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Prevalence of non-confounded HIV-associated neurocognitive impairment in the context of plasma HIV RNA suppression

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Abstract HIV-associated neurocognitive disorder is known to occur in the context of successful combination antiretroviral therapy (cART; plasma HIV RNA <50 copies/ml). Here, we newly provide an analysis of its prevalence and nature in the absence of medical or psychiatric confounds that may otherwise inflate the prevalence rate. We enrolled a cohort of 116 advanced HIV+individuals on cART (51% virally suppressed (VS)). They were screened for active Hepatitis C, current substance use disorder and were assessed with standard neuropsychological (NP) testing. Our results showed that out of the entire sample, NP impairment occurred in 18.1% (21/116) in VS individuals which was not statistically different from the 24.1% (28/116) that were found to be NP-impaired and not VS. In comparison with NP-normal-VS persons, NP impairment in VS individuals was associated with shorter duration of current cART and lower pre-morbid ability. Higher cART CNS penetration effectiveness tended to be associated with lesser cognitive severity in NP-impaired VS individuals. Current CD4 cell count, depression symptoms and past CNS HIV-related diseases did not specifically account for persistent NP impairment in VS individuals. In conclusion, despite suppression of systemic viral load, non-confounded HIV-related NP-impairment prevalence reached 18.1%. Of the potential explanations for this persistent deficit, a "burnt-out" form of the disease and immune reconstitution inflammatory syndrome were the less likely explanations, while a shorter current cART duration and lower pre-morbid intellectual capacity were significant. Nonetheless, predictive modelling with these last two factors misclassified 27% and had low sensitivity (43%) emphasising that other yet-to-be-defined factors were operative.

Keywords HIV/AIDS · Antiretroviral treatment · Neurological complications · Neuropsychological functions · HIV-associated dementia · HIV RNA

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Introduction

In the era of combination antiretroviral therapy (cART), HIV-associated neurocognitive impairment (HAND) is still common (30–50% depending on HIV disease stage) even occurring in the context of successful cART—most simply defined as maximal viral load suppression in the plasma (HIV RNA <50 copies/ml).

By inspecting a series of large observational cohort studies, we were able to retrieve a 20–30% prevalence rate of neuropsychological (NP) impairment in HIV-positive (HIV+) individuals with viral suppression the plasma (21% from Robertson et al. (2007), 21% from Sevigny et al. (2004) and 29% from the CNS HIV Anti-Retroviral Therapy Effects Research Study (Heaton et al. 2009)). A number of other studies did not present enough data to compute the NP impairment prevalence rate in the context of undetectable plasma viral load; however, these studies showed no significant relationships between NP impairment and plasma viral load levels (Bhaskaran et al. 2008; Valcour et al. 2004).

Several reasons have been suggested for this relatively high prevalence (Brew 2004). We will briefly overview

some that have already been evaluated and others that remain to be thoroughly explored.

First, some NP confounds common in the HIV population could be operative. This would be principally *current* substance use disorders, but this is an unlikely significant confound in studies that have screened out or analysed separately these individuals (Heaton et al. 2009). And if not, a systematic effect of substance use disorders on NP functions is not evident (Byrd et al. 2009). Another factor could be current major depressive disorder, but there is cumulative evidence that it is not compounding NP deficits in most HIV+ individuals (Carter et al. 2003; Cysique et al. 2007; Goggin et al. 1997). Lastly, co-infection with Hepatitis C Infection (HCV) has been associated with worse NP functioning (Hilsabeck et al. 2005). The above-mentioned studies have not clearly reported whether co-infected HCV individuals were included. Therefore, part of the prevalence of NP impairment in VS HIV+ patients may be related to HCV infection.

Second, another explanation for continued NP impairment in the context of suppressed viral load in the plasma is that chronic low-level HIV replication occurs separately in the brain (Cinque et al. 2007; Cunningham et al. 2000; Deeks et al. 2001) especially in advanced HIV infection even potentially with very low CSF HIV RNA levels between one and 49 copies/ml (Letendre et al. 2009). Nonetheless, cART initiation frequently leads to viral suppression in the plasma and CSF (Ellis et al. 2000; Letendre et al. 2004; Roberston et al. 2004).

