# HIV Proviral DNA Associated With Decreased Neuropsychological Function

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*The authors previously found a strong association between elevated HIV proviral DNA (HIV DNA) and a diagnosis of HIV-1-associated dementia (HAD) vs. normal cognition. It is unclear whether HIV DNA globally affects the diagnosis of HAD or whether the effect is limited to individual neuropsychological deficits. This exploratory study examined baseline HIV DNA and its association with individual neuropsychological deficits. HIV DNA was significantly associated with baseline neuropsychological deficits independent of age, ethnicity, IQ, and plasma HIV-1 RNA levels. However, HIV DNA did not predict future changes in neuropsychological deficits. The data suggest that HIV DNA and neuropsychological deficits may co-vary over time.*

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Progress in understanding the pathogenesis of HIV-1-associated dementia continues to be made, but details on how the neuropathogenic pathways interact with each other are not completely understood.[1–6] By identifying key elements involved in HIV-1-associated dementia (HAD) pathogenesis, we may be able to target interventions to treat or prevent it. Recently, we performed a cross-sectional study and found an association between circulating HIV-1 proviral DNA (HIV DNA) levels and HAD, independent of plasma HIV-1 RNA levels.[7] This remains the only prior investigation of the association between HIV DNA and HAD. In the study, we tested the null hypothesis of no association between HAD and HIV DNA in specimens from individuals at opposite ends of the cognitive diagnostic spectrum: HAD and normal cognition. We used the American Academy of Neurology (AAN) diagnostic criteria for HAD, which were established in the pre-HAART era, and found a significant association of HIV DNA with

HAD (OR=2.83; 1.57–5.08, p<0.001).[7,8] We hypothesized that HIV DNA levels may affect different areas of the brain uniquely, thus leading to specific neuropsychological deficits. If HIV DNA is shown to associate differentially with specific neuropsychological deficits, this may suggest that specific areas of the brain are affected differently. Therefore, focusing on neuropsychological deficits to clinically characterize patients may provide an advantage over using a diagnosis of HAD.[7] In the current HAART era, markers for HAD, a diagnosis which relies on global neuropsychological deficits, remain to be identified.[1,9,10] Though additional studies are necessary to establish HIV DNA as a marker for HAD, the use of HIV DNA as a prognostic marker for neuropsychological deficits could potentially be a clinical and research tool. A recent report[11] by other investigators found that HIV DNA levels predicted HIV-1 disease progression to AIDS. Rouzioux et al.[11] suggested that HIV DNA levels could be a useful clinical marker to help define the best time to initiate treatment. The study supported the possibility that HIV DNA may be involved in disease pathogenesis and prompted us to look at its association with neuropsychological deficits.

In this exploratory study, we analyzed an expanded data set to explore the association of HIV DNA with specific neuropsychological deficits. The objectives were to assess the relationship of baseline HIV DNA to baseline and yearly neuropsychological deficits for 2 years, and to determine whether baseline HIV DNA predicts subsequent neuropsychological deficits. Based on our earlier observation suggesting that HIV DNA may be predominant in circulating monocytes/macrophages, we hypothesized that HIV DNA levels and neuropsychological deficits would be transient and both would co-vary over time.[7]

## METHOD

### Cohort and Clinical Data

Cases analyzed from the Hawaii Aging with HIV Cohort (HAHC) for this study matched those previously reported.[7] From the previously reported 49 subjects, 44 individuals completed at least two annual follow-up visits and comprised the cohort for the current study. The current study was limited to those reported in our earlier study[7] (i.e., those with HAD and normal cognition), because the intent of this study was to follow up

and extend the analyses of individuals enrolled in the cohort over subsequent years. The original report studied randomly selected individuals enrolled in the HAHC and diagnosed with HAD and normal cognition but did not include those with intermediate neuropsychological deficits.[7] The rationale was to try to assess the value of HIV DNA on extreme opposite ends of neurocognitive diagnoses, HAD and normal cognition, which resulted in a skewed percentage of HAD cases. In actuality, the number of HAD cases in the HAHC is better represented in a recent analysis of HAD cases in older (25.2%) and younger (13.7%) individuals.[12] The diagnosis of HAD was made after individual cases were discussed in a consensus conference involving two neurologists, two neuropsychologists, and a geriatrician.[12] HIV dementia cases were defined with the American Academy of Neurology criteria using all clinical data obtained during the study visit.[8] A diagnosis of HIV dementia required an abnormality in at least two cognitive domains, including attention/concentration, speed of information processing, abstraction/reasoning, visuospatial skills, memory/learning and speech/language, and either an abnormality in motor function or a decline in motivation/emotional control.

