Can high central nervous system penetrating antiretroviral regimens protect against the onset of HIV-associated neurocognitive disorders?

Matteo Vassallo[a,b], Jacques Durant[a], Virginie Biscay[a], Christine Lebrun-Frenay[c], Brigitte Dunais[d], Muriel Laffon[c], Alexandra Harvey-Langton[a], Jacqueline Cottalorda[e], Michel Ticchioni[f], Helene Carsenti[a], Christian Pradier[d] and Pierre Dellamonica[a]

Objective: To assess changes over time in neuropsychological test results (NPr) and risk factors among a regularly followed HIV-infected patient population.

Methods: Prospective cohort of HIV-infected patients randomly selected to undergo neuropsychological follow-up. Test score was adjusted for age, sex and education. Patients were divided into five groups: normal tests, neuropsychological deficit (one impaired cognitive domain), asymptomatic neurocognitive disorders (ANIs), mild neurocognitive disorders (MNDs) and HIV-associated dementia (HAD). Demographic and background parameters including CSF drug concentration penetration effectiveness (CPE) score 2010 were recorded. Changes in NPr and associated risk factors were analyzed.

Results: Two hundred and fifty-six patients underwent neuropsychological tests and 96 accepted follow-up approximately 2 years later. The groups were comparable. Upon neuropsychological retesting, six patients improved, 31 worsened and 59 were stable. The proportion of patients with HIV-associated neurocognitive disorders (HANDs) rose from 26 to 45%, with ANIs and MNDs still mostly represented. Most patients initially diagnosed with HANDs remained stable, five of 25 showed clinical improvement and three of 25 deteriorated. Of 33 patients with normal tests, four deteriorated, whereas 24 of 38 with initial neuropsychological deficit had poorer NPr, and contributed most of the new HAND cases. Patients with clinical deterioration had a lower CPE score both at inclusion (6.9 vs. 8.1; $P = 0.005$) and at the end of follow-up (7.2 vs. 7.8; $P = 0.08$) than those with improved or stable performance. This was confirmed by multivariate analysis.

Conclusion: Patients with higher CPE scores upon inclusion and at the end of follow-up were at lower risk of clinical worsening, suggesting that combination antiretroviral therapy with better CSF penetration could protect against cognitive deterioration.

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[a]Department of Infectious Diseases, L'Archet Hospital, University of Nice, [b]Department of Internal Medicine, Cannes General Hospital, [c]Department of Neurology, Pasteur Hospital, [d]Department of Public Health, L'Archet Hospital, [e]Virology Laboratory Unit, L'Archet Hospital, and [f]Immunology Laboratory Unit, L'Archet Hospital, University of Nice, France.

Correspondence to Matteo Vassallo, MD, Cannes General Hospital, Department of Internal Medicine, 15 avenue des Broussailles, 06400 Cannes (France).

E-mail: m.vassallo@ch-cannes.fr
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Background

The prevalence of HIV-associated neurocognitive disorders (HANDs) remains high (15–50%) in the era of combination antiretroviral therapy (cART) [1–7].

Such persistence of HANDs may reflect a failure of antiretrovirals to reverse neurological damage, result from prolonged survival or illustrate the effects of sustained central nervous system (CNS) inflammation [1,8]. Other authors have suggested a potential neurotoxic role of antiretrovirals in the persistence of HANDs [9].

New insights in the treatment of HANDs have been provided by the concentration penetration effectiveness (CPE) score, which ranks antiretrovirals according to their capability to penetrate into the CNS [10].

Indeed, brain penetration of antiretrovirals appears crucial to achieve the goal of maximal HIV suppression, but it is difficult to assess how well cerebrospinal fluid (CSF) drug concentrations reflect parenchymal diffusion of molecules [1].

Moreover, dynamics of cognitive changes over time have been essentially studied on patients initiating or modifying treatment and results are contradictory in terms of the clinical benefits of choosing drug combinations with high CNS penetration [11–14].

Indeed, Cysique *et al.* [11] showed that high CNS-penetrating drugs are linked to greater improvement in neuropsychological performance, whereas Marra *et al.* [12] showed clinical worsening when switching to high penetrating regimens.

An ongoing unanswered question is whether antiretrovirals with high CNS penetration protect against cognitive deterioration, and at present there is no evidence to support the initiation of cART with better CNS-penetrating molecules for preventing HANDs [1–16].