Third, immune reconstitution inflammatory syndrome (IRIS), following treatment initiation, may be responsible in some cases for a paradoxical neurological deterioration, despite improvements in HIV viral load and CD4 cell count (Riedel et al. 2006). However, when considering the finding of a study which investigated the NP response of HIV+ individuals with IRIS (defined as CD4 lymphocyte counts <50 before and >100 cells/ml after cART), we determined that at baseline, the proportion of patients with undetectable viral load who were NP-impaired or not did not differ (74% versus 70%; (McCutchan et al. 2007)). Therefore, IRIS could be explanatory only in a minority.

Fourth, some individuals may present with a "burnt out" form of the disease. In some cases, HAND may not have completely resolved on previous cART and presents with irreversible cognitive deficits, through neuronal loss (Rumbaugh and Nath 2006). This burnt out form of the disease has been found to predict further cognitive decline (Cysique et al. 2006; Stern et al. 2001). However, whether this is a major cause of NP impairment in individuals with plasma viral load suppression remains unclear.

Fifth, antiretroviral drug toxicities in brain tissue may be responsible for some NP impairment. While plausible, the data demonstrating such neurotoxcity are still sparse (Schweinsburg et al. 2005).

Sixth, chronic low level immune activation despite systemic viral suppression may damage brain tissue per se and, in some patients, facilitate the expression of neurodegenerative diseases such as Alzheimer's Diseases, Parkinson's disease and vascular cognitive impairment (Brew et al. 2008; Valcour and Paul 2006).

Lastly, some HIV+ individuals may be more susceptible to the development of cognitive disorders and this may reflect *less cognitive reserve* (Stern 2002). The role of cognitive reserve (passive and active cognitive efficiency to compensate for brain injury) has been demonstrated in various neurological disorders as well as in HIV infection (Basso and Bornstein 2000; Stern et al. 1996). However, its role in persistent NP impairment in the context of successful treatment has not been investigated.

The first aim of our study is to determine the prevalence of NP impairment in the context of maximal plasma viral load suppression in a cohort of advanced HIV-infected individuals (N=116), screened for major NP confounds (current substance use disorder and Hepatitis C virus positive serology) and who were on cART.

Based on the above-mentioned literature, we hypothesised that NP impairment in VS HIV+ individuals would *not* be associated with low current immune function or higher levels of depressive and anxiety complaints.

Moreover, because we had collected the presence of previous CNS-related diseases in our cohort, we hypothesised that "burnt out form of the disease" would *not* be specifically associated with NP impairment in VS individuals.

In addition, we tested the possibility of ART toxicity on NP functions using the CNS penetration rank score (Letendre et al. 2008). As such, we expected that greater CNS penetration effectiveness (CPE) rank in the impaired VS individuals may be associated with worse NP impairment.

Lastly, we hypothesised that lower cognitive reserve would be associated with NP impairment specifically in the NP-impaired VS group.

Methods

Participants

Between August 2001 and December 2002, 138 HIV-infected individuals from the outpatient clinics at St. Vincent's Hospital, Sydney, Australia, were invited to participate in a prospective study of the neurological and NP complications of HIV disease. The inclusion criteria were advanced HIV disease (stage C3, 1993 Centres for Diseases Control and Prevention Classification), being on cART (at least three ART drugs (Gulick

and Staszewski 2002; Yeni et al. 2002)) and being clinically stable.

Individuals were excluded if they had a history of or a current psychotic disorder, current untreated major depression, current other neurological disease (current CNS opportunistic infections, current neurological disorder unrelated to HIV), active syphilis, head injury with loss of consciousness greater than 1 h and a current drug use disorder. Patients with previous brain HIV-related disease were included as long as there had been clinical resolution on cART at least 6 months prior to study entry (see (Cysique et al. 2004b) for further details). Eight (6.8%) participants were positive for HCV antibody. Twenty participants declined to participate, but these did not differ from the patients who agreed to participate for demographic and laboratory factors. One patient could not follow the test instructions and could not be included. One did not come for the scheduled assessments. The demographic, clinical and laboratory characteristics of the 116 advanced HIV-infected individuals who completed the study examination are presented in Table 1.

