Altered neuropsychological performance and reduced brain volumetrics in people living with HIV on integrase strand transfer inhibitors

Jane A. O'Halloran[a], Sarah A. Cooley[b], Jeremy F. Strain[b], Anna Boerwinkle[b], Robert Paul[c], Rachel M. Presti[a] and Beau M. Ances[b,d]

Objectives: Neuropsychiatric symptoms have been reported in people living with HIV (PLWH) on integrase strand transfer inhibitors (INSTIs) in postmarketing analysis. Limited data exist regarding brain integrity (function and structure) in PLWH prescribed INSTIs compared with other HIV treatment regimens.

Design: A cross-sectional analysis of PLWH on combined antiretroviral therapy aged more than 18 years at a single institution.

Methods: Neuropsychological tests were administered to calculate domain deficit scores in learning/memory, executive function and motor/psychomotor domains. Cortical and subcortical volumes from MRI were obtained using the FreeSurfer software suite (v5.3).

Results: Of 202 participants, median age 55 (48, 60) years old, 49% were on INSTI-based combined antiretroviral therapy. PLWH on INSTIs were similar to individuals on non-INSTIs in terms of age, sex, race, education years, smoking history, depression scores, psychiatric medication use, presence of hepatitis C infection, history of substance use, HIV infection duration and recent or nadir $CD4^+$ T-cell count. Participants in the INSTI group performed worse than non-INSTI users in the verbal learning and memory domain [1.5 (interquartile range 0, 2.5) versus 1 (0, 2); $P = 0.016$]. The INSTI and non-INSTI groups were similar for other cognitive domains. Frontal, brain stem and cerebellar volumes were reduced in INSTI compared with non-INSTI users (all $P = <0.05$).

Conclusion: We demonstrated modest differences in learning/memory performance and smaller brain volumes in PLWH on INSTI-based regimens compared with non-INSTI users. Prospective studies are needed to define mechanisms and the clinical significance of reduced brain integrity in PLWH on INSTIs.

AIDS 2019, **33**:1477–1483

Keywords: antiretroviral therapy, brain volumetrics, HIV, integrase strand transfer inhibitors, neuroimaging, neuropsychological performance

[a]Division of Infectious Diseases, Department of Medicine and, [b]Department of Neurology, Washington University School of Medicine, [c]Missouri Institute of Mental Health, University of Missouri St. Louis, and [d]Hope Center, Washington University in St. Louis, St. Louis, Missouri, USA.

Correspondence to Jane A. O'Halloran, MB, BCh, BAO, PhD, Division of Infectious Diseases, Department of Medicine, Washington University School of Medicine, 4523 Clayton Ave, Campus Box 8051, St. Louis, MO 63110, USA.

Tel: +1 314 454 8354; e-mail: janeaohalloran@wustl.edu

Received: 20 January 2019; revised: 20 March 2019; accepted: 24 March 2019.

DOI:10.1097/QAD.0000000000002236

ISSN 0269-9370

Introduction

HIV-associated neurocognitive disorder (HAND) continues to occur in people living with HIV (PLWH), even in the era of combined antiretroviral therapy (cART) [1–3]. The prevalence of HAND is less common among virally suppressed PLWH when compared with demographically similar individuals with detectable viral load [4]. Similarly, studies report lower frequencies of progressive neuropsychological decline [5,6] and/or structural brain changes in virally suppressed PLWH [7]. However, concerns remain about iatrogenic effects of cART on brain integrity (function and structure), which may contribute to HAND. The nonnuclease reverse transcriptase inhibitors (NNRTI), especially efavirenz (EFV), have been linked to incident neuropsychiatric adverse events and worsening cognition [8,9]. NNRTIs have been replaced as first line therapy by integrase strand transfer inhibitors (INSTIs).

Although INSTIs were well tolerated in clinical trials, concerns have emerged regarding the risk of neuropsychiatric symptoms. Several postmarketing studies have reported insomnia and depressive symptoms among PLWH who initiated dolutegravir (DTG)-based [10–12] or raltegravir (RAL)-based regimens [13–15]. However, studies of the effects of INSTIs on brain function and structure are lacking. To address this gap in knowledge, we examined neuropsychological performance and brain volumetrics in a cohort of PLWH on INSTI-based regimens compared with a well matched group of PLWH receiving non-INSTI-based regimens.

