were eligible if they were 40 years and above. HIV-uninfected participants were frequency matched in 1:1 ratio by sex, education and 5-year age categories to HIV cases, who were randomly selected from a sample of 1216 HIV-uninfected individuals recruited either from persons receiving HIV voluntary counseling and testing or routine physical examination at local Center for Disease Prevention and Control during the same study period, and were eligible if they were 40 years and above and also HIV-seronegative at the time of enrollment. The study was approved by the Institutional Review Board of Fudan University, Shanghai, China. All subjects provided informed consent prior to enrollment.

Data Collection

A standardized structured questionnaire was administered face-to-face by trained health staff to collect information on demographics, smoking, illicit drug use, and medical history regarding hypertension, diabetes and cardiovascular events (e.g., coronary artery disease). Physical examinations of height, weight, and blood pressure (BP) were carried out after the questionnaire has been completed. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Hypertension was defined as systolic BP $\geq$ 140 mmHg or diastolic BP $\geq$ 90 mmHg, or current use of antihypertensive therapy.

All HIV-related characteristics were extracted from CNISAPC. Nadir CD4 count was defined as the lowest ever measured CD4 count between HIV diagnosis and the present survey. Current CD4 count was defined as the most recent CD4 count (within 2 months prior to the survey or within 1 month after the survey).

Depression and Insomnia Assessment

Depressive symptoms were measured by the 10-item version of Zung Self-Rating Depression Scale (Li et al. 2011; Zung 1973). Insomnia symptoms were measured based on Jenkins's 4-item sleep questionnaire (Jenkins et al. 1988). Presence of insomnia symptoms was based on answers with "on most nights" or "on every night" to 1 or more questions.

Neurocognitive Assessment

All participants underwent face-to-face neurocognitive testing conducted by trained health staff using both the International HIV Dementia Scale (IHDS) and the Chinese version of Mini-mental State Examination (MMSE) in each participant. The two scales were chosen for three primary reasons: first, both are brief, easy to administer and highly applicable to resource-limited countries (Kamminga et al. 2013); second, IHDS is designed to identify HIV-associated dementia which is a subcortical dementia and has been confirmed to have high sensitivity to detect HAND among HIV-positive patients (Dang et al. 2015; Sacktor et al. 2005), and MMSE is originally developed to screen for cortical dementia and is the most widely used cognitive impairment screening instrument (Oshinaike et al. 2012); third, the pattern of NCI in the aged HIV-infected population is complex and includes symptoms of both cortical and subcortical dysfunctions (Cohen et al. 2015; Scott et al. 2011).

IHDS covers 3 domains: memory registration and recall, motor speed; psychomotor speed; each of these subtests is rated on a scale of 0–4. The cutoff score for defining NCI is 10 (Sacktor et al. 2005). Chinese version of MMSE takes the subjects' education into account to define NCI if MMSE $\leq$ 19 for those with no formal education; MMSE $\leq$ 22 for those with

primary school education (≤ 6 years); MMSE ≤ 26 for those with junior school education or above (≥ 7 years) (Zhang et al. 2006). It has a high sensitivity (90.8%) and specificity (93%) in the detection of dementia in the Chinese populations (Zhang et al. 2006). It covers the five domains: orientation of place and time, registration, attention and calculation, recall, language and visual construction.

Statistical Analysis

Analyses were performed using SAS software (version 9.11). Differences between groups were assessed by χ^2 test, Fisher's exact test, Student's t-test, ANOVA or Kruskal-Wallis test as appropriate. A series of ANCOVA were run to test for main effects of age (40–49, 50–59 vs ≥ 60 years) and HIV serostatus (yes vs no) and the potential interaction between two variables on the neurocognitive scores of interest, controlling for education, depressive symptoms and hypertension which were associated with age or/and HIV infection as well as NCI based on bivariate analysis. Tukey post-hoc analyses comparing adjusted means were performed on all significant interactions in ANCOVA. Univariable and multivariable logistic regressions were performed to explore the determinants of NCI using the IHDS and MMSE, respectively. Variables with $p < .10$ in univariable analysis were included in multivariable model. Backward selection was used with retention at a significance level of $p < .10$. Sensitivity analysis was conducted to assess the robustness of the results using an IHDS score cut-off point of ≤ 9 for defining NCI, as suggested by Hosein and colleagues that it might be more appropriate for identifying NCI in those with low education level (2015).

