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Factors Related to HIV-Associated Neurocognitive Impairment Differ With Age

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Abstract

Over 50% of HIV-infected (HIV+) persons are expected to be over age 50 by 2015. The pathogenic effects of HIV, particularly in cases of long-term infection, may intersect with those of age-related illnesses and prolonged exposure to combined antiretroviral therapy (cART). One potential outcome is an increased prevalence of neurocognitive impairment in older HIV+ individuals, as well as an altered presentation of HIV-associated neurocognitive disorders (HAND).

METHODS—In this study, we employed stepwise regression to examine 24 features sometimes associated with HAND in forty older (55–73 years of age) and thirty younger (32–50 years of age) HIV+, cART-treated participants without significant central nervous system confounds.

RESULTS—The features most effective in generating a true assessment of the likelihood of HAND diagnosis differed between older and younger cohorts, with the younger cohort containing features associated with drug abuse that were correlated to HAND, and the older cohort containing features that were associated with lipid disorders mildly associated with HAND.

CONCLUSION—As the HIV-infected population grows and the demographics of the epidemic change, it is increasingly important to re-evaluate features associated with neurocognitive impairment. Here we have identified features, routinely collected in primary care settings that

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provide more accurate diagnostic value than a neurocognitive screening measure among younger and older HIV-individuals.

Keywords

HIV; aging; neurocognitive tests; HAND

Introduction

With the success of combined anti-retroviral therapy (cART), the HIV-infected (HIV+) population is living longer. Over 25% of HIV+ adults in the United States are now over the age of 50, and over 50% are expected to be over the age of 50 by 2015 (Heaton et al. 2011). In this aging population, the pathogenic effects of HIV, especially in those with a long duration of infection, may intersect with those of age-related illnesses and the effects of long-term use of cART. Several broad categories of pathologies associated with HIV infection, aging, and long-term cART exist, including lipid disorders, B-cell lymphomas, and neurocognitive disorders (Lamers et al. 2012; Herndier et al. 1994; Bandaru et al. 2013). As such, it is now important that the unique medical challenges posed by the aging HIV+ population be delineated.

HIV-associated neurocognitive disorder (HAND) is one of the most common medical complications of HIV infection (Schouten et al. 2011). It can have a devastating impact on day-to-day functioning (Heaton et al. 2004), and may affect adherence to treatment, resulting in increased morbidity; therefore, it is important to identify HAND early and to begin effective intervention. However, HAND diagnosis remains highly dependent on neuropsychological test batteries that were developed in the pre-cART era, and validated primarily in younger cohorts for whom age-related co-morbidities were not considered. Investigating the pathogenesis of HAND in older HIV+ adults presents unique challenges (Gannon et al. 2011). Long-term exposure to cART and multiple co-morbid conditions that affect the brain may modify the mechanisms that lead to HAND in older HIV+ adults, resulting in a different clinical presentation than that described previously (Everall et al. 2009; Sacktor et al. 2007; Morgello et al. 2001; Heaton et al. 2011; Erlandson et al. 2014). As such, the current diagnostic schema for HAND may not adequately capture the true complexity of neurocognitive impairments that result from both HIV and other age-related factors (such as vascular diseases), and may fail to consider the multifaceted approach required for effective treatment. In addition, the study of HAND has often focused on relatively few potential causative factors at one time (Dwyer et al. 2014; Heaton et al. 2010; Cysique and Brew 2011). As such, a more comprehensive examination of factors affecting neurocognitive functioning in HIV+ adults is needed.

Finally, from a pragmatic perspective in the current age of managed healthcare, it is important to minimize the burdens of assessment for HAND. In research settings, HAND is generally identified via a comprehensive neurological examination and neuropsychological testing, in addition to neuroimaging, virologic, and medical assays. However, such testing is quite expensive and burdensome to patients, making it less feasible to screen a large number of patients in most clinical settings. At present, brief neurocognitive screening measures

such as the HIV dementia scale (HDS) (Power et al. 1995), the International HIV Dementia Scale (Sacktor et al. 2005) and others (Zipursky et al. 2013; Milanini et al. 2014) are commonly used to detect HAND in primary or secondary care settings. However, many reviewers opine that these scales have low accuracy (Haddow et al. 2013; Zipursky et al. 2013), especially in milder forms of the disorder. But the availability of data (e.g., virologic, medical, demographic, behavioral, and psychosocial) collected within such clinical environments raises the possibility that consideration of these varied data in clinical screening can improve the detection of HAND without the necessity of comprehensive neurocognitive testing.

