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Effect of Aging on Neurocognitive Function by Stage of HIV Infection: Evidence from the Multi-Center AIDS Cohort Study

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Summary

Background—The demography of the HIV epidemic in the United States has shifted toward older age. The objective of this study was to determine the relationship between the processes of aging and HIV infection on neurocognitive impairment.

Methods—We examined the impact of aging, HIV infection (by disease stage), and their interaction across five neurocognitive domains: information processing speed, executive function, episodic memory, working memory, and motor function. Longitudinal data from the Multi-Center AIDS Cohort Study were analyzed to address this question utilizing control for duration of

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[Study descriptor: "MACS HIV, Aging and Cognition Study"]

Declaration of Interests

Dr. Miller is the author of the CalCAP Reaction Time program used in this study. Funding for this study was provided by the NIH. Otherwise, we declare that we have no conflicts of interest.

Contributors Section

Dr. Miller was involved in the study design, data collection, data analysis, data interpretation, and writing of the manuscript; Dr. Cox in the study design, data analysis, data interpretation, and writing of the manuscript; Ms. Reynolds in the data analysis, data interpretation, and preparation of the manuscript figure; Dr. Becker in the study design, data collection, data interpretation, and writing of the manuscript; Dr. Martin in data interpretation and writing of the manuscript; Dr. Selnes in the study design and data collection; Dr. Ostrow in the study design, data interpretation and writing of the manuscript; and Dr. Sacktor in data collection, data interpretation and writing of the manuscript.

serostatus (in a sub-analysis) as well as controls for other factors affecting cognition Analyses were by linear mixed models for longitudinal data.

Findings—There was a total of 5,086 participants (47,886 visits) in the analytic sample (2,278 were HIV-seropositive participants contributing 20,477 visits; 2,808 were HIV-seronegative control participants contributing 27,409 visits). Direct negative effects of HIV disease progression and aging were observed on all neurocognitive domains. Deleterious interaction effects were also observed in the domains of episodic memory and motor function.

Interpretation—Evidence for a greater than expected impact of aging was found on episodic memory ($p=.03$) and motor function ($p=.02$) with advanced stages of HIV infection. This suggests that these two domains are most susceptible to the progression of neurocognitive impairment due to aging amongst the HIV infected. This deficit pattern suggests differential damage to the hippocampus and basal ganglia, specifically nigrostriatal pathways. Older people with HIV infection should be targeted for regular screening for HIV-associated neurocognitive disorder, particularly with tests referable to the episodic memory and motor domains.

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Introduction

Until the advent of effective antiretroviral therapy (ART) in the mid-1990s, the prevalence of older adults living with HIV infection was low. By 2010, however, older adults (> age 50) crossed the 50% threshold of AIDS cases in San Francisco, which began a trend expected to become nationwide in 2020. Older age continues to be predictive of excess mortality today in the era of effective ART – despite suggestions in the literature that increasing age might be associated with higher antiretroviral (ARV) adherence¹ and despite adjustment for “natural aging”, which accounts for more than 50% of mortality in those 45.² The prevalence of HIV-associated neurocognitive disorders (HAND) appears to have increased as well, primarily as a function of longer survival times and aging in the era of effective ART, although there is also an increasing number of newly infected older adults.³ Studies of neurocognitive dysfunction among older individuals with HIV have increased in number in the past 15 years, but results have been inconsistent. Neurocognitive dysfunction and HIV-associated neurocognitive disorders in older individuals with HIV have been focused upon as high priorities in the field, and thus systematic attempts to identify and resolve the sources of these inconsistencies are needed.