Procedure

All participants were tested with a standard NP battery assessing six cognitive domains: speed of information processing, executive function, learning, memory, motor and verbal (See Table 2; Cysique et al. 2004b). In addition, all participants completed standard questionnaires assessing current depressive, anxiety and stress symptomatology (Lovibond and Lovibond 1995). Pre-morbid abilities were assessed using the National Adult Reading Test (Nelson and Willison 1982).

All participants signed an informed consent form and the affiliated research institutions (The Ethics Committee of St. Vincent's Hospital and the University of New South Wales, Sydney, Australia), and ethics committees approved the research protocol.

Table 1 Demographic, clinical and laboratory characteristics of the study group

	Advanced HIV+
N	116
Age (years)	48.7 (9.2)
Educational level (years)	14.08 (2.8)
Gender (% men)	100%
Estimated HIV duration (years)	12.0 (5.0)
Nadir CD4 cells count (count/μl)	76 (64) [median=65]
Current CD4 cells count (count/μl)	355 (228) [median=326]
Log $_{10}$ plasma HIV RNA (detectable)	4.2 (1.1) [median=4.4]
Virally suppressed (mL/copy <50)	51% (*N*=59)
cART duration (years)	5 (2) [median=5]
Current treatment duration (months)	19 (17) [median=12]
CPE [a]	1.9 (0.8) [median=2]
Depression [b]	7.2 (7.4)
Anxiety [b]	5.5 (6.3)

CPE CNS penetration effectiveness

[a] CNS penetration Effectiveness was based on Letendre et al. (2008) definition

[b] Depression, Anxiety and Stress Scale

Table 2 Neuropsychological test battery

Cognitive ability Domains	Individual Neuropsychological measures
Speed Information processing	Trail Making test A (time in second) [a]
	Symbol Digit Modalities Test total correct (written) [b]
Executive function	Trail Making test B (time in second) [a]
Motor	Grooved Pegboard Dominant hand (time in second) [a]
	Grooved Pegboard non dominant hand (time in second) [a]
Learning	California Verbal Learning Test Total Learning [c]
Memory	California Verbal Learning Test long-delay free recall [c]
Verbal	Controlled Oral Word Association test: Verbal Fluency (total letter FAS or CFL) [a]
	Semantic Fluency (total animal) [a]

[a] Normative data used for these measures were developed by Heaton et al. 2004 (Norms for Caucasian individuals were retained)

[b] Normative data used for this measure were developed by Uchiyama et al. 1994

[c] Normative data used for these measures were developed by Norman et al. 2000

Data analysis

Definition of NP impairment

First, raw neuropsychological scores were transformed into scaled scores (with a mean of 10 and a standard deviation of 3 for all NP measures except the Symbol Digit Modalities Test (SDMT)) which was transformed into age, gender and education *z* scores. The SDMT *z* scores were transformed into *T* scores using a linear transformation (Strauss et al. 2006). The scaled scores for the rest of the NP measures were transformed into demographically corrected *T* scores for age, education and gender following the Heaton et al. (2004) methodological approach. The battery *T* scores were then averaged into a mean *T* scores (*T* scores have a mean of 50 and a standard deviation of 10)—see Table 2.

Second, we used the Global Deficit Score (GDS) approach to determine the overall classification of impair-

ment status on the battery (see Carey et al. (2004) for detailed description). Briefly, demographically corrected T scores were converted to deficit scores according to the following criteria: $T > 39 = 0$ (normal), $39 \geq T \geq 35 = 1$ (mild impairment), $34 \geq T \geq 30 = 2$ (mild to moderate impairment), $29 \geq T \geq 25 = 3$ (moderate impairment), $24 \geq T \geq 20 = 4$ (moderate to severe impairment), $T < 20 = 5$ (severe impairment). Deficit scores were averaged across the test battery to compute the GDS. The GDS can be analysed as a continuous variable indicating number and severity of neurobehavioral deficits across the entire test battery or as a cut-off of ≥0.50 that can be used to classify overall NP impairment. Using the memory complaints as a surrogate of functional decline, we were able to classify each case as either having Asymptomatic Neurocognitive Impairment (ANI) or Mild Neurocognitive Disorder (MND) or HIV-Associated Dementia (HAD). In the cohort, global impairment rate reached 42.2%, and this was significantly different from 10% in a demographically comparable HIV-control group ($p < .0001$; see Cysique et al. 2011 for more details). It should be noted that when compared to HIV-controls, global NP impairment was 35% ($p < .02$) in the VS HIV+ subgroup and global NP impairment was 50% ($p < .0002$) in the not virally-suppressed (NVS) HIV+ subgroup. Furthermore, among the NP-impaired HIV+ participants, 7.7% had ANI, 23.3% had MND and 11.2% had HAD.