In this study, we evaluated extant clinical data from cohorts of both older and younger HIV+ individuals enrolled in a longitudinal study conducted by the National Neurological AIDS Bank at the University of California, Los Angeles (UCLA NNAB) in order to determine those features most predictive of HAND in differently aged groups. We hypothesized that information obtained via standard medical examinations would be more useful in detecting HAND as compared to the HDS, and that those features would differ between older and younger groups.

Methods

Data from participants enrolled in the UCLA NNAB were used for the analyses. The UCLA NNAB is a member of the National NeuroAIDS Tissue Consortium (NNTC) (Morgello et al. 2006). The NNTC was founded in 1998 to respond to researchers' need for well-characterized human tissues and fluid samples and to study the mechanisms of HIV neurological disease. The NNAB uses standardized NNTC protocols to assess and classify neurocognitive impairment and to assign diagnoses according to established criteria (Morgello et al. 2006; Woods et al. 2004; Antinori et al. 2007). NNAB recruits adult volunteers with advanced HIV infection to enroll in the study. Eligibility is as follows: willing and able to give an informed consent or had a legal guardian to do so; agreed to donate brain and other tissues in the event of death; had a CD4+ count <50 cells/mm^3 at enrollment and/or one or more of the following conditions: systemic lymphoma or other malignancy, mycobacterium avium complex, wasting with loss of ≥30% body weight, primary central nervous system (CNS) lymphoma, progressive multifocal leukoencephalopathy, congestive heart failure, renal failure, end-stage liver disease, or serum albumin <3.2 g/dL. Once enrolled, participants continue to be followed in the event that their health improves. All participants or their legal guardians are consented in accordance with UCLA IRB-approved protocols. The subjects are both male and female, from a variety of ethnicities, racial backgrounds and socioeconomic groups. All study material is coded in accordance with NNAB protocols.

Participants

The primary NNAB dataset contained over 200 living HIV+ persons aged 21–80 with a variety of CNS conditions. From this primary dataset we identified 70 cART-treated HIV+ participants that met our inclusion criteria, ranging in age from 32–73 years (Figure I). For inclusion in the study, we required that each patient have associated data for all parameters

of interest for at least one time point. Longitudinal data was not was considered in the study. In the case that a single patient received all tests on a single day more then once, only the last time point, where all variables were collected was considered for our analysis. The histogram of patient age provides a natural breakpoint of five years to divide the participants into two categories of younger and older patients. Thirty of these participants were 32–50 years of age with a mean age of 43.8±5.62 and a mean known duration of their HIV infection of 17.7±6.79 years. Forty were aged 55–73 years with a mean age of 61.1±4.56 years and a mean known duration of their HIV infection of 19.3±6.14 years. Duration of known HIV infection (years infected) was calculated as the number of years from the first positive HIV serology to the time of participant assessment for this study; however, the precise time of infection was rarely available and was likely to be of longer duration. Interestingly, the mean length of infection for the both cohorts was quite long (17.7 – 19.3 years), thus, each cohort represents individuals with moderately successful cART treatment over time. These two age-stratified datasets were used in our analysis to identify features related to HAND and global deficit score (GDS).

Procedures

As part of the standard NNAB protocol, participants were asked to complete a standardized medical and neurological examination including administration of the HDS performed by a board-certified neurologist who specializes in HIV neuro-disease; a standardized set of neuropsychological tests; a psychiatric/substance abuse inventory based on the Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition DSM-IV (DSM-IV 2000), or Composite International Diagnostic Interview (CIDI) (Kessler and Ustun 2004), or the Psychiatric Research Interview for Substance and Mental Disorders (PRISM) (Hasin et al. 1996); the Beck Depression Inventory-Second Edition (BDI) (Beck et al. 1996); a urine screen for drugs of abuse; a blood draw for complete blood count (CBC) including white blood count, hemoglobin, hematocrit, and platelet count; CD4+ cell subsets, plasma HIV viral load, HCV serology (at entry) and RPR (syphilis serology); an optional lumbar puncture for cerebrospinal fluid (CSF) cell count, glucose, total protein, VDRL, and CSF HIV viral load; and in a subset of subjects, brain magnetic resonance imaging (MRI). In all cases, aggressive efforts were made to review and abstract the participants' current medical records and verify their cART regimens and adherence. In addition, all participants were asked to sign a release of medical information so that their healthcare providers could be contacted and medical records obtained on a regular basis.

