Original article

Revised central nervous system neuropenetration-effectiveness score is associated with cognitive disorders in HIV-infected patients with controlled plasma viraemia

Nicoletta Ciccarelli[1], Massimiliano Fabbiani[1], Manuela Colafigli[1], Enrico Maria Trecarichi[1], Maria Caterina Silveri[2], Roberto Cauda[1], Rita Murri[1], Andrea De Luca[3], Simona Di Giambenedetto[1]*

[1]Institute of Clinical Infectious Diseases, Catholic University of the Sacred Heart, Rome, Italy
[2]Memory Clinic, Catholic University of the Sacred Heart, Rome, Italy
[3]University Division of Infectious Diseases, Siena University Hospital, Siena, Italy

*Corresponding author e-mail: manuela76@inwind.it

Background: The objective of our study was to compare two different central nervous system penetration-effectiveness (CPE) scores for the prediction of cognitive dysfunction in HIV-infected patients.

Methods: We performed a cross-sectional single cohort study, consecutively enrolled during routine outpatient visits. HIV-infected subjects on antiretroviral therapy with plasma HIV RNA<50 copies/ml were included. A neuropsychological battery was administered. Each patient was classified as cognitively impaired on the basis of results obtained in age-, gender-, education- and nationality-matched healthy HIV-negative subjects. Self-reported adherence to antiviral therapy was measured on a 0–100 visual analogue scale. CPE rank was calculated for each antiretroviral regimen based on rules proposed by the CHARTER group in the 2008 original version (orCPE rank) and the 2010 revised version (revCPE rank). Neuroeffectiveness categories were analysed based on cutoffs of ≥1.5 (orCPE rank) or ≥6 (revCPE rank).

Results: A total of 101 patients were enrolled (66% male, median age 47 years, median education 13 years); mean adherence was 81%. orCPE rank ≥1.5 and revCPE rank ≥6 were observed in 85.0% and 78.2% of patients, respectively (*P*=0.31). Asymptomatic neurocognitive impairment (ANI) was diagnosed in 50 (49.5%) subjects. In a multivariable model, after adjusting for nationality, adherence and nadir CD4⁺ T-cell count, orCPE rank did not show an association with cognitive performance (*P*=0.704). By contrast, patients with revCPE rank ≥6 (OR 0.32, 95% CI 0.11, 0.95; *P*=0.039) and adherence ≥80% (OR 0.39, 95% CI 0.15, 0.99; *P*=0.047) showed a decreased risk of cognitive impairment.

Conclusions: A high prevalence of ANI was observed in virologically suppressed HIV-infected individuals. The revCPE rank showed improved association with neurocognitive dysfunction over the orCPE rank. Moreover, a relationship between cognitive impairment and adherence to antiretroviral therapy was found.

Introduction

Combination antiretroviral therapy (cART) has markedly changed the prognosis of HIV-infected patients, reducing AIDS-related morbidity and mortality [1]. However, the prevalence of HIV-associated neurocognitive disorders (HAND), especially asymptomatic and milder forms, remains high even in patients on a stable and successful cART [2–4]. Nevertheless, a progressive improvement of neurocognitive abilities has been observed in longitudinal studies using virologically suppressive antiretroviral treatment [5,6].

Possible reasons explaining the sustained prevalence of HAND are the increasing numbers of older individuals with HIV infection [7–9], comorbidities (HCV coinfection and cardiovascular disease) [10,11], drug resistance, poor treatment adherence [12] and also poor central nervous system (CNS) penetration of some antiretroviral agents [4,13]. Low CNS penetration of antiretroviral agents could be one of the reasons explaining why viral replication can be demonstrated in a proportion of cerebrospinal fluid (CSF) samples obtained by subjects with controlled plasma viraemia [14,15].

