J. Neurovirol.
DOI 10.1007/s13365-014-0242-x

HIV-associated neurocognitive disorder in Australia: a case of a high-functioning and optimally treated cohort and implications for international neuroHIV research

Lucette A. Cysique · Robert K. Heaton · Jody Kamminga · Tammy Lane · Thomas M. Gates · Danielle M. Moore · Emma Hubner · Andrew Carr · Bruce J. Brew

Received: 24 November 2013 / Revised: 28 January 2014 / Accepted: 7 February 2014

Abstract The Australian HIV-infected (HIV+) population is largely comprised of high-functioning men who have sex with men (MSM). Like other English-speaking countries, Australia mostly relies on US neuropsychological normative standards to detect and determine the prevalence of neurological disorders. Whether the US neuropsychological (NP) normative standards are appropriate in Australian HIV+ MSM has not been established. Ninety virally suppressed HIV+ and 49 HIV-uninfected (HIV−) men (respectively 86 and 85 % self-reported MSM; mean age 54 and 56 years, mean premorbid verbal IQ estimate 110 and 111) undertook standard NP testing. The raw neuropsychological data were transformed using the following: (1) US standards as uncorrected scaled scores and demographically corrected *T* scores (US norms); and (2) *z* scores (without demographic corrections) derived from Australian comparison group scaled scores (local norms). To determine HIV-associated neurocognitive disorder prevalence, we used a standard definition of impairment based upon a battery-wide summary score: the global deficit score (GDS). Impairment classification (GDS≥0.5) based on the local norms was best at discriminating between the two groups (HIV−=14.3 % vs. HIV+=53.3 %; $p<0.0001$). This definition was significantly associated with age. Impairment classification based on the US norms yielded much lower impairment rate regardless of the HIV status (HIV−=4.1 % vs. HIV+=14.7 %; $p=0.05$), but was associated with historical AIDS, and not age. Both types of summary scores were associated with reduced independence in activities of daily living ($p\leq 0.03$). Accurate neuropsychological classifications of high (or low) functioning individuals may need country-specific norms that correct for performance-based (e.g., reading) estimates of premorbid cognition in addition to the traditional demographic factors.

Keywords HIV-associated neurocognitive disorder · Neuropsychological functions · Normative data · HIV/AIDS

Electronic supplementary material The online version of this article (doi:10.1007/s13365-014-0242-x) contains supplementary material, which is available to authorized users.

L. A. Cysique · T. M. Gates · A. Carr · B. J. Brew
St. Vincent's Clinical School, University of New South Wales, Sydney, Australia

L. A. Cysique · J. Kamminga
Neuroscience Research Australia, Sydney, Australia

L. A. Cysique · T. Lane · B. J. Brew
Neurology and Imaging and HIV Departments, St. Vincent's Hospital, Sydney, Australia

L. A. Cysique · J. Kamminga · T. M. Gates · D. M. Moore · E. Hubner · A. Carr · B. J. Brew
St. Vincent's Hospital Centre for Applied Medical Research, Sydney, Australia

R. K. Heaton
HIV Neurobehavioral Research Center (HNRC), Department of Psychiatry, University of California at San Diego, San Diego, CA, USA
URL: http://hnrc.hivresearch.ucsd.edu/

A. Carr
HIV, Immunology and Infectious Diseases Unit, St. Vincent's Hospital, Sydney, Australia

L. A. Cysique (✉)
Neuroscience Research Australia, PO Box 1165, Randwick NSW, Australia
e-mail: lcysique@unsw.edu.au

Published online: 03 April 2014

Introduction

The sociodemographic characteristics of HIV at-risk populations vary across the world (UNAIDS 2012). This represents a major challenge for reliably estimating the prevalence of HIV-associated neurocognitive disorder (HAND). In Australia, the main risk group for HIV infection remains men who have sex with men (MSM; >80 %) (The Kirby Institute 2012), and among those many have high premorbid functioning (Law et al. 2011). The Australian HIV epidemic is also characterized by a relatively good treatment response for HIV-infected (HIV+) persons and one of the highest nationally reported rates of viral undetectability *for those on combination antiretroviral therapy* (CART) (>85 % undetectable) (Law et al. 2011; The Kirby Institute 2012). However, the recently released 2013 Australian HIV Surveillance report indicates that out of the total HIV population who needs to be on CART, only 53 % are (The Kirby Institute 2013).

It is in this context that the current study takes place. The original aim was to assess the effect of HIV and aging on brain functions, as the HIV+ persons in Australia are surviving through older age (Cysique et al. 2013; Lane et al. 2012). Therefore, the current study is by design composed of middle-aged men (median age = 55) with chronic HIV infection (median HIV duration=20 years) and with stable CART.

As for similar cohorts in other parts of the world, for example, the US MACS cohort (Sacktor et al. 2002) and the North West London cohort (Garvey et al. 2011), a majority of the HIV+ MSM in these cohorts are highly educated (both formal and informal education) and high functioning in addition to being successfully treated. In these cohorts, recent reports of long-term stability of neurocognitive functioning (Cole et al. 2007) and low prevalence of HAND (Garvey et al. 2011) may have been over-generalized in that they were interpreted as evidence of low disease morbidity in general and due to successful CART.

In Western English-speaking countries (Australia, UK, and Canada), and in neuropsychology beyond the field of neuroHIV, there is a reliance on US normative standards to interpret neuropsychological performance. The US normative samples typically represent the current American demographic in terms of age, education, gender, and ethnicity (including migration history and acculturation (Manly et al. 2004)). These norms therefore intrinsically embed performance levels that, while representing the general American population, may not be appropriate for specific subpopulations in the USA and in other countries; this issue that has been recently raised in a UK neuroHIV study (Winston et al. 2013).

In all cases, the use of appropriate normative data is central to valid interpretation of neurocognitive performance. There are two schools of thought in neuropsychology on this matter. Some have advocated the use of large samples, which provide uncorrected and corrected normative standards (corrections for the main demographic effects that are relevant to a given country) (Heaton et al. 2004b). Others argue that relatively smaller local samples, which are as close as possible to the demographic and other (cultural, intellectual) characteristics of a clinical sample are more appropriate (Mitrushina et al. 2005). In many countries, there are no population norms and therefore a matched local control group may be the best option. There are three main issues with having local norms as the default choice in Australia and these are as follows: (1) The use of local comparison groups has variable and uncontrolled ascertainment biases by nature (Williams and Cottle 2011), and tends to be based on smaller samples because of relatively restricted research funding (Australian Neuroscience Society 2010). (2) The collection of a relatively small local sample for a study demands a lot of resources for relatively limited practical use. (3) Relatively small local norms may include sample-specific demographic or other background effects that are otherwise unusual in larger normative samples.