Criterion Variables

HAND was established based on the results of the procedures described above. HAND was determined via consensus conference by the study neurologist and neuropsychologist, with the consideration of the participants' neuropsychological test scores and other pertinent data, including medical and substance use history and psychosocial background. Participants found to have neurocognitive impairment (NCI) attributable to other disease processes including head trauma, severe psychiatric disorders, learning disorder, metabolic encephalopathy, cerebral opportunistic infections, tumors, etc. were excluded from this study. The remaining participants were given a HAND classification based on either the previous AAN criteria (Nomenclature and research case definitions for neurologic

manifestations of human immunodeficiency virus-type 1 (HIV-1) infection. Report of a Working Group of the American Academy of Neurology AIDS Task Force 1991) if their evaluation occurred prior to the publication of the newer HAND research criteria in 2007, or according to the "Frascati" criteria if after 2007 (Antinori et al. 2007). Because the NNTC included a "subsyndromic" impairment classification since its inception, and because the criteria for MCMD and HAD (AAN) remained essentially identical to MND and HAD (Antinori et al 2007), we were able to group participants from both diagnostic eras. For simplicity, we use the Frascati designations in this paper, as follows: neurocognitively normal (0), asymptomatic neurocognitive impairment (1), possible minor neurocognitive disorder (2), probably MND (3), possible HIV–associated dementia (4), probable HAD (5). The Global Deficit Score (GDS) was determined by averaging individual neuropsychological (NP) domain deficit scores (Carey et al. 2004). The test battery is shown in Table I.

Modeling Variables

For each patient, 24 features routinely collected as part of the NNAB protocol were used as input for our statistical analysis to determine those features that best predicted, or explained variance in, HAND and GDS. Table II provides a description of the mean and standard deviation or the frequency for these features for both the entire participant set in addition to the younger and older cohorts.

Nadir absolute CD4+ cell count was determined by chart review and/or participant recollection. Tobacco smoking was determined by self-report, participant examination and/or chart review. Depression was determined by the BDI. Chronic renal disease was assessed by self-report and/or review of medical records including recent measurements of creatinine (Cr) and glomerular filtration rate (GFR). Hypertension was assessed by self-report, review of medications, chart review, and review of patient's serial blood pressures taken on multiple NNAB visits. Hyperlipidemia was assessed by self-report, review of current medications, and chart review of serum lipid panels. Diabetes was assessed by self-report, use of medications specific for diabetes, chart review for elevated hemoglobin A1C or elevated fasting blood sugars (≥100mg/dL). Lipodystrophy was determined by NNAB physical examination looking for evidence of abnormalities such as facial lipoatrophy, centripetal fat accumulation, and/or wasting of fat in the extremities, and confirmed by anthropomorphic measurements at each study visit. Cardiac disease was determined by participant history, medication review (prescription of one or more medications specific for cardiac disease) and/or medical record review demonstrating abnormal cardiac function. Liver disease was determined by self-report, physical examination, and review of medical records for elevated liver enzymes, elevated alpha fetoprotein, or abnormal liver biopsy. Cerebrovascular disease was assessed by the NNAB neurological exam and history as well as medication review and review of medical records, including neuroimaging scans when available. Cocaine or methamphetamine use was assessed via urine toxicology; we focused on these two drugs due to their consistent association with additive neurocognitive problems in HIV+ individuals (Rippeth et al. 2004; Carey et al. 2006; Levine et al. 2006; Meade et al. 2011; Gaskill et al. 2009; Silverstein et al. 2012) and because they are recognized as an intersecting presenting condition of HIV infection (High et al. 2012). The study neurologist

administered the HDS test. The HDS test generates a score between from 0–16, which was used in a continuous manner for these analyses. An HDS score of ≤10 was considered to be an indication of impairment (Power et al. 1995).

