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Review

Does highly active antiretroviral therapy improve neurocognitive function? A systematic review

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Highly active antiretroviral therapy (HAART) reduces the incidence of human immunodeficiency virus (HIV) dementia (HAD), whereas the overall prevalence appears to have increased. Recent changes to diagnostic nosology have emphasized the presence of neurocognitive deficits. Uniform methods of ascertaining neuropsychological impairment and excluding confounding causes are critical to between-study comparison. We conducted a systematic review on all studies that use single-cohort prospective treatment effect design that reported on the neurocognitive or neuropsychological profile of individuals commencing HAART. Fifteen 15 relevant studies were included. A large number of studies using observational or cross-sectional designs were excluded, as these do not allow for a within-subject description of pre- and post-HAART predictive factors. Eleven studies reported a significant improvement in neurocognitive status or neuropsychological profile over an average study period of 6 months. Variable or nonreporting of HAART regimens in these studies did not allow for an analysis of individual agent or regimen effectiveness. The results show that although HAART does improve cognition, it does not appear to fully eradicate impairments. The methods used in this research differ widely and therefore comparison across studies is difficult. Studies examining the long-term effects of HAART on HIV-associated neurocognitive disorders (HANDs) using uniform methods of data collection are needed, together with clear reporting of HAART regimens. *Journal of NeuroVirology* (2010) **16,** 101–114.

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Introduction

Prior to the widespread use of highly active antiretroviral therapy (HAART), infection with human immunodeficiency virus (HIV) resulted in HIV-associated dementia (HAD) in about 15% of individuals (McArthur *et al*, 1993). Less severe forms of HIV-associated neurocognitive disorders (HANDs) are found in about 30% to 60% of people living with HIV/AIDS (acquired immunodeficiency syndrome) (Grant *et al*, 2005; McArthur *et al*, 1993). The advent of HAART has substantially altered the nature of these disorders, although they frequently persist (Sacktor *et al*, 2002; Grant, 2008). Specifically, HAART has reduced the incidence of HAD, but the prevalence appears to be increasing (McArthur, 2004; Nath *et al*, 2008). In addition, the clinical presentation of HAD has changed (Brew, 2004). It has been suggested that the subcortical features previously thought to be characteristic may be less prominent (Cysique *et al*, 2004). More recently, efforts to predict response to HAART have intensified. Currently it is thought that people who initiate HAART and achieve plasma viral suppression (Sacktor *et al*, 2003) and cerebrospinal fluid (CSF) viral suppression (Letendre *et al*, 2004) and who use CSF penetrating regimens accrue the most benefit (Letendre *et al*, 2004; Ferrando *et al*, 2003).

Central to the characterization and description of HAND is the use of a universal diagnostic classification. The original criteria of the American Academy of Neurology, proposed in 1991, recognized two main forms: that of HAD, and a less severe minor

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cognitive and motor disorder (MCMD) (Janssen *et al*, 1991). This system emphasized the presence of behavioral and personality changes. The limitations of this approach, particularly in the face of both a growing understanding of HAND and the use of HAART, include a lack of emphasis on the cognitive deficits in HIV, as well as the presence of these deficits in the absence of overt functional decline in some individuals (Antinori *et al*, 2007). These limitations were addressed in a set of newer research criteria, proposed by the HIV Neurobehavioral Research Center (HNRC) and published in 2007 (Antinori *et al*, 2007). They now include a category of asymptomatic neuropsychological impairment (ANI), and also address the more widespread neurocognitive deficits that are thought to occur in HIV. The ANI category together with mild neurocognitive disorder (MND) require that neuropsychological deficits corresponding to at least one standard deviation below age-appropriate norms in at least two cognitive domains exist. A diagnosis of HAD is made when two or more domains reveal deficits of at least two standard deviations below the norm (Antinori *et al*, 2007). In addition, other causes of cognitive disorder need to be excluded, and some measure of function must be provided. Widespread use of this approach would go a long way to standardize studies of HAND, but may not always be possible or practical, particularly in resource-limited settings.

These clinical case definitions are now known to represent the underlying neuropathology, namely HIV encephalitis, and demonstrate a sensitivity and specificity of 67% and 92%, respectively, for the HNRC categories (Cherner *et al*, 2002, 2007). As indicated above, these neuropathological changes are now thought to involve various cognitive domains. In fact, if systemic disease factors are controlled for, HAD is characterized by severe deficits in learning, motor coordination, verbal fluency, and memory, whereas moderate deficits are observed in attention and processing speed (Cysique *et al*, 2006). These represent a range of deficits across subcortical and cortical domains. In order to ascertain whether neuropsychological deficits are indeed related to HIV-related neuropathology, it is therefore necessary to assemble a range of neuropsychological tests that measure the brain regions thought to be typically affected by HIV (Grant, 2008). Clinical and research batteries differ widely in their selection of tests, duration, and spread across cognitive domains.