Because of the global nature of neuroHIV research, these issues demand making difficult choices regarding the selection of normative standards. These choices may sometimes be suboptimal and this is probably reflected in the wide variability of HAND prevalence data that have been published so far in the CART era (Kamminga et al. 2013). In Australian neuroHIV research, there are two choices: using US norms or collecting local control data keeping in mind particular HIV demographics as mentioned above.

In assessing the effect of HIV and aging on brain functions in the current cohort of HIV+ and HIV-uninfected (HIV−) healthy controls, which is mainly composed of MSM with high premorbid functioning, we noted that the US normative standards performed suboptimally (see Lane et al. 2012). In the current paper, we therefore assessed whether the use of American population norms versus a local normative reference affected the validity, the nature and the profile of HAND.

The aims of our study were as follows:

1. To determine the rate of neuropsychological impairment in Australian HIV− versus HIV+ individuals using US normative standards (US norms);
2. To compare the HIV effects on neuropsychological impairment generated from the US normative standards versus impairment generated from the demographically comparable local HIV− control group (local norms);
3. To determine which clinical disease and laboratory markers, as well as non-HIV markers impairment risks (i.e., cardiovascular diseases as the cohort was middle-aged per design) predict the degree of impairment and the presence of impairment.

Methods

Participants

Between June 2009 and July 2012, 139 males aged 45 years old and above were enrolled into the HIV and Brain Aging Research Program, a prospective study investigating the effects of HIV infection on the brain in middle-aged persons. Of those 139 participants, 90 were HIV+ and 49 HIV−. HIV+ participants were recruited through the HIV and Neurology Clinics at St. Vincent's Hospital, Sydney. Fifteen HIV+ individuals had been diagnosed with HAND at some point in the past and our analyses were conducted with and without these cases. Eligible HIV+ participants were: at least 45 years old, on stable CART for at least 6 months, had a nadir CD4 equal to or below 350 cells/mm^3, had known HIV duration equal to or greater than 5 years, and had no active opportunistic disease. The 49 HIV− controls were recruited in the metropolitan area of Sydney using community newspapers, community websites, as well as posters and brochures placed at St. Vincent's Hospital, the University of New South Wales campuses, and the Holdsworth House general practice in Darlinghurst, Sydney. To meet eligibility criteria, control participants were required to be HIV negative on an ELISA test within the past 3 months. Moreover, they were screened for any history of acute cardiovascular disease (CVD) events (see Table 2 legend for exact definition). The majority of the control group participants self-identified as MSM (>85 %), which probably reflects that participants "self-selected" to support research involving their HIV+ counterparts.

Both HIV− and HIV+ participants were excluded from the study based on the following criteria: having a history of neurological disorders predating HIV diagnosis in the HIV+ group such as epilepsy, traumatic brain injury, Parkinson's Disease, Multiple Sclerosis, Alzheimer's disease, or Vascular Dementia; or psychiatric disorders on the psychotic axis (e.g., schizophrenia); current substance use disorders (within 12 months of study enrolment); history of loss of consciousness (≥30 min); and being non-proficient in English (see Lane et al. 2012 for English proficiency assessment details). All participants with English as a second language (N=4 in HIV+ group and N=2 in HIV − group; see Table 1) considered themselves fluent and stated that they preferred to be assessed in English. Participants were not excluded on the basis of current depressive symptoms or past substance use disorders that predated study entry by 12 months. Recreational use of marijuana was not set as a criterion for exclusion because it would exclude a large number of HIV+ individuals. Hepatitis C (HCV) status was recorded from the participants' medical records (HCV is actively screened both in tertiary and primary care in Australia) and if HCV+, participants were included only if successfully treated and/or inactive: N=2 in the HIV+ group (inactive HCV was defined as undetectable HCVRNA). All participants were assessed at their preferred time and without current illnesses that would prevent optimal cognitive performance

Ethics

All individuals signed an informed consent before participating in the study and the St. Vincent's Hospital and The University of New South Wales Human Research Ethics Committees approved our protocol.

Procedure

Detailed procedures are reported in Lane et al. (2012). Briefly, we used a standard neuropsychological test battery covering seven ability domains, and that is in widespread use for NeuroAIDS research in the USA (Heaton et al. 2010; Table S1 in supplemental file).

Data analysis

To assess our first aim, we used a battery-wide summary score: the Global Deficit Score (GDS) (Blackstone et al. 2012; Carey et al. 2004; Heaton et al. 2004b). The standard GDS cutoff of ≥0.5 is an established definition of impairment for HIV-related brain injury and that virtually guarantees meeting the international criteria for HAND (Antinori et al. 2007; Blackstone et al. 2012). We first developed the *impairment rate computations based on American population norms* (*US norms*). Using US population normative data (Brandt and Benedict 2001; Heaton et al. 2004b), raw scores were converted to normally distributed and demographically uncorrected scaled scores and then demographically corrected T scores (see norming procedure details in supplemental files). T scores were then transformed into deficit scores and averaged to create the GDS. Second, we developed the *impairment rate computations based on local Australian scaled scores* (*local norms*). To develop a local normative reference, we used the 49 HIV− control participants' demographically uncorrected scaled scores (see Table S2) and transformed them into z scores. z scores were then transformed into deficit scores and averaged to create the GDS.

Note that scaled scores, T scores, and z scores are standard scores that have the same linear properties. Moreover, the GDS can be computed from both T scores and z scores (see GDS computation details in Supplemental files). Therefore, for both the US and local norms, we used a GDS greater than or equal to 0.5 as it has typically been used as a cutoff for defining

Table 1 Demographic characteristics in the HIV+ and HIV− groups

	HIV−	HIV+	*P*
N	49	90	–
Age	54.2±6.6	56.1±7.6	NS
Age >60 years old	22.4 %	33.3 %	NS
Education	15.1±2.6	14.4±2.6	NS
Gender (% male)	100 %	100 %	–
Ethnicity (% Anglo-Australian)	96.0 %	93.0 %	NS
WAIS-III VIQ[a]	111.8±6.1	110.1±5.6	NS
HIV risk groups (%MSM)	85 %	86 %	–
Employed %	62.0 %	55.6 %	NS
Depressive complaints[b]	10.2 %	18.9 %	NS
IADL[d] decline %	6 %	29 %	<0.002
Mild/≥ moderate cognitive symptoms[c]	8.2 %/0 %	17.8 %/12.2 %	<0.007