Neuradapt is a study on the prevalence and risk factors for neurocognitive impairment in a population of randomly selected HIV-infected patients. In a cross-sectional study, we previously showed that microbial translocation, hepatitis C co-infection and high HIV-DNA proviral load were risk factors for HANDs [7]. We subsequently performed a follow-up analysis, in order to measure changes over time in neuropsychological performance and to identify factors linked to clinical deterioration.

In particular, we focused on the CPE score and its potential impact on clinical outcome.

Methods

Study design and participants

We randomly selected HIV-1-infected patients above 18 years of age among patients followed in the Department of Infectious Diseases at Nice University Hospital. No limits were set concerning $CD4^+$ cell count or HIV viral load.

Exclusion criteria included active opportunistic infection, a change in psychotropic therapy within the past 3 weeks or any neurological history. Patients were asked to provide informed consent. The study was approved by the Montpellier Ethics Committee.

Each patient performed a wide range of neuropsychological tests administered by a single trained neuropsychologist.

Tests explored a wide spectrum of cognitive domains: learning and recall episodic memory, attention/concentration, working memory, executive functions, language, visual agnosia and motor/psychomotor speed.

The following neuropsychological tests were performed:

(1) Mini Mental State Evaluation (MMSE) for evaluation of global cognitive function
(2) Grober and Buschke test for episodic memory (learning and recall)
(3) 'Four seconds' Paced Auditory Serial Addition Task (PASAT) for attention/concentration and working memory
(4) Stroop test for attention/concentration and speed of information processing
(5) Modified Card Sorting test for executive functions
(6) Motor and Psychomotor test (timed finger tapping and timed alternating hand sequence test) for motor and psychomotor speed abilities
(7) Verbal Fluency test for executive functions and language
(8) Protocole Montreal-Toulouse d'Evaluation des Gnosies Visuelles for visual agnosia

The neuropsychological scores from each test were transformed into z-scores as described elsewhere [12], and were adjusted for age, sex and years of education, using standardized norms. The mean duration of tests was 90 min per patient.

According to the American Academy of Neurology (AAN) revised criteria [17], the definition of HAND includes the three following categories:

(1) Asymptomatic neurocognitive disorder (ANI), involving at least two cognitive domains and documented by a performance of at least 1 SD below the mean on neuropsychological tests, without interference in everyday functioning. The asymptomatic characteristics of

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impairment were defined by the Instrumental Activity of Daily Living short version battery and by interviewing the patients and their family.
(2) Mild neurocognitive disorder (MND), involving at least two cognitive domains and documented by a performance of at least 1 SD below the mean on neuropsychological tests, with mild interference in daily functioning.
(3) HIV-associated dementia (HAD), involving at least two cognitive domains and documented by performing below 2 SD from the normative mean on neuropsychological tests, with marked interference in daily functioning.

According to their neuropsychological test results, patients were classified into two main groups:

(1) Those with HANDs (i.e. ANI, MCD or HAD)
(2) Those without HANDs [patients included in this category could have either normal tests, or one cognitive domain impaired, with 1 or 2 SD below the mean (which we defined as neuropsychological deficit)]

Demographic parameters and background measurements at inclusion

In order to correlate results to neuropsychological test group, the following parameters were recorded at inclusion for each patient: age, sex, education, comorbid conditions [hypertension, smoking, dyslipidemia, illicit drug use (IDU), diabetes], use of psychotropic molecules (benzodiazepines, antidepressants, carbamates and antiepileptic drugs), inclusion and nadir $CD4^+$ and $CD8^+$ T-cell count, HIV-RNA viral load (Abbott Real-time PCR), HIV-DNA viral load (Abbott Real-time PCR), viral hepatitis markers and type, duration and 2010 CPE score [9] of current ART upon inclusion.

Patient follow-up

Patients included in the Neuradapt study continued regular follow-up with clinical evaluation and blood tests. Those who also accepted to repeat neuropsychological evaluation were submitted to the same panel of tests as upon inclusion, approximately 2 years later, in order to identify any changes, and continued to participate in the study.

The following parameters were considered during follow-up: $CD4^+$ and $CD8^+$ T-cell count, HIV-RNA viral load, viral hepatitis markers, changes of cART and type of antiretroviral therapy, and CPE score at the end of follow-up.