Methods

Patient population and study design

We performed a cross-sectional analysis of eligible PLWH enrolled in ongoing research studies conducted at our institution between February 2012 and June 2017, who were 18 years or older, on stable cART and who had neuropsychological performance assessment and neuroimaging results. Participants were excluded if they had less than 7 years of education; a history of confounding neurological disorders including epilepsy, dementia or stroke; current or past opportunistic central nervous system infection; a history of brain injury with loss of consciousness for greater than 30 min; or evidence of intoxication on the day of assessment. All participants provided informed written consent approved by the institutional review board at Washington University in Saint Louis (WUSTL). Participants in this analysis were representative of PLWH followed at the WUSTL Infectious Diseases Clinic (clinic population 70% men, 70% African American, median age 45 years old).

Clinical and radiological assessments

Demographic data, HIV parameters including cART history, plasma $CD4^+$ T-cell counts and HIV RNA, medications (including psychiatric medications) and history of recent substance use (self-reported and urine drug screen verified) were collected. Date of HIV diagnosis was verified using medical records.

Neuropsychological assessment

Neuropsychological performance was evaluated to identify potentially clinically relevant differences between the two groups [16,17]. Neuropsychological tests were divided into three domains: executive function, learning/memory and motor/psychomotor speed. Executive function was assessed using Letter Number Sequencing [18], Trail Making Test B (Trail B) [19], Letter fluency (FAS) [20] and Verb fluency [21]. Learning/memory was assessed by Hopkins Verbal Learning Test-Revised [22] total score across three learning trials and total score on the delayed trial [22]. Motor/psychomotor speed was assessed by the Trail Making Test A (Trail A) [19], Grooved Pegboard dominant and nondominant hands [23] and Digit-Symbol [18]. Each raw score was converted to a standardized score using demographically corrected norms [18,24–28]. T scores were then converted to a deficit score by assigning a value from 0 (normal) to 5 (severe impairment) for each test [29]. Within each domain, tests were averaged to form a domain deficit score (DDS). DDS scores were averaged to form the total deficit score (TDS). Scores greater than or equal 0.5 were considered abnormal.

Mood and sleep assessment

Depressive symptoms were assessed using the Beck Depression Inventory II [30]. Pittsburgh Sleep Quality Index (PSQI) [31], Epworth Sleepiness Scale [32] and Stanford Sleepiness Scale [33] were used to assess daytime somnolence and sleep quality.

Imaging acquisition

Neuroimaging was performed using a 3T Siemens Tim Trio MR scanner (Siemens AG, Erlangen, Germany) with a 12-channel head coil. A high-resolution, three-dimensional, sagittal, magnetization-prepared rapid gradient echo scan T1 scan was acquired (repetition time = 2400 ms, echo time = 3.16 ms, flip angle = 8, inversion time = 1000 ms, voxel size = $1 \times 1 \times 1$ μl voxels, $256 \times 256 \times 256$ acquisition matrix, 162 slices).

Volumetrics

All cortical and subcortical volumes were obtained using the FreeSurfer software suite (v5.3) (Martinos Center, Harvard University, Boston, Massachusetts, USA). Each individual's FreeSurfer segmentation was rigorously inspected and corrected when necessary by a trained research technician. Frontal [frontal pole, precentral gyrus, inferior frontal gyrus (pars opercularis, pars orbitalis, par triangularis)], parietal (superior and inferior

regions), temporal (transverse, inferior and superior temporal regions), occipital (lateral occipital, lingual and cuneus), cerebellar and brain stem regions were examined. Each volume was adjusted for intracranial volume to correct for head size.

Statistical analysis

Continuous variables were expressed as median and interquartile range (IQR) or mean and SD according to distribution. Categorical variables were expressed in percentages. Between-group differences were compared using Mann–Whitney *U* tests or Students *t* tests depending on the distribution of the variable being examined. A binary logistic regression model was used to assess the association between clinical parameters and neuropsychological performance. Variables that were significantly different between the two groups (*P* values < 0.05) were included in the multivariate model. In addition, some variables that were considered clinically relevant, but did not differ between the groups, were also included. *P* values less than 0.05 were considered statistically significant. Analyses were performed using IBM SPSS Statistics for Window, version 24 (IBM SPSS Corp., Armonk, New York, USA) and GraphPad Prism version 7.0 (GraphPad Software Inc, San Diego, California, USA).

Results

Of the 202 participants included in the study, the median (IQR) age was 55 (48, 59) years old, 152 (75%) were men and 136 (67%) were African American. A total of 99 (49%) were on INSTI-based ART regimens, and 103 (51%) were taking non-INSTI-based regimens. Baseline demographics are shown in Table 1.