Other factors that impact on HAART-related outcomes include study design, longitudinal construct validity of neuropsychological testing, and numerous treatment and disease variables. In a recent substantive review, Cysique and Brew clearly delineate differences between cross-sectional cohort designed studies, prospective observational cohort studies and prospective treatment effect studies (Cysique and Brew, 2009). The cross-sectional studies are largely limited by uncontrolled cohort effects (see Sacktor *et al*, 2002; Ferrando *et al*, 1998), whereas the prospective observational studies tend to include cohorts already on HAART who have either switched regimens or followed neuropsychological changes whilst on HAART (see Tozzi *et al*, 1999; McCutchan *et al*, 2007). Prospective treatment effect cohort studies offer the advantage of describing a range of pretreatment variables, which may either predict or be associated with positive or adverse outcomes. These are then carried into the study in a case-controlled manner. The issue of longitudinal construct validity refers to whether tests or subtests can be considered appropriate for measuring neuropsychological functions over time. It is possible that some functions may improve de facto, but that change over time may also be affected by the specific function reaching a plateau due to persistence of deficits, practice effects, the severity of the deficit at baseline, or disease-specific factors (Suarez *et al*, 2001; Rabbitt *et al*, 2004; Cysique *et al*, 2009).

Disease-specific factors that may impact on outcomes in HAND include viral resistance, HAART-related neurotoxicity, central nervous system (CNS) penetration of HAART, the effects of aging and comorbidities, viral clade, and molecular biology. In particular, it is well established that HAART has reduced the incidence of severe forms of HAND, such as HAD, whereas there is clear evidence that at least milder forms persist (see Sacktor *et al*, 2002; Robertson *et al*, 2007). Viral resistance may follow individual nonadherence and systemic resistance, the infection of individuals with resistant strains of virus, or the development of intraindividual (CNS in particular) resistance (Verbiest *et al*, 2001; Cunningham *et al*, 2000). CNS compartment resistance, whereby the CNS acts like a reservoir of HIV, may be affected by limited or even differential penetration of individual antiretroviral drugs (see below) (Cunningham *et al*, 2000). The issue of antiretroviral toxicity has been addressed to a limited extent in the literature, and is based on theories of systemic toxicity, scanty magnetic resonance spectroscopy (MRS) studies, and *in vitro* evidence (Cysique and Brew, 2009; Schweinsburg *et al*, 2005; Piccinini *et al*, 2005). This type of antiretroviral neurotoxicity is independent of the phenomenon of neuroIRIS (immune reconstitution inflammatory syndrome), which is thought to be rare but may result in worsening neurocognitive function despite HAART use (Venkataramana *et al*, 2006).

A related factor is the penetration of antiretrovirals through the blood-brain barrier. The ability of these agents to pass into the brain, depending on their protein binding, molecular size, and lipophilicity, has led to the development of a *CNS penetration effectiveness* (CPE) rank system (Letendre *et al*, 2008). Although several studies have shown that regimens with a relatively high CPE rank (>2) resulted in better neurocognitive outcomes (see Letendre *et al*, 2004), it is not well known whether these regimens may produce neurotoxicity,

whether the benefits will persist, or if the HAART-related improvements to date have been observed in individuals with poor baseline neuropsychological performance or worse levels of immunosuppression. A recent prospective treatment effect study reported that regimens containing a higher CPE rank score were effective in suppressing CSF viral loads but were associated with worse neurocognitive performance (Marra *et al*, 2009). Long-term studies that examine both the neurocognitive profile and the CPE rank, as well as potential measures of antiretroviral neurotoxicity, will be needed to resolve these issues.

The question of whether viral subtype or clade is responsible for differences in HAND has not been studied well enough in clinical populations. For instance, the neurovirulence of HIV clade C has been associated with less severe forms of neurocognitive impairment in some studies, but with equally deleterious effects in others (Kanki *et al*, 1999; Kiwanuka *et al*, 2008; Gupta *et al*, 2007). Variability has been attributed to differences in the dicysteine motif within the neurotoxic region of B-Tat, producing a greater (or lesser) degree of Tat-induced apoptosis (Ranga *et al*, 2004; Mishra *et al*, 2008). However, other viral proteins such as gp120 may be as neurotoxic. The clade sequence, levels of proviral DNA and Tat protein, together with their impact on neuropsychological functions and neuroimaging findings, are the subjects of a study currently being conducted by our group. These clade and viral neurotoxicity studies are needed to better understand mechanisms of HAND. However, where these studies are conducted across different regions with differing culture and language effects on neuropsychological test performance, the need for standard approaches to clinical characterization of HAND becomes more pressing. A possible clade-specific difference has already emerged in our preliminary work, wherein we found that HIV-positive participants performed as well as HIV-negative controls on the Grooved Pegboard Test, a measure consistently used to ascertain whether HIV associated subcortical neuropathology exists (Sacktor *et al*, 1996; Joska *et al*, 2009)

Given that prospective treatment effect studies afford many advantages to better understand the impact of viral, treatment, and other individual factors on HAART, this systematic review will undertake to examine all such published studies. In particular, the methods of classifying of HAND will be discussed with a view to describing an approach that allows for comparison across studies.