Results

Participant Characteristics

Characteristics of 345 HIV-infected and 345 uninfected participants were summarized in Table 1. HIV-infected group was similar to HIV-uninfected group except the HIV-infected group had a lower proportion of hypertension and more depressive and insomnia symptoms ($p < .05$). With regards to HIV-related characteristics, the median time since HIV diagnosis was 3.0 years. About 87% was receiving cART, with the median treatment duration of 2.2 years.

In both HIV-infected and HIV-uninfected participants, compared to the age groups of 40–49 and 50–59 years, the oldest age group (60–82 years) were significantly less likely to have at least middle school education, but significantly more likely to have hypertension and a history of diabetes. HIV-infected participants aged 50–59 years were significantly less likely to have current CD4 count ≥ 500 cells/μL (Table 1).

Prevalence of Neurocognitive Impairment by HIV Serostatus and Age Group

As shown in Table 1, using cut-off of ≤ 10 for IHDS, 46.7% of HIV-infected participants were detected to have NCI compared to 15.1% of the uninfected participants ($p < .01$). Using the MMSE, 17.1% of HIV-infected participants were detected to have NCI compared with 2.6% of the uninfected participants ($p < .01$) (Table 1). In multivariable models adjusting for sex, education, BMI, current alcohol use, current smoker, hypertension, history of diabetes, history of cardiovascular events and depressive and insomnia symptoms, HIV infection is associated with NCI using the IHDS and MMSE, respectively (OR, 4.98 for IHDS using cut-off of ≤ 10; 95% CI, 3.24–7.66; $p < .001$; OR, 8.49 for MMSE; 95% CI, 3.78–19.07; $p < .001$). Furthermore, in both groups, the highest prevalence of NCI was observed in the age group of 60–82 years ($p < .05$), and such association (60–82 vs 40–49 years) remained significant (OR, 2.87 for IHDS using cut-off of ≤ 10; 95% CI, 1.73–4.76; $p < .001$; OR, 4.18 for MMSE, 95% CI, 1.99–8.77; $p < .001$) after adjusted for aforesaid potential confounding variables.

Main and Interaction Effects of HIV Serostatus and Age on Neurocognitive Performance

In ANCOVA model adjusting for education, depressive symptoms and hypertension, significant main effects of HIV and age on NCI were observed for all domains and IHDS and MMSE composite scores except for the main effect of HIV on attention and calculation ($p = 0.070$). Significant interaction effects were observed for motor speed, orientation, registration and recall, and also marginally significant interaction effects were observed for IHDS and MMSE composite scores ($p = 0.094$ and $p = 0.099$, respectively) (Table 2). Post-hoc analyses showed that interaction effect on recall was mainly attributable to the superior performance of the HIV-uninfected group aged 40–49 years and the inferior performance of the HIV-infected group aged 60–82 years, whereas the interaction effects on motor speed, orientation and registration were mainly attributable to the inferior performance of the HIV-infected group aged 60–82 years. Such attributions were also observable in Fig. 1a–d, showing that HIV-infected group aged 60–82 years had the much lower scores on these four domains than other five subgroups.

Factors Associated with NCI in HIV-Infected Patients Only

As shown in Table 3, in multivariable models, older age, more depressive symptoms, and history of nevirapine (NVP) treatment (vs efavirenz or EFV) were associated with NCI using IHDS with a cut-off of ≤10 and MMSE. Also, lower education