Neuropsychological testing follow-up

For each patient, comparison between neuropsychological testing results at inclusion and at the end of follow-up allowed three situations to be identified to changes in AAN subgroups of impairment:

(1) Clinical improvement
(2) Clinical worsening
(3) Clinical stability

In the HAND group, change over time was defined as a switch in impairment subgroup (i.e. ANI, MND and HAD).

Among the non-HAND group, changing from NT to one cognitive domain 2 SD below the mean was considered as worsening (or conversely as improvement), whereas in case of a change from normal tests to one cognitive domain 1 SD below the mean, patients were considered as stable.

Statistical analysis

Patients with either improvement or stable neuropsychological tests were compared with those with clinical worsening.

Means were compared using Student's *t*-test and analysis of variance (ANOVA), and independent risk factors were identified by multivariate analysis. A *P*-value less than 0.05 was considered significant.

Results

Characteristics of patients at inclusion and comparison with excluded patients

From December 2007 to July 2009, 256 patients underwent neuropsychological tests, and 96 of them accepted to continue neuropsychological follow-up, from 2009 to 2011.

Among the 160 patients who did not repeat neuropsychological evaluation, the main reasons for exclusion were lack of interest in continuing the study or noncompliance with the study schedule. One patient died during follow-up. Among patients who refused to continue follow-up, 24 of 160 presented with HANDs (15%), whereas 136 of 160 did not have HANDs (85%). Among these 24 patients with HANDs not continuing the study, the main subgroups of impairment included ANI (14/24) and MND (8/24), whereas only two patients had HAD.

Among the 49 patients initially diagnosed with HANDs, 25 continued follow-up (51%), whereas 71 of 207 patients without HANDs accepted neuropsychological retesting (34%).

Participants and nonparticipants to follow-up were comparable with regard to age, sex, mean and nadir $CD4^+$ cell count, detectable HIV-RNA viral load, HIV-DNA viral load, HBV and HCV co-infection, smoking,

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Table 1. Characteristics of patients at inclusion.

	Total population	Patients without HANDs [*n* (%) or mean (SD)]	Patients with HANDs [*n* (%) or mean (SD)]	*P*
Number of patients	96	71	25	
Men	77 (80)	56 (79)	21 (84)	0.79
Age (years)	48 (11)	46 (11)	48 (10)	0.26
Previous IDU	16 (17)	11 (15)	5 (20)	0.84
Duration of HIV infection (years)	12 (7.5)	11.5 (7.5)	13.6 (7.5)	0.23
Hepatitis C co-infection	23 (24)	14 (20)	9 (36)	0.17
HIV-RNA (copies/ml) at inclusion	10760 (34828)	9772 (27738)	13528 (50228)	0.65
Patients with HIV-RNA <40 copies/ml	56 (58)	42 (59)	14 (56)	0.9
Mean $CD4^+$ cell count at inclusion (cells/μl)	551 (272)	546 (271)	567 (278)	0.74
Mean $CD4^+$ nadir (cells/μl)	265 (182)	275 (181)	235 (185)	0.34
CPE score at inclusion	7.8 (1.7)	7.6 (1.6)	8.1 (1.9)	0.21
Months on last cART at inclusion	24.6 (20.5)	25.4 (21.1)	22.6 (19.2)	0.59

cART, combination antiretroviral therapy; CPE, concentration penetration effectiveness; HANDs, HIV-associated neurocognitive disorders; IDU, illicit drug use.

hypertension, alcohol use, IDU, dyslipidemia and use of psychotropic molecules (data not shown).

Mean duration of follow-up was 22.4 months [95% confidence interval (CI) 21.5–23.3]. Table 1 summarizes participants' main characteristics.

Neuropsychological testing follow-up

Among the 96 patients who participated, 25 (26%) were defined as suffering from HANDs (13% ANI, 10% MND and 3% HAD) upon initial testing.

Upon neuropsychological retesting, six patients showed clinical improvement, 31 had worsened and 59 were stable, resulting in 43 patients presenting with HANDs (45%). The majority of HAND cases consisted of ANI (26%) and MND (16%), whereas the proportion of HAD remained stable at 3% (Fig. 1).

Among the 25 patients with HANDs at inclusion, 17 remained stable (68%), three worsened (12%) and five improved (20%).