Results

Nature of studies

The majority of studies identified were conducted in the USA, where clade B is predominant ($n = 11$); the remainder consists of one each completed in Brazil and Thailand, and two in Uganda (Table 1) (Carvalhal *et al*, 2006; Valcour *et al*, 2009; Sacktor *et al*, 2006, 2009). Where reported, almost all studies were done in infectious diseases clinics or in research projects that were associated with such clinics. Sample sizes of HIV-positive individuals included in these studies range from 14 to 126, with one large study including 303 individuals. The mean sample size was 69, with a median of 49. Most studies report good follow-up rates, with only two studies managing to review less than 80% of recruited subjects (67.7% and 71.4%, respectively). The mean age of participants was 37.05 years, and ranges from 29.7 to 45.2 years. Studies report a wide range of gender distribution, with the mean percentage of men included being 66%. In most cases, the degree of immunosuppression at study entry was significant, with a mean CD4 cell count in all included studies of 179.2 (53–392.2). This mean improved to 285.8 after HAART use (148.5–337). (Note that the post-HAART CD4 count for the study reporting a higher CD4 count at study entry was not provided.) Similarly, the pre-HAART mean viral load in $\log_{10}$ copies was 4.64 and improved to 3.29 post-HAART.

Measures

The clinical assessment of neurocognitive disorders requires the exclusion of confounding causes (see Table 2). Most studies ($n = 10$) utilize either a psychiatric history or make use of rating scales to exclude participants who suffer from psychiatric disorders. Of those that use rating scales, two use the Center for Epidemiology rating scale for Depression (CES-D), and one each use the Hamilton Depression Rating Scale and Thai Depression Inventory. Patients with current psychiatric disorders are generally not included in studies of HAND. Similarly, 4 of the 13 studies do not formally report on the screening of substance use disorders. Those that do, use a combination of self-report and clinician-interview, with only two using formal drug testing procedures. Only two studies formally report on the exclusion of concomitant neurological problems. Most utilize some type of standardized clinical or neurologic examination. Only one study, which aimed to correlate the use of HAART with magnetic resonance spectroscopy findings, utilized formal neuroimaging to exclude intracranial pathology (Chang, 1999). Regarding the reporting of functional assessment, only four studies note this, with three reporting impairment of function using the Karnofsky score. In these, the scores range from 66 to 84.

The prevalence of neurocognitive disorder is noted in nine studies, with three utilizing the Memorial Sloan Kettering (MSK) score. Many of the studies recruited participants from specialized clinics, and in most cases, sought to include people with established HAND. The prevalence of people who had normal MSK ratings ranges from 4% to 69%, whereas 21% to 48% had "equivocal" ratings, 10% to 61% had stage 1 scores, and one study

Table 1 Descriptive variables of studies examining neurocognitive function before and after initiating HAART

Author	Country	Setting	Sample size	Follow-up rate	Age	Education in years	Men %	Pre-HAART CD4	Post HAART CD4	Pre-HAART viral load	Post-HAART viral load
Baldewicz 2004	USA	Research clinic	59 HIV+ and 55 HIV−	91.2	29.7	14.2	100	392.2	Not reported	Not reported	Not reported
Carvalhal 2006	Brazil	Infectious diseases centers	14	71.4	35.5	8.4	57	134.6	239.1	4.56	<80 to 25 000
Chang 1999	USA	Infectious diseases centers	16 HIV+ and 15 HIV−	100	44.3	Not reported	88	163	274	Not reported	Not reported
Clifford 2005	USA	Infectious diseases centers	303	93.4	37	Not reported	81	219	Not reported	4.74	Not reported
Cohen 2001	USA	Infectious diseases centers	126 (55 received HAART)	100	33.2	12.2	0	64.9	119.4	77978	48226
Cysique 2009	USA	Research clinic	37	18	39.7	13.6	86.5	195.6	Not reported	4.9	50% LDL at week 12
Marra 2003	USA	Not specified	Total 25; 13 HAART naïve	88	34.5	13	92.9	207	Not reported	4.73	Not reported
Marra 2009	USA	Research clinic	79 (44 naïve)	60	39	13	83.5	111	Not reported	4.86	Not reported
Parsons 2006	USA	Health Care system	65	67.7	41.4	12.3	64	239.8	316.95	4.25	3.13
Robertson 2004	USA	Infectious diseases centers	48	100	38.77	12.54	62.5	225.81	310.52	4.56	2.64
Sacktor 2000	USA	MACS cohort infectious diseases clinic	33	100	38.5	13	88.5	Not reported	Improved by 60	Not reported	<1 in responders
Sacktor 2003	USA	MACS cohort infectious diseases clinic	49	100	45.2	% college: 57–70	100	281	337	4.35	Responder: 2.4
Sacktor 2006	Uganda	Infectious diseases Clinic, Mulago Hospital	23	91	32.8	8.7	23	71	176	Not reported	Not reported
Sacktor 2009	Uganda	Infectious diseases clinic, Kampala	102 HIV+ and 25 HIV−	92	34.2	HIV+ 9.1 (4.3); HIV− 10.3 (4.2)	29	129	272	Not reported	Not reported
Valcour 2009	Thailand	Infectious diseases/neurology clinics, HIV testing centers	30	93.3	32	6	33	23	190	5.3	All LDL, but 1