Statistical models

For each age group and also with all participants pooled together as a single dataset, stepwise regression using StatView (SAS International) was used to identify multiple linear regressions relating patient features to the dependent variable of HAND or GDS. For each of these dependent variables we first considered HDS score on its own to evaluate the utility of this single metric in clinical evaluation. For each of the dependent variables above we then used a standard process of stepwise regression to evaluate multiple linear regressions using all available subject features. Stepwise regression resulted in multiple linear regressions that used as few terms as possible with maximal correlation (R^2) to the dependent variable. Terms in the regressions were reviewed to ensure that an appropriate p-value had been attained and that coefficients associated with the features were reasonable.

Results

HAND

When combining all 70 participants and identifying variables of greatest concern using stepwise regression, a two-term linear regression was identified with correlation to HAND (y = −0.120 (HDS) + 0.041 (BDI) + 2.234; adj R^2 = 0.135). All terms in this model are significant to the p<0.05 level. However, examining HDS on its own relative to HAND provided a weaker correlation of adj R^2 = 0.071, thus indicating the limitations of this test on its own in a cART-exposed, longer-lived patient cohort.

When examining only participants in the younger cohort (n=30), stepwise regression identified a 4-term model (y = −0.110 (years infected) + 0.091 (age) − 0.356 (Bld hemoglobin) + 3.416 (cocaine/methamphetamine) + 3.788; adj R^2=0.492). All terms in this model were significant to the p<0.05 level. Interestingly, cocaine/methamphetamine use on its own provided a stronger correlation to HAND (adj R^2=0.130) than HDS on its own (adj R^2=0.005).

When examining only the older cohort (n=40), stepwise regression identified a model with three terms that generated a useful regression (y = 0.077 (years infected) + 0.108 (BDI) − 0.766 (hyperlipidemia) − 0.236; adj R^2=0.345). Only BDI was significant to p<0.0001 in this model, all other terms were significant to p<0.05. HDS on its own provided a weaker correlation of adj R^2=0.094 to HAND in the older cohort. A summary of these regressions is provided in Figure IIA.

Global deficit score

When combining all 70 participants and using GDS as the dependent variable, stepwise regression resulted in a four term model (y = −0.093 (HDS) − 0.018 (age) + 0.015 (BDI) − 0.292 (diabetes) + 3.004; adj R^2=0.290). Of these terms, only HDS, age, and BDI were significant to the p<0.05 level. Diabetes (p=0.0567) was retained in the model in light of its

large coefficient. HDS on its own generated a weak correlation with GDS (adj R^2=0.145) over the entire cohort.

When examining the younger cohort, a 6-term model was realized (y = − 0.111 (HDS) − 0.028 (years infected) − 0.134 (Bld hemoglobin) − 0.721 (liver disease) − 0.096 (# comorbid) + 1.664 (cocaine/methamphetamine) + 5.432; adj R^2=0.758). This model included all the terms that correlated to HAND for this cohort. Of these terms, only the number of comorbid conditions was not statistically significant at the p=0.05 level. (p=0.0598). HDS, Bld hemoglobin, and cocaine/methamphetamine were all significant to the p<0.0001 level. HDS on its own for the younger cohort had a much weaker correlation of adj R^2=0.271 to GDS.

When examining the older cohort, a 3-term model was realized (y = −0.071 (HDS) + 0.647 (liver disease) + 0.391 (gender) + 0.079; adj R^2=0.289). All of these terms were significant (p<0.02) with the exception of gender (p=0.0570). HDS on its own resulted in a weaker correlation of adj R^2=0.106 to GDS for the older cohort. A summary of these regressions is given in Figure IIB. Table III provides a summary of all results by dependent variable and by cohort age.

Discussion

In this study we sought to determine which variables, routinely collected in primary care settings, predicted both HAND diagnosis and neurocognitive impairment. In addition, we determined if these variables differed between older and younger HIV+ individuals. Not surprisingly (Zipursky et al. 2013), in the overall sample the HDS was weakly correlated with GDS but not HAND, suggesting that it is a poor indicator of neurocognitive dysfunction compared to approaches that consider multiple features. This is consistent with recent studies that have found the HDS to be of limited utility in identifying the majority of cART-exposed individuals with HAND (i.e., those with mild impairment) (Bottiggi et al. 2007; Smith et al. 2003; Cross et al. 2013). The model was strengthened when HDS was combined with BDI. This finding is also not unexpected, as there is reason to believe that depression is related to HAND both via molecular and behavioral avenues (Atkinson et al. 2008; Leserman 2008; Dantzer and Kelley 2007; Raison et al. 2006; Fialho et al. 2013); however, the relationship is far from unequivocal.