Ethnicity: In HIV− group: 1 Asian-Australian; 1 Middle-Eastern/Mediterranean Australian. In HIV+ group: 1 Asian-Australia, 1 Indigenous Asian-Australian, 2 Middle-Eastern/Mediterranean Australian, 1 South American Australian. All but one had secondary education in English, and this participant had secondary education in Spanish and had lived in Australia for 30 years

NS non-significant statistical difference (at least $p>0.15$); Mean SD otherwise notified; *MSM* Men who have sex with men

[a] Predicted WAIS-III Verbal IQ (VIQ) according to Sullivan et al. (2000): Australian Age-Education and Premorbid Cognitive/Intellectual Estimates for the WAIS-III

Formula: 101.32−0.58(NARTerr)+4.18(Educ)

In NESB formula: 85.54+5.0(Educ)+0.2(Age)−2.87(Sex)

Age = age in years; Sex: 1 = Male; 2 = Female; Educ = education level: 1 = less than 9 years; 2=9 to 10 years; 3=11 to 12 years; 4=13 to 15 years; 5=16 or more years; *NARTerr*: National Adult Reading Test Error scores (NART 2nd Ed, Nelson, 1991)

[b] This was based on the published clinical cutoffs for the BDI-II and the DASS (see "Methods") and included mild, moderate, and severe depressive complaints. Moderate depressive complaints reached 2 % in the HIV− group and none were severely depressed. Moderate depressive complaint reached 8.9 % in the HIV+ group and 3.3 % has severe depressive complaints

[c] This was based on the PAOFI (see Methods), cutoffs for mild symptoms was PAOFI≥5<11; and moderate symptoms >11. These cutoffs were based on the current samples' data distributions

[d] Instrumental Activities of Daily Living (IADL) Heaton et al. (2004a)

"impairment." This cutoff indicates that, on average, an individual is at least mildly impaired on at least half of the tests in the battery (Heaton et al. 2004b). When possible, and for clarity of the results and illustrations, we refer to US norm-based GDS or *T* scores versus local norm-based GDS or *z* scores.

To assess our second aim, we used the following two strategies: First, we examined the effects of demographics on neuropsychological performance in the *HIV− group only*. We conducted Pearson correlations between age and education separately and the uncorrected global scaled score, and then used the US norm-based global *T* scores. These global scores represent an average of the neuropsychological performance across the test battery and are normally distributed. Second, to compare the HIV effects on neuropsychological impairment generated from the USA vs. local norms, we generated Cohen's *d* effect sizes between HIV− and HIV+ groups on the seven cognitive domains mean *T* scores and global *T* score as well as on the seven cognitive domains mean *z* scores and global *z* score.

To assess our third aim, we used the GDS within the HIV+ group as the dependent variable and the disease and laboratory characteristics as well as Instrumental Activities of Daily Living (IADL) and depressive symptoms as the independent variables. The analyses were run using the two types of GDS (US normed versus local normed GDS), as dichotomous and continuous outcomes in order to determine the effects of predictors on the presence and severity of impairment (using χ^2, or logistic regression, and *t* test, or linear regression as appropriate). The current cohort was recruited to assess the effect of aging and HIV on the brain. One aspect of brain aging in HIV+ middle-aged individuals that is being increasingly recognized is the effect of CVD (Wright et al. 2010); hence this was included in the current study (see Table 2 and legend).

For this study, statistical significance was set at the conventional $p\leq0.05$ and effect sizes were used to provide transparency regarding magnitude of differences independently of the *p* values. Effect sizes (Cohen's *d*) and coefficient of correlation (*r*) were computed using the Effect Size

Table 2 Disease and laboratory characteristics in the HIV+ group

HIV disease characteristics	HIV+ group	Interquartile range
Estimated HIV duration (Median years)	20.6	14.6–25.5
% AIDS	72.2 %	–
% AIDS defining illness	46.7 %	–
Nadir CD4 (cells/mL median)	180	60–286
Current blood CD4 (cells/mL, median)	528	342–721
Current blood CD8 (cells/mL, median)	805	629–1150
% plasma HIV RNA (undetectable)	98.0 %	–
% CSF HIV RNA (undetectable)[a]	97.4 %	–
HIV treatment characteristics		
Current cART duration (months)	24	18–48
High CPE rank score (>7)[b]	76.6 %	–
Non-HIV aging (CVD) characteristics	HIV+ group	% Intermediate to High risk
Median/range Framingham score (10-year risk of CVD)[c]	18.3/0–80	52.2 %
Median/range D.A.D. score (12-month CVD risk)[d]	0.8/0–6.3	16 %
Past acute CVD[e]	17.8 %	–

Undetectable: HIV RNA assay with a limit of detection at 50 copies/mL. The majority of patients (>95 %) reported a high to very high level of adherence as confirmed by a high level of plasma viral load non-detectability

[a] N=38 who had lumbar puncture

[b] CPE: Central Nervous System Penetration Efficiency(Letendre 2011)

[c] We used the 2008 Framingham definition(D'Agostino et al. 2008). An intermediate to high risk was defined as score >15

Note that by design the non-HIV aging characteristics mainly consisted of CVD risk markers (see Cysique et al. 2013 for more details on the CVD protocol)

[d] D.A.D.: 12-months Data Collection on Adverse events of Anti-HIV Drugs(Friis-Moller et al. 2010). An intermediate to high risk was defined as score >1.5. Note that for both these CVD risk scores, age is the predominant factor in the predictive equation. Therefore, for our third aim analyses, there was a need to control and examine to what degree any CVD and neuropsychological score association may be driven by age. This is especially important since the US norm-based T scores have the age-effect removed and the local norm-based z scores do not

[e] CVD: cardiovascular diseases: atrial fibrillation, myocardial infarction, congestive heart failure, peripheral arteriosclerosis, carotid/coronary arteriosclerosis. Note that the current Framingham 2008 or D.A.D. formula does not include previous CVD events. Therefore, in our sample, the 17.8 % of HIV+ individuals with past CVD events have CVD risk scores moderated by both their past CVD history and the effects of successful CVD treatment. HIV− individuals were screened for history of past acute CVD events

Determination Program (Lipsey and Wilson 2001). Statistical analyses were conducted using the statistical package JMP 10, 2013 SAS Institute Inc.