The HAHC protocol, assessment battery, and demographic characteristics of the individuals are described elsewhere.[7,12] Briefly, the HAHC is a collaboration between the University of Hawaii and Johns Hopkins University to evaluate older (50 years of age or higher) and younger (20 to 39 years of age) HIV-1-seropositive individuals. Major exclusion criteria included the following: major psychiatric disorder including bipolar disorder, schizophrenia, and active major depression; head injury with loss of consciousness for more than 1 hour; CNS opportunistic infection; learning disability; and neurological disease, such as major stroke, multiple sclerosis, or delirium. English was the primary language for all individuals. Broad community-based recruitment techniques were implemented, including recruitment from AIDS service organizations, through advertisement in local newspapers, referrals from community physician clinics, and participation in local HIV/AIDS events. Participants were recruited from all major islands of Hawaii and were living in Hawaii.

Participant evaluations included demographics, medical history, the macroneurological examination as used in the Adult AIDS Clinical Trials Group (including the United Parkinson's Disease Rating Scale to examine for extrapyramidal signs), medication/adherence his-

tory, DSM-IV-based substance abuse/dependence inventory, immunologic and virologic laboratory tests, and neuropsychological testing.[13,14] The 80-minute neuropsychological test battery assessed multiple cognitive domains affected by HIV-1 and included the following: Choice and Sequential Reaction Time from the California Computerized Assessment Package (CalCAP), the Rey Auditory Verbal Learning Test (RAVLT), Rey Osterreith Complex Figure (RCF) Copy and Recall, Trail Making Test, Parts A and B, Wechsler Adult Intelligence Scale–Revised (WAIS-R) Digit Symbol, Grooved Pegboard (dominant and nondominant hands), Verbal Fluency Test (FAS), Animal Naming, Boston Naming Test (BNT), the WAIS-R Digit Span (Forward and Backward), and Timed Gait. Depression symptomatology was assessed using the Beck Depression Inventory (BDI). This neuropsychological test battery was adapted from that used in the NorthEast AIDS Dementia (NEAD) cohort.[15]

Various normative data were required due to the use of a comprehensive test battery and the inclusion of both younger and older subjects. The normative data were selected as the best possible dataset for this population with a long history of applications in HIV-1 research (e.g., Multicenter AIDS Cohort Study [MACS]). Application of these norms was guided by the clinical neuropsychologists on the team. Normative neuropsychological data for individuals with a high school or greater education were derived from the MACS consisting of 733 HIV-1-seronegative subjects with risk profiles similar to the Hawaii cohort. For individuals with less than a high school education, normative neuropsychological data from the AIDS Link to IV Experience study (N = 150) were used.[16] These two normative sets have few individuals over 54 years old. Thus, for individuals over 54, alternative published normative data were used.[17,18] Normative data for the RCF were taken from alternative published norms for individuals over 59 years old and the main MACS normative set for individuals under 60 years old.[19] A similar battery with a large overlap in norms was shown to be appropriate for HIV-1-infected individuals of similar ethnic diversity.[20] All test results were transformed to z scores using appropriate age and education-matched normative data sets. Scores for cognitive domains (i.e., motor skills/motor speed; verbal memory; visual memory; working memory, attention, and concentration; learning; recognition memory; visuospatial abilities; executive functioning; language) were calculated by averaging the z scores of the neuropsychological tests corresponding to the domains they were intended to measure (Table 1).