For the purpose of this study, only the HIV+ group was considered. Therefore, to investigate relations between NP impairment (NP-impaired versus NP-normal) and plasma viral load status (VS versus NVS; plasma HIV RNA detection was conventionally set as >50 copies/ml), four groups were defined and compared using ANOVA: NP-normal and VS N=38/116 (32.7%); NP-normal and NVS N=29/116 (25%); NP-impaired and VS N=21/116 (18.1%) and NP-impaired and NVS N=28/116 (24.1%).

This four group's analysis strategy was employed to better define the nature of NP impairment in the VS individuals. Therefore, for the following analyses, we used our group of interest: "NP-impaired-VS" as the *reference* group to which others were compared using the Dunnett's methods to control for types I and II errors following one-way ANOVA. This method is less conservative than the Bonferroni corrections (Perneger 1998) but still accounts for multiple comparisons. Statistical analyses were conducted with Statistical Package JMP version 8 (SAS Inc).

Results

Groups' demographic characteristics and NP status

The four defined groups did not differ in terms of age ($F_{(112)}$=1.36; p=.26) and education ($F_{(112)}$=1.65; p=.18). In addition, post hoc Tukey HSD shows no additional differences between groups at $p < .05$. By design, they differed on GDS as follows: NP-normal-VS group (GDS=0.15±0.14); NP-normal-NVS group (GDS=0.19±0.18); NP-impaired-VS group (GDS=1.21±0.85) and NP-impaired-NVS group (GDS=1.35±0.99); ($F_{(112)}$=31.4; $p < .0001$). Post hoc Tukey HSD shows that as expected both the NP-impaired groups had significantly lower GDS than both NP-unimpaired groups and that both types of groups did not differ between themselves.

Groups' clinical and laboratory characteristics

We found that in comparison with other groups, the NP-impaired VS group did not differ in terms of HIV duration, nadir CD4-T cell count, overall cART duration and self-reported depressive and anxiety symptoms. In addition, we found that the NP-impaired VS group did not differ from the NP-normal VS group for current CD4-T cell count, proportion of individuals with past CNS HIV-related diseases and haemoglobin (see Table 3).

The NP-impaired VS group had an average current treatment duration of 17 months which was not different from the NP-normal NVS group but tended to be less than the NP-normal VS group. Using the Letendre et al. (2008) CPE score, we found that the NP-impaired VS group did not differ from the NP-normal VS for the CPE but that it had a higher CPE in comparison with the NP-normal NVS group. Results were similar when individuals with current HAD were excluded. When including only individuals with current cART duration of at least 3 months, we also found similar results. Using the dichotomous CPE (≥2), we found that the NP-impaired VS group showed the highest proportion of individuals with a high CPE, although it only differed significantly from the NP-normal-NVS group. Further analyses demonstrated that only within the NP-impaired VS group did the individuals with higher CPE (CPE>2) tend to show a lesser degree of NP impairment although not significant due to small sample size (High CPE (N=10), GDS=1.05±0.38 vs. Low CPE (N=11), GDS=1.36±1.12; Cohen's d=0.36). A higher GDS means greater cognitive impairment.

Lastly, we found that the NP-impaired VS group obtained lower pre-morbid IQ than both NP-normal groups, but did not differ from the NP-impaired NVS group.

HAND severity and relation to viral suppression

When selecting only individuals with impairment, we found that individuals with viral suppression were more likely to be classified as ANI rather than HAD as compared to individuals who were not virally suppressed ($p < .05$; see Fig. 1).