The two cART groups did not differ in rates of current substance use, and rates of smoking and alcohol consumption were similar for both groups. There was no difference in depressive symptoms as measured by the Beck Depression Inventory II or the proportion of participants on medication(s) to treat psychiatric conditions overall or by class (Supplementary Table 2, http://links.lww.com/QAD/B476). The median (IQR) number of psychiatric medications was 0 (0, 1) for both groups. There was no difference in the proportion of participant that were prescribed more than one psychiatric medication [non-INSTI 19 (18%) compared with the INSTI group 24 (24%); $P = 0.31$].

There was no difference in daytime somnolence, sleep quality or sleep disturbance between the two groups [global PSQI score (non-INSTI 7 (4, 10) versus INSTI 7

Table 1. Baseline characteristics.

Characteristics	Non-INSTI, $n = 103$	INSTI, $n = 99$	*P* value
Age in years (median, IQR)	55 (45, 60)	54 (50, 58)	0.91
Males, *N* (%)	78 (76)	74 (75)	0.87
Black, *N* (%)	69 (67)	67 (68)	0.92
Education in years, mean (SD)	13 (3)	13 (2.7)	0.58
Right handedness, *N* (%)	88 (86)	84 (85)	0.77
Beck Depression Inventory-II (median, IQR)	10 (2, 17)	7 (4, 16)	0.99
Psychiatric medications, *N* (%)	38 (37)	46 (47)	0.17
BMI (median, IQR)	26.5 (23.5, 31)	26.2 (22.7, 29.4)	0.27
Substance use			
Positive urine drug screen, *N* (%)	67 (65)	59 (60)	0.42
Cannabis	53 (52)	44 (44)	
Cocaine	11 (11)	14 (14)	
Opioids	5 (5)	6 (6)	
Methamphetamine	2 (2)	8 (8)	
Benzodiazepines	19 (18)	15 (15)	
Self-reported illicit drug use, *N* (%)	56 (54)	42 (42)	0.09
Cannabis	40 (39)	33 (33)	
Cocaine	8 (8)	11 (11)	
Opioids	8 (8)	3 (3)	
Methamphetamine	1 (1)	1 (1)	
Benzodiazepines	9 (9)	8 (8)	
Prescribed opiate therapy	11 (11%)	7 (7%)	0.38
Alcohol use (self-reported), *N* (%)	60 (58)	60 (61)	0.73
Current smoker, *N* (%)	53 (52)	46 (47)	0.48
Hepatitis C, *N* (%)	8 (8)	10 (10)	0.56
Testosterone replacement therapy	4 (4)	6 (6)	0.48
HIV parameters			
Duration of HIV infection (median, IQR)	185 (89, 263)	200 (109, 264)	0.76
Duration of current regimen (months; median, IQR)	60 (24, 89)	18 (6, 35)	<0.001
Nadir $CD4^+$ (cells/μl) (median, IQR)	185 (35, 302)	128 (22, 274)	0.42
Recent $CD4^+$ (cells/μl) (median, IQR)	604 (446, 834)	548 (321, 782)	0.10
HIV RNA < 20 copies/ml, *N* (%)	85 (83)	79 (80)	0.33
HIV RNA < 200 copies/ml, *N* (%)	95 (97)	91 (95)	0.50

INSTI, integrase strand transfer inhibitor; IQR, interquartile range.

(4, 11)); $P = 0.79$]; Epworth Sleepiness Scale [non-INSTI 8 (5, 12) versus INSTI 7 (4, 9); $P = 0.09$] and Stanford Sleepiness Scale [non-INSTI 2 (1, 3) versus INSTI 2 (1, 3); $P = 0.79$]. There was no difference in the self-reported or confirmed length of time since HIV diagnosis between the groups. Nadir and recent $CD4^+$ T-cell counts were similar in both groups as were the proportion of participants with HIV RNA less than 200 or less than 20 copies/ml. For the participants on an INSTI-based regimen, 40 (40%) were on RAL, 29 (29%) on elvitegravir (ETG) and 30 (30%) on DTG.

Although there were no differences between the groups in the proportion of participants on protease inhibitors, a higher proportion of participants in the non-INSTI group were on NNRTIs compared with those in the INSTI group [67 (65%) versus 19 (19%); $P < 0.001$]. The most commonly used NNRTI was EFV with 43 (42%) individuals prescribed this medication in the non-INSTI group compared with 6 (6%) in the INSTI group ($P < 0.001$). Significantly, the proportion of participants who had received EFV as part of a previous regimen was similar for both groups [non-INSTI 34 (33%) compared with INSTI 39 (39%); $P = 0.35$].