Plasma HIV-1 RNA levels (VL) and CD4 cell counts were performed by a certified clinical laboratory, as previously reported.[7]

## Specimens and HIV DNA Assay

HIV DNA, normalized to the number of copies of HIV-1 proviral DNA per $10^6$ cells, was measured as previously reported from peripheral blood mononuclear cells.[7] The assays were set up with independent standard curves measuring the relative ratios of HIV DNA copy number to cellular equivalent genomic DNA along with appropriate positive and negative controls and reported as HIV DNA copy per $10^6$ cells.[7]

## Statistical Analysis

We examined the association between HIV DNA and each of the nine neuropsychological deficits in a series of multilevel longitudinal regression models. The level one variable in the model included initial neuropsychological deficits and annual rates of change. Given the exploratory aim of this study, p values were not adjusted

**TABLE 1. Cognitive Domains Associated With Neuropsychological Tests**

| Cognitive Domain | Neuropsychological Test |
| --- | --- |
| Motor skills and motor speed | Grooved Pegboard, dominant hand<br>Grooved Pegboard, nondominant hand<br>Trail Making Test, Part A<br>WAIS-R Digit Symbol Subtest<br>Timed Gait<br>CalCap Choice<br>CalCap Sequence |
| Verbal memory | RAVLT Immediate Recall<br>RAVLT Delayed Recall |
| Visual memory | Rey-Osterreith Complex Figure Test–Immediate Recall Trial<br>Rey-Osterreith Complex Figure Test–Delayed Recall Trial |
| Working memory, attention, and concentration | WAIS-R Digit Span Subtest<br>RAVLT Trial 1<br>RAVLT Interference Trial |
| Recognition memory | RAVLT Recognition |
| Learning | RAVLT Total |
| Visuospatial abilities | Rey-Osterreith Complex Figure Test–Copy Trial |
| Executive functioning | Controlled Oral Word Association Test<br>Odd Man Out<br>Trail Making Test, Part B |
| Language | Boston Naming Test<br>Animal Naming Test |

WAIS-R = Wechsler Adult Intelligence Scale-Revised; RAVLT = Rey Auditory Verbal Learning Test

for multiple endpoints and thus were construed to be complementary to the regression coefficients' indications of the association strength for each neuropsychological deficit rather than strict hypothesis tests. All analyses were conducted using SAS® v9.1 PROC MIXED specifying maximum likelihood as the estimation method and an unstructured covariance matrix. The temporal variability within each deficit was estimated in two ways: 1) fixed effect for time, and 2) probability of the residual variance of each individual's trajectory around the overall mean trajectory. We examined the association between HIV DNA and baseline neuropsychological deficit and annual rate of change of each deficit, as indicated by the TYPE III fixed effect for HIV DNA after it was added to the unconditional growth model. To determine whether the obtained estimates were attributable to other patient characteristics, we added age, ethnicity and premorbid IQ. To determine whether associations between HIV DNA and each deficit were present in individuals with undetectable plasma HIV RNA levels, we repeated the univariate analyses using only those with undetectable levels.

## RESULTS

Characteristics and demographics of the subjects are summarized in Table 2. The mean age at entry was 46.2 (SD = 10.77) years with the mean number of years of education being 14.14 (SD = 2.56). The mean BDI score was 9.39 (SD = 9.09) and the mean Karnofsky score was 88.92 (SD = 6.99). The mean duration of HIV-1 infection as self-reported was 9.2 (SD = 4.9) years with nadir CD4 cell count reported as 217 cells/μL (SD = 167.43).

The decrement in baseline of each neuropsychological deficit associated with HIV DNA is plotted in Figure 1, and adjusted for age, ethnicity, and estimated premorbid IQ, where ethnicity and IQ are not confounded with cognitive diagnosis. For each unit increase in $\log_e$ of HIV DNA, there is a decrease in neuropsychological deficit. Neuropsychological deficits were significantly associated with baseline HIV DNA in all deficits except for one: visuospatial abilities (regression coefficients range from $-0.27$ to $-0.10$, $p < 0.01$) (Table 3). The effect of HIV DNA on neuropsychological deficits remained significant after adjusting for age, ethnicity, and estimated premorbid IQ. When analyses were repeated using only individuals with undetectable plasma HIV-1 RNA levels, the association between neuropsychological deficits

and baseline HIV DNA remained significant (N = 26, $p < 0.01$). The effect for time in the unconditional growth model was significant in only two of the nine domains: visual memory (regression coefficient = 0.18, SE = 0.04, $p < 0.0001$) and executive functioning (regression coefficient = 0.22, SE = 0.04, $p < 0.0001$). However, the variance component for residual variance in change over time was significant for only one domain: motor skills and motor speed (z = 2.48. $p < 0.01$). In this exploratory analysis, baseline HIV DNA baseline was not associated with neuropsychological deficit change over the subsequent 2 years.