The majority of patients newly diagnosed with HANDs came from the subgroup of patients with neuropsychological deficit, who worsened in 24 of 38 cases, whereas only three of 25 patients with initial normal tests contributed to new cases of HANDs.

The main cognitive deteriorations were identified for executive functions (16 cases), speed of information processing (13 cases) and recall memory (12 cases), followed by working (8 cases) and learning (6 cases) memory.

Figure 2 summarizes clinical outcomes for the HAND and non-HAND groups, according to changes in cART during follow-up. In the HAND group, a change of

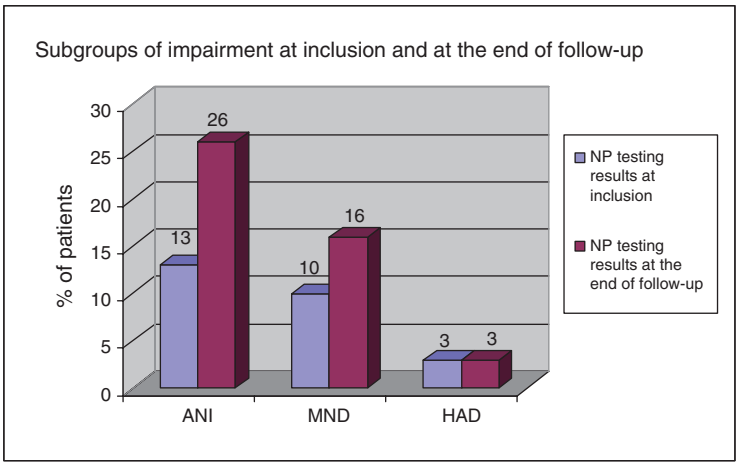

Fig. 1. Subgroups of impairment at inclusion and at the end of follow-up.

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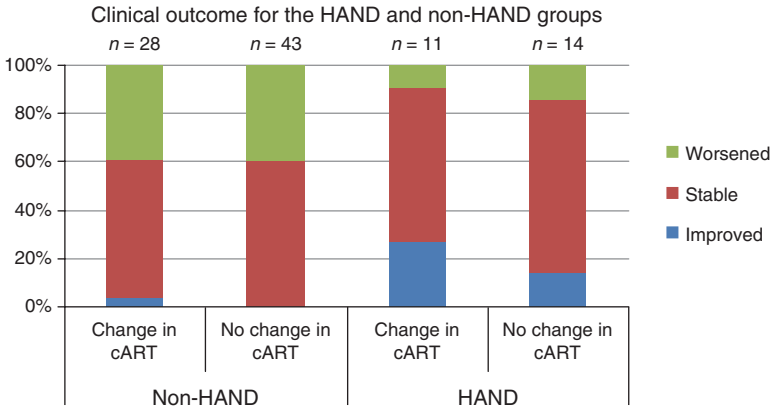

Fig. 2. Clinical outcome for the HAND and non-HAND groups.

antiretroviral regimen was more frequently due to virological failure than to side effects or comorbid conditions (7 vs. 4 patients), differing from the non-HAND group (11 vs. 17 patients, respectively).

Course of neuropsychological deficit, asymptomatic neurocognitive disorder, mild neurocognitive disorder and HIV-associated dementia over time

Because the role of ANI as a genuine impairment category is debated [12], we studied the outcome over time in this subgroup: among 12 patients initially diagnosed as presenting with ANI, eight maintained the same performance, two improved and two progressed to MND.

Among 13 patients initially diagnosed with MND or HAD, nine were stable, three improved and one worsened.

Among the 38 patients with an initial diagnosis of neuropsychological deficit (thus not classified in the HAND group), 11 evolved towards ANI and six towards MND.

Factors linked to changes in neuropsychological performance

Comparison between patients with either improvement or stable neuropsychological tests and those with clinical worsening showed that lower CPE scores at inclusion (6.9 vs. 8.1; $P = 0.005$) and at the end of follow-up (7.2 vs. 7.8; $P = 0.08$), and longer duration of exposure to their current cART regimen (31 vs. 22 months; $P = 0.06$) were associated with clinical deterioration (Table 2).

After adjustment for potential confounding factors, CPE scores at inclusion and at the end of follow-up were still independently related to neuropsychological performance (Table 3).