In order to try to optimize cART regimen for patients with HAND, a CNS penetration-effectiveness (CPE) scoring system was first derived in 2008 [16] using a hierarchical approach, which considered clinical efficacy, pharmacokinetics and pharmacological characteristics of each drug; this original version (orCPE) assigns a score of 0, 0.5 or 1 to each antiretroviral drug according to its increasing neuropenetration or neuroeffectiveness. During subsequent years, several studies have shown that better penetration of antiretroviral drugs in the CNS, as estimated by the orCPE score, is associated with a lower CSF viral load [16,17] suggesting that antiretrovirals with good CNS penetration might positively affect cognition in HIV-infected patients. Nevertheless, studies evaluating the relationship between neuroactive antiretrovirals and cognitive performance have reported controversial results [3,5,18–21].

In early 2010, a revised version was released (revCPE) [22]; this version assigns a score from 1 to 4 to each antiretroviral drug according to its increasing neuropenetration or neuroeffectiveness. The revCPE seemed to better predict virological control in CSF; however, to date, no single study has demonstrated an association between revCPE and neuropsychological performance [23,24]. Moreover, no standard cutoff value that better predicted CSF viral suppression or neuropsychological performance has been clearly established for this novel score, but there is evidence showing that a cutoff ≥6 is highly predictive of CSF viral suppression [25].

The aim of our study was to investigate the association of the two CPE versions with the risk of cognitive dysfunction in a cohort of patients on cART with plasma HIV RNA<50 copies/ml.

Methods

Subjects

This cross-sectional single cohort study consecutively enrolled virologically suppressed HIV-infected subjects during routine outpatient visits from November 2008 to February 2010; patients were excluded if their age was <18 years, or in case of active or known past CNS opportunistic infections, history of neurological disorders, active psychiatric disorders, alcoholism or drug abuse, decompensated liver disease or cirrhosis, and linguistic difficulties for non-native patients.

This study was approved by the local Institutional Ethics Committee of the Catholic University of S Heart Largo a Gemelli (Rome, Italy). All subjects provided informed consent prior to enrolment.

The following demographic, clinical and laboratory variables were collected for each subject at the time of neuropsychological examination: gender, age, education, ethnicity, risk factors for HIV infection, coinfection with HBV or HCV, history of AIDS-defining events, current antiretroviral regimen, concomitant medications, $CD4^+$ T-cell count, $CD4^+$ T-cell count nadir and HIV-1 viral load. In addition, self-reported adherence to cART was measured on a 0–100 visual analogue scale using a previously validated questionnaire [26].

Neuropsychological examination

All patients underwent a Mini Mental State Examination (MMSE) to assess general cognitive status, and a comprehensive neuropsychological battery exploring memory (immediate and delayed recall of Rey's words, delayed recall of Rey's figure, forward digit span and forward spatial span), attention and executive functions (Stroop test, trail making test B, backward digit span, backward spatial span, drawings and double barrage), visuospatial and constructional functions (Rey's figure copy), speed of mental processing (WAIS digit symbol), language (letter fluency), logical reasoning skill (Raven's matrices). The scores obtained on each task were adjusted for age, gender and education on the basis of normative data available for the Italian population. The Instrumental Activities of Daily Living (IADL) scale was also administered.

It has been previously demonstrated that neurologically healthy subjects do not necessarily score above the normative cutoff in all tasks included in a composite battery [27]. Thus, in order to allow a reliable interpretation of the general performance of HIV-infected patients and consequently avoid overestimation of cognitive impairment, we selected an historical age-, gender-, education- and nationality-matched control population (30 subjects; 19 men and 11 women) who received the same full neuropsychological examination. Control subjects had no history or risk factor for neurological impairment and were not taking any medication deemed to affect cognitive abilities. They were recruited among students (≥18 years of age), hospital personnel, patients' caregivers or relatives. All subjects were volunteers. They did not receive any financial remuneration for participating.

On the basis of the number of tasks with pathological scores observed in the control population (no control subject performed pathologically on >2 tasks), HIV-infected patients were considered cognitively impaired if they scored below the normative cutoff on ≥3 tests. A similar method has been used in a previous study [23], yielding a prevalence of neurocognitive disorders comparable to other historical cohorts.

Moreover, according to standard criteria [2], cognitive disorders were classified into three categories on the basis of their increased severity: asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorders (MND) and HIV-associated dementia (HAD). We distinguished MND from ANI in case of the presence of self- or proxy report of decline in ≥2 IADLs [2].