## DISCUSSION

Much progress has been made in understanding the pathogenesis of HAD, but the mechanisms leading to disease progression are still not completely delineated.[21–24] We previously reported that high HIV DNA levels were associated with HAD and hypothesized that HIV DNA, independent of plasma HIV-1 RNA levels, was involved in HAD pathogenesis.[7] In our current exploratory study, we expanded our prior results with a more complete dataset using less restrictive endpoints. We demonstrated that HIV DNA was significantly associated with baseline neuropsychological deficits in all

**TABLE 2. Demographic and Disease Characteristics of Cohort (N = 44)**

|  | Mean | SD | Range |
|---|---|---|---|
| Age at visit (in years) | 46.20 | 10.77 | 43.07 |
| Education (in years) | 14.14 | 2.56 | 16.00 |
| BMI | 25.96 | 4.96 | 22.06 |
| Depression (BDI) | 9.39 | 9.09 | 41.00 |
| Functioning (Karnofsky) | 88.92 | 6.99 | 30.00 |
| CD4 cell count (absolute #) | 458.95 | 297.64 | 1209.00 |
| CD4 cell count nadir | 216.74 | 167.43 | 614.00 |
| Duration of infection (in years) | 9.20 | 4.90 | 17.10 |
| Log of viral load | 6.48 | 3.06 | 7.83 |
| $\log_e$ of HIV DNA | $-13.10$ | 2.89 | 12.47 |

|  | % |
|---|---|
| Sex (male) | 84% |
| On HAART | 75% |
| Ethnicity | |
|   Caucasian | 52% |
|   Asian–Pacific Islander | 36% |
|   Other | 11% |
| Cognitive Dx | |
|   Normal | 48% |
|   HAD | 52% |

BMI = body mass index; BDI = Beck Depression Inventory (range = 0–63); Karnofsky = Karnofsky Performance Scale (range = 0–100); HAD = HIV-associated dementia

but one domain (visuospatial abilities), but did not predict subsequent changes in neuropsychological deficits. Although not shown yet, we hypothesize that HIV DNA levels and neuropsychological deficits are transient and both factors may co-vary over time; however, the limitations of this exploratory study cannot conclusively rule out any potential role for HIV DNA as a predictive marker. The lack of predictive value is best understood against the backdrop of minimal temporal variation that was available for the analysis. Only two deficits (visual memory and executive functioning) showed a significant effect for time in the unconditional growth models,