Table 2 Clinical and neuropsychological characteristics

Author	Substances	Psychiatric	Neurologic exam	Neuroimaging	Function	Neurocognitive prevalence	HAART used and duration	Test battery	NP baseline	NP outcome
Baldewicz 2004	Clinical interview, but not reported	Hamilton Depression Rating Scale; SCID depression	Clinical examination	Not reported	Not reported	Asymptomatic at baseline	Included NRTIs but not specified; duration not specified	FT, Ruff 2 and 7 Selective Attention Test, CVLT, TMT B, SCWT, DSS-W-R	All domains reported as *F*-scores and significantly different from HIV− controls	Average *z*-score by domain over time: AIDS fine motor 0.2, attention 0.4, memory 0.55, executive 0.4, speed of processing 0.3
Carvalhal 2006	N/A	Not reported	Clinical examination	Not reported	Not reported	Not reported	AZT, 3TC, EFV; duration 6 months	Verbal Fluency Test,[a] Logical Memory, Visual Recognition Test, Word Span, SCWT	NPZ6 0.05	NPZ6 0.075 (ns)
Chang 1999*	Urine toxicology negative	Not specified—excluded on history	Neurologic examination—exclusion	No MRS changes except NA/CR elevated in BG at baseline	Karnofsky 80.6 (50–100)	All patients recruited had cognitive motor complex	Various; duration 9.1 (3–14) months	HDS plus neuropsychological evaluation not reported, providing Karnofosky and ADC staging	HDS 10.3	HDS 12.2
Clifford 2005*	On history, IDU 1 current, 29 previous	CES-D (median score 12), State-Trait Anxiety Inventory (median 55)	Not reported	Not reported	Not reported	Not reported	EFV and non-EFV groups; duration 24 weeks	TMT A/B, DSC-W-III, NPZ3	−0.09 (EFV) and −0.03 (non-EFV) *z*-score	0.51 and 0.61 medians in groups (sig)
Cohen 2001*	Interview for alcohol: 46% alc, 20.6% IDU, and 38.9% illicit subs within last 6 months	CES-D 22.6	Not reported	Not reported	Not reported	None HIV-D, high prevalence of impairment but figures of NCD status not reported	PI, plus NRTI/ NNRTI; duration 28.4 (15.3) weeks	GP D, CTM 1/2, COWAT, FWL	HAART SD: CT1 49.8 (19.9), CT2 106.5 (31.8), COWAT 24.2 (8.4), GP D 87.0 (36.5), FWL 3.1 (1.1)	HAART SD (change): CT1 41.3 (11.0; sig), CT2 89.6 (19.0; sig), COWAT 22.5 (−1.0), GP D 81.0 (8.6; sig), FWL 3.4 (0.3)
Cysique 2009	Clinical interview	Clinical interview for psychotic disorder	Neurologic history only	Not done	Not reported	All impaired at baseline with average GDS 1.44 (0.93)	Not specified; CPE rank mean 1.4, duration 48 weeks	GP D and ND, PASAT, TMT A and B, Letter Fluency (F, A, S)	GDS 1.44 (0.93)	13.5% improvement at 12 weeks, 40.9% at 36 weeks, and 33.3% at 48 weeks

Table 2 *(Continued)*

Author	Substances	Psychiatric	Neurologic exam	Neuroimaging	Function	Neurocognitive prevalence	HAART used and duration	Test battery	NP baseline	NP outcome
Marra 2003*	Not reported	Not reported	Standard neurologic examination	Not reported	Not reported	Only NPZ reported	Indinivir, AZT, and others; duration 8 weeks	TG, GP D, FT ND, Digit Symbol Tests[a]	NPZ4 = −0.31 (−0.83 to 1.01)	NPZ not specifically reported, but improved significantly
Marra 2009	Not reported	Medical history	Standard neurologic examination	Not reported	Not reported	Only NPZ reported: 43/79 impaired	NNRTI regimens at 39% of visits, duration 52 weeks	NPZ4: timed gait, GP dominant, digit symbol, FT nondominant; NPZ8: add RAVLT, GP nondominant, TMT A and B, FT dominant, CalCAP	NPZ4 = −0.29 (−0.96 to 0.14); NPZ8 = −0.24 (−0.70 to 0.15)	NPZ4 in those on 3 ARVs was 0.36 (sig); those on 4 was −0.58 (ns)
Parsons 2006	Current substance abuse—alcohol 16 drinks per month, cocaine 0.85 days per month, cannabis 0.85 days per month	1/3 current depression, 34.5% current anxiety on history	Assessed on history	Not reported	Not reported	Not specified	Not specified; duration 6 months	Ruff 2 and 7 SAT, PASAT, computerized reaction time tasks, DS,[a] TMT A and B, SW, SCWT, AVLT,[a] Complex Figure Test–IM and DR,[a] GP,[b] FT, TG	*z*-score −0.78	*z*-score −0.55 (ns)
Robertson 2004*	Not reported	Not specified	ACTG full evaluation using a weighted scoring approach	Not reported	Quality of life scale/ MSK scale	MSK scores—69% normal, 21% equivocal, 10% stage 1	Not specified; duration 6 months	Ruff 2 and 7 SAT, PASAT, computerized reaction time tasks, DS,[a] TMT A/B, SCWA, COWAT, RAVLT, ROCF, GP,[a] FT, TG, Vocabulary—WAIS-R	Total *z*-score −0.74	Total *z*-score −0.52
Sacktor 2000*	Not reported	Not reported	Clinical examination	Not reported	Not reported	HAD 61% at baseline	Various including PI; duration 2 years	GP D/ND	23/30 had GP ND *z*-score < −1.0	23/33 GP ND improved
Sacktor 2003	Screened on history but not reported	Not reported	Screened on history but not reported	Not reported	Not reported	11/49 probable HAD, 34/49 possible HAD	Not specified; duration not specified, minimum 6 months	DSMT and TMT B	Symbol digit −1.45; TMT B −0.825	Symbol digit −1.025; TMT B −0.225