A substantial body of evidence shows that older age is associated with an increased likelihood of HIV-associated neurocognitive disorders, particularly of HIV-associated dementia and, less so, of mild neurocognitive disorder and HIV-associated neurocognitive impairment taken generally (across systemic HIV disease stages).^{4,5} During the transitional period to effective ART, Hardy et al.⁶ reported on a sample of 257 men in which older HIV infected persons (mean= 44.5 years) performed worse than younger persons (M=31.5 years) on a number of neuropsychological (NP) tests. As expected, those in the late symptomatic stage/AIDS performed worse than those at earlier stages. Subsequently, Hinkin et al.⁷ reported an investigation of the interaction between age [< 40 , 40-49, 50] and HIV disease

category [HIV–, HIV+ (non-AIDS), and HIV+ (AIDS)] and demonstrated that age acted as a significant risk factor for HIV-associated NCI in late-stage systemic disease. Like Hardy et al.⁶, those 50 or older who had progressed to AIDS had a greater rate of NCI than those in other groups. Subsequently, it was reported that HIV-associated NCI was not consistently worse with age across domains and that there remained a large inter-individual variation in NP performance among older HIV-infected persons.⁸ Regarding the large inter-individual variation found in older persons, longer periods of follow-up and greater use of control variables for NP performance, particularly for medical co-morbidities, depressed mood, and alcohol/substance use, may improve the consistency of results in this area of research. Another influence of concern that has been noted in the area but not generally assessed as a specific type of control is the duration of HIV infection – as opposed to the effect of aging itself.⁹

In summary, limitations of the work published so far include the truncation of the oldest age range and the incomplete use of controls for other possible influences on neurocognitive function beyond education, ethnicity, and stage of HIV disease. The need to control for additional factors, such as medical comorbidities common in the general population that affect cognition (e.g., diabetes, hypertension, coronary artery disease, cerebrovascular disease, thyroid disease), has been increasingly acknowledged. Furthermore, controls for depressed mood, use of alcohol, psychoactive substances, or psychotropic drugs, history of hepatitis C virus infection, pain, and fatigue also need to be considered routinely. Thus, we aimed to examine the hypothesis that aging interacts with the effect of HIV infection on neurocognitive impairment and simultaneously to address the limitations of published work by using the Multicenter AIDS Cohort Study (MACS) dataset, which has long-term longitudinal data on participants examined semi-annually over many years, allowing the employment of a number of selected controls of importance for other effects on neurocognitive functioning.

Methods

Study Design

The MACS is an ongoing, prospective cohort study of the natural and treated history of HIV infection among men who have sex with men in the United States. Men were enrolled at four study sites: Baltimore, Maryland/Washington, DC; Chicago, Illinois; Los Angeles, California; and Pittsburgh, Pennsylvania. A total of 6,972 men have been enrolled in the study since its inception in April, 1984 (4,954 from 4/2/84–4/8/85; 668 from 4/1/87–3/16/95, and 1,350 from 10/4/01–8/20/03). Participants return every six months for an interview, physical examination, and collection of blood for laboratory testing. The assessments cover physical health, medical treatments, and sexual and stimulant use behaviors. More information about the MACS study, including data collection instruments, can be found at <http://www.statepi.jhsph.edu/macs/mac.html>.

Participants/Study Population

In the original MACS cohort from the mid-1980s, eligibility criteria were limited to: homosexual or bisexual men of at least 18 years of age who were able and willing to give

informed consent and had no active malignancy or immunosuppression by virtue of a medical condition or prescribed therapy. For the 2001–2003 cohort, date of first use of ART must have been documented along with a documented plasma HIV load and a CD4 cell count within six months prior to initiation. This study received institutional review board approval from Northwestern University (Evanston, IL), University of California, Los Angeles (Los Angeles, CA), the University of Pittsburgh (Pittsburgh, PA), and the Johns Hopkins Bloomberg School of Public Health (Baltimore, MD). Participants signed a written informed consent form in the English language. Strict privacy and limited access to individual identifiers is assured through a Certificate of Confidentiality issued by the National Institutes of Health.