Patients with clinical worsening did not differ for smoking, hypertension or diabetes (data not shown).

In order to assess if cognitive changes were linked not only to CPE scores but also to any difference in the class of antiretrovirals, patients were classified into the following three groups:

(1) Patients receiving or having received cART including protease inhibitors during follow-up
(2) Patients who did not receive PI-containing cART during follow-up
(3) Patients without cART during follow-up

The main combination for users consisted of two nucleotide reverse transcriptase inhibitors (NRTIs) and a protease inhibitor, whereas in PI-sparing regimens, the main treatment consisted of two NRTI and a non-nucleoside reverse transcriptase inhibitor (NNRTI), followed by three NRTIs.

Among the 31 patients with clinical worsening, 17 (55%) received cART with a protease inhibitor during follow-up, nine (29%) without, whereas five (16%) were not treated.

Among the other 65 patients who did not have clinical progression, 34 (52%) had a protease inhibitor, 24 (37%) did not and seven (11%) were treatment-naive.

Differences between the two groups were not statistically significant.

Patients with stable treatment during follow-up

In order to exclude a potential bias linked to changes in cART during follow-up, we focused selectively on the 57 patients whose treatment was not modified: even in this group, patients with improvement or stability (38/57, 67%) differed from those with worsening (19/57, 33%) in

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Table 2. Comparison according to clinical outcome.

	Patients with clinical stability or improvement [*n* (%) or mean (SD)]	Patients with clinical worsening [*n* (%) or mean (SD)]	*P*
Number of patients	65	31	
Men	54 (83)	23 (74)	0.45
Age (years)	47 (11)	45 (11)	0.48
Previous IDU	11 (17)	5 (16)	0.99
Hepatitis C co-infection	16 (25)	7 (23)	0.99
HIV-RNA (copies/ml) at inclusion	9721 (34656)	12900 (35655)	0.68
HIV-RNA (copies/ml) at the end of follow-up	7400 (26624)	14785 (51000)	0.35
Patients with HIV-RNA <40 copies/ml at the end of follow-up	49 (75)	23 (74)	0.99
Mean $CD4^+$ cell count (cells/μl) at the end of follow-up	554 (291)	546 (231)	0.89
Mean $CD4^+$ nadir (cells/μl)	258 (187)	278 (174)	0.61
HIV-DNA at inclusion	613 (1692)	444 (724)	0.63
Years of HIV infection	12.8 (7.6)	10.4 (7.1)	0.14
CPE score at inclusion	8.1 (1.8)	6.9 (1)	0.005
CPE score at the end of follow-up	7.8 (1.5)	7.2 (1.1)	0.08
Change of treatment during the follow-up	27 (42)	12 (39)	0.97
Months on last cART at inclusion	21.7 (18.3)	31 (23.7)	0.06

cART, combination antiretroviral therapy; CPE, concentration penetration effectiveness; IDU, illicit drug use.

terms of CPE score at inclusion (8.1 vs. 7.1; $P=0.03$), whereas they did not differ for the duration of their last ART (25.8 vs. 35.7 months; $P=0.15$).

The main cognitive abilities to worsen were executive functions (11 cases), recall memory (10 cases) and speed of information processing (8 cases).

Aviremic patients

Thirty-seven patients with persistently undetectable viral load during follow-up were studied in order to see if any change in neuropsychological performance was observed: 27 of 37 patients were initially defined as not impaired, whereas 10 of 37 had HANDs at inclusion.

Follow-up showed that 24 of 37 patients were stable or improved, whereas 13 of 37 had clinical worsening. Clinical worsening was mainly observed in executive functions (8 cases), recall memory (7 cases) and speed of information processing (4 cases).

Even in this patient subgroup, those with clinical worsening had a lower CPE score than the others (7.0 vs. 8.1; $P=0.01$)

Discussion

We conducted a longitudinal study investigating changes in neuropsychological performance in an HIV-infected

Table 3. Logistic regression.