Table 1 Characteristics of Study Participants

	No. (%), mean ± SD or median (IQR).									
	HIV-infected individuals				p^a	HIV-uninfected individuals				p^a
	Total	40–49 y	50–59 y	60–82 y		Total	40–49 y	50–59 y	60–82 y	
Subjects	345	173	88	84		345	173	88	84	
Age, y	52.7 ± 9.5	45.9 ± 2.8	54.3 ± 3.0	66.6 ± 4.9	<.001	52.8 ± 9.4	45.4 ± 2.8	54.3 ± 3.1	66.5 ± 5.7	<.001
Male	268 (77.7)	135 (78.0)	68 (77.3)	65 (77.4)	0.987	268 (77.7)	135 (78.0)	68 (77.3)	65 (77.4)	0.987
Education					<.001					<.001
Illiterate	43 (12.5)	10 (5.8)	10 (11.4)	23 (27.4)		43 (12.5)	10 (5.8)	10 (11.4)	23 (27.4)	
Primary	119 (34.5)	49 (28.3)	28 (31.8)	42 (50.0)		119 (34.5)	49 (28.3)	28 (31.8)	42 (50.0)	
Middle school or above	183 (53.0)	114 (65.9)	50 (56.8)	19 (22.6)		183 (53.0)	114 (65.9)	50 (56.8)	19 (22.6)	
BMI[b], kg/m^2					0.578					0.962
< 18.5	30 (8.7)	15 (8.7)	6 (6.8)	9 (10.7)		6 (1.7)	4 (2.3)	1 (1.1)	1 (1.2)	
18.5–23.9	228 (66.1)	110 (63.6)	59 (67.1)	59 (70.2)		178 (51.7)	91 (52.6)	44 (50.0)	43 (51.8)	
≥ 24	87 (25.2)	48 (27.7)	23 (26.1)	16 (19.1)		160 (46.5)	78 (45.1)	43 (48.9)	39 (47.0)	
Current alcohol use	23 (6.7)	15 (8.7)	3 (3.4)	5 (5.9)	0.261	34 (9.9)	14 (8.1)	8 (9.1)	12 (14.3)	0.128
Current smoker	88 (25.5)	51 (29.5)	20 (22.7)	17 (20.2)	0.221	103 (29.9)	50 (28.9)	31 (35.2)	22 (26.2)	0.202
Ever used illicit drugs[b]	5 (1.4)	5 (2.9)	0 (0)	0 (0)	0.079	0 (0)	0 (0)	0 (0)	0 (0)	NA
Comorbid conditions										
Hypertension[b]	82 (23.8)	34 (19.7)	18 (20.5)	30 (35.7)	0.012	110 (31.9)	43 (24.9)	27 (30.7)	40 (47.6)	0.001
History of diabetes	19 (5.5)	5 (2.9)	4 (4.6)	10 (11.9)	0.017	21 (6.1)	3 (1.7)	3 (3.4)	15 (17.9)	<.001
History of cardiovascular events	13 (3.8)	6 (3.5)	1 (1.1)	6 (7.1)	0.124	13 (3.8)	2 (1.2)	2 (2.3)	9 (10.7)	0.001
Depressive symptoms[b]	16.4 ± 4.9	16.7 ± 4.8	16.0 ± 5.6	16.2 ± 4.5	0.521	13.4 ± 3.8	13.0 ± 3.7	13.3 ± 3.6	14.1 ± 4.2	0.070
Insomnia symptoms[b]	71 (20.6)	34 (19.7)	20 (22.7)	17 (20.2)	0.841	36 (10.4)	10 (5.8)	6 (6.8)	20 (23.8)	<.001
HIV-related characteristics										
Time since HIV diagnosis, y	3.0 (1.5–4.6)	2.9 (1.5–4.9)	2.7 (1.3–4.3)	3.5 (2.0–4.6)	0.340					
Nadir CD4 count ≥ 200 cells/μL	153 (44.3)	77 (44.5)	31 (35.2)	45 (53.6)	0.053					
Current CD4 count, cells/μL					0.048					
< 350	167 (48.4)	78 (45.1)	49 (55.7)	40 (47.6)						
350–499	99 (28.7)	53 (30.6)	24 (27.3)	22 (26.2)						
500–799	70 (20.3)	41 (23.7)	13 (14.8)	16 (19.1)						
≥ 800	9 (2.6)	1 (0.6)	2 (2.3)	6 (7.1)						
Type of antiretroviral treatment					0.251					
ART naive	45 (13.0)	25 (14.4)	9 (10.2)	11 (13.1)						
Ever 2NRTI + NVP	130 (37.7)	70 (40.5)	26 (29.6)	34 (40.5)						
Ever 2NRTI + EFV	129 (37.4)	57 (32.9)	43 (48.9)	29 (34.5)						
Ever (2NRTI + EFV) and (2NRTI + NVP)	39 (11.3)	21 (12.1)	9 (10.2)	9 (10.7)						
Other	2 (0.6)	0 (0)	1 (1.1)	1 (1.2)						
Duration on cART (n = 300), y	2.2 (0.9–3.7)	2.0 (0.9–3.6)	2.1 (0.8–3.8)	2.6 (0.9–3.6)	0.945					
Current HIV viral load < 400 copies/mL (n = 231)	214 (92.6)	110 (94.0)	56 (91.8)	48 (90.6)	0.697					
Neurocognitive impairment										
NCI using IHDS[b]										
≤ 10	161 (46.7)	68 (39.3)	41 (46.6)	52 (61.9)	0.003	52 (15.1)	16 (9.3)	5 (5.7)	31 (36.9)	<.001
≤ 9	119 (34.5)	43 (24.9)	32 (36.4)	44 (52.4)	<.001	30 (8.7)	6 (3.5)	2 (2.3)	22 (26.2)	<.001
NCI using MMSE[b]	59 (17.1)	68 (12.1)	41 (14.8)	52 (29.8)	0.002	9 (2.6)	2 (1.1)	2 (2.3)	5 (5.9)	0.074