For the purposes of this study of the MACS cohort, the following exclusion criteria were used: history of CNS opportunistic infections or tumors or treatment with chemotherapy; presence of non-HIV-associated neurological disease; history of major psychiatric disorder (e.g., psychosis); current, severe alcohol or substance use disorder; collagen vascular disease; thyroid disease; chronic obstructive pulmonary disease; emphysema; congestive heart failure; angina pectoris; myocardial infarction within the prior six months; hepatic failure; renal failure; daily use of systemic steroids (catabolic or anabolic), narcotic/opioid analgesics, or immunostimulant/immunosuppressive medications; and participation in blinded trials of non-FDA-approved ARVs. Those with a history of IV drug use were relatively few in number and were not excluded.

Procedures

Independent variables follow: Age was determined by proof of date of birth. HIV clinical disease stage was used as an index of disease progression and determined by the revised CDC staging system for HIV infection in which there are three stages: (A) asymptomatic, (B) early symptomatic, and (C) late symptomatic/clinically defined AIDS – adding “0” to code for HIV-seronegative participants at each visit. An algorithm was specifically developed for use on the MACS database for this purpose.

Dependent variables follow: NP testing was administered by the standardized MAC NP test protocol. NP outcomes were captured by five domain scores. (1) Information Processing Speed was comprised of the Symbol-Digit Substitution Test, measuring visuoperceptual and motor processes, and the Simple and Choice Reaction Time from the CalCAP. (2) Episodic Memory was comprised of verbal and visual memory using the summed recall across trials 1–5 on the Rey Auditory Verbal Learning Test (RAVLT), delayed recall on the RAVLT, and the copy and delayed recall measures on the Rey-Osterreith Complex Figure. (3) Executive Function was comprised of the Trail Making Test (TMT) Part B and the interference trial from the Stroop. (4) Measurement of motor function was comprised of the Grooved Pegboard Task, yielding time to place small metal pegs with keys along one side into slotted holes as quickly as possible with the non-dominant hand. (5) Working Memory was measured with a one-back procedure from the foregoing CalCAP reaction time test.

Control variables were utilized in line with our effort to optimize control for extraneous sources of variance in NP outcomes in this study, we used the following variables: educational level:¹⁰ < 8th grade, 9–11th grade, HS graduation, some college or degree, and

some graduate school or degree]; race and ethnicity:¹¹ White, non-Hispanic vs. all other categories; and income [concurrent annual income category at each visit: < \$20,000, \$20,000-40,000, and > \$40,000] (the foregoing by self-report); time since seroconversion: months at each visit (in a sub-sample analysis) by actual date of seroconversion (or date of study entry as a proxy), coding HIV-seronegative participants as “0”; ART era: before and after 1/1/96 (adopted as the beginning of the era of effective ART); medical co-morbidities [diabetes diagnosis:¹² defined by self-report on at least 2 consecutive visits or by a fasting glucose level above 125 mg/dl on at least two consecutive visits (with a consecutive visit defined as the next available visit within two years); hypertension diagnosis:¹³ defined by self-report on at least two consecutive visits or blood pressure above 140 mm Hg systolic and 90 mm Hg diastolic on at least two consecutive visits; and hepatitis exposure history: for types B (metabolic effects) and C (metabolic effects and direct CNS effects)¹⁴ [by HBV surface antigen status positive lifetime and HCV antibody status positive lifetime]; global nutritional status¹⁵ defined as total body weight [relative change from the prior visit (%)] and body mass index (BMI) [underweight (<18.5), normal (18.5 - 24.9), overweight (25.0-29.9), and obese (>30.0)] (obtained by weighing the participant); depressed mood level per the Center for Epidemiology-Depression (CES-D) Scale¹⁶; fatigue level:¹⁷ self-reported fatigue over the prior two weeks; and pain:¹⁸ self-report by number of types (headache, joint, abdominal, muscle, and urinary) present [0= 0-1, 1= 2-3, and 2= 4-5 types present]. Alcohol and psychoactive substances requiring control were reduced to alcohol use:¹⁹ categorical variable based on frequency of use by a MACS-derived algorithm; cigarette smoking:²⁰ MACS-derived algorithm generating total pack-years; and cannabis²¹ and nitrite inhalant (“popper”) use frequencies²² (none vs. any use) [all by self-report]. Psychotropic medication use²³ was controlled by use at assessment derived from self-report based upon relevant drugs listed across psychotropic categories. HIV-specific control variables (e.g., CD4 nadir, plasma HIV load, ARV adherence and CNS-penetration scores) could not be employed because these variables cannot be properly defined for HIV-seronegative participants. Insufficient data were available to allow control for cholesterol and triglyceride levels, renal and hepatic function, and laboratory measures of general nutritional status.