	Neurocognitive worsening vs. neurocognitive improvement or stability		
	Adjusted OR	95% CI	*P*
CPE score at inclusion	0.54	0.3–0.9	0.01
Months on last therapy at inclusion	1	1–1.1	0.09
Age	1	0.9–0.9	0.8
Benzodiazepines	1.6	0.2–10.5	0.62
Antidepressants	1.62	0.3–8.9	0.57
Previous IDU	0.99	0.2–4.3	0.99
Viral replication during follow-up	1	0.2–5.1	0.99
Sex (female)	1.37	0.4–4.8	0.62
CPE score at the end of follow-up	0.65	0.4–1	0.04
Benzodiazepines	3.01	0.6–15.4	0.19
Antidepressants	1.2	0.3–5.8	0.77
Age	1.01	0.9–1.1	0.58
Viral load at inclusion	1	1.0–1.0	0.34
Treatment changes during follow-up	0.86	0.3–2.4	0.77
Sex (female)	1.86	0.6–5.9	0.29

CI, confidence interval; CPE, concentration penetration effectiveness; IDU, illicit drug use; OR, odds ratio.

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population regularly followed at Nice University Hospital. We explored factors potentially associated with neuropsychological worsening, and in particular, our goal was to study whether high CNS-penetrating regimens could protect against cognitive deterioration.

During a 2-year follow-up period, the proportion of patients with a diagnosis of HANDs increased, most of them displaying mild cognitive disorders, whether symptomatic or not. The main novel domains of impairment concerned executive functions, learning and working memory.

We showed that patients with clinical worsening had lower CPE scores at inclusion and at the end of follow-up. Even in the subgroups of patients who either did not change treatment or remained aviremic during follow-up, differences were significant.

The majority of novel HAND diagnosis concerned patients with neuropsychological deficit, whereas in those with completely normal tests upon inclusion, neuropsychological performance remained generally stable.

Although the degree of impairment changed over time in certain cases, the majority of patients diagnosed with HANDs at inclusion were stable during follow-up and only six of them showed clinical improvement.

If confirmed by other studies on larger numbers of patients, our results suggest that once neurocognitive disorders are diagnosed, they generally remain stable over time, whereas novel cognitive deterioration could be prevented by high CNS-penetrating regimens.

Letendre *et al.* [18] showed that a CPE score greater than a median value of 7 was associated with a significantly smaller proportion of patients with a CSF viral load above 2 copies/ml. Our data show that patients with clinical worsening have a median CPE score of 6.9 at inclusion. Unfortunately, we did not perform lumbar punctures during the follow-up, thus we can only speculate that lower penetrating regimens were linked to higher risks of viral replication and immune activation in CSF.

Our results are in contrast with other studies in favor of neurotoxicity of antiretrovirals, such as that by Robertson *et al.* [9], who showed that treatment interruption could provide a clinical benefit, and Marra *et al.* [12], who found that higher CSF-penetrating regimens were associated with poorer neurocognitive performance. Unfortunately, our study lacked drug monitoring in the CSF during follow-up, so that we can only suggest the possibility of a therapeutic window as an explanation for the effectiveness of ART in the CNS. Indeed, Letendre [19] suggested that the goal of ART is to achieve a range of concentrations in the CNS that allow a control of viral replication and immune activation, thus reducing the risk of brain injury. Only when overstepping a critical threshold might antiretrovirals be associated with neurotoxicity [19].

The low number of patients who improved could be explained by the study design, as this was not an interventional trial on patients with HANDs failing or starting treatment, but rather a follow-up of the natural course of neurocognitive performance in the cART era in a randomly selected population. However, it is interesting to note that improvement was mainly observed among patients with HANDs who changed therapy as a consequence of virological failure.

The increased number of patients with learning memory deficit is in favor of a cortical–subcortical pattern of impairment previously described by other authors [1,20]. This fact could be explained by the accelerated aging process observed in the HIV-infected population and by the high number of associated comorbid conditions. Indeed, Ances *et al.* [21] found that functional brain demands observed via functional MRI in HIV-infected patients were equivalent to 15–20 years older HIV-negative individuals, suggesting that HIV and aging are independent factors for body frailty.

Even aviremic patients were at risk of evolving toward neurocognitive deterioration, confirming what has been previously described by Simioni *et al.* [22], who found a high prevalence of HANDs even in long-standing aviremic patients.

Progressors and nonprogressors had the same proportions of protease inhibitor-including and protease inhibitor-sparing antiretroviral regimens, thus suggesting that differences in clinical outcome are not associated to a specific class of antiretrovirals, but rather to penetration properties of molecules. A slightly higher, although not significant, proportion of patients did not receive treatment in the progressors group during the follow-up.