The most common prescribed ART regimens for the INSTI group were tenofovir, emtricitabine (FTC), cobicistat, ETG (25%); abacavir (ABC) or tenofovir, lamivudine, DTG (16%) and ABC or tenofovir, FTC, RAL (14%). In the non-INSTI group, the most common regimens were tenofovir, FTC, EFV (38%); tenofovir, FTC, darunavir, ritonavir (12%) and tenofovir, FTC, atazanavir, ritonavir (11%). Within the INSTI group, 10% of participants were receiving nucleoside reverse transcriptase inhibitor-sparing regimens compared with 3% in the non-INSTI group. Reflecting the more recent approval of INSTIs, participants in the non-INSTI group had been on their current regimens for longer period compared with the INSTI group (60 versus 18 months; $P < 0.001$).

The learning/memory DDS was higher (worse) in the INSTI group compared with the non-INSTI group [1.5 (0, 2.5) versus 1 (0, 2); $P = 0.016$] (Table 2). This remained significant after correction for nadir $CD4^+$ T-cell count, duration of current cART regimen, current NNRTI or protease inhibitor use, current psychiatric medication use or having previously received another cART regimen [odds ratio 3.9 (confidence interval 1.4, 11.8); $P = 0.012$]. When INSTIs were included in the model as DTG or non-DTG INSTI, both DTG and non-DTG remained significant (Table 3). The proportion of PLWH with abnormal learning/memory domain scores (primarily within learning and retention) was significantly higher in the INSTI group compared with the non-INSTI group [73 (74%) versus 61 (59%), $P = 0.029$]. There was no difference in executive function or motor/psychomotor DDS. Participants in the INSTI group had worse TDS than those in the non-INSTI group [0.75 (0.33, 1.25) versus 0.5 (0.25, 1); $P = 0.049$] that primarily reflects deficits in the learning/memory domain score. The proportion of PLWH with abnormal TDS was also significantly higher in the INSTI group compared with the non-INSTI group [70 (71%) versus 57 (55%), $P = 0.024$].

Table 2. Between group domain and total deficit scores.

Deficit scores	Non-INSTI, $n = 103$		INSTI, $n = 99$		*P* value
Learning/memory	1	(0, 2)	1.5	(0, 2.5)	0.016
Executive function	0.25	(0, 0.75)	0.5	(0, 1)	0.85
Psychomotor/ Processing speed	0	(0, 0.5)	0	(0.5)	0.98
Total deficit	0.5	(0.25, 1)	0.75	(0.33, 1.25)	0.049

Data presented are median (IQR). INSTI, integrase strand transfer inhibitors; IQR, interquartile range.

Table 3. Multivariable analysis of learning/memory domain deficit scores.

Variable	Odds ratio	95% CI	*P* value
Current dolutegravir use	4.7	1.2, 18.4	0.028
Current nondolutegravir use	3.7	1.2, 11.7	0.026
Current NNRTI use	1.2	0.4, 3.4	0.7
Current protease inhibitor use	1.2	0.4, 3.2	0.8
Previous ART	1.1	0.4, 2.8	0.8
Current psychiatric medications	0.7	0.3, 1.4	0.3
Duration of current ART	1.0	0.9, 1.1	0.3
Nadir $CD4^+$ T-cell count	1.0	0.9, 1.0	0.4

ART, antiretroviral therapy; CI, confidence interval; NNRTI, nonnucleoside reverse transcriptase inhibitor. Variables that were significantly different between the two groups (*P* values <0.05) were included in the multivariate model. In addition, some variables that were clinically significant but did not differ between the groups were also included.

As the effects observed could be due to exposure to multiple cART regimens, we performed an additional analysis within a subset of participants (44, 21.7%) who were on their first cART regimen (11 on INSTI-based regimens and 33 on non-INSTI-based regimens). We observed worse performance in the learning/memory domain in the INSTI group [2.5 (0.5, 3) compared with the non-INSTI group 1 (0.125, 2); $P = 0.021$]. No significant differences were seen in the executive function or motor/psychomotor domains when comparing the two subgroups. Participants on their first cART regimen had similar demographics to the overall cohort: median age 54 years old (IQR 40, 63), 73% African American, 68% men, 39% using psychiatric medication(s) and history of substance use (61%). Similarly, for those on first ART regimens there was no difference in age, sex, race, substance use history or use of psychiatric medication between INSTI and non-INSTI-based regimens (all $P > 0.05$).