Statistical Analysis

Analyses were conducted using visit-based (rather than participant-based) sets of linear mixed models for longitudinal data.²⁴ Age was employed as a continuous measure, and HIV disease stage was characterized as an ordinal variable at four levels as aforementioned. Each model included a random participant effect to account for repeated measurements on the same participant. Analysis of residuals was used to check the required assumptions of normally distributed errors with constant variance; if necessary, outcome variables were log transformed to stabilize the variance or produce a more normal error distribution. NP outcome measures were not adjusted for age or ethnicity. NP outcomes were evaluated using the age and HIV disease stage variables to examine main effects and by the interaction of these two variables to examine evidence for the hypothesized, deleterious synergistic effect. All qualifying visits were included from the beginning of NP testing in the MACS. We analyzed four separate sets of models: Model 1 was the “Full Model on the Entire Sample” with independent variable predictors for age, HIV disease stage, and an age × HIV disease

stage interaction term as well as all control variables. In Model 2 we used a “Reduced Model on the Entire Sample”, which eliminated all non-significant control variable predictors from Model 1 – as a confirmatory model. Model 3 added a single control to the set – “Full Model Adding Time Since Seroconversion” – on a sub-sample with data available to estimate this parameter. Model 4 was the “Full Model Without Time Since Seroconversion on the Seroconversion Sub-Sample”, which was conducted as another confirmatory model (like Model 2) to identify any possible factors in the outcome that might have been related to the sub-sample composition.

Role of the Funding Source

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Results

The sample was comprised of a total N = 5,086 participants, of whom 2,278 were HIV-seropositive and 2,808 were HIV-seronegative. The total number of visits analyzed was 47,886, of which 20,477 were contributed by HIV-seropositive individuals and 27,409 were contributed by HIV-seronegative individuals. The distribution of age at baseline and other sample characteristics are shown in Table 1. On initial recruitment, slightly over 10% of HIV-seronegative participants were ≥ 50 years of age, and 5% of HIV-seropositive persons recruited were ≥ 50 years old over the same time period. However, these analyses employed age as a continuous variable with time-varying entries by study visit calendar date. For the purposes of characterizing the cohort, we designated those ≥ 50 years of age as “older” – as per the CDC. For the HIV-seropositive participants, those ≥ 50 were in the mid-50s with very few truly elderly participants over 65, as would be expected by the demography of older age in HIV infection in the USA. There were more participants with an educational level of high school or less in the HIV-seropositive sub-sample and, commensurately, a higher frequency of those with college or greater education in the HIV-seronegative sub-sample, particularly the older HIV-seronegative group. There were also more minority participants in the HIV-seropositive sub-sample, as expected from national demographics. There were no significant differences by age category in HIV disease stage at baseline, although there were somewhat more patients with Stage C/AIDS in the older HIV-seropositive group. There was also a somewhat higher CD4 cell nadir and concurrent CD4 cell count in the older HIV-seropositive sub-group, although the sizes of these differences were not likely to be clinically significant. The frequency of detectable plasma viral load was highly comparable between age groups.

Baseline NP scores are shown by domain in Table 2. Neuropsychological domain scores were generally lower (but not always significantly so) in HIV-seropositive participants than

in HIV-seronegative participants (table 2). However, when HIV disease stage was accounted for, lower performance on all five neuropsychological domain scores was significantly associated with advanced disease stage (table 2).