Abbreviations: *cART* combination antiretroviral therapy, *BMI* body mass index, *EFV* efavirenz, *IHDS* International HIV Dementia Scale, *IQR* interquartile range, *NA* not applicable, *NCI* neurocognitive impairment, *NRTI* nucleoside reverse transcriptase inhibitor, *NVP* nevirapine, *MMSE* Mini-mental State Examination, *SD* standard deviation

[a] p calculated using χ^2 test, Fisher's exact test, ANOVA or Kruskal-Wallis test as appropriate

[b] $p < .05$ when comparing HIV-infected and uninfected group using χ^2 test, Fisher's exact test, or ANOVA where applicable

level and current smoker were associated with NCI only using the IHDS with a cut-off of ≤ 10, while hypertension was associated with NCI only using the MMSE. In terms of HIV-related variables, only current CD4 count ≥ 800 cells/μL was negatively associated with NCI using the IHDS with a cut-off of ≤ 10.

In subgroup analysis restricted to those on cART (n = 300), similar variables were found to be significantly associated with NCI using IHDS with a cut-off of ≤ 10 and MMSE, respectively. But, current CD4 count ≥ 800 cells/μL was no longer significantly associated with NCI using the IHDS with a cut-off of ≤ 10. It is possibly due

Table 2 Mean and Standard deviation as well as the main and interaction effects given by the ANCOVA for Scores on IHDS and MMSE and All domains by Age group and HIV Serostatus

Variables	40–49 y		50–59 y		60–82 y		Effects (F values)[a]		
	HIV+ (n = 173)	HIV- (n = 173)	HIV+ (n = 88)	HIV- (n = 88)	HIV+ (n = 84)	HIV- (n = 84)	HIV	Age	HIV × Age
IHDS composite score	10.4 ± 1.8	11.7 ± 0.8	10.1 ± 2.1	11.7 ± 0.7	8.9 ± 3.0	10.6 ± 1.7	81.3**	14.0**	2.4†
Memory registration and recall	3.4 ± 0.9	3.8 ± 0.4	3.4 ± 0.9	3.9 ± 0.3	3.0 ± 1.1	3.5 ± 0.7	45.7**	3.5*	0.5
Motor speed	3.7 ± 0.6	3.9 ± 0.3	3.6 ± 0.6	3.9 ± 0.2	3.2 ± 0.9	3.6 ± 0.6	33.2**	19.5**	4.1*
Psychomotor speed	3.3 ± 0.8	3.9 ± 0.3	3.2 ± 0.9	3.9 ± 0.4	2.7 ± 1.3	3.5 ± 0.8	88.1**	11.7**	1.5
MMSE composite score	28.3 ± 3.3	29.6 ± 1.0	27.7 ± 4.2	28.9 ± 2.0	25.0 ± 5.7	27.3 ± 3.0	28.5**	14.3**	2.3†
Orientation	9.9 ± 0.8	10.0 ± 0.0	9.8 ± 0.8	9.9 ± 0.3	9.4 ± 1.4	9.9 ± 0.3	16.1**	2.6†	6.5**
Registration	2.8 ± 0.5	2.9 ± 0.2	2.7 ± 0.7	2.9 ± 0.3	2.4 ± 0.9	2.7 ± 0.4	16.7**	16.4**	3.7*
Attention and calculation	4.5 ± 1.2	4.8 ± 0.5	4.5 ± 1.1	4.6 ± 1.1	3.8 ± 1.5	3.8 ± 1.3	3.3†	9.4**	1.6
Recall	2.7 ± 0.6	2.9 ± 0.2	2.6 ± 0.8	2.9 ± 0.3	2.2 ± 1.0	2.7 ± 0.5	43.9**	7.1**	3.2*
Language and visual construction	8.4 ± 1.3	8.8 ± 0.5	8.1 ± 1.7	8.6 ± 0.9	7.3 ± 2.1	8.0 ± 1.4	18.1**	10.4**	1.3