Table 3 Four groups' comparisons on laboratory and clinical data

	NP-impaired VS	NP-normal VS	NP-normal NVS	NP-impaired NVS	*p* Value
N	21	38	29	28	–
Estimated HIV duration (years)	10.2 (5.8)	11.4 (5.1)	13.4 (4.1)	12.4 (4.8)	.12
Nadir CD4 cells count (count/μl)	89.0 (60.2)	62.0 (63.8)	84.1 (62.5)	77.3 (69.7)	.38
Current CD4 cells count (count/μl) [a]	479.7 (215.0)	416.7 (197.9)	273.5 (199.2)	261.0 (242.4)	.0003
Past CNS HIV-related involvement [b]	19%	18.4%	6.9%	29.6%	.18
Overall cART duration (years)	4.6 (1.5)	5.0 (1.7)	5.5 (1.5)	4.7 (2.4)	.33
Current treatment duration (months) [c]	16.8 (12.9)	26.9 (18.8)	17.4 (15.7)	9.4 (12.3)	.0007
CPE (all sample) [d]	2.20 (0.53)	2.01 (0.76)	1.5 (0.99)	1.93 (0.99)	.03
CPE>2 (all sample) [e]	47.6%	43.2%	24.1%	35.7%	.32
CPE (*HAD excluded*) [f]	2.26 (0.53)	2.01 (0.76)	1.5 (0.99)	1.94 (0.88)	.03
CPE>2 (*HAD excluded*) [g]	52.9%	43.2%	24.1%	31.6%	.19
CPE (≥3 months current cART)	2.31 (0.54) *N*=16	1.97 (0.78) *N*=34	1.81(0.90) *N*=21	1.88 (0.86) *N*=18	.27
CPE>2 (≥3 months current cART) [h]	62.5%	41.2%	28.6%	33.3%	.18
Haemoglobin [i]	146.5 (14.1)	145.0 (12.6)	137.5 (22.9)	133.8 (15.2)	.02
Estimated full IQ (weighted for education) [j]	110.6 (9.64)	116.8 (8.05)	117.5 (6.94)	114.7 (9.54)	.02
Depressive symptoms (DASS)	7.3 (7.8)	7.2 (6.1)	5.9 (6.5)	8.4 (9.3)	.67
Anxiety symptoms (DASS)	6.5 (9.3)	4.4 (4.1)	4.1 (4.8)	7.6 (7.1)	.09

VS virally suppressed; *NVS* non-virally suppressed; *HAD* HIV-associated dementia

CPE was based on Letendre et al. (2008) definition. Post hoc comparisons were made with Dunnets' Controls method. Non-significant planned contrasts: estimated HIV duration, nadir CD4, Overall cART duration, CNS penetration Index (≥3 months current cART) and depressive as well as anxiety symptoms

[a] NVS groups≠VS groups ($p<.003$)

[b] NP-impaired detectable group≠NP-normal detectable group ($p<.03$)

[c] NP-impaired VS group tends to have lower current treatment duration than NP-normal VS group ($p=.06$)

[d] NP-impaired VS group has a higher CPE compared to NP-normal NVS group ($p<.02$)

[e] NP-impaired VS group tends to have a CPE >2 more often than for the NP-normal NVS group ($p=.08$)

[f] (HAD excluded) NP-impaired VS group has a higher CPE than NP-normal NVS ($p=.01$)

[g] (HAD excluded) NP-impaired VS group has a higher CPE compared to NP-normal NVS group ($p<.05$)

[h] (≥3 months on current cART) NP-impaired VS tended to have a CPE >2 more often than the NP-impaired NVS ($p=.09$) and the NP-normal NVS group ($p=.01$)

[i] NP-impaired VS group had higher haemoglobin that the NP-impaired NVS group ($p=.03$)

[j] NP-impaired VS group had lower estimated pre-morbid IQ than both NP-normal groups ($p<.02$)