Table 1. Characteristics of patients and controls

Characteristic	Patients (*n*=101)	Controls (*n*=30)	*P*-value
Male	66 (65.3)	19 (63.3)	0.83
Median age, years (IQR)	47 (42–52)	50 (36–62)	0.51
Median education, years (IQR)	13 (8–13)	13 (10–15)	0.14
Non-Italian born	8 (7.9)	1 (3.3)	0.68
Heterosexual	43 (42.6)	–	–
Past injecting drug users	18 (17.8)	–	–
HCV coinfection	23 (22.8)	–	–
Past AIDS-defining events	23 (22.8)	–	–
Past suboptimal antiretroviral therapy	27 (49.1)	–	–
Median time from HIV diagnosis, years (IQR)	11.8 (7.2–16.9)	–	–
Median time on antiretroviral therapy, years (IQR)	9.6 (5.1–11.8)	–	–
Duration of current cART regimen ≥12 months	75 (74.3)	–	–
Median current CD4$^+$ T-cell count, cells/μl (IQR)	620 (454–827)	–	–
Median CD4$^+$ T-cell count nadir, cells/μl (IQR)	171 (62–264)	–	–
CD4$^+$ T-cell count nadir <200 cells/μl	60 (61.2)	–	–
CD4$^+$ T-cell count nadir 200–350 cells/μl	30 (30.6)	–	–
CD4$^+$ T-cell count nadir >350 cells/μl	8 (8.2)	–	–
cART adherence ≥80%	64 (63.4)	–	–
orCPE rank ≥1.5	86 (85.1)	–	–
revCPE rank ≥6	79 (78.2)	–	–

Values are expressed as *n* (%) unless indicated otherwise. cART, combination antiretroviral therapy; orCPE, original central nervous system penetration-effectiveness; revCPE, revised central nervous system penetration-effectiveness.

Neuroeffectiveness of combination antiretroviral therapy regimens

CPE rank was calculated for each cART regimen according to two definitions. orCPE rank was calculated based on rules proposed in the 2008 original version [16], which was slightly modified on the basis of increasing knowledge of CNS penetration of novel antiretroviral drugs [28–30]. In this version, a score of 1 (abacavir, zidovudine, nevirapine, fosamprenavir/ritonavir, indinavir/ritonavir, lopinavir/ritonavir and maraviroc), 0.5 (emtricitabine, lamivudine, stavudine, efavirenz, fosamprenavir, atazanavir, atazanavir/ritonavir, darunavir/ritonavir, indinavir and raltegravir) and 0 (all other drugs) was assigned to each antiretroviral drug according to its decreasing neuropenetration or neuroeffectiveness. revCPE rank was calculated based on the 2010 revised version [22]. In this version a score of 1 (tenofovir, zalcitabine, nelfinavir, ritonavir, saquinavir/ritonavir, saquinavir, tipranavir/ritonavir and enfuvirtide), 2 (didanosine, lamivudine, stavudine, etravirine, atazanavir/ritonavir, atazanavir and fosamprenavir), 3 (abacavir, emtricitabine, delavirdine, efavirenz, darunavir/ritonavir, fosamprenavir/ritonavir, indinavir, lopinavir/ritonavir, maraviroc and raltegravir) and 4 (zidovudine, nevirapine and indinavir/ritonavir) was assigned to each antiretroviral drug according to its increasing neuropenetration or neuroeffectiveness. Regimens were considered as effective for the treatment of CNS infection if CPE scored above predefined cutoffs: orCPE rank ≥1.5, which was the median orCPE rank value and was used as cutoff in previous studies [16] and revCPE rank ≥6, because it was the median value in our population and, moreover, a previous study indicated a cutoff of ≥6 as highly predictive of CSF viral suppression [25].