All data are raw scores

Abbreviations: *IHDS* International HIV Dementia Scale, *MMSE* Mini-mental State Examination

† $p < .1$; *$p < .05$; **$p < .01$

[a] All models adjusted for education, depressive symptoms and hypertension

to the fact that among HIV-infected patients on cART, none of them with current CD4 count ≥ 800 cells/μL (n = 7) had NCI using IHDS or MMSE. Of note, duration on cART was negatively associated with NCI using the MMSE. In addition, among HIV-infected individuals without treatment (n = 45), only current smoker and hypertension were significantly associated with NCI using the IHDS with a cut-off of ≤ 10, and only depressive symptoms were significantly associated with NCI using the MMSE (data not shown).

Sensitivity Analysis

We repeated all the analysis using an IHDS score cut-off point of ≤ 9 for defining NCI. About 34.5% of HIV-infected participants were detected to have NCI compared to 8.7% of the uninfected participants ($p < .01$). Such association remained significant (OR, 5.73; 95% CI, 3.44–9.55; $p < .001$) after adjusting potential confounders. Similarly, the highest prevalence of NCI with a cut-off of ≤ 9 was observed in the age group of 60–82 years ($p < .05$), and such association (60–82

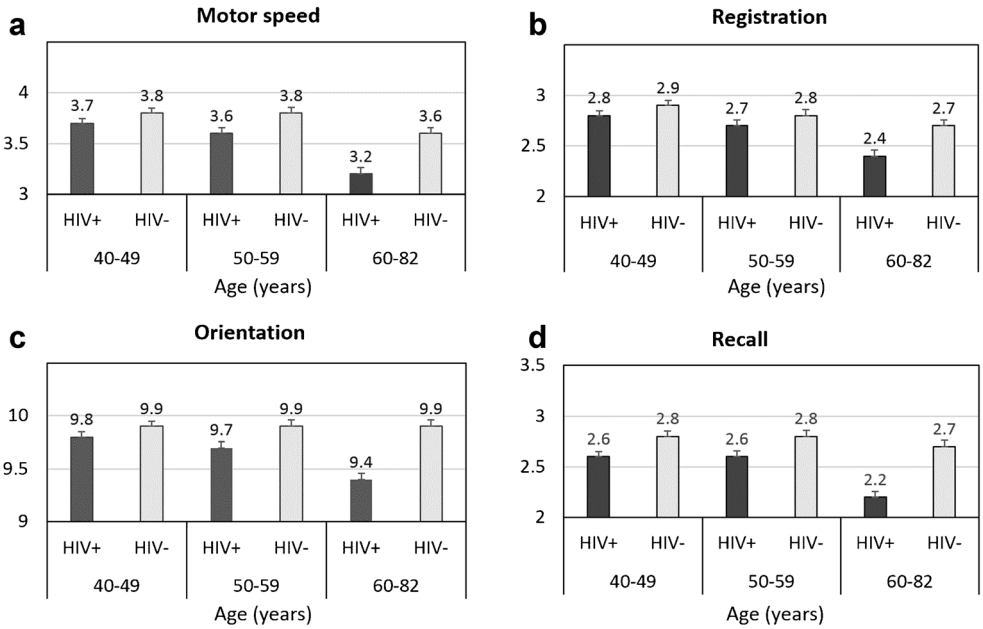

Fig. 1 Estimated means and standard errors of motor speed, recall, orientation and registration scores by HIV serotatus and age group. Adjusted for education, depressive symptoms and hypertension