The Full Model/Full Sample Model 1 results in Table 3 show that older age was significantly associated with lower performance in all five NP outcome domains. Negative HIV disease stage effects shown in the baseline differences were maintained in the full model/full sample results. A significant age $\times$ HIV disease stage interaction was noted in information processing speed, executive functioning and working memory. A marginally significant interaction was noted for motor function. The Reduced Model/Full Sample results (Model 2; data not shown) eliminating non-significant control variables recapitulated the results of the full models, including the impact of controls, which were in the expected directions. Each control was significant in the analyses, with the exception of cannabis use and lifetime history of HBV infection.

The Full Model with the Sub-Sample Adding Time since Seroconversion (Model 3) analysis had an N=4,234 with N= 1,638 HIV-seropositive participants, of which 1,120 were seroprevalent at study baseline, and 518 seroconverted while enrolled in the study; there were 2,596 HIV-seronegative participants. For seroprevalent participants, date of study baseline was conservatively taken as time since seroconversion. Time since seroconversion was statistically significant for three domains – information processing speed, episodic memory, and executive function – and all relationships were positive in direction. Negative aging main effects from the full model were maintained. The impact of HIV disease stage on NP performance was greater, and in the expected negative direction in this model. Age $\times$ HIV disease stage interactions were eliminated for information processing speed and executive function but were significant and negative for motor function and episodic memory (which had changed in direction from positive to negative) (see Figure). While a positive interaction was observed for working memory, the directions of the changes observed over increased progression from HIV disease stages A to C were in the negative pattern consistently – as predicted. Analysis of this sub-sample using the Full Model (i.e., Model 4, without including the “time since seroconversion” control) showed that the results (data not shown) predominantly reverted to those of the Full Model/Full Sample (Model 1), which, as anticipated, were once again contrary to prediction in the directions of the interactions.

Discussion

As expected, a primary effect of aging was observed across models consistently demonstrating decreased performance with older age on all five cognitive domains. Likewise, a primary effect of systemic HIV disease severity (HIV disease stage) was observed consistently on all domains, with the lowest performance predominantly in the late symptomatic stage/AIDS. A number of controls were significant in the expected directions (particularly ethnicity, education, income, antiretroviral therapy era, diabetes, hypertension, depressed mood level, pain, fatigue, body mass index, total body weight, and history of HCV infection). In the Full Model/Full Sample (Model 1) analysis, interactions of age with HIV disease stage were present in all domains but episodic memory. The direction indicated

that older HIV-seropositive individuals performed better than their younger counterparts, with respect to older and younger HIV-seronegative controls, except for the motor domain; similar positive interactions of age with HIV disease stage have been reported previously using models in which duration of HIV serostatus was not able to be controlled.⁹

The addition of a control for time since seroconversion to this model in a sub-sample where the data were available in the MACS cohort demonstrated better performance with longer duration of HIV infection in information processing speed, episodic memory, and executive function. Such an effect might be driven by variance in the lower end of the range of this time period related to a more effective suppression of viral load on ARV regimens and greater immune reconstitution. In this analytic model, the former interactions of aging with HIV disease stage suggesting better performance in older HIV-seropositive participants were either eliminated or shifted direction, with the exception of motor function still showing a lower performance and working memory (showing positive but decreasing associations toward late stage disease). With serostatus duration controlled, the results yielded the anticipated aging interaction effect in which the lowest performance occurred with older age and later disease stage in the specific domains of motor function and episodic memory. One limitation of the study is that participants undergoing NP testing could have experienced intercurrent medical events impacting their cognitive function between visits; however, our analytic model would have controlled for the impact of many of these events and such events were recorded and uncommon. Overall, the results clearly demonstrate an impact of controlling for the specific factor of time since infection separately from age. Chronological age represents not only simply time since birth but also the onset of a specific physiological process of “aging” that has a debilitating cognitive impact beginning at about age 50 in HIV infection.