Results

Demographic characteristics of the study samples are presented in Table 1, and HIV disease, HIV treatment, and CVD risk characteristics are presented in Table 2.

Note also that 15/90 (17 %) cases had been diagnosed with past HAND; therefore, the prevalence data was determined with and without those 15 cases.

First aim: rate of neuropsychological impairment in Australian HIV− versus HIV+ individuals

Figure 1 presents the global impairment rates for the two study groups using the two types of impairment definitions. Panel a provides the data for the entire group and panel b provides the data after exclusion of past HAND cases. We found that the local norm-based GDS provided significantly higher rates of impairment in both groups. All impaired cases detected by US norm-based GDS were also impaired by local norm-based GDS (17.8 %), while 40 % were impaired (Panel A) as classified by local norm-based GDS but not by the US norm-based GDS.

Second aim: to compare the HIV effects on neuropsychological impairment generated from the US norm-based GDS vs. local norm-based GDS

Because demographic effects can mask or influence any HIV effect, we first estimated the magnitude of any demographic effects in the HIV− group. Table 3 presents the correlations between age, education, and the uncorrected scaled scores versus demographically corrected US T scores. As expected, age exerted a negative influence on the uncorrected scores,

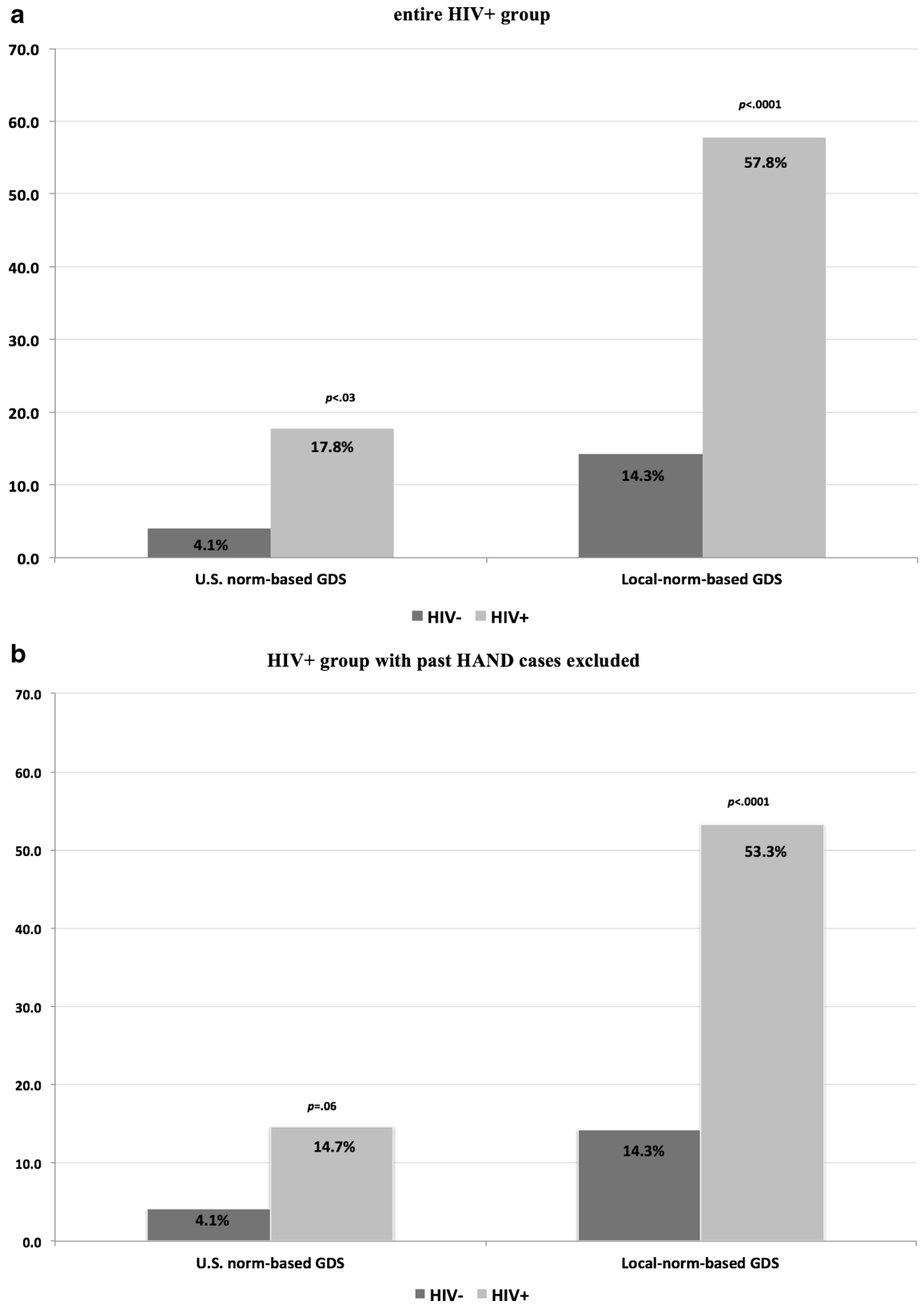

Fig. 1 Neuropsychological impairment prevalence rates in the study samples. Panel **a** entire HIV+ group. Panel **b** HIV+ group with past HAND cases excluded. Panels **a** and **b** within each of the scoring procedures, the USA versus local norms yield to significant differences ($p<0.001$) in HAND overall impairment rate. Panel **a** age was significantly associated with impaired status on the local norm-based GDS (mean age impaired=58.38±8.02; unimpaired=52.92±5.65; $p=0.0003$), but not on the US norm-based GDS (mean age impaired=54.76±6.55; unimpaired=56.36±7.80; $p=0.40$). Education was not different between impairment definitions ($p>0.45$)

Table 3 Age and education correlations on the uncorrected global scaled score in the 49 HIV− individuals

	Scaled scores		*T* scores		Comparative *P*[a]
	r	*P*	*r*	*p*	
Age	−0.32	*<0.03*	*0.15*	*0.32*	*0.01*
Education	0.25	*0.05*	*−0.13*	*0.38*	*0.03*
NART estimated FSIQ	0.25	*0.08*	–	–	–

Note correlations between demographic factors are: education and age correlation: Pearson $r=-0.10$ $p=0.50$; Education and NART FSIQ correlation: Pearson $r=0.41$ $p=0.004$; NART FSIQ and age correlation: Pearson $r=0.14$ $p=0.32$

[a] The correlation comparisons between scaled scores and *T* scores were conducted using http://www.quantpsy.org/corrtest/corrtest.htm program. First, each correlation coefficient is converted into a *z* score using Fisher's *r*-to-*z* transformation. Then, making use of the sample size employed to obtain each coefficient, these *z* scores are compared using formula 2.8.5 from Cohen and Cohen (1983, p. 54). *P* value one-tailed are reported

while education exerted a positive influence on neuropsychological performance. When considering the US *T* scores, we observed that the demographic corrections successfully diminished demographic influences, but actually showed small, non-significant trends towards over-corrections. That is, compared to the US standards, the Australian HIV− group performed slightly better than expected for their age and education.