We found a significantly increased risk of clinical deterioration in patients with neuropsychological deficit compared to those with normal tests. However, the role of asymptomatic impairments, that is ANI and neuropsychological deficit, is debated, and certain authors warn against the risk of overestimating neurological disorders [23,24]. Although some patients evolved to symptomatic forms of HANDs, that is, to MND, the majority of patients with ANI remained stable and those with neuropsychological deficit worsened to ANI, so that no conclusion can be drawn concerning the risk of clinical evolution under these conditions. Further studies and longer follow-up are needed in order to determine whether these conditions should really be considered in the same way as symptomatic forms of HANDs.

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The study has many limitations, especially in terms of the evaluation of cognitive performance over time. For each patient, we looked for any change in degree of impairment according to the AAN classification criteria, whereas other authors measured a global cognitive score. Our method is interesting for its evaluation of interference with daily living and for the long period of neuropsychological testing, but underestimation or overestimation of neuropsychological performance cannot be excluded in patients remaining in the same impairment group.

Moreover, the minority of patients with multiple changes of cART during follow-up may introduce a potential bias for the analysis of CPE scores, as these were only measured upon inclusion and at the end of our study. However, even in the subgroup of patients who did not change cART during follow-up, the CPE score was significantly associated with clinical outcome, thus excluding the potential bias of treatment modification.

The fact that patients with clinical worsening had almost significant longer periods of exposure to cART at inclusion could allow to speculate that longer periods of exposure to less CSF-penetrating drug combinations could increase the risk of neuropsychological test deterioration. However, these results were not confirmed in the subgroup of patients who did not change treatment, so that this hypothesis needs to be elucidated via larger studies.

Further insights into the protective role of the high CNS-penetrating drugs could be provided by the antiretroviral monocyte efficacy score, which was recently introduced by Shikuma *et al*. [25], although it still lacks data for several molecules and needs further studies before being routinely applied to HAND studies [26].

In conclusion, our study shows that over a follow-up period of 2 years, the proportion of cases of HANDs increased and patients with lower CNS-penetrating regimens carried a higher risk of clinical deterioration. The clinical significance of neuropsychological deficit and ANI still needs to be elucidated.

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Author contributions: conceived and designed the study: M.V., J.D., C.L.F., C.P. and P.D.

Performed the study: M.V., V.B., M.L., A.H.L., J.C., M.T. and H.C.

Analyzed the data: M.V., J.D., B.D. and C.P.

Wrote the manuscript: M.V. and B.D.

Edited the manuscript: J.D., B.D., C.L.F., M.L. and P.D.

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Conflicts of interest

There are no conflicts of interest.

References

1. Mc Arthur JC, Steiner J, Sacktor N, Nath A. **Human immunodeficiency virus associated neurocognitive disorders: mind the gap.** *Ann Neurol* 2010; **67**:699–714.
2. Robertson KR, Smurzynski M, Parsons TD, Wu K, Bosch RJ, Wu J, *et al*. **The prevalence and incidence of neurocognitive impairment in the HAART era.** *AIDS* 2007; **21**:1915–1921.
3. Woods SP, Moore DJ, Weber E, Grant I. **Cognitive neuropsychology of HIV-associated neurocognitive disorders.** *Neuropsychol Rev* 2009; **19**:152–168.
4. Heaton RK, Clifford DB, Franklin DR, 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.
5. Ellis RJ, Badiee J, Vaida F, Letendre S, Heaton RK, Clifford D, *et al*. **CD4 nadir is a predictor of HIV neurocognitive impairment in the era of combination antiretroviral therapy.** *AIDS* 2011; **25**:1747–1751.
6. 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.
7. Vassallo M, Dunais B, Durant J, Carsenti-Dellamonica H, Harvey-Langton A, Cottalorda J, *et al*. **Relevance of lipopolysaccharide levels in HIV-associated neurocognitive impairment: the Neurdapt study.** *J Neuroviral* 2013; **19**:376–382.
8. Ancuta P, Kamat A, Kunstman KJ, Kim EY, Autissier P, Wurcel A, *et al*. **Microbial translocation is associated with increased monocyte activation and dementia in AIDS patients.** *Plos One* 2008; **3**:e2516.
9. Robertson KR, Su Z, Margolis DM, Krambrink A, Halvir DV, Evans S, *et al*. **Neurocognitive effects of treatment interruption in stable HIV+ patients in an observational cohort: ACTG 5170.** *Neurology* 2010; **74**:1260–1266.