Table 2 *(Continued)*

Author	Substances	Psychiatric	Neurologic exam	Neuroimaging	Function	Neurocognitive prevalence	HAART used and duration	Test battery	NP baseline	NP outcome
Sacktor 2006*	Clinical interview, but not reported	Psychiatric history	Standard neurologic examination	Not reported	Karnofsky score, mean 66	MSK scores—4% normal, 35% equivocal, 61% stage 1	3TC/D4T/NVP (n = 18), AZT/3TC/TEN (n = 5); duration 6 months	WHO-UCLA AVLT, GP D/ND, DSMT, Timed Gait, CT 1/2, DS F/B, Karnofsky Performance Scale, MSK	z-scores: WHO-UCLA AVLT total −1.7, GP D −0.4, GP ND −0.2, CT1 −1.2, CT2 −1.5, DSF −0.7, DSB −0.7	z-scores: AVLT −0.1, GP D 0.2, GP ND 0.3, CT1 −0.1, CT2 −0.3, DSF −0.2, DSB −0.2
Sacktor 2009*	Clinical interview, but not reported	Psychiatric history	Standard neurologic examination	Not reported	Karnofsky HIV+ 84 (8.5); HIV− 98 (4.1)	MSK scores—12% normal, 48% equivocal, 33% stage 1, 7% stage 2	Triommune (stavudine, lamivudine, andnevirapine); duration 6 months	WHO-UCLA AVLT, Timed Gait, Finger Tapping, GP D/ND, DSMT, CT 1/2, DS F/B, Category Naming,[a] Karnofsky Performance Scale, MSK	z-scores: AVLT total −1.2, CT1 −1.7, CT2 −2.8 SDMT −0.8, GP D 0, GP ND −0.7, FT −1.0, TG 2.7, Verbal Fluency −0.4	z-scores: AVLT total −0.1, CT1 −0.4, CT2 −1.3, SDMT −0.3, GP D 0.4, GP ND 0.3, FT −0.5, TG −1.8, Verbal Fluency 0
Valcour 2009*	Interview and urine screen	Thai depression inventory 19.5	Clinical examination	MRI brain	Not reported	12/27 (44%) HAD	NNRTI based; D4T/3TC/NVP (n = 24); duration 48 weeks	IHDS, RAVLT, Timed Gait, DSMT, NPZ	IHDS 10.2; NPZ composite score −0.62	NPZ comp 0.29

*Studies in which there was significant improvement in NP outcome after initiating HAART.Abbreviations used for neuropsychological tests: ADC = AIDS Dementia Complex; AVLT = Auditory Verbal Learning Test; COWAT = Controlled Oral Word Association Test; CTM 1/2 = Color Trails 1 and 2; CVLT = California Verbal Learning Test; DSMT = Digit Symbol Modalities Test; DSS-W-R = Digit Symbol Subtest WAIS-R; DSC-W-III = Digit Symbol-Coding Subtest—WAIS III; DS = Digit Symbol; DSS-WR = Digit Symbol Subtest—WAIS-R; DS F/B = Digit Span Forwards and Backwards; FT= Finger Tapping; FWL = Four Word Learning; GP D/ND = Grooved Pegboard dominant hand/nondominant hand; HDS = HIV Dementia Scale; IHDA = International HIV Dementia scale; Complex Figure Test–IM and DR = Complex Figure Test—Immediate memory and delayed recall; MSK = Memorial Sloan Kettering Dementia Stage; NPZ = Neuropsychological Z-score (composite); RAVLT = Rey Auditory-Verbal Learning Test; ROCF = Rey-Osterrieth Complex Figure; SAT= Selective Attention Test; SCWT = Stroop Color-Word Test; SW = Stroop Word; TMT A/ B = Trail Making Test A/B; TG= Timed Gait; WHO-UCLA AVLT = World Health Organization-University of California-Los Angeles Auditory Verbal Learning Test.[a]Test not specified. [b]Dominance not specified.

reports a prevalence of 7% of stage 2 scores. Three other studies report a prevalence of HAD ranging from 22.4% to 61% (Sacktor *et al*, 2000, 2003).

Neuropsychological test batteries
In the studies included in this review the neuropsychological test batteries vary widely. In general terms, half of the studies include formal tests of verbal learning, with three using the California Auditory Verbal Learning Test, three the Rey Auditory Verbal Learning Test, and one an unspecified verbal learning test. Psychomotor speed is tested using the Trail-Making Test B (TMT B) in seven instances, and the Color Trails 2 in two instances. In addition, the Grooved Pegboard (either dominant hand or non-dominant, or both) is used in eight of the batteries. Executive functions are assessed using a variety of tests, including the Stroop Color-Word Test ($n = 4$), and components of the trail-making tests (TMT B or Color Trails 2). The Digit Symbol Substitution Test, a test of attention and speed of processing, is used in 10 batteries.