Figure 2 presents the standardized differences (Cohen's *d* effect sizes) between the HIV− and HIV+ groups for the domain and global *T* scores (US norms) as well as *z* scores (local norms). The two sets of norms generated overall a similar profile. But the magnitude of effect sizes was greater when the local norms were used.

Third aim: relationships between impairment definitions, disease markers, and clinical significance, Table 4

Considering the HIV disease factors first, we found that historical AIDS was associated with impaired status using the US norm-based GDS ($p=0.05$). Second, we found significant effects of CVD risk scores (which have a large age component) when using the local norm-based GDS ($p=0.003$). However, age is a major component of the CVD risk score (Table 2 legend) and because age remains an uncorrected effect in the local norm-based GDS, the significant association between CVD and the this impairment definition was found to be essentially driven by this "age-CVD effect" (see Table 4 legend for further details on this result).

Finally, when considering the clinical significance of impairment status, we found that a decrease in IADL independence was associated with worse cognitive functioning on both US and local norm-based impairment definitions (Table 4). In contrast, we did not detect an effect of depressive complaints on impairment status.

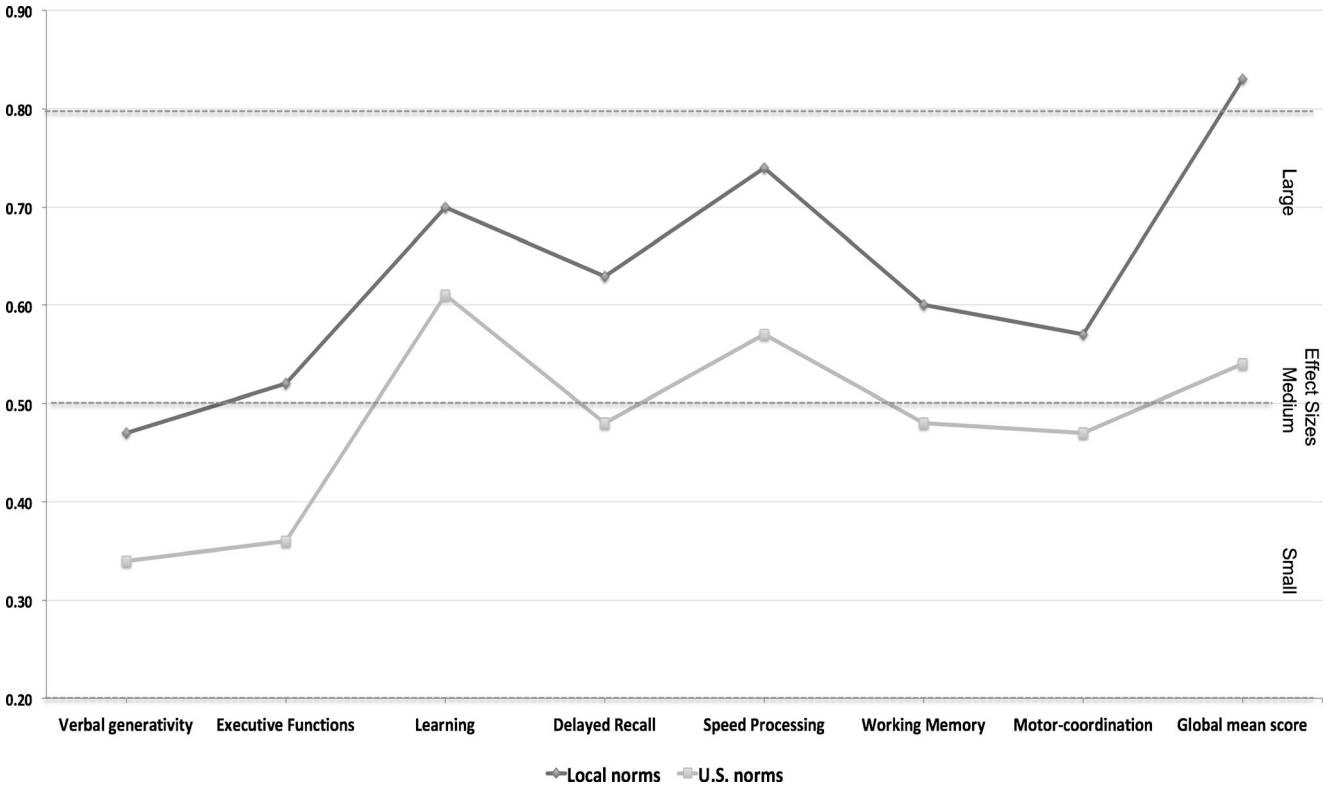

Fig. 2 Effect sizes for the domain and global mean US norm-based and local norm-based scores between the HIV− and HIV+ group

Discussion

Our study assessed whether the use of US norms versus local norms led to significantly different overall neuropsychological impairment rates (validity), and/or led to significant differences in the factors affecting neuropsychological impairment (determinants) or significant differences in patterns of neuropsychological performance (profile).

On the question of validity, the answer is that the local norms yielded a substantially larger HIV effect size, and higher estimated prevalence of HAND than the US norms, albeit with lack of demographic corrections. Note that the standard GDS method and 0.5 cutoff is intended to produce a specificity of approximately 85 % rate for impairment classifications (i.e., about15% false positive), which tends to optimize the balance between sensitivity and specificity (Heaton et al. 2004b; Taylor and Heaton 2001). In fact, the false positive rate for the local norm-based GDS is close to optimal (14.3 % versus only 4.1 % for the US norm-based GDS, Fig. 1); and unsurprisingly, this is associated with a much higher HIV+ impairment rate. In contrast, the US norms apparently underestimated the rate of neuropsychological impairment in both groups.