Overall, participants on INSTIs had lower total grey volume and subcortical grey volumes compared with

those receiving non-INSTI regimens. Frontal, brain stem and cerebellar volumes were smaller for the INSTI group (all $P < 0.05$) (Supplementary Table 3, http://links.lww.com/QAD/B476). There was no significant difference in other regional cortical or subcortical white matter volumes between the groups.

Discussion

Antiretroviral drugs have previously been associated with neuropsychiatric symptoms including dizziness, sleep disturbance, abnormal dreams, anxiety and depression. Despite this, limited data exist in relation to the effect of specific antiretroviral drugs on neuropsychological function [34]. The primary aim of this study was to determine if differences existed in neuropsychological function and brain structure in PLWH on INSTI-based cART compared with a well matched group on non-INSTI-based cART. Here, we demonstrated worse learning/memory performance and smaller regional brain volumes in PLWH on INSTI-based regimens. This could be due to multiple possible causes including direct neurotoxicity of the INSTI cART regimens themselves, variation in cerebrospinal fluid (CSF) concentrations of different cART agents, the effect of a recent switch of regimen to an INSTI-based regimen or different drug interactions between INSTI versus protease inhibitor or NNRTI-based cART.

Although not definitive, direct neurotoxicity has been reported *in vitro* with ART. cART has been shown to lead to oxidative stress and neuronal damage and may account for some of the observed reductions in brain volumes [35]. A recent autopsy study demonstrated higher likelihood of neuronal phospho-tau lesions in the putamen of patients on darunavir, whereas ritonavir use was associated with marked microgliosis in the putamen, both suggestive of cerebral degenerative changes. However, there was insufficient INSTI use to allow for their assessment [36]. Significantly, a recent study in primary rat neuroglial cultures demonstrated neurotoxicity of ETG but not RAL or DTG [37]. Clinically, concerns have been raised regarding increased prevalence of neural-tube defects (NTD) in infants born to mothers treated with DTG at the time of conception. In a surveillance study that is currently ongoing in Botswana, the prevalence of NTD in those who received DTG-based therapy was 0.94% compared with 0.12% in those in non-DTG-based regimens. Neurotoxicity concerns have resulted in cART guideline changes for women of childbearing age. However, limited data exist on differences in brain volumes according to type of cART in PLWH [38].

Interindividual variabilities in CSF penetration of antiretrovirals may contribute to the relative risk of neuropsychiatric side effects. Higher CSF concentrations of certain medications can produce neurotoxicity, whereas lower concentrations may increase viral replication and inflammation in the central nervous system [39,40]. Neuropsychiatric symptoms in PLWH have been associated with interindividual variability in CSF concentration of RAL [41]. EFV use was associated with improvement in neuropsychological testing, likely due to viral suppression; however, higher blood levels of EFV corresponded with worse neuropsychological performance [42]. The expression of neuropsychiatric symptoms may be due to complex interactions among HIV, cART and the host.

Previous studies have demonstrated neuropsychological dysfunction in individuals with both sleep disturbances and depression [43,44]. High prevalence of sleep disturbances have been reported in PLWH and have been associated with a myriad of factors including depression and specific antiretroviral drugs [45]. However, we did not observe differences in subjective sleep measures between the groups. Of note in a recent study that demonstrated increased DTG peak concentration in older (>60 years) PLWH, there was also no differences in sleep quality noted at 3 or 6 months [46].

Empirical data on INSTIs and neuropsychological function are limited. A small prospective study reported decline in neuropsychological function after 24 weeks of RAL in virally suppressed PLWH at least 60 years old [47]. Of note, a recent pilot study included comprehensive assessment of cerebral function parameters including cognitive function, CSF parameters and MRI imaging in 20 patients who switched from a RAL-based regimen to a DTG-based regimen and did not demonstrate changes in any parameters [48]. Here we present data indicating a modest worsening in the learning and memory domain of PLWH on INSTI-based regimens. We also observed significant lower brain volumes, especially within the frontal, brain stem and cerebellar regions. Frontotemporal connections are involved in multiple cognitive functions including learning and memory, and are affected in PLWH [49].