This evidence documenting an increased impact of aging by HIV disease stage on motor function and episodic memory performance has neuroanatomical referents. For motor function, the neuroanatomical referent is the basal ganglia, which has been documented to be impacted early in HIV brain infection. Of note, Parkinsonism has been observed in HIV infection and related to lowered dopamine in the CSF and brain tissue of HIV infected patients.²⁵ For episodic memory, the neuroanatomical referent is the hippocampus, wherein dysfunction and atrophy have been noted to occur independently with both aging²⁶ and HIV infection²⁷ as well as in a deleterious interaction between aging and HIV infection.²⁸ Several studies have documented these regions to be of particular concern for damage in the setting of older persons with HIV infection. A critical review reported that HIV infection has been associated with greater than age-related brain atrophy in the basal ganglia and hippocampus.²⁹ This has been confirmed by a recent study of brain morphometry in an older HIV infected cohort.³⁰ The review²⁹ indicated that fMRI studies reported evidence for greater effects than those expected by aging alone in HIV infected persons by brain region, though these effects varied when other neuroimaging techniques were employed. One neuroimaging study³¹ used a longitudinal analysis and revealed evidence for a greater-than-expected impact of aging in selected brain regions over a 6-month to 8-year interval within a cohort of HIV-infected individuals who were in good overall health and did not have clinical evidence for dementia. Another relevant study³² showed age-dependent changes in brain activation in response to tasks of increasing attentional load that differed amongst three

groups, with HIV and aging acting synergistically (i.e., interactively) to exacerbate brain activation abnormalities in different brain regions. These results suggest that a neurologically adaptive mechanism in the attention network may be operating to compensate for decreased neural efficiency. Along a separate line, the protective role of cognitive reserve in older HIV infected patients also deserves further study.³³

In summary, our results demonstrate evidence for region-specific increases of deleterious aging effects with worsening systemic stage of HIV infection. We employed a well-controlled, longitudinal design of an HIV-seropositive group versus an HIV-seronegative control group. These results are buttressed by other recent studies examining brain tissue changes using neuroimaging techniques. We suggest that our NP results provide evidence that there is a differential worsening of the deleterious impact of aging on neurocognitive function when there is a higher level of systemic HIV disease progression – specifically on the neurocognitive domains of episodic memory and motor performance. That is, the magnitude of the impairment in these domains is greater than the sum of the independent, negative effects of age and HIV disease stage.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1. Plots of Adjusted Domain Scores and Fitted Regression Lines from the Multi-Variable Models for the Relationships Observed between Age on Episodic Memory and Motor Function According to Late CDC Disease Stage/AIDS Versus HIV Seronegative Status

This figure shows the adjusted domain scores together with the fitted regression lines for the effect of age in late stage HIV disease (AIDS) versus those with HIV-seronegative status from the multi-variable models for the Full Model/Full Sample Analysis and for the Full Model /Sub-Sample Analysis Adding Time since Seroconversion into the model. The AIDS and HIV-seronegative sub-samples were selected to display the results from the opposite poles of the HIV disease stage variable used here on the domains of episodic memory and

motor function. In the model adding time since seroconversion, participants with AIDS (solid line) performed more poorly in older age than the HIV-seronegative control participants (broken line) in both domains. The lack of any pattern in the residual error scattergrams of both groups (aside from the downward trends consistent with the regression on age) supports the validity of the analytic models employed.