Our HAND prevalence is higher than those reported in slightly younger, virally controlled cohorts (Heaton et al. 2010; 41 %) and this possibly represents the effect of age and age-related diseases. However, it may also reflect some lack of precision of the local norm-based *z* scores, particularly for classifying individual participants; as the local norm-based *z* scores were not demographically corrected, hence impairment estimates with this method were biased by demographic effects (i.e., age and education). Nevertheless, while classification biases probably occurred at the individual participant level, our two groups were comparable with respect to all major demographics (i.e., age, education and gender) as well as our best estimate of premorbid cognition (i.e., WAIS-III predicted VIQ). Therefore, while demographic biases undoubtedly occurred (in both directions) at the individual level, the HAND prevalence may not have been significantly biased at the general population level.

The estimated HAND prevalence in the current study is higher than in a comparable English cohort, which also mostly included highly educated MSM, who were virally suppressed and had an average age of 53 years (HAND prevalence 19 %; Garvey et al. 2011). This study used the brief computerized CogState battery with its large US and UK normative standards (N=800) that allow age and gender corrections, but not education corrections. By contrast, estimated HAND prevalence in our cohort is lower than that reported in (Simioni et al. 2010) in an optimally treated Swiss cohort (HAND prevalence >70 %). Their sample comprised mostly men, aged in their late 40s, of which 73 % had at least a high school education. Some were on current methadone treatment suggesting that the cohort included participants who had acquired HIV infection through intravenous drug use (the education level in this subgroup was not specifically provided), but HIV infection transmission mode in the overall group was not documented. In addition, some had had previous HIV-related CNS opportunistic infections. Lastly, it is unclear which neuropsychological normative standards were used in this study.

These varying prevalence rates are concerning as they are drawn from similar types of Western cohorts where educational and cultural similarities are thought to allow the use of US normative standards. This phenomenon is likely due to the lack of optimal demographic corrections for the neuropsychological tests that were used in each of those studies (Strauss et al. 2006). This extreme variation in estimated prevalence rate calls for the careful examination of limitations to generalizability of US norms to other English-speaking countries in general and especially in subgroups that may be characterized by unusually high or low premorbid cognitive functioning. A recent NeuroAIDS panel (Joseph et al. 2013) has also emphasized the need for this country-specific effort to improve neuroHIV research standards.

The unusually high level of premorbid functioning in our sample constrains generalization of our findings to the rest of the Australian population. Our results do not suggest that US norms would also perform suboptimally in a more average Australian sample until this has been addressed empirically. Still, accurate neuropsychological classifications of high (or low) functioning individuals may need country-specific norms that correct for performance-based (e.g., reading) estimates of premorbid cognition in addition to the traditional demographic factors as also suggested by other Australian research (Green et al. 2008).

Our results are partially representative of HIV populations on CART in other countries including Europe (Munoz-Moreno et al. 2008) or the US (Heaton et al. 2010), as the level of undetectability for plasma HIV RNA in our cohort was very high (>95 %); however, the high rate of successful viral suppression on CART is comparable to treated participants of the Australian HIV observational database (N=2439), especially if mortality rate is taken into account (Law et al. 2011). This might serve as a reference for international NeuroAIDS research as well as for Australian HIV research if we consider those who should be on CART and are not (up to 47 %), and are therefore likely to initiate CART only when they become symptomatic or have AIDS (The Kirby Institute 2013). Based on our optimal impairment definition, we found that HAND was detected in a substantial proportion of this optimally treated sample. We confirm that HAND occurs despite what is considered optimal HIV care on CART (Cysique et al. 2011). On the basis of our results, there are concerning implications when more representative cohorts are considered (e.g., those who have initiated CART later than recommended, or cases with multiple psychiatric and

Table 4 Disease and laboratory characteristics predictions of the GDS-based impairment (Correlation coefficients *r* are reported)

HIV disease characteristics	US norm-based GDS	Local norm-based GDS
HIV duration (years)[a]	0.02	0.02
% AIDS (CDC 1993)[b]	0.15	0.08
% AIDS defining illness (yes/no)[b]	0.20 *	0.06
Nadir CD4 (cells/mL)[a]	0.04	0.02
Nadir CD4 <200 (cells/mL)[a]	0.02	0.01
Current blood CD4 (cells/mL)[a]	0.01	0.07
Immune recovery (CD4 *minus* nadir)[a]	0.03	0.06
Current blood CD8 (cells/mL)[a]	0.07	0.06
Current CART duration (months)[a]	0.11	0.10
High CPE rank score (>7)[b]	0.05	0.06
2008 Framingham score (high/low risk)[b]	0.09	0.33 **
D.A.D. score (high/low risk)[b]	0.02	0.25 *
Past acute CVD (yes/no)[b]	0.14	0.16
Significant decrease in IADL[a]	0.33*	0.36 **
Depressive complaints (BDI-II total score)[a]	0.18	0.18

For clarity we present results for

[a] The continuous GDS as the dependent variable or

[b] The GDS dichotomous definition (impaired vs. unimpaired) as the dependent variable

Both analyses were initially run, but the results' selection in the table provides the best data fits whether significant or non-significant results are presented. D.A.D.: 12-months Data Collection on Adverse events of Anti-HIV Drugs. An intermediate to high risk was defined as score >1.5. With AIDS=26.2 % impaired; without an AIDS=10.4 % impaired (US norm-based GDS) (χ^2 (1)=4, p=0.05). With high Framingham (data available in 88)=72.3 % impaired; with low Framingham=39.0 % impaired (local norm-based GDS) (χ^2 (1)=9.9, p<0.002). With high D.A.D.=85.7 % impaired; with low D.A.D.=51.3 % impaired (local norm-based GDS) (χ^2 (1) = 5.6, p<0.02). To investigate the age-CVD effect, we ran a logistic regression model with the *z* score GDS (impaired versus unimpaired) as the outcome and the Framingham score as predictor, while adding age as a covariate. We examined the same model using the D.A.D. score, which also includes an age component. We found that when age was used as a covariate, the relationship between the local norm-based GDS and CVD risk scores became non-significant (p>0.30). In addition, the partial correlation (partialled with respect to age) between the Framingham score and the continuous local norm-based GDS was $r_{(1.2.3)}$=0.13 (p=0.69), and was $r_{(1.2.3)}$=0.12 (p=0.26) between the D.A.D. score and the continuous local norm-based GDS, indicating that only a modest non-age-related CVD effect contributes to worse neurocognitive functioning. When investigating the individual components of the CVD risk scores on neurocognitive impairment, we found negligible effects across the board (r=0.05–0.08). A significant decrease in Instrumental Activities of Daily Living (IADL) independence was associated with worse neurocognitive functioning on the US norm-based GDS (*t* ratio=−2.2, p=0.03) and on the local norm-based GDS (*t* ratio=−2.6, p=0.01). A significant decrease in IADL independence is defined as a decrease in at least two activities of daily living

*p≤0.05; **p≤0.01

neurological confounds, which are fairly common in HIV+ persons including in Australia (The Kirby Institute 2013)). In fact, the largest American study including a more diverse range of HIV+ individuals found a substantially increased rate of impairment in those with higher comorbidity burdens (Heaton et al. 2010), and only 54 % of that unselected sample had low comorbidity levels. These findings argue that further research into the long-term effects of HIV and age on the brain is needed to document HAND prevalence and functional impact in HIV+ persons with broader socioeconomic status and geographical background, as well as including more women and HIV+ persons with comorbidities.