Statistical analysis

Comparisons between groups were based on Student's *t*-test (for continuous variables) and the χ^2 test or, when appropriate, Fisher's exact test (for categorical variables). The association between variables and cognitive impairment was analysed by univariate and multivariate logistic regression analysis; variables showing a nearly significant trend at univariate analysis (*P*-value <0.075) were included in the multivariate model. All analyses were performed using the SPSS version 13.0 software package (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

A total of 101 HIV-infected patients were evaluated for this study. Baseline characteristics of the patient population are detailed in Table 1. At the time of neuropsychological examination, 23 (22.8%) patients were HCV-coinfected and 23 (22.8%) had past AIDS-defining events. Median (IQR) orCPE rank and revCPE rank were 1.5 (1.5–2.0) and 6 (6–7) respectively; orCPE

Table 2. Scores obtained by patients and controls on each neuropsychological test

Neuropsychological test	Mean score (SD)			Pathological performances, %		
	Patients (*n*=101)	Controls (*n*=30)	*P*-value	Patients (*n*=101)	Controls (*n*=30)	*P*-value
Mini Mental State Examination	27.92 (2.10)	29.10 (0.88)	<0.001	14.9	0.0	0.022
Immediate recall of Rey's words	38.39 (8.41)	42.3 (8.01)	0.025	21.8	3.3	0.026
Delayed recall of Rey's words	7.53 (2.60)	8.77 (2.62)	0.025	27.7	13.3	0.147
Digit span (forward)	5.65 (1.24)	5.77 (1.19)	0.658	19.8	13.3	0.592
Digit span (backward)	4.18 (1.19)	4.47 (1.33)	0.273	13.9	3.3	0.189
Spatial span (forward)	4.77 (0.89)	5.43 (0.90)	0.001	31.7	6.7	0.005
Spatial span (backward)	3.82 (0.98)	4.10 (1.18)	0.197	1.0	0.0	1.000
Constructional task (Rey's figure)	31.64 (3.79)	32.71 (2.64)	0.163	16.8	3.6	0.119
Delayed recall of Rey's figure	13.77 (6.36)	15.09 (5.35)	0.318	7.0	0.0	0.346
Stroop test (errors)	1.68 (3.12)	0.60 (0.87)	0.002	10.6	16.7	0.525
Stroop test (time), s	10.00 (9.00)	22 (12.00)	0.075	21.8	10.0	0.191
Trail-making test B (errors)	0.92 (1.24)	0.78 (0.92)	0.425	11.9	7.4	0.733
Trail-making test B (time), s	141.00 (65.00)	130 (48.00)	0.592	5.9	0.0	0.339
Drawings	4.61 (1.87)	5.17 (1.44)	0.093	22.4	13.3	0.436
Raven's matrices	28.95 (5.28)	30.78 (3.97)	0.082	7.1	0.0	0.346
Letter fluency	34.94 (11.79)	37.47 (11.47)	0.302	9.9	3.3	0.455
Wais digit symbol	8.79 (2.60)	9.57 (2.58)	0.153	16.7	13.9	0.761
Double barrage	0.96 (0.04)	0.98 (0.02)	<0.001	9.9	0.0	0.115
Number of pathological tasks	2.94 (2.99)	1.33 (0.84)	<0.001	–	–	–

rank ≥1.5 and revCPE rank ≥6 were observed in 85.1% and 78.2% of patients, respectively (*P*=0.31).

Despite virological suppression at the time of the evaluation, only 64/101 (63.4%) patients self-reported an adherence to cART ≥80%.

When compared with HIV-infected patients, the control HIV-negative population did not show significant differences in gender (male 65.3% versus 63.3%; *P*=0.83), education (mean 11.78 years [SD 3.43] versus mean 12.80 years [SD 2.93]; *P*=0.14) and age (mean 47.43 years [SD 8.28] versus mean 49.47 years [SD 16.37]; *P*=0.51; Table 1).

Neuropsychological examination

Overall, 50 (49.5%) patients were classified as cognitively impaired. All showed a profile of ANI and none revealed a cognitive profile of MND or HAD.