When examining the young vs. old cohorts, positive urine toxicology for cocaine/methamphetamine, years of known infection, age, and blood hemoglobin in the younger population become useful for predicting HAND, whereas in the older population a small and different set of features were significant (depression, hyperlipidemia, and known years of infection). The finding that hyperlipidemia may be associated with neurocognitive disorders in older HIV+ individuals agrees with other studies that suggest there is a cerebrovascular component to the development of NCI (Foley et al. 2010; Becker et al. 2009; Cysique et al. 2010; McCutchan et al. 2012). This finding could also indicate increased inflammation in the older cohort, as both HIV dementia and hyperlipidemia have been linked to inflammatory cytokines (Gongvatana et al. 2012; Shiramizu et al. 2011; Bandaru et al. 2013; Bernstein et al. 2006; Lo et al. 2007; Correia et al. 2013). The number of known years

infected is considered as an important feature for both the younger and older cohorts, but was not statistically significant in the best multiple linear regression associated with HAND over all participants, suggesting that this might be the result of a limited participant sampling. In all cases when predicting HAND, these multiple linear regressions outperformed HDS on their own, indicating the need for additional features to be used in combination with that screening measure. Further, the difference between HDS on its own and the use of a multiple linear regression for the prediction of HAND was pronounced in the younger cohort. Such a result confirms the need for additional participant features for detecting HAND in both young and older cART-treated cohorts so that improved models can be developed.

With GDS as the dependent variable, HDS remained important for the sample as a whole and in both age groups. However, beyond this one feature, each division of the data by age resulted in different features that enhanced the regression to GDS, demonstrating that NCI in the two groups may have different etiological factors contributing to HAND. As was the case with HAND, prediction of GDS in the younger cohort benefited the most from the addition of other parameters in addition to HDS, presenting a drastic improvement over HDS alone. The younger cohort model made use of more terms than those that were indicative of HAND: years known infected, blood hemoglobin, cocaine/methamphetamine use, liver disease, and number of co-morbidities. This set of features may have its own internal correlations, for example cocaine/methamphetamine use could result in low hemoglobin due to poor nutrition, is often associated with alcohol abuse, which could result in liver disease and increase the number of co-morbidities due to overall bad health combined HIV infection. This finding further underscores the importance of these features when examining younger HIV+ patients for neurocognitive issues. The features associated with GDS in the older cohort were different from those associated with HAND, thus highlighting the need to consider a wider range of variables when predicting HAND in older individuals. In the older cohort, it is interesting that hyperlipidemia was correlated to HAND and liver disease was correlated to GDS because uncontrolled hyperlipidemia can lead to liver disease (Yang 2004). Table IV compares the difference between using the HDS on its own relative to HAND or GDS versus the multiple linear regression with additional terms.

Using stepwise regression we have identified combinations of commonly collected clinical features relevant for these HIV- and age-related impairments. Clearly this approach would benefit from the examination of a larger number of participants. As the HIV+ population ages, this contemporary and quantitative method could be used to understand the contributions of multiple viral, age, and cART-related factors in the pathogenesis of NCI. Here we have elucidated the relative importance of the different clinical factors that are often measured as HAND or GDS.

For appropriate diagnosis, statistical methods that can handle the complex and multi-factorial features that may lead to neurocognitive impairment are necessary to identify older HIV+ individuals at the highest risk. Moreover, the development of a method that can incorporate a wide range of newer biological tests in the pipeline, including MRI (Li et al. 2011), novel biomarkers (Burdo et al. 2011), and information about the CNS brain penetration effectiveness (CPE) of cART (Shapshak et al. 2011) would be a highly valuable