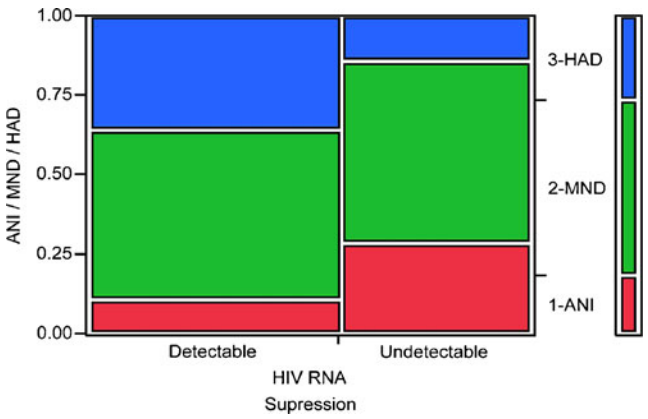

Fig. 1 HAND categories and relation to HIV RNA suppression. ANI vs. HAD are statistically different at $p<05$. MND vs. HAD were not statistically different

Predicting NP impairment in VS HIV+ individuals?

Finally, to test the predictive power of a model that would differentiate NP-impaired from NP-normal in the VS sub-sample, we conducted a multivariate logistic regression analysis with NP impairment status as the outcome variable and current treatment duration as well as estimated pre-morbid IQ as predictors (the two variables that were significantly different between the NP-impaired group and NP-normal group). We found that the overall model was significant ($\chi^2_{(2)}=10.7$; $p<.005$). In addition, treatment duration remains a unique predictor in the model (Wald statistic, $p=.05$; OR=1.04; CI=1.00–1.08) as well as estimated pre-morbid IQ (Wald statistic, $p<.03$; OR=1.09; CI=1.02–1.17). The sensitivity is 43% and the specificity 89%, while the predictive value of a positive test is 69% and the negative 74%. Overall misclassification rate is of 27%.

Discussion

This study showed that in an advanced HIV+ cohort, 18.1% (21/116) were NP-impaired in the context of maximal viral suppression. Of the potential explanations for this persistent deficit, only a shorter current cART duration and lower pre-morbid intellectual capacity were significant. Nonetheless, predictive modelling with these factors misclassified 27% and had low sensitivity (43%) emphasising that other yet-to-be-defined factors were operative.

This result is somewhat marginally lower than other studies which determined the prevalence of NP impairment to be 20–29% (1–3). This still represents a non-negligible amount of HIV+ individuals, and it may increase as people survive longer (Dore et al. 2003). In our cohort, the overall NP impairment rate for both VS and NVS individuals, corrected for demographic factors, was 42%. This is consistent with previous reports in similar advanced HIV population in the cART era (Sacktor et al. 2002).

Among the factors that relate to current NP impairment in the VS group, especially in comparison with the NP-normal VS group, was current treatment duration. The results appear to confirm that stability on treatment is an important factor for normal NP functioning (Cole et al. 2007). It may also suggest that NP-impaired VS persons have been undetectable for shorter periods compared to their NP-normal counterparts. This would imply that the NP-impaired VS group is still in the process of improving. However, this does not entirely explain our results. Indeed, the median current treatment duration in our interest group was 13 months which was in fact slightly longer than in the NP-normal-NVS group for example (11 months). Still in our group of interest, five participants (24%) had a treatment duration of less than 3 months (which is a window for the first maximal phase of recovery (Cysique et al. 2009)), but this was not statistically different from the NP-normal NVS group (28%).

An alternative explanation is that these individuals have remained VS but that regimens were proactively changed due to antiretroviral drug resistance, peripheral toxicity or side effects. Other reasons for non-stability in treatment are a lack of adherence. For the current cohort, this is an unlikely explanation as they had reported high average levels of adherence (96.8±7% (Cysique et al. 2006)). Moreover, non-adherent HIV+ persons often have detectable plasma viral load. So, while treatment stability may explain why the current NP-normal VS are more likely to be free of cognitive deficits, it does not fully explain the persistence of NP impairment in VS HIV+ cases.

Our finding that estimated pre-morbid IQ is lower in the NP-impaired VS group when compared to the NP-normal and that educational level did not differ is interesting. Still, the average difference in terms of IQ points is actually small (six points or 1/6 of one IQ SD unit). Also, our NP-impaired group obtained pre-morbid levels that are still well within the normal range. Consequently, the meaning of this difference should be interpreted with caution. One interpretation that is currently popular is that pre-morbid IQ may represent cognitive reserve (related to environmental and genetic factors (Stern 2002)). As such, individuals with less reserve will demonstrate clinical signs of CNS injury in higher proportion than those with higher reserve. Cognitive reserve (Stern 2002) is also conceptualised as an active process representing more efficient compensatory mechanisms in the face of a disease. While interesting, these interpretations are only possibilities. Nonetheless, they constitute new hypotheses that need to be explored.