Raw scores and the proportion of subjects scoring below the normative cutoff on each task in HIV-infected patients and control subjects are summarized in Table 2. Overall, patients performed below the cutoff on a higher number of tasks than control subjects (mean 2.94 [SD 2.99] versus mean 1.33 [SD 0.84]; *P*<0.001). Moreover, patients obtained worse mean scores than HIV-negative controls on all tasks, although a significant difference was reached only for MMSE (*P*<0.001), immediate recall of Rey's words (*P*=0.025), delayed recall of Rey's words (*P*=0.025), spatial span (forward; *P*=0.001), Stroop test (errors; *P*=0.002) and double barrage (*P*<0.001).

Similarly, the proportion of pathological scores was always higher in patients than in controls, except for Stroop test (errors; 11% versus 17%; *P*=0.525); a significant difference was reached for MMSE (15% versus 0%; *P*=0.022), immediate recall of Rey's words (22% versus 3%; *P*=0.026), and spatial span (forward; 32% versus 7%; *P*=0.005).

In HIV-infected patients, a lower proportion of ANI was observed when cART regimens with revCPE≥6 were prescribed (44% versus 68%; *P*=0.048). By contrast, no differences were observed when comparing regimen with orCPE > or <1.5 (50% versus 47%; *P*=0.812).

Similarly, analysing each single task, a lower proportion of pathological scores was observed at delayed recall of Rey's figure (28.6% versus 71.4%; *P*=0.005) and at double barrage (50% versus 60%; *P*=0.007) when cART regimens with revCPE≥6 were prescribed. Conversely, no differences in any test were observed when comparing regimens with orCPE > or <1.5.

Factors associated with asymptomatic neurocognitive impairment: comparison of different CPE rank

Factors associated with ANI were identified by univariate and multivariate logistic regression analysis (Table 3). At univariate analysis, revCPE≥6 showed a nearly significant trend toward a negative association with ANI (OR 0.37, 95% CI 0.14, 1.01; *P*=0.052) while no relationship was demonstrated for orCPE (OR 1.14, 95% CI 0.38, 3.43; *P*=0.812). Among the other variables, adherence ≥80% emerged as significant protective factors (OR 0.40, 95% CI 0.17, 0.92; *P*=0.032), while a trend toward an association was observed for

Table 3. Factors associated with asymptomatic neurocognitive impairment

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P*–value	OR (95% CI)	*P*-value
Sex (male versus female)	0.89 (0.39, 2.02)	0.778	–	–
Age (per 10 years more)	0.75 (0.46, 1.22)	0.249	–	–
Education (per 1 year more)	0.90 (0.80, 1.02)	0.093	–	–
Non-Italian born patients (versus Italian born)	8.14 (0.96, 68.81)	0.054	7.59 (8.44, 68.22)	0.071
Injecting drug users	0.78 (0.28, 2.17)	0.636	–	–
HCV coinfection	0.73 (0.20, 1.86)	0.511	–	–
Duration of infection (per 1 year longer)	0.95 (0.89, 1.01)	0.099	–	–
Time on antiretroviral therapy (per 1 year longer)	0.96 (0.88, 1.04)	0.315	–	–
Past AIDS-defining events	0.92 (0.36, 2.32)	0.855	–	–
$CD4^+$ T-cell count nadir				
<200 cells/mm^3 (reference)	1	–	1	–
200–350 cells/mm^3	1.07 (0.44, 2.57)	0.881	0.89 (0.34, 2.33)	0.810
>350 cells/mm^3	0.13 (0.01, 1.15)	0.067	0.17 (0.01, 1.58)	0.119
Time on current cART>12 months	0.97 (0.40, 2.38)	0.953	–	–
Adherence ≥80%	0.40 (0.17, 0.92)	0.032	0.39 (0.15, 0.99)	0.047
orCPE rank ≥1.5	1.14 (0.38, 3.43)	0.812	–	–
revCPE rank ≥6	0.37 (0.14, 1.01)	0.052	0.32 (0.11, 0.95)	0.039
$CD4^+$ T-cell count (per 100 cells more)	0.98 (0.87, 1.11)	0.748	–	–

cART, combination antiretroviral therapy; orCPE, original central nervous system penetration-effectiveness; revCPE, revised central nervous system penetration-effectiveness.