asset to the medical community. Such models may require nonlinear multivariate models such as neural networks or support vector machines that are able to merge the information from significantly different types of data (images, demographics, etc.) and determine a classification/probability of neuropsychological condition based on age. Cysique et al. (Cysique et al. 2010) developed a screening algorithm for neuropsychological impairment on a similarly sized cohort of individuals using support vector machines that used age, CD4+ cell count, past CNS HIV-related diseases, and current treatment duration to classify neurocognitively impaired vs. normal individuals. Our study has made use of many more features than those used by Cysique et al. (Cysique et al. 2010) and has also focused on the identification of age-specific features that can be used to diagnose HAND in older individuals. A recent study by the same group used age and neurodiagnosis in various statistical analyses and found no significant interaction of the two variables (Cysique et al. 2011). Noted in that analysis is that the other cohort consisted of a homogenous group of primarily educated men, whereas our data sets contained patients from diverse backgrounds, including 15.7% women. In the Cysique study, the age separation between the means of the two age groups was a seven years, whereas in our study the difference between the means was 17.2 years. Moreover, we considered varied types of pathological features occurring over a long period of time. In the younger cohort we found features that are likely synergistic, and as such may have more total impact on CNS injury. For example, low blood hemoglobin is a correlate of comorbidities and drug use, both of which were identified as meaningful correlates of HAND. In the older cohort it is likely that new biomarkers for NCI are required for adequate diagnosis. Therefore, our findings differ from the study by Cysique et al. primarily because of the greater diversity of our cohort, an increased age spread (a 14 year difference between the means of the two age groups in our cohort) and the inclusion of multiple risk factors in the analysis. Further, our data supports Becker et al.'s recent determination that non-HIV factors are significant in older neurocognitively impaired individuals (Becker et al. 2011).

Continuous re-evaluation of the diagnostic methods and scales used to assess HAND are necessary because both therapies and HIV disease pathogenesis change with time (Gandhi et al. 2010; Becker et al. 2011). This is especially the case for the growing number of older, cART-treated HIV+ individuals, where there is concern that other age related features that influence neurological decline should be considered, such as duration of infection, cardiovascular disease or lipodystrophy. The features found in this analysis that were associated with HAND or GDS in older vs. younger HIV+ individuals would be greatly enhanced with more data as these individuals continue to age. Our initial evaluation in this direction suggests that additional focus should be applied toward a revised method for NP evaluation in the older HIV+ population.

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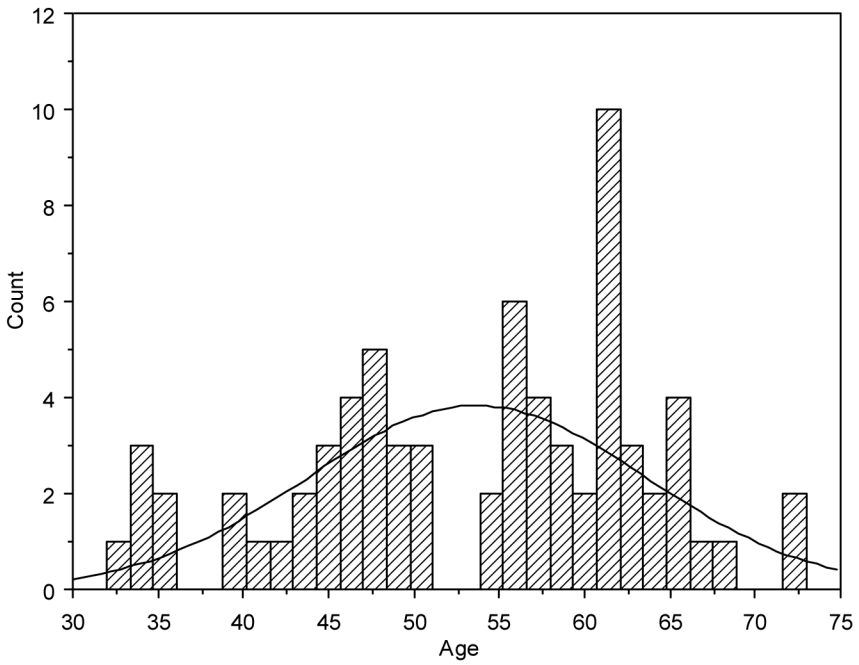

Fig. I. Histogram of Patient Age

The bar graph shows the distribution of age in the two categories (younger vs. older) given a threshold at 53 years of age.