With regards to the question of possible determinants of the neuropsychological impairment, we found that the local norm-based GDS yielded an impairment classification that was significantly associated with age and age-CVD risk. On the other hand, the US norm-based GDS was uniquely associated with historical AIDS. This result emphasizes the impact that selection of a particular normative dataset can have on what conclusions are drawn regarding the nature of HAND. It also reinforces the careful attention to possible needs for risk-population norms, which would allow researchers to assess the detailed connections between CVD, age and HAND using optimal classification standards.

One of our most interesting findings was the strong evidence for the clinical significance of the detected neuropsychological impairment, and this was observed using both local and US standards. We interpret this finding as supporting the inclusion of mild forms of HAND in addition to the moderate to severe forms as detected by the US norms (Heaton et al. 2010).

On the question of the profile of neuropsychological impairment, we showed that the selection of different sets of norms had a major impact on the magnitude of effect sizes but not on the general pattern of performance. Deficits were present especially in learning (episodic memory) and speed of information processing; these are well-recognized hallmarks of HAND in the CART era (Woods et al. 2009). These results imply that norms with greater sensitivity to impairment should be selected in order to allow for timely initiation of both pharmalogical and behavioral interventions for HAND.

Acknowledgments We would like to thank Dr. Mark Bloch, director of the Holdsworth House General Practice for facilitating the co-enrolment of his HIV− cohort into the HIV and aging cohort. We would also like to thank the HIV physicians and the nursing staff at the Immunology and Infectious Diseases Department of St. Vincent's Hospital for their support and investment in the study. Last but not least, we would like to give a special thanks to all our participants for their time and involvement in the project.

Conflict of interest Lucette A. Cysique: This study was supported by the National Health and Medical Research Council of Australia project grant ID568746 (Cysique CIA/PI), the 2009–2012 postdoctoral Brain Science UNSW fellowship (Cysique), 2012 Mercks Sharp Dome (MSD) partial salary support for 2012, the National Health and Medical Research Council of Australia Career Development Fellowship APP1045400 (Cysique CIA/PI), and the Peter Duncan Neurosciences Unit (Head Prof. Bruce Brew). MSD had no direct participation in the current study design,

data analyses, and interpretation. Dr. Cysique has otherwise no conflict of interest with the organizations that funded this research. Robert K. Heaton, Jody Kamminga, Tammy Lane, Thomas M. Gates, Danielle M. Moore, and Emma Hubner have no conflict of interest with the organizations that funded this research. Andrew Carr has received grants from the National Health and Medical Research Council of Australia, has received research funding, consultancy fees, lecture and travel sponsorships from MSD, and has served on advisory boards for MSD. Bruce J. Brew has received grants from the National Health and Medical Research Council of Australia, had received payment as board member for MSD, and received travel/accommodation expenses covered or reimbursed by MSD.

References

Antinori A, Arendt G, Becker JT, Brew BJ, Byrd DA, Cherner M, Clifford DB, Cinque P, Epstein LG, Goodkin K, Gisslen M, Grant I, Heaton RK, Joseph J, Marder K, Marra CM, McArthur JC, Nunn M, Price RW, Pulliam L, Robertson KR, Sacktor N, Valcour V, Wojna VE (2007) Updated research nosology for HIV-associated neurocognitive disorders. Neurology 69:1789–1799

Australian Neuroscience Society (2010) Australian health & medical research funding summary. http://www.ans.org.au/uploads/documents/ANSweb_A&NZResearch%20funding.pdf

Blackstone K, Moore DJ, Franklin DR, Clifford DB, Collier AC, Marra CM, Gelman BB, McArthur JC, Morgello S, Simpson DM, Ellis RJ, Atkinson JH, Grant I, Heaton RK (2012) Defining neurocognitive impairment in HIV: deficit scores versus clinical ratings. Clin Neuropsychol 26:894–908

Brandt J, Benedict RH (2001) Hopkins verbal learning test-revised. Professional manual. Psychological Assessment Resources, Inc., Lutz

Carey CL, Woods SP, Gonzalez R, Conover E, Marcotte TD, Grant I, Heaton RK (2004) Predictive validity of global deficit scores in detecting neuropsychological impairment in HIV infection. J Clin Exp Neuropsychol 26:307–319

Cohen J, Cohen P (1983) Applied multiple regression/correlation analysis for the behavioral sciences. Erlbaum: Hillsdale, NJ

Cole MA, Margolick JB, Cox C, Li X, Selnes OA, Martin EM, Becker JT, Aronow HA, Cohen B, Sacktor N, Miller EN (2007) Longitudinally preserved psychomotor performance in long-term asymptomatic HIV-infected individuals. Neurology 69:2213–2220

Cysique LA, Brew BJ (2011) Prevalence of non-confounded HIV-associated neurocognitive impairment in the context of plasma HIV RNA suppression. J Neurovirol 17:176–83

Cysique LA, Moffat K, Moore DM, Lane TA, Davies NW, Carr A, Brew BJ, Rae C (2013) HIV, vascular and aging injuries in the brain of clinically stable HIV-infected adults: a (1)H MRS study. PLoS One 8:e61738

D'Agostino RB Sr, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, Kannel WB (2008) General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation 117:743–753

Friis-Moller N, Thiebaut R, Reiss P, Weber R, Monforte AD, De Wit S, El-Sadr W, Fontas E, Worm S, Kirk O, Phillips A, Sabin CA, Lundgren JD, Law MG (2010) Predicting the risk of cardiovascular disease in HIV-infected patients: the data collection on adverse effects of anti-HIV drugs study. Eur J Cardiovasc Prev Rehabil 17:491–501