Table 3 Factors associated with neurocognitive impairment using the IHDS and MMSE in HIV-infected participants only (n = 345)

	NCI using IHDS (≤ 10)				NCI using MMSE			
	Crude OR (95% CI)	p	Adjusted OR (95% CI) [a]	p	Crude OR (95% CI)	p	Adjusted OR (95% CI)[a]	p
Age, y								
40–49	1.00	–			1.00		1.00	
50–59	1.35 (0.80–2.26)	0.260	1.77 (0.98–3.21)	0.060	1.26 (0.60–2.64)	0.551	1.38 (0.62–3.07)	0.433
60–82	2.51 (1.47–4.29)	<.001	2.91 (1.52–5.58)	0.001	3.07 (1.60–5.89)	<.001	3.20 (1.57–6.54)	0.001
Male	0.76 (0.46–1.26)	0.293			0.49 (0.26–0.90)	0.021	0.48 (0.24–0.92)	0.039
Education								
Illiterate	1.00	–	1.00	–	1.00			
Primary	0.44 (0.21–0.93)	0.031	0.51 (0.22–1.21)	0.127	0.75 (0.32–1.74)	0.502		
Middle school or above	0.27 (0.13–0.56)	<.001	0.33 (0.14–0.78)	0.011	0.57 (0.25–1.29)	0.179		
BMI, kg/m^2								
< 18.5	1.67 (0.78–3.61)	0.189			1.00 (0.36–2.78)	1.000		
18.5–23.9	1.00	–			1.00			
≥ 24	1.31 (0.80–2.15)	0.285			1.13 (0.59–2.15)	0.717		
Current alcohol use	2.26 (0.93–5.48)	0.071			1.38 (0.49–3.87)	0.542		
Current smoker	1.96 (1.20–3.21)	0.007	2.78 (1.58–4.90)	<.001	0.89 (0.46–1.72)	0.731		
Hypertension	1.76 (1.06–2.90)	0.028			2.95 (1.63–5.34)	<.001	2.57 (1.34–4.94)	0.005
History of diabetes	1.61 (0.63–4.11)	0.317			1.80 (0.62–5.20)	0.279		
History of cardiovascular events	1.35 (0.44–4.10)	0.597			2.24 (0.67–7.53)	0.193		
Depressive symptoms	1.11 (1.06–1.16)	<.001	1.13 (1.07–1.19)	<.001	1.09 (1.03–1.15)	0.004	1.09 (1.03–1.16)	0.006
Insomnia symptoms	2.03 (1.19–3.46)	0.009			1.74 (0.92–3.29)	0.088		
Time since HIV diagnosis, y	0.97 (1.09–1.06)	0.511			0.90 (0.79–1.02)	0.093		
Nadir CD4 count ≥ 200, cells/μL	0.78 (0.51–1.19)	0.241			1.49 (0.85–2.61)	0.166		
Current CD4 count, cells/μL								
< 350	1.00	–	1.00	–	1.00		1.00	
350–499	0.64 (0.39–1.06)	0.081	0.60 (0.34–1.06)	0.080	0.96 (0.51–1.81)	0.910	1.17 (0.58–2.35)	0.669
500–799	0.89 (0.51–1.56)	0.681	0.85 (0.45–1.60)	0.607	0.38 (0.15–0.96)	0.039	0.40 (0.15–1.08)	0.070
≥ 800	0.12 (0.01–0.96)	0.046	0.06 (0.01–0.57)	0.014	0.51 (0.06–4.20)	0.529	0.62 (0.07–5.82)	0.678
Type of antiretroviral treatment								
ART naive	0.87 (0.44–1.71)	0.676	0.87 (0.41–1.85)	0.712	0.83 (0.34–1.98)	0.666	0.93 (0.36–2.38)	0.872
Ever 2NRTI + NVP	1.00	–	1.00		1.00		1.00	
Ever 2NRTI + EFV	0.38 (0.23–0.63)	<.001	0.39 (0.22–0.69)	0.001	0.36 (0.17–0.75)	0.007	0.39 (0.18–0.86)	0.020
Ever (2NRTI + EFV) and (2NRTI + NVP)	0.72 (0.36–1.46)	0.362	0.70 (0.33–1.53)	0.373	1.77 (0.81–3.87)	0.152	2.31 (0.98–5.43)	0.056
Other	0.97 (0.86–1.10)	0.621			0.79 (0.65–0.95)	0.013		
Current HIV viral load < 400 copies/mL	0.95 (0.35–2.56)	0.920			0.80 (0.22–3.02)	0.766		