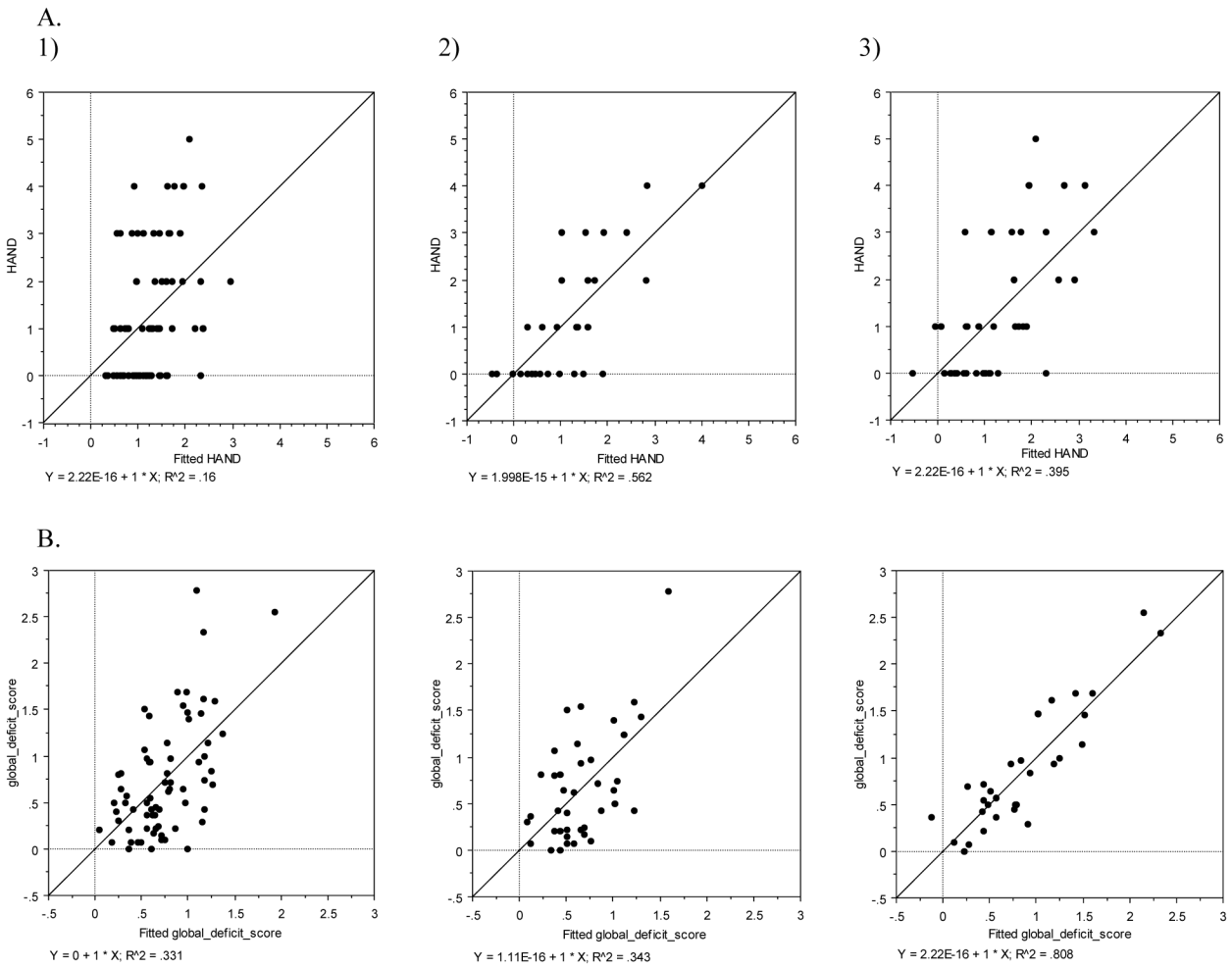

Fig. II. Multiple Regression Plots

A) HAND relative to the output of three stepwise regressions (fitted HAND) for 1) all patients, 2) the young cohort, and 3) the old cohort being examined. B). Global deficit score relative to the output of three stepwise regressions (fitted global deficit score) for 1) all patients, 2) the young cohort, and 3) the old cohort being examined.

Table I

Neurological domains and measures for the calculation of GDS.