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10. Letendre S, Marquie-Beck J, Capparelli E, Best B, Clifford D, Collier AC, *et al*. **Validation of the CNS Penetration-Effectiveness rank for quantifying antiretroviral penetration into the central nervous system.** *Arch Neurol* 2008; **65**:65–70.
11. Cysique LA, Vaida F, Letendre S, Gibson S, Cherner M, Woods SP, *et al*. **Dynamics of cognitive change in impaired HIV-positive patients initiating antiretroviral therapies.** *Neurology* 2009; **73**:342–348.
12. Marra CM, Zhao Y, Clifford DB, Letendre S, Evans S, Henry K, *et al*. **Impact of combination antiretroviral therapy on cerebrospinal fluid HIV RNA and neurocognitive performance.** *AIDS* 2009; **23**:1359–1366.
13. Evers S, Rahmann A, Schwaag S, Frese A, Reichelt D, Hussdedt IW. **Prevention of AIDS dementia by HAART does not depend on cerebrospinal fluid penetrance.** *AIDS Res Hum Retroviruses* 2004; **20**:483–491.
14. McCutchan JA, Wu JW, Robertson K, Koletar SL, Ellis RJ, Cohn S, *et al*. **HIV suppression by HAART preserves cognitive function in advanced, immune-reconstituted AIDS patients.** *AIDS* 2007; **21**:1109–1117.
15. The MIND Exchange Working Group. **Assessment, diagnosis and treatment of human immunodeficiency virus (HIV)-associated neurocognitive disorders (HAND): a consensus report of the Mind Exchange Program.** *Clin Infect Dis* 2013; **56**:1004–1017.
16. Tozzi V, Balestra P, Salvatori MF, Vlassi C, Liuzzi G, Giancola ML, *et al*. **Changes in cognition during antiretroviral therapy: comparison of 2 different ranking systems to measure antiretroviral drug efficacy on HIV-associated neurocognitive disorders.** *J Acquir Immune Defic Syndr* 2009; **52**:56–63.
17. Antinori A, Arendt G, Becker JT, Brew BJ, Byrd DA, Cherner M, *et al*. **Updated research nosology for HIV-associated neurocognitive disorders.** *Neurology* 2007; **69**:1789–1799.
18. Letendre S, McClernon D, Ellis R, Munoz-Moreno J, Way L, Franklin D, *et al*. Persistent HIV in the central nervous system during treatment is associated with worse ART penetration and cognitive impairment (Abstract 484b) *16th Conference on Retrovirus and Opportunistic Infections (CROI)*, 8–11 February 2009, Montreal, Canada.
19. Letendre S. **Central nervous system complications in HIV disease: HIV-associated neurocognitive disorders.** *Top Antivir Med* 2011; **19**:137–142.
20. Scott JC, Woods SP, Carey CL, Weber E, Bondi MW, Grant I. **Neurocognitive consequences of HIV infection in older adults: an evaluation of the 'cortical' hypothesis.** *AIDS Behav* 2010; **15**:1187–1196.
21. Ances BM, Vaida F, Yeh MG, Liang CL, Buxton RB, Letendre S, *et al*. **HIV infection and aging independently affect brain function as measured by functional magnetic resonance imaging.** *J Infect Dis* 2011; **201**:336–340.
22. 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.
23. Gisslen M, Price RW, Nilsson S. **The definition of HIV-associated neurocognitive disorders: are we overestimating the real prevalence?** *BMC* 2011; **11**:356.
24. Torti C, Focà E, Cesana BM, Lescure FX. **Asymptomatic neurocognitive disorders in patients infected by HIV: fact or fiction?** *BMC* 2011; **9**:138.
25. Shikuma CM, Nakamoto B, Shiramizu B, Liang CY, DeGruttola V, Bennet K, *et al*. **Antiretroviral monocyte efficacy score linked to cognitive impairment in HIV.** *Antiviral Ther* 2012; **17**:1233–1242.
26. Price RW, Swanson R. **Targeting chronic central nervous system HIV infection.** *Antiviral Ther* 2012; **17**:1227–1231.

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