The current study has several limitations. Although the groups are well matched for baseline demographics as well as HIV clinical variables, the cross-sectional design means that it is subject to the inherent biases associated with this study design and does not allow examination of causal pathways. As is common in the management of PLWH for several years, the majority of study participants had previous cART treatment but data on the reason for switching regimens were not available. Although many study participants were likely switched to regimens with better safety and tolerability profiles as part of routine standard of care, we cannot rule out potential channelling bias introduced by these switches. To account for this, the use of previous cART was included in our regression

model. To address this further, we examined the cohort of participants who were on their first cART regimen. Although the cohort was small, the learning/memory DDS was also worse in the subgroup on INSTIs in this analysis. This study is also prone to survival bias as some participants may have discontinued non-INSTI drugs prior to the time of analysis because of neuropsychiatric adverse events. Also as the non-INSTI group had been taking their current regimen much longer than the INSTI group, the non-INSTI group may be selected for participants who tolerate NNRTI or protease inhibitor therapy. Finally, data on the participant's functional or menopausal status were not available [48].

In conclusion, in this large cohort of PLWH, the use of INSTI-based regimens were associated with modestly reduced neuropsychological performance in the learning and memory domain as well as lower brain volumes when compared with their counterparts on non-INSTI-based regimens. These findings emphasize the importance of clinical monitoring of PLWH being switched to INSTI-based regimens. Longitudinal studies with preplanned hypotheses are needed to confirm the observed findings and explore potential underlying mechanisms.

Acknowledgements

The study was supported by grants from the National Institute of Nursing Research (NINR) R01-NR015738, R01-NR012657 and R01-NR014449 and the National Institute of Mental Health (NIMH) R01-MH118031, BrightFocus Foundation A2018817F.

Conflicts of interest

There are no conflicts of interest.

References

1. Simioni S, Cavassini M, Annoni JM, Rimbault Abraham A, Bourquin I, Schiffer V, *et al*. **Cognitive dysfunction in HIV patients despite long-standing suppression of viremia.** *AIDS* 2010; **24**:1243–1250.
2. Heaton RK, Clifford DB, Franklin DR Jr, Woods SP, Ake C, Vaida F, *et al*. **HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER Study.** *Neurology* 2010; **75**:2087–2096.
3. Heaton RK, Franklin DR, Ellis RJ, McCutchan JA, Letendre SL, Leblanc S, *et al*. **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.
4. Su T, Schouten J, Geurtsen GJ, Wit FW, Stolte IG, Prins M, *et al*. **Multivariate normative comparison, a novel method for more reliably detecting cognitive impairment in HIV infection.** *AIDS* 2015; **29**:547–557.
5. Sacktor N, Skolasky RL, Seaberg E, Munro C, Becker JT, Martin E, *et al*. **Prevalence of HIV-associated neurocognitive disorders in the Multicenter AIDS Cohort Study.** *Neurology* 2016; **86**:334–340.
6. Heaton RK, Franklin DR Jr, Deutsch R, Letendre S, Ellis RJ, Casaletto K, *et al*. **Neurocognitive change in the era of HIV combination antiretroviral therapy: the longitudinal CHARTER study.** *Clin Infect Dis* 2015; **60**:473–480.
7. Underwood J, Cole JH, Leech R, Sharp DJ, Winston A, CHARTER Group. **Multivariate pattern analysis of volumetric neuroimaging data and its relationship with cognitive function in treated HIV disease.** *J Acquir Immune Defic Syndr* 2018; **78**:429–436.