The finding that individuals with viral suppression have a less severe form of HAND implies that the nature of the disease, in this instance, may be different from non-VS individuals.

Our cohort did not include individuals with current substance abuse disorders and a very small proportion who were co-infected with HCV (6.8%), and these last individuals were *not* more likely to be NP-impaired than the rest of the group. This was due to the fact that their HCV diagnosis was not recent and that they did not have active HCV. HCV is actively treated in Australian Tertiary healthcare, especially in the context of co-infection with HIV. Moreover, individuals with a diagnosis of current major depression were included only if stable on their psychotropic regimen and again were not more likely to be NP-impaired than the rest of the group. Therefore, these potential NP confounds could not explain the observed HIV-related impairment rate in our cohort. In addition, current self-reported symptoms of depression and anxiety did not differ between the defined NP-impaired and viral load detection groups. Altogether, our cohort's low rate of confounding conditions may help explain why our rate of NP impairment in the VS individuals was marginally lower than elsewhere reported (Robertson et al. 2007).

No HIV+ individuals presented with acute cognitive disturbances and recovering immune functions compatible with IRIS. Moreover, we found that the NP-normal VS group had comparable CD4 cell counts to the NP-normal VS group making IRIS an unlikely factor for current NP impairment. This is in agreement with previous literature showing that over the long-term IRIS is not associated with NP deterioration (McCutchan et al. 2007).

A past CNS HIV-related disease (clinically resolved 6 months prior study entry) appears to be a more significant factor in the sub-group who were impaired and had detectable viral load. This would suggest that for the NP-impaired VS individuals, our group of interest, past HIV-related brain injury is not a single significant cause. No such finding has been previously reported in the NeuroAIDS literature as most

studies tend to exclude individuals with past CNS HIV-related insults or such previous CNS HIV-related disorders were not accounted for.

In this study and as previously reported (Trillo-Pazos et al. 2004), we did not find evidence for a decisive role of the cART CPE in explaining the difference in NP-impairment status between VS groups. However, we found tentative evidence that within the NP-impaired VS group, the individuals with a lower CPE showed greater cognitive severity. The result is in accordance with previous reports which have also found a lower degree of cognitive severity in *NP-impaired participants* on higher CNS penetrating regimens (Cysique et al. 2004a, 2009). This suggests that some HIV+ individuals could be more optimally treated even when plasma HIV viral load is undetectable. Moreover, it suggests that ARV CNS neurotoxicity may not be substantial.

Another explanation that we cannot definitively exclude and that may be one of the most plausible in the context of chronic HIV infection is that there is ongoing viral replication in the CNS despite maximal viral suppression in the plasma, due to increasing CNS compartmentalization with advanced HIV infection (Cunningham et al. 2000; Letendre et al. 2009). Still, in our cohort, the regimens with the highest CPE were observed in both VS groups, and they have been shown to efficiently reduce HIV RNA in the CSF compartment at least 1 year after initiation (Cysique et al. 2004a).

Finally, our study suggests that new pathogenetic axes as potential explanations for persistent cognitive deficits in the cART era need to be explored (Brew et al. 2008). One would be a neurodegenerative process that may be facilitated chronic brain HIV infection (Churchill et al. 2009; Trillo-Pazos et al. 2004). The second neuropathological axis is vascular cognitive impairment due to the increasing prevalence of cardio-vascular diseases in chronically HIV-infected individuals (Wright et al. 2010).

Our study had several limitations which may detract from our findings. First, the cohort was composed of advanced HIV+ men, and the results could be different not only in less advanced HIV+ individuals but also in women. We were not able to obtain CSF HIV RNA to determine in how many cases HIV replication may have been active in the CNS. However, it should be said that undetectable viral level in the plasma remains the recommended clinical guideline to assess efficient cART. Lastly, in some instances, the sub-sample sizes were relatively small and may have led to reduced power to detect significant differences.

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