non-Italian nationality (*P*=0.054) and a nadir $CD4^+$ T-cell count >350 cells/μl (*P*=0.067 when compared to a nadir $CD4^+$ T-cell count <200 cells/μl). In order to test the potential association with ANI of the two CPE versions, we performed two sets of multivariate analyses in which the orCPE or the revCPE were each adjusted for variables showing a trend (*P*<0.075) towards an association with cognition in univariate analysis. A relationship with ANI could not be demonstrated for orCPE (OR 0.77, 95% CI 0.21, 2.91; *P*=0.70, after adjusting for nadir $CD4^+$ T-cell count, non-Italian born status, and adherence ≥80%). Conversely, a revCPE rank≥6 (adjusted OR [aOR] 0.32, 95% CI 0.11, 0.95; *P*=0.039) showed an independent association with a reduced odds of ANI. Moreover, in this model, adherence ≥80% (aOR 0.39, 95% CI 0.15, 0.99; *P*=0.047) also showed an independent negative association with ANI.

Discussion

The importance of neuropenetration of antiretroviral drugs for the prevention of neurocognitive disorders in HIV-infected patients is increasingly recognized. We performed a comprehensive neuropsychological investigation in a cohort of patients on antiretroviral therapy with plasma HIV RNA<50 copies/ml. A high prevalence (49.5%) of ANI was observed, in-line with previous findings from other cohorts [4,31]. This observation underscores the importance of often unrecognized subclinical cognitive disorders in HIV-infected patients. Although executive functions and memory abilities were confirmed as the most vulnerable functions in HIV-infected patients [31], the deficit was not confined to these cognitive domains and resulted in an extensive asymptomatic cognitive impairment.

The proportion of MND observed in our population was lower than that reported in other cohorts, usually ranging from 4% to 12% [3,4]. The main reason for this finding could be that our cohort included only patients having virologically and immunologically controlled HIV infection; however, difficulties to access outpatient health-care services and the possibility to receive home caring (a service available in our hospital, Policlinico a Gemelli, Rome, Italy) for patients with more severe cognitive dysfunction could be additional explanations.

In the past years, there has been an evolution of CPE score on the basis of new knowledge about CNS penetration and effectiveness of antiretrovirals [22]. In our study, two different scoring systems used to measure cART neuroeffectiveness were compared. The main finding was the demonstration of an independent association between revCPE rank ≥6 and a better neurocognitive performance, while no association was observed for the orCPE rank. This observation is in-line with the evidence of a stronger correlation between CSF viral load suppression and revCPE rank when compared with the orCPE rank [22]. Our results suggest that targeting cART regimens on the basis of optimal revCPE rather than orCPE could represent an improvement for the treatment of HAND. However, since cross-sectional studies do not allow the assessment of causal relationships between the investigated factors, further

longitudinal studies should be performed to better explore our findings.

Unitil now, few studies had investigated the association between revCPE and cognition in HIV-infected patients [23,24,32] and none had previously demonstrated an association between suboptimal revCPE and neurocognitive dysfunction. In a previous study exploring predictors of cognitive impairment [23], a significant association with revCPE rank was not observed; however, the investigated population showed a greater heterogeneity in terms of viroimmunological features and medical history and this could have potentially influenced the results.

In the present study, a homogeneous population including only subjects with controlled viral replication was selected. Despite this, ANI was not negligible and its prevalence increased in subjects treated with suboptimal revCPE. These results suggest that prescribing cART regimens with optimal revCPE rank could represent a primary goal also in the treatment of patients with well-controlled plasma viral load. Our data seem apparently in contrast with those from a recent study [32], in which both original and revised versions of CPE rank were not associated with cognition in a population of HIV-infected subjects on stable cART with suppressed plasma viraemia. Nevertheless, the authors administered a different neuropsychological battery, their population was older than ours, and they observed a very low rate of neuropsychological impairment: thus, their data are not applicable to our population. Moreover, in that study adherence-related behaviours were not evaluated and this could have influenced their findings.