Abbreviations: *ART* antiretroviral therapy, *BMI* body mass index, *CI* confidence interval, *EFV* efavirenz, *NCI* neurocognitive impairment, *NVP* nevirapine, *NRTI* nucleoside reverse transcriptase inhibitor, *OR* odds ratio

[a] Variables with $p < .10$ in univariable analysis were included in multivariable model, backward selection used with retention at a significance level of $p < .10$

vs 40–49 years) remained significant (OR, 3.28; 95% CI, 1.88–5.72; $p < .001$) in multivariable model. Again, similar as using a cut-off of ≤ 10 for IHDS (Table 3), age, education, depressive symptoms, current CD4 count ≥ 800 cells/μL and history of NVP treatment were independently associated with NCI using IHDS with a cut-off of ≤ 9 at significance level of $p < .05$ except for current smoker (data not shown). In subgroup analysis restricted to those on cART (n = 300), similar variables as in all HIV-infected participants were found to be significantly associated with NCI using IHDS with a cut-off of ≤ 9 except for current CD4 count ≥ 800 cells/μL (data not shown).

Discussion

Approximately a half of HIV-infected participants were detected to have NCI using the IHDS, which were similar to previous reports from Africa (Cross et al. 2013; Oshinaike et al. 2012), but higher than reports from developed countries (Ku et al. 2014). The discrepancy may be due to the older age of participants or/and the later initiation of cART in developing countries in these studies. In contrast, 17.1% of participants had NCI using the MMSE. This was consistent with previous observations that MMSE detected a lower rate of NCI than IHDS, possibly because of lacking sensitivity to HIV-related subcortical dysfunctions (Oshinaike et al. 2012). Consistent with other research (Bonnet et al. 2013; Oshinaike et al. 2012), HIV-infected patients were more likely to be cognitively impaired than similar but uninfected individuals. Furthermore, the prevalence of NCI was highest in the oldest age group. These support the previous findings that HIV and aging are independent risk factors for reduced neurocognitive performance (Ciccarelli et al. 2012; Valcour et al. 2011).

Importantly, in contrast to previous neuropsychological studies identifying either no interaction effect or interaction effect only on verbal memory (Ciccarelli et al. 2012; Scott et al. 2011; Seider et al. 2014; Valcour et al. 2011), we observed significant interaction effects between HIV infection and age on motor speed, orientation, registration and recall. Some neuroimaging studies also identified the interaction effects between HIV and aging in selective brain functions (Chang et al. 2013; Kuhn et al. 2017). This may be due to the fact that our study included a relatively large sample of older HIV-infected cases aged over 60 years, as suggested by Scott et al. that a lag occurs between when brain changes and when changes can be observed on neuropsychological tests (Seider et al. 2014). Post hoc analysis further indicated that the interaction effects on motor speed and recall were mainly attributed to the youngest HIV-uninfected age group and the oldest HIV-infected age group, whereas interaction effects on orientation and registration were mainly attributed to the oldest HIV-infected age group. These support the evidence that HIV infection and older age act synergistically to affect some domains of cognitive function. It is possible that HIV accelerates age-associated cognitive decline (Cohen et al. 2015; Hellmuth et al. 2014) but it is also possible that age exacerbates the adverse effects of HIV on NCI among older HIV-infected patients as prevalence of co-morbidities is rapidly increasing (Cysique and Brew 2014). Our findings further suggest that among HIV-infected population, different cognitive domains have different dynamic changes with age as a combined effect of HIV infection and aging, which may be attributed to different mechanisms.