8. Ma Q, Vaida F, Wong J, Sanders CA, Kao YT, Croteau D, *et al*. **Long-term efavirenz use is associated with worse neurocognitive functioning in HIV-infected patients.** *J Neurovirol* 2016; **22**:170–178.
9. Ciccarelli N, Fabbiani M, Di Giambenedetto S, Fanti I, Baldonero E, Bracciale L, *et al*. **Efavirenz associated with cognitive disorders in otherwise asymptomatic HIV-infected patients.** *Neurology* 2011; **76**:1403–1409.
10. Clotet B, Feinberg J, van Lunzen J, Khuong-Josses MA, Antinori A, Dumitru I, *et al*. **Once-daily dolutegravir versus darunavir plus ritonavir in antiretroviral-naive adults with HIV-1 infection (FLAMINGO): 48 week results from the randomised open-label phase 3b study.** *Lancet* 2014; **383**:2222–2231.
11. Raffi F, Rachlis A, Stellbrink HJ, Hardy WD, Torti C, Orkin C, *et al*. **Once-daily dolutegravir versus raltegravir in antiretroviral-naive adults with HIV-1 infection: 48 week results from the randomised, double-blind, noninferiority SPRING-2 study.** *Lancet* 2013; **381**:735–743.
12. Walmsley SL, Antela A, Clumeck N, Duiculescu D, Eberhard A, Gutierrez F, *et al*. **Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection.** *N Engl J Med* 2013; **369**:1807–1818.
13. Gray J, Young B. **Acute onset insomnia associated with the initiation of raltegravir: a report of two cases and literature review.** *AIDS Patient Care STDS* 2009; **23**:689–690.
14. Eiden C, Peyriere H, Peytavin G, Reynes J. **Severe insomnia related to high concentrations of raltegravir.** *AIDS* 2011; **25**:725–727.
15. Harris M, Larsen G, Montaner JS. **Exacerbation of depression associated with starting raltegravir: a report of four cases.** *AIDS* 2008; **22**:1890–1892.
16. Gonzalez R, Heaton RK, Moore DJ, Letendre S, Ellis RJ, Wolfson T, *et al*. **Computerized reaction time battery versus a traditional neuropsychological battery: detecting HIV-related impairments.** *J Int Neuropsychol Soc* 2003; **9**:64–71.
17. Levine AJ, Hinkin CH, Castellon SA, Mason KI, Lam MN, Perkins A, *et al*. **Variations in patterns of highly active antiretroviral therapy (HAART) adherence.** *AIDS Behav* 2005; **9**:355–362.
18. Wechsler D. *WAIS-III: Wechsler adult intelligence scale*. San Antonio: Psychological Corporation; 1997.
19. Reitan RM, Davison LA. *Clinical neuropsychology: current status and applications*. New York: Hemisphere; 1974.
20. Borkowski JG, Benton AL, Spreen O. **Word fluency and brain damage.** *Neuropsychologia* 1967; **5**:135–140.
21. Piatt AL, Fields JA, Paolo AM, Troster AI. **Action (verb naming) fluency as an executive function measure: convergent and divergent evidence of validity.** *Neuropsychologia* 1999; **37**:1499–1503.
22. Benedict RH, Schretlen D, Groninger L, Brandt J. **Hopkins Verbal Learning Test–Revised: normative data and analysis of inter-form and test-retest reliability.** *Clin Neuropsychol* 1998; **12**:43–55.
23. Matthews CG, Klove H. *Instruction manual for the adult neuropsychology test battery*. Madison, WI: University of Wisconsin Medical School; 1964.
24. Piatt AL, Fields JA, Paolo AM, Koller WC, Troster AI. **Lexical, semantic, and action verbal fluency in Parkinson's disease with and without dementia.** *J Clin Exp Neuropsychol* 1999; **21**:435–443.
25. Heaton RK, Miller SW, Taylor MJIG. *Revised comprehensive norms for an expanded Halstead Reitan Battery: demographically adjusted neuropsychological norms for African American and Caucasian adults*. Lutz: Psychological Assessment Resources, Inc; 2004.
26. Gladsjo JA, Schuman CC, Evans JD, Peavy GM, Miller SW, Heaton RK. **Norms for letter and category fluency: demographic corrections for age, education, and ethnicity.** *Assessment* 1999; **6**:147–178.