Neurocognative Domain	Test	Reference
I. Working Memory	Letter–Number Sequencing	WAIS–III; Wechsler, 1997 (Wechsler 1997)
	PASAT Trial 1	Wiens, Fuller, & Crossen, 1997 (Wiens et al. 1997)
II. Motor	Grooved Pegboard, dominant and nondominant hand	Klove, 1963 (Klove 1963)
III. Information Processing Speed	Digit Symbol	WAIS–III; Wechsler, 1997 (Wechsler 1997)
	Symbol Search	WAIS–III; Wechsler, 1997 (Wechsler 1997)
	Trail Making Test–Form A	Battery A., 1944 (Battery 1944)
IV. Learning	HVLT–Revised Learning Trials total	Shapir et al., 1999 (Shapiro et al. 1999)
	BVMT–Revised Learning Trials total	Benedict et al., 1996 (Benedict et al. 1996)
V. Memory	HVLT–Revised Free Recall	Shapiro et al., 1999 (Shapiro et al. 1999)
	BVMT–Revised Free Recall	Benedict et al., 1996 (Benedict et al. 1996)

Table II

Sample Characteristics.

Variable (units)	All Patients Mean (SD) (*n*=70)	Younger Cohort Mean (SD) (*n*=30)	Older Cohort Mean (SD) (*n*=40)
HAND	1.24 (1.40)	1.20 (1.32)	1.28 (1.47)
GDS	0.74 (0.62)	0.85 (0.64)	0.65 (0.59)
HDS	12.2 (3.1)	12.7 (2.7)	11.8 (3.3)
Years infected (years)	18.61 (6.43)	17.70 (6.79)	19.30 (6.14)
Age (years)	53.7 (10.0)	43.9 (5.6)	61.1 (4.6)
Absolute CD4+ count (cells/mm^3)	411.46 (303.55)	299.87 (241.11)	495.15 (320.98)
Plasma viral load (IU/L)	14,036.14 (50,163.34)	23,994.63 (62,103.08)	6,567.05 (38,087.31)
Nadir CD4+ count (cells/mm^3)	202.01 (211.69)	134.47 (143.26)	252.68 (240.59)
Bld Hemoglobin (g/L)	13.8 (1.8)	13.4 (2.2)	14.1 (1.5)
BDI	11.76 (9.47)	13.53 (11.03)	10.43 (8.00)
# Comorbidities	2.41 (1.65)	2.07 (1.28)	2.68 (1.85)

Variable	All Patients (%)	Younger Cohort (%)	Older Cohort (%)
HCV	25.7	20.0	30.0
Chronic renal disease	13.2	10.0	15.8
Lipodystrophy	27.5	20.1	32.5
Tobacco smoking	48.6	46.7	55.0
Hypertension	50.7	40.0	59.0
Diabetes	21.7	23.3	20.5
Cardiovascular	24.6	24.1	25.0
Liver disease	7.1	3.3	10.0
Cerebrovascular	10.4	13.8	7.8
Hyperlipidemia	39.1	26.7	48.7
Cocaine/Meth	8.5	3.3	12.5
Race			
Black	34.3	40.0	30.0
Hispanie (Caucasian)	17.1	30.0	7.5
White	38.6	23.3	50.0
Other (Native American)	10.0	6.7	12.5
Gender			
Male	84.3	90.0	80.0
Female	15.7	10.0	20.0

Table III

Features Identified Through Stepwise Regression. Terms marked by asterisk have the highest coefficient in each of the realized stepwise regressions.

Dependent Variable	All Patients	Younger Cohort	Older Cohort
HAND	HDS* BDI	Years infected Age Bld hemoglobin Cocaine/meth*	Years infected BDI* Hyperlipidemia
GDS	HDS Age BDI Diabetes*	HDS Years Infected Bld hemoglobin Liver disease # Comorbid Cocaine/meth*	HDS Liver disease* Gender

Table IV

Differences in HIV dementia scale (HDS) vs. multiple linear regression (MLR) correlation (adjusted R^2) to HAND and GDS given different age cohorts.

Dependent Variable		All Patients Combined	Younger Cohort	Older Cohort
HAND	HDS	0.071	0.005	0.094
	MLR	0.135	0.492	0.345
GDS	HDS	0.145	0.271	0.106
	MLR	0.290	0.758	0.289