Use of HAART
A wide range of HAART regimens are reported and there was no emergent trend. Studies where these are specified note regimens based on non-nucleotide reverse transcriptase inhibitors (NNRTIs) (efavirenz [EFV] in two cases, nevirapine in two cases), whereas in others protease inhibitor-based regimens are reported ($n = 3$). The duration of use ranges from 8 weeks to 2 years, but most ($n = 8$) utilize an average study period of 6 months. In studies reporting non-significant neuropsychological improvement, the HAART regimen is noted in two of three cases: in the one study a combination of AZT, 3TC, and EFV was used, whereas in the other an unspecified combination of NNRTIs was used. These regimens both rank CPE > 2.

Neuropsychological outcomes
Studies included in this review report on neuropsychological outcomes in a number of different ways (see Table 2). In some instances, neuropsychological data are compared to an HIV-negative group. Most of the included studies ($n = 11$) note a significant improvement in neuropsychological function of individuals following HAART initiation. In most instances, investigators make use of *z*-scores based on population norms (7 of the 11 studies), with most using a composite *z*-score based on combinations of neuropsychological tests (NPZ). It was not possible to generate a pooled effect due to the variability in the number of tests used for calculating the NPZ scores in different studies (for example, NPZ4 or NPZ6). In two studies where composite *z*-scores pre- and post-HAART are reported, the scores improved from −0.74 to −0.52 (Robertson *et al*, 2004) and −0.62 to 0.29 (Valcour *et al*, 2009), respectively. There were three studies that do not find significant improvements in neuropsychological function following initiation of HAART. In one, the authors report that this may be explained by the fact that HAART may improve more severe HAND (such as HAD), as opposed to milder forms, and that their sample size was small (14 participants) (Carvalhal *et al*, 2006). In another study, the specific focus was on hepatitis C coinfection, and although there was a trend to improvement on HAART, it does not reach significance (Parsons *et al*, 2006). The remaining study reports separately on HAART responders and nonresponders; there were more nonresponders than responders (39 versus 19). No reason for this disparity is provided (Sacktor *et al*, 2003).

Quality of studies
When we conducted a review of the quality of the studies, using the method described in Methods, we found that most are high-quality studies ($n = 8$), with only one study rating less highly. This particular study was published as a brief report, and could have excluded certain clinical parameters for the sake of brevity. What is striking is that most studies do not report on or address all of those factors that may be considered as comprising a detailed and high-quality study of HAND. For example, four studies do not report on any assessment of substance misuse and only two note any neuroimaging findings. In addition, only four studies formally report on functional assessment. It may be suggested that more formal reporting of these issues are needed to fully appreciate the complexity of the diagnostic issues in HAND.

Discussion

To our knowledge this is the first systematic review examining the effect of initiating HAART in a prospective treatment effect cohort of people with HIV. Our findings support the existing literature that, in general, the initiation of HAART results in improvement of neuropsychological function. Although the duration of treatment most often reported was only 6 months, improvement was neither full nor universal. Factors contributing to the variety of treatment responses include genetic vulnerabilities, comorbid substance abuse, viral resistance and neurovirulence factors, and host immune and inflammatory responses. These have only been explored to a limited extent in these prospective cohort studies. In addition, these studies vary greatly in their methodologies, leading to difficulties in interpreting and collating these findings.

In this review, a significant improvement in either neurocognitive status or neuropsychological profile was reported in 11 of the 15 studies. It was not possible, due to the variability of reporting, to conduct formal meta-analysis, although this would clearly be desirable. In most instances these

improvements were noted across a number of different neuropsychological domains. It may be possible in subsequent reviews or meta-analyses to identify whether particular domains improve more than others and over what period of time. Deficits reflective of a loss of cortical neurons, for example, may be more persistent than ones suggesting white matter damage, which may be reversible. Such studies may best employ specific neuroimaging techniques coupled to neurocognitive assessment. In studies that did not find significant improvement in neuropsychological function, it is suggested that the nature of HAND studied may have been a factor. In particular, it is now known that although HAD occurs less commonly in the HAART era, milder forms are becoming more frequent (McArthur, 2004). In this way, it is possible that HAART has a greater mitigating effect on severe HAND, and less so on milder neurocognitive disorders.

We also note that different investigators report on this field very differently. In the first instance, there is little uniformity in the selection of neuropsychological tests. Although there is general agreement about the nature of HIV-related neurocognitive impairment, test batteries vary both in length and structure. It could be argued that a greater uniformity would lead to improved comparability across not only different regions (and viral clades), but also between different study questions (for example, some studies examine coinfections whereas others examine CSF viral loads). Few studies include a description or classification of HAND. Although it is understandable that the key to understanding the mechanism of neuropsychological change requires that such scores are reported in detail, the provision of diagnostic categories and prevalence would again aid in the understanding of regional differences in severity and course. Other challenges identified in this review are that sample sizes were mostly small, with most studies including less than 100 participants, although follow-up rates are generally very high. These cohorts do allow for intraindividual comparison, but they are limited in their ability to report on categories of HAND and the associated factors or predictors of severe types of cognitive disorder.