**FIGURE 1.   Neuropsychological Deficits Associated With Unit Increase in Log$_e$ of HIV DNA Copies Per Cell**
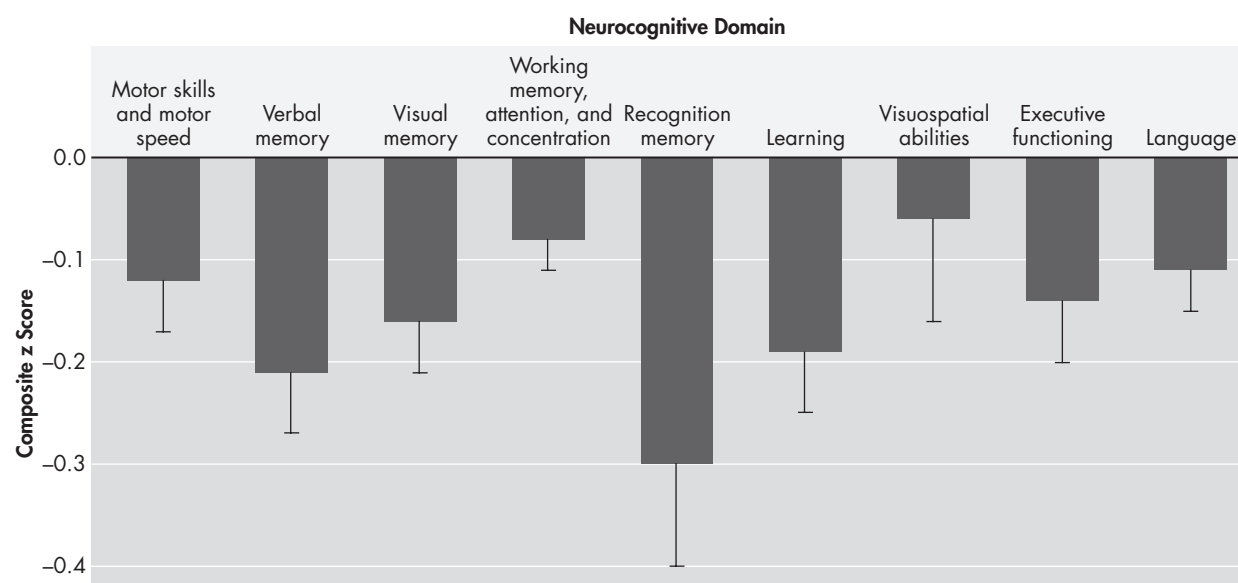


Error bars represent Standard Error for regression coefficient in a multilevel longitudinal model. Effects and standard errors are adjusted for age, ethnicity, and estimated premorbid IQ. No significant effects were observed for annual rate of change.

**TABLE 3.   Association between HIV DNA at Entry and Neuropsychological Deficit**

| Neurocognitive Domain | | Univariate Model | | | Full Model | | |
|---|---|---|---|---|---|---|---|
| | | β | (SE) | p | β | (SE) | p |
| Motor skills/motor speed | Status at Entry | −0.15 | (0.04) | <0.01 | −0.12 | (0.05) | <0.05 |
| | Annual Rate of Change | <0.01 | (0.02) | 0.58 | <0.01 | (0.02) | 0.47 |
| Verbal memory | Status at Entry | −0.24 | (0.05) | <0.0001 | −0.21 | (0.06) | <0.001 |
| | Annual Rate of Change | <0.01 | (0.02) | 0.73 | < 0.01 | (0.02) | 0.68 |
| Visual memory | Status at Entry | −0.18 | (0.05) | <0.001 | −0.16 | (0.05) | <0.01 |
| | Annual Rate of Change | > 0.01 | (0.02) | 0.77 | −0.01 | (0.02) | 0.51 |
| Working memory, attention, & concentration | Status at Entry | −0.10 | (0.03) | <0.001 | −0.08 | (0.03) | <0.05 |
| | Annual Rate of Change | >−0.01 | (0.01) | 0.89 | >−0.01 | (0.01) | 0.95 |
| Recognition memory | Status at Entry | −0.28 | (0.09) | <0.01 | −0.30 | (0.10) | <0.01 |
| | Annual Rate of Change | −0.01 | (0.03) | 0.68 | −0.01 | (0.03) | 0.69 |
| Learning | Status at Entry | −0.22 | (0.06) | <0.001 | −0.19 | (0.06) | <0.01 |
| | Annual Rate of Change | >−0.01 | (0.03) | 0.73 | <0.01 | (0.03) | 0.92 |
| Visuospatial abilities | Status at Entry | −0.20 | (0.10) | 0.06 | −0.06 | (0.11) | 0.61 |
| | Annual Rate of Change | 0.05 | (0.04) | 0.21 | −0.03 | (0.04) | 0.38 |
| Executive functioning | Status at Entry | −0.24 | (0.06) | < 0.001 | −0.14 | (0.06) | <0.05 |
| | Annual Rate of Change | 0.02 | (0.02) | 0.37 | 0.03 | (0.02) | 0.15 |
| Language | Status at Entry | −0.14 | (0.04) | <0.01 | −0.11 | (0.05) | <0.05 |
| | Annual Rate of Change | >−0.01 | (0.02) | 0.73 | >−0.01 | (0.02) | 0.98 |

β = regression coefficient for the fixed effect of HIV DNA; SE = standard error; p = probability of obtaining coefficient assuming the true value = 0. Effects and standard error in full model are adjusted for age, ethnicity, and estimated premorbid IQ.

indicating that the average trajectory over 2 years was fairly flat. The time effect alone can be assessed on the outcome without any additional predictors.