In terms of HIV-related and treatment factors, we found that a much lower prevalence of NCI, comparable to the prevalence in HIV-uninfected individuals, was seen in those with current CD4 count above 800 cells /μL, which is the lower tail of the CD4 count distribution in HIV-infected persons and associated with ART initiation at earlier stage of HIV infection (Le et al. 2013). This may explain the findings from a previous study that low prevalence of NCI was observed among early diagnosed and treated HIV-infected patients (Crum-Cianflone et al. 2013). Also, we found that NVP in comparison to EFV was associated with more NCI, which appears to conflict with other reports indicating that EFV is associated with cognitive disorders (Ciccarelli et al. 2011; Winston et al. 2012). However, in these studies the drug for comparison was either not NVP (Ciccarelli et al. 2011) or undefined (Winston et al. 2012). NVP has a higher central nervous system (CNS) penetration-effectiveness (CPE) rank than EFV and high CPE is associated with poor neuropsychological tasks (Libertone et al. 2014). Animal studies indicated that both NVP and EFV had CNS toxicity (Romão et al. 2011; Streck et al. 2008). These combined with our results suggest the possibility that NVP may increase the risk for NCI. But, two possible explanations should be noted. First, NVP is recommended to be prescribed to patients with lower CD4 count as compared to EFV. The other is that clinicians avoid to use EFV in patients with history of psychiatric disorders or suspected to have some level of NCI.

Other factors for NCI identified in HIV-infected patients included lower education level, smoking, hypertension, depressive and insomnia symptoms. Cognitive reserve has been found to be a protective factor for older HIV-positive adults who are at high risk for cognitive decline, and education is an important component of cognitive reserve (Foley et al. 2012; Morgan et al. 2012). It should be also noted that education and depression may be the factors impacting neuropsychological testing performance (Antinori et al. 2007). The association of depression with NCI was consistent with other research (Cross et al. 2013) and should be noted because it is highly prevalent in HIV-infected patients. Current guidelines recommend the initiation of ART in all HIV-infected individuals regardless of CD4 count. Consistent with other studies (Wright et al. 2010, 2015), the association of overweight and hypertension with NCI underscores the importance of attention to the metabolic side effects of treatment and its combined effects with HIV infection and aging on NCI.

Our study had several limitations. We conducted a cross-sectional study, hence could not assess temporality or causation between factors of interest and the development of NCI. Second, NCI was detected by IHDS and MMSE, a full battery of neurocognitive tests to diagnose NCI was not administered. The major issue with IHDS is its relatively lower specificity when using a high cut-off point for positive screen although with high sensitivity (Goodkin et al. 2014), but our sensitivity analysis revealed that there is not much change in significant variables identified when using a cut-off of ≤ 9 for IHDS. In addition, the relatively short duration of treatment limited the

ability to explore the impact of metabolic changes associated with treatment on the development of NCI.

In conclusion, we found that HIV and aging act synergistically on several domains of cognitive function, and also such interaction effects are mainly attributed to the inferior performance of older HIV-infected patients. Additional follow-up studies are warranted to observe the trajectories of cognitive changes among HIV-infected versus HIV-uninfected individuals with NCI. In addition, our findings suggest that early diagnosis of HIV infection and early treatment initiation that restoring or maintaining CD4 count above 800 cells/μL may prevent or reverse the presence of NCI, but extra attention should be given to the metabolic changes and other adverse effects due to long-term treatment and their impact on the development of NCI.

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Authors' Contributions Y. D. and N. H. conceived and designed the study. Y. D. and H. L. supervised the participant recruitment and data collection. M. G., W. S., and Q.W. recruited the participants and collected data. Y. D. analyzed the data and wrote the first draft of the manuscript. All authors contributed to data interpretation and writing of the manuscript.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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