Garvey L, Surendrakumar V, Winston A (2011) Low rates of neurocognitive impairment are observed in neuro-asymptomatic HIV-infected subjects on effective antiretroviral therapy. HIV Clin Trials 12:333–338

Green A, Garrick T, Sheedy D, Blake H, Shores A, Harper C (2008) Repeatable battery for the assessment of neuropsychological status (RBANS): preliminary Australian normative data. Aust J Psychol 60:72–79

Heaton RK, Marcotte TD, Mindt MR, Sadek J, Moore DJ, Bentley H, McCutchan JA, Reicks C, Grant I (2004a) The impact of HIV-associated neuropsychological impairment on everyday functioning. J Int Neuropsychol Soc 10:317–331

Heaton RK, Miller SW, Taylor MJ, Grant I (2004b) Revised comprehensive norms for an expanded Halstead-Reitan Battery: demographically adjusted neuropsychological norms for African American and Caucasian adults Scoring Program. Psychological Assessment Resources, Odessa

Heaton RK, Clifford DB, Franklin DR Jr, Woods SP, Ake C, Vaida F, Ellis RJ, Letendre SL, Marcotte TD, Atkinson JH, Rivera-Mindt M, Vigil OR, Taylor MJ, Collier AC, Marra CM, Gelman BB, McArthur JC, Morgello S, Simpson DM, McCutchan JA, Abramson I, Gamst A, Fennema-Notestine C, Jernigan TL, Wong J, Grant I (2010) HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER Study. Neurology 75:2087–2096

Joseph J, Achim CL, Boivin MJ, Brew BJ, Clifford DB, Colosi DA, Ellis RJ, Heaton RK, Gallo-Diop A, Grant I, Kanmogne GD, Kumar M, Letendre S, Marcotte TD, Nath A, Pardo CA, Paul RH, Pulliam L, Robertson K, Royal W 3rd, Sacktor N, Sithinamsuwan P, Smith DM, Valcour V, Wigdahl B, Wood C (2013) Global NeuroAIDS roundtable. J Neurovirol 19:1–9

Kamminga J, Cysique LA, Lu G, Batchelor J, Brew BJ (2013) Validity of cognitive screens for HIV-associated neurocognitive disorder: a systematic review and an informed screen selection guide. Curr HIV/AIDS Rep 10:342–55

Lane TA, Moore DM, Batchelor J, Brew BJ, Cysique LA (2012) Facial emotional processing in HIV infection: relation to neurocognitive and neuropsychiatric status. Neuropsychology 26:713–722

Law MG, Woolley I, Templeton DJ, Roth N, Chuah J, Mulhall B, Canavan P, McManus H, Cooper DA, Petoumenos K (2011) Trends in detectable viral load by calendar year in the Australian HIV observational database. J Int AIDS Soc 14:10

Letendre S (2011) Central nervous system complications in HIV disease: HIV-associated neurocognitive disorder. Top Antivir Med 19:137–142

Lipsey M, Wilson D (2001) Practical meta-analysis. Sage Publications, London

Manly JJ, Byrd DA, Touradji P, Stern Y (2004) Acculturation, reading level, and neuropsychological test performance among African American elders. Appl Neuropsychol 11:37–46

Mitrushina M, Boone KB, Razani J, D'Elia LF (2005) Handbook of normative data for neuropsychological assessment, 2nd edn. Oxford University Press, Oxford

Munoz-Moreno JA, Fumaz CR, Ferrer MJ, Prats A, Negredo E, Garolera M, Perez-Alvarez N, Molto J, Gomez G, Clotet B (2008) Nadir CD4 cell count predicts neurocognitive impairment in HIV-infected patients. AIDS Res Hum Retrovir 24:1301–1307

Nelson H, Willison J (1991). National Adult Reading Test (NART). Test manual, 2nd edn. NFER-NELSON: Windsor, UK

Sacktor N, McDermott MP, Marder K, Schifitto G, Selnes OA, McArthur JC, Stern Y, Albert S, Palumbo D, Kieburtz K, De Marcaida JA, Cohen B, Epstein L (2002) HIV-associated cognitive impairment before and after the advent of combination therapy. J Neurovirol 8:136–142

Simioni S, Cavassini M, Annoni JM, Rimbault Abraham A, Bourquin I, Schiffer V, Calmy A, Chave JP, Giacobini E, Hirschel B, Du Pasquier RA (2010) Cognitive dysfunction in HIV patients despite long-standing suppression of viremia. AIDS 24:1243–1250

Strauss E, Sherman EMS, Spreen O (2006) A compendium of neuropsychological tests: administration, norms, and commentary. Oxford University Press, Oxford

Sullivan R, Senior G, Henessy M (2000) Regression equations: Australian age-education and premorbid cognitive/intellectual

estimates for the WAIS-III In: Assessment Psychology Online: http://www.assessmentpsychology.com/iq-estimates-3.htm

Taylor MJ, Heaton RK (2001) Sensitivity and specificity of WAIS-III/WMS-III demographically corrected factor scores in neuropsychological assessment. J Int Neuropsychol Soc 7:867–874

The Kirby Institute (2012) HIV, viral hepatitis and sexually transmissible infections in Australia annual surveillance report 2012. In: Institute TK (ed) The University of New South Wales, Sydney, NSW 2052

The Kirby Institute (2013) HIV, viral hepatitis and sexually transmissible infections in Australia annual surveillance report 2013. In: Institute TK (ed) The University of New South Wales, Sydney, NSW 2052

UNAIDS (2012) UNAIDS Report on the global AIDS epidemic 2012. WHO: (Digital version)

Williams JM, Cottle CC (2011) A correction for recruitment bias in norms derived from meta-analysis. Psychol Assess 23:856–864

Winston A, Arenas-Pinto A, Stohr W, Fisher M, Orkin CM, Aderogba K, De Burgh-Thomas A, O'Farrell N, Lacey CJ, Leen C, Dunn D, Paton NI (2013) Neurocognitive function in HIV infected patients on antiretroviral therapy. PLoS One 8:e61949

Woods SP, Moore DJ, Weber E, Grant I (2009) Cognitive neuropsychology of HIV-associated neurocognitive disorders. Neuropsychol Rev 19:152–168

Wright EJ, Grund B, Robertson K, Brew BJ, Roediger M, Bain MP, Drummond F, Vjecha MJ, Hoy J, Miller C, Penalva de Oliveira AC, Pumpradit W, Shlay JC, El-Sadr W, Price RW (2010) Cardiovascular risk factors associated with lower baseline cognitive performance in HIV-positive persons. Neurology 75: 864–73