In this model, the coefficients indicate the amount of change in the outcome that is attributable to a unit of change in the predictor. The direction of change is indicated by the sign of the beta. In this case, the positive sign of the betas indicate improved performance in the two outcomes, which could possibly be due to a practice effect. The fact that only these two outcomes were significant suggests that there may be too little temporal variability in the data for the question of HIV DNA's impact on subsequent change to be adequately posed.

The one deficit (motor skills and motor speed) that showed a significant residual variance component for change over time in unconditional growth models suggests that little variation was available to be explained by HIV DNA or other predictors added to the model. The residual variance is the variance that is not explained by the fixed and random effects in the mixed model. The mixed model allowed for testing of the residual variance of the trajectory of motor skills and motor speed to determine whether it was statistically different. Thus, the findings suggest the possibility that the lack of association may be partly a function of the small amount of change that was available to be explained to begin with, and that if the amount of change were increased, for instance, by prolonging the period of observation, the predictor would have a better chance of being associated with change over time.

The study is limited by including only subjects with normal cognition and HAD, excluding individuals with mild or intermediate neuropsychological deficits, thus limiting the generalizability of the results.[7] An additional limitation of interpreting the results of the study is the absence of comparable and adequate neuropsychological norms for the entire subject group, particularly the norms used for the older subjects in which data for comparable education levels were lacking. Thus, the results of this study should be taken in the context that various norms for the subject groups may place limitations on the comparable standard scores and diagnoses.

HIV DNA has been studied by other investigators[11] to assess HIV-1 disease progression and has been found to predict progression to AIDS. Rouzioux et al.[11] reported on a cohort of individuals who were not on antiretroviral treatment initially but subsequently were put on therapy; and demonstrated that HIV DNA was a marker for progression to AIDS, independent of plasma HIV-1 RNA levels.[11] In our previous study, to assess the association of HIV DNA with HAD, we used the AAN diagnostic criteria for HAD, which are based on combined functional impairments and neuropsychological deficits.[1,8,12,25] The HIV-1-associated cognitive deficits now observed in developed countries may be less severe and their trajectories more varied than the dementia label implies. Nevertheless, even in an era where viremia in developed countries is declining among HIV-1-infected individuals, HAD and milder neurocognitive diagnoses clearly carry clinically relevant functional implications.

In the current study, we looked specifically at neuropsychological deficits for associations with HIV DNA in an attempt to identify focal deficits that might be affected by HIV DNA. Because we believe that HIV DNA could potentially co-vary and affect neuropsychological deficits over time, future studies should focus on: increasing the amount of explainable temporal variation by analyzing neuropsychological deficits over a longer duration in order to assess the predictive value of HIV DNA on neuropsychological deficits; sampling older individuals whose rate of change over a given period is likely to be greater; and including subjects with intermediate neuropsychological deficits.

In conclusion, the results of this study suggest that the neuropsychological deficits associated with HIV DNA levels may be global in nature. Any forthcoming studies to assess the association between HIV DNA and subsequent neuropsychological deficits should require periods of observation in excess of 2 years to address the predictive value of HIV DNA. It is possible that the lack of association of baseline HIV DNA levels with subsequent neuropsychological deficits may suggest that HIV DNA and neuropsychological deficits co-vary over time. Similar to the scenario where plasma HIV-1 RNA levels fluctuate with nonadherence of HAART, HIV DNA copies in monocytes/macrophages may also change through some as-of-yet unidentified influence. Thus, if HIV DNA influences neuropsychological deficits, resulting in the two entities co-varying over time, this fact may need to be taken into consideration in developing future treatment or preventative strategies.

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