Interestingly, in a recent study on a large cohort a low CPE rank was associated with higher frequency of CNS diseases and death [33]. Although neuropsychological examination was not available in that population, these data suggest that neuropenetration of antiretroviral drugs should be taken into account to improve the outcome in the long-term care of HIV-infected patients.

According to previous studies [12,34] we also found evidence of a relationship between adherence and neurocognitive performance; in particular, a strong association between a level of adherence ≥80% and a better memory performance was demonstrated. Adherence and cognitive function are likely to be reciprocally related [34], because it is plausible that cognitive disorders, especially memory impairment [35,36], might lead to a decline in adherence to cART and, on the other hand, a poor adherence might contribute to a rebound of viral replication in CNS with development of cognitive impairment. It is worth noting that, in our population, the association between adherence and cognitive performance was demonstrated in the setting of suppressed plasma viraemia. It could be hypothesized that adherence levels needed to achieve undetectable viral load in plasma might not be the same needed to achieve undetectable viral load in CSF. Indeed, it has been shown that undetectable plasma viral load does not exclude CSF escape [14]. Suboptimal adherence, together with poor CNS penetration of antiretroviral drugs, could be a potential explanation for this finding. Unfortunately, no CSF samples were available in our population to confirm this hypothesis.

In our population, variables related to severity of the HIV infection, such as current and nadir $CD4^+$ T-cell counts, or time from HIV diagnosis, were not significantly associated with neuropsychological performance. A possible reason for this finding could be that our cohort included only asymptomatic patients with undetectable viral load.

We acknowledge that our study can have some limitations because uncontrolled biases can occur in cross-sectional studies performed in routine clinical practice: regimens with higher CPE rank scores could have been selected for patients at higher risk of neurocognitive impairment. Moreover, the clinical status at time of commencing cART could influence antiretroviral selection and consequently CPE score, thus representing a potential confounder in cross-sectional or retrospective studies investigating CPE [33]. Furthermore, we have to consider that CPE score can show ongoing evolution on the basis of novel data about CNS penetration and effectiveness of antiretrovirals, especially recently introduced drugs. Moreover, the potential benefit associated with neuro-effective cART in terms of prevention of neurocognitive impairment did not seem to translate into an improvement in overall survival in an HIV-positive population [37]. Finally, our control group was of small size and not completely comparable to HIV-infected patients for potentially relevant variables other than age, gender, education and nationality (that is, socio-economic factors). Thus, additional controlled longitudinal studies are needed to confirm our findings and to better understand the interaction between neuroeffectiveness and the prognosis of HIV infection.

In conclusion, the neuroeffectiveness of cART regimens largely depends on drug penetration and on the consistency with which the medications are taken. Our study suggests that the revCPE rank represents a step forward in estimating the penetration of antiretroviral drugs in the CNS and confirmed the importance of good treatment adherence in order to prevent cognitive disorders. Longitudinal investigations and routine neuropsychological examinations are warranted to better understand the dynamics of the relationship between adherence, neuroeffectiveness of antiretroviral drugs and cognitive impairment.

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MF received speakers' honoraria from Abbott Virology, Merck Sharp & Dohme and Janssen-Cilag. MC has been a paid consultant for Merck Sharp & Dohme, Italy and was employed by Bristol–Myers Squibb, Italy, from 10 May 2010 to 28 February 2011. MCS received travel grants from Novartis and Lundbeck and research support from the Catholic University of Rome. RC is an advisor for Gilead and Janssen-Cilag, received speakers' honoraria from ViiV, Bristol–Myers Squibb, Merck Sharp & Dohme and Janssen-Cilag, and research support from 'Fondazione Roma'. RM received speakers' honoraria from Abbott, Gilead and Bristol–Myers Squibb. ADL received speaker's honoraria and fees for attending advisory boards from GlaxoSmithKline, Gilead, ViiV Healthcare, Abbott Virology, Janssen-Tibotec, Siemens Diagnostics and Monogram Biosciences. SDG received speakers' honoraria and support for travel meetings from Gilead, Bristol–Myers Squibb, Abbott, Boehringer Ingelheim, Janssen-Cilag and GlaxoSmithKline. All other authors declare no competing interests.

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