A key issue that has emerged in the understanding of neurocognitive change or improvement over time is the duration of treatment and the point at which follow-up assessment is made. A recent study has highlighted the variability of this improvement, noting that in some individuals improvement occurs within the first weeks of HAART, whereas for the majority of individuals this may occur after up to a year (Cysique *et al*, 2009c). These findings seem to contribute to the notion of the variable course of HIV dementia (HIV-D), as noted by Nath and others (Nath *et al*, 2008; McArthur, 2004). The "early improvement" group might be associated with a greater degree of baseline impairment, and with clinical and immunological features suggestive of an inflammatory process, as well as with good viral suppression on HAART (Wojna and Nath, 2006). Discriminating between those with active disease and those with "burnt out" or stable deficits may not only provide indicators as to factors driving disease activity, but may also be relevant to developing targeted or adjuvant treatments. Given that the majority of people living with HIV/AIDS (PLWHA) continue to improve from 6 months, the importance of following these individuals up to 1 year and probably beyond is critical to understanding further the effects of HAART in the long term.

Research into the predictors of response to HAART is essential to informing the clinical practice likely to produce the best outcomes. The measurement of peripheral blood CD4 count and viral load is considered standard practice before and during HAART. In addition to a low baseline CD4 nadir being predictive of HIV-D, the suppression of peripheral viral load has consistently been linked to better neurocognitive outcomes in the face of good adherence to HAART (Nath *et al*, 2008). The role of CSF analysis is less clear, with good CNS penetrating HAART being associated with suppression of CSF viral load and good neurocognitive outcomes in some studies, but with either failure to suppress or adverse neuropsychological performance in others (Letendre *et al*, 2004; Cysique *et al*, 2009a; Marra *et al*, 2009). In this review, of the studies reporting neurocognitive improvement on HAART, only three reported on baseline and follow-up peripheral viral loads. In all three there was significant improvement in this parameter, and in all cases suppression of peripheral viral load was directly associated with suppression of CSF viral load. Corresponding measures of CNS inflammation were examined only in one study using MRS (Chang, 1999). In one other study, peripheral monocyte HIV DNA was associated with poorer neuropsychological performance at 48 weeks, suggesting that the peripheral pool of infected monocytes may stimulate ongoing CNS inflammation (Valcour *et al*, 2009). Further cohort studies wherein other measures of immune and inflammatory response (such as cytokines), inflammatory protein (for example amyloid), and imaging markers (such as diffusion tensor imaging) are addressed should be conducted. Other baseline characteristics, such as antiretroviral drug resistance, may predict neurocognitive outcome. In a recent study, it was reported that the presence of antiretroviral resistance mutations may be associated with diminished neurovirulence (Hightower *et al*, 2009).

The importance of obtaining locally derived population normative data is central to the neuropsychological characterization of impairment. In general the approach has been to generate these data from either matched or similar groups of individuals within the population under study. The degree to which these groups are regarded as similar is often

based on the cultural and language expression of the group in question, and it is these parameters that drives the development of new normative data sets (Manly, 2005). Although other demographic factors such as education are well known to exert significant effects on test performance, there may be other difficult-to-measure group variables that also do so and that may result in the overdiagnosis of HAND (Grant, 2008). So, although good normative data represent an essential starting point for conducting research into HAND, the deconstruction of cultural and linguistic variables may be needed to make a test battery truly relevant to the group under study (Manly, 2005).

Much of the literature examining neurocognitive disorders could not be included in this review, mainly due to the absence of cohort-type studies. In many instances, studies were carried out comparing different HAART-naive and HAART-using participants. Many studies we initially found were excluded because they did not make use of formal neuropsychological measures. This has been emphasized by many as the key to the diagnosis of HAND (Antinori *et al*, 2007b). This analysis was limited by the small number of included studies, but we believe that our findings remain important and valid. In particular, the variability among studies and their differing approaches was evident.

There is clearly then a need for further studies examining the effect of HAART in a cohort of well-characterized individuals, and preferably making use of tools that allow for comparison with other studies. Given the constraints of resource-limited settings in terms of time and skills, we would recommend that a neuropsychological battery for use in international settings might include tests of the following domains: attention, learning and memory, motor coordination and processing speed, and verbal fluency. Tests selected for use require age- and educational-appropriate norms, and should be properly translated into the local language. A longer battery has been used successfully in cross-cultural settings (see Cysique *et al*, 2007; Cherner *et al*, 2008). In addition, we recommend the use of a brief activities of daily living scale—we have adapted the Lawton Brody Scale for this purpose (Lawton and Brody, 1969). An assessment of neurologic status is a prerequisite, and should be structured to examine neurological functions affected in HIV/AIDS. Structured or semistructured clinical interviews are needed to establish substance use history and psychiatric disorder status. Together, this approach will allow at least for some standardisation across studies and regions. In order to address the issue of treatment effect, it is suggested that studies clearly report on HAART regimen used, duration, and possibly CPE rank. The reporting of neuropsychological test means and standard deviations would allow for potential meta-analytic approaches.

Methods

Search strategy

The search for studies was conducted using four approaches:

(1) Using a key word search of the following databases conducted on 12 March 2009:
   (i) PubMed: HIV [mh] OR Acquired Immunodeficiency Syndrome [mh] OR AIDS [tw] OR HIV [tw]) AND (Anti-retroviral Therapy, Highly Active [mh] OR HAART [tw]) AND (Cogniti* Disorders [mh] OR memory [mh] OR memor* [tw] OR cognition [mh] OR cogniti* [tw] OR AIDS Dementia Complex [mh] OR Neuropsychological Tests [mh]). All clinical types of studies on adults were included.
   (ii) PsycINFO: AIDS and HAART and NEURO.*
(2) Reviewing the reference sections of articles found in this way and searching for relevant publications.
(3) Using a hand search to review the tables of contents of key journals, searching for relevant publications. These key journals included: *AIDS*, *AIDS and Behaviour*, *AIDS Care and STDs*, *Archives of Neurology and Neurology*.
(4) Personal communication with key researchers in the field. This was defined as first authors of studies included.