27. Norman MA, Moore DJ, Taylor M, Franklin D Jr, Cysique L, Ake C, *et al*. **Demographically corrected norms for African Americans and Caucasians on the Hopkins Verbal Learning Test-Revised, Brief Visuospatial Memory Test-Revised, Stroop Color and Word Test, and Wisconsin Card Sorting Test 64-Card Version.** *J Clin Exp Neuropsychol* 2011; **33**:793–804.
28. Lucas JA, Ivnik RJ, Smith GE, Ferman TJ, Willis FB, Petersen RC, *et al*. **Mayo's Older African Americans Normative Studies: norms for Boston Naming Test, Controlled Oral Word Association, Category Fluency, Animal Naming, Token Test, WRAT-3 Reading, Trail Making Test, Stroop Test, and Judgment of Line Orientation.** *Clin Neuropsychol* 2005; **19**:243–269.
29. Carey CL, Woods SP, Gonzalez R, Conover E, Marcotte TD, Grant I, *et al*. **Predictive validity of global deficit scores in detecting neuropsychological impairment in HIV infection.** *J Clin Exp Neuropsychol* 2004; **26**:307–319.
30. Beck AT, Steer RA, Ball R, Ranieri W. **Comparison of beck depression inventories-IA and -II in psychiatric outpatients.** *J Pers Assess* 1996; **67**:588–597.
31. Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. **The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research.** *Psychiatry Res* 1989; **28**:193–213.
32. Johns MW. **A new method for measuring daytime sleepiness: the Epworth sleepiness scale.** *Sleep* 1991; **14**:540–545.
33. Hoddes E, Zarcone V, Smythe H, Phillips R, Dement WC. **Quantification of sleepiness: a new approach.** *Psychophysiology* 1973; **10**:431–436.
34. Dalwadi DA, Ozuna L, Harvey BH, Viljoen M, Schetz JA. **Adverse neuropsychiatric events and recreational use of efavirenz and other HIV-1 antiretroviral drugs.** *Pharmacol Rev* 2018; **70**:684–711.
35. Akay C, Cooper M, Odeleye A, Jensen BK, White MG, Vassoler F, *et al*. **Antiretroviral drugs induce oxidative stress and neuronal damage in the central nervous system.** *J Neurovirol* 2014; **20**:39–53.
36. Soontornniyomkij V, Umlauf A, Soontornniyomkij B, Gouaux B, Ellis RJ, Levine AJ, *et al*. **Association of antiretroviral therapy with brain aging changes among HIV-infected adults.** *AIDS* 2018; **32**:2005–2015.
37. Stern AL, Lee RN, Panvelker N, Li J, Harowitz J, Jordan-Sciutto KL, *et al*. **Differential effects of antiretroviral drugs on neurons in vitro: roles for oxidative stress and integrated stress response.** *J Neuroimmune Pharmacol* 2018; **13**:64–76.
38. Sanford R, Fellows LK, Ances BM, Collins DL. **Association of brain structure changes and cognitive function with combination antiretroviral therapy in HIV-positive individuals.** *JAMA Neurol* 2018; **75**:72–79.
39. Anderson AM, Munoz-Moreno JA, McClernon DR, Ellis RJ, Cookson D, Clifford DB, *et al*. **Prevalence and correlates of persistent HIV-1 RNA in cerebrospinal fluid during antiretroviral therapy.** *J Infect Dis* 2017; **215**:105–113.
40. Letendre SL, Ellis RJ, Everall I, Ances B, Bharti A, McCutchan JA. **Neurologic complications of HIV disease and their treatment.** *Top HIV Med* 2009; **17**:46–56.
41. Calcagno A, Cusato J, Simiele M, Motta I, Audagnotto S, Bracchi M, *et al*. **High interpatient variability of raltegravir CSF concentrations in HIV-positive patients: a pharmacogenetic analysis.** *J Antimicrob Chemother* 2014; **69**:241–245.
42. Clifford DB, Evans S, Yang Y, Acosta EP, Ribaudo H, Gulick RM, *et al*. **Long-term impact of efavirenz on neuropsychological performance and symptoms in HIV-infected individuals (ACTG 5097s).** *HIV Clin Trials* 2009; **10**:343–355.
43. Miller MA. **The role of sleep and sleep disorders in the development, diagnosis, and management of neurocognitive disorders.** *Front Neurol* 2015; **6**:224.
44. Burt DB, Zembar MJ, Niederehe G. **Depression and memory impairment: a meta-analysis of the association, its pattern, and specificity.** *Psychol Bull* 1995; **117**:285–305.
45. Allavena C, Guimard T, Billaud E, De la Tullaye S, Reliquet V, Pineau S, *et al*. **Prevalence and risk factors of sleep disturbance in a large HIV-infected adult population.** *AIDS Behav* 2016; **20**:339–344.
46. Elliot ER, Wang X, Singh S, Simmons B, Vera JH, Miller RF, *et al*. **Increased dolutegravir peak concentrations in people living with HIV aged 60 and over and analysis of sleep quality and cognition.** *Clin Infect Dis* 2019; **68**:87–95.
47. Vera JH, Jackson A, Dickinson L, Else L, Barber T, Mora-Peris B, *et al*. **The pharmacokinetic profile of raltegravir-containing antiretroviral therapy in HIV-infected individuals over 60 years of age.** *HIV Clin Trials* 2015; **16**:39–42.
48. Moro-Peris B, Else L, Vera-Rojas J, Petersen C, Khan M, Penchala SD, *et al*. **Cerebral function parameters in people living with HIV switching integrase inhibitor**. *Conference on Retroviruses and Opportunistic Infections*, Seattle; 2019.
49. Sanford R, Ances BM, Meyerhoff DJ, Price RW, Fuchs D, Zetterberg H, *et al*. **Longitudinal trajectories of brain volume and cortical thickness in treated and untreated primary human immunodeficiency virus infection.** *Clin Infect Dis* 2018; **67**:1697–1704.