The search strategy and retrieved articles are shown in Figure 1.

Inclusion and exclusion criteria

We included peer-reviewed published studies in which a clinical sample received a neuropsychological and neuromedical assessment before or during early treatment (defined as within 1 month of commencement) of HAART, and again within 24 months. A minimum treatment period of 2 months was required. A clear categorization of EITHER a neurocognitive disorder OR of global/overall neuropsychological status in patients needed to be reported at both time points. The included studies were defined as prospective treatment effect cohort studies.

We excluded cross-sectional and prospective observational studies where comparisons were made between treatment-naïve and HAART-treated groups or where neuropsychological changes over time were assessed in participants already using HAART/not HAART naïve. Our primary aim was to describe the pretreatment factors that may predict or be associated with HAND outcomes. In addition, the dynamics of neuropsychological profile and neuropsychological change are known to be different in individuals who are not HAART naïve (for example,

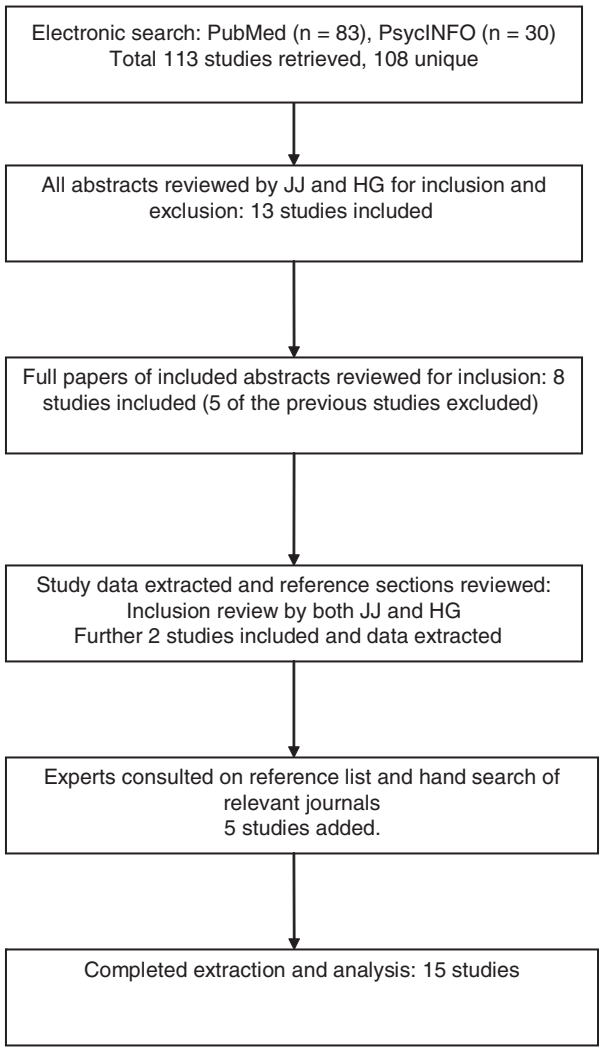

Figure 1 Results of search strategy.

see Robertson *et al* [2007], wherein it is reported that treatment interruption resulted in improved neuropsychological function). We also excluded studies of children and studies where the neurocognitive status OR neuropsychological profile was not reported at the two time points.

Study sorting
All articles retrieved on electronic search were loaded into a single Reference Manager database (see Figure 1). Duplicates were removed. This left 108 studies. Using the criteria set out above, the database was reviewed by two of the authors, independently and respectively (J.J. and H.G.), to ascertain reliability of inclusion and exclusion. The kappa was 0.76. Where there was disagreement, the non-included study was discussed and a decision made as to its suitability. After this stage, 15 studies were identified. The papers were reviewed to establish suitability in terms of two criteria: they needed to report neuropsychological or neurocognitive profile in the same sample at the two time points. Duplicate publications from the same data set were omitted. Once the electronically retrieved articles had been sorted, these were reviewed and data extracted using a spreadsheet with key fields. The reference sections of papers reviewed in this way were then screened for other potential studies. Additional studies were discussed between the two reviewers and data extracted. Finally, we wrote to all first authors requesting their willingness to review the reference list and to suggest any papers or studies that they felt needed to be included. A final list of 15 studies was reached.

We also reviewed the quality of studies using a simple Likert-type scale of three areas: (1) Assessment—Did the study utilize a neuropsychological test battery including at least three domains of function, and was this repeated both before initiating and after a period of time on HAART? (2) Reporting—Did the study report on the full neuropsychological assessment both before and after HAART, and did it indicate whether the first assessment occurred prior to initiating HAART? and (3) Confounders—Did the study report on the assessment of potential confounding factors such as neurological conditions, psychiatric disorders, or substance misuse? Each domain was rated on a scale of 0 for no, 1 for partly, and 2 for yes. In this way, high-quality studies could be viewed as scoring between 4 and 6, intermediate-quality studies between 2 and 3, and lower-quality studies less than 3.

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