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Table 1

Sociodemographic and Clinical Characteristics of the Sample

		HIV+ 50	HIV+ <50	HIV- 50	HIV- < 50	Overall	p Value
Sample Size at Baseline		115	2163	267	2541		
Sample Size at Last Visit		471	1962	890	1763		
Cohort Sub-Sample Size at Baseline	1984	47/115 (41%)	1376/2163 (64%)	209/267 (78%)	1856/2541 (73%)	3488/5086 (69%)	<0001
	1987	15/115 (13%)	250/2163 (12%)	11/267 (4%)	157/2541 (6%)	433/5086 (9%)	
	2001	53/115 (46%)	537/2163 (25%)	47/267 (18%)	528/2541 (21%)	1165/5086 (23%)	
N of Visits		3125	17352	6832	20577	5086	
Cohort Sub-Sample by Visits	1984	2223/3125 (71%)	11459/17352 (66%)	6148/6832 (90%)	16283/20577 (79%)	36113/47886 (75%)	<0001
	1987	315/3125 (10%)	2142/17352 (12%)	215/6832 (3%)	1160/20577 (6%)	3832/47886 (8%)	
	2001	587/3125 (19%)	3751/17352 (22%)	469/6832 (7%)	3134/20577 (15%)	7941/47886 (17%)	
Baseline Age		54.0 (4.1)	35.3 (6.3)	55.3 (5.2)	36.2 (7.0)	37.2 (8.3)	<0001
Age by Visits		54.5 (4.1)	38.6 (6.2)	56.4 (5.7)	39.1 (6.5)	42.4 (9.2)	<0001
Baseline Education	less than HS	6/115 (5%)	133/2163 (6%)	11/267 (4%)	113/2541 (4%)	263/5086 (5%)	<0001
	HS	18/115 (16%)	327/2163 (15%)	29/267 (11%)	284/2541 (11%)	658/5086 (13%)	
	Some College	35/115 (30%)	714/2163 (33%)	50/267 (19%)	665/2541 (26%)	1464/5086 (29%)	
	College degree	13/115 (11%)	464/2163 (21%)	31/267 (12%)	641/2541 (25%)	1149/5086 (23%)	
	College plus	42/115 (37%)	521/2163 (24%)	146/267 (55%)	825/2541 (32%)	1534/5086 (30%)	
	Missing	1/115 (1%)	4/2163 (0%)	–	13/2541 (1%)	18/5086 (0.35%)	
Race and Ethnicity	White, non- Hispanic	75/115 (65%)	1456/2163 (67%)	223/267 (84%)	1918/2541 (75%)	3672/5086 (72%)	<0001
	other	40/115 (35%)	707/2163 (33%)	44/267 (16%)	621/2541 (24%)	1412/5086 (28%)	
	Missing	–	–	–	2/2541 (0.08%)	2/5086 (0.04%)	
Baseline Annual Income Level	<20,000	31/115 (27%)	477/2163 (22%)	39/267 (15%)	488/2541 (19%)	1035/5086 (20%)	<0001
	20,000–39,999	21/115 (18%)	276/2163 (13%)	68/267 (25%)	488/2541 (19%)	853/5086 (17%)	
	40,000	27/115 (23%)	201/2163 (9%)	98/267 (37%)	463/2541 (18%)	789/5086 (16%)	
	Refused to answer	3/115 (3%)	36/2163 (2%)	10/267 (4%)	52/2541 (2%)	101/5086 (2%)	
	Missing	33/115 (29%)	1173/2163 (54%)	52/267 (19%)	1050/2541 (41%)	2308/5086 (45%)	
Seropositive Months from Enrollment		23.3 (30.8)	26.1 (28.4)			25.9 (28.5)	0.027
Months from Seroconversion		65.3 (68.4)	33.4 (29.0)			35.3 (33.2)	0.012

		HIV+ 50	HIV+ <50	HIV- 50	HIV- <50	Overall	p Value
Months From Known or Imputed Seroconversion		71.1 (44.8)	50.4 (30.3)			51.2 (31.1)	<.0001
Antiretroviral Therapy Era by Visits	Before 01/01/96	641/3125 (21%)	9800/17352 (56%)	2231/6832 (33%)	14062/20577 (68%)	26734/47886 (56%)	<.0001
	01/01/96-present	2484/3125 (79%)	7552/17352 (44%)	4601/6832 (67%)	6515/20577 (32%)	21152/47886 (44%)	
HIV Clinical Disease Stage	A (HIV+ asymptomatic)	44/115 (38%)	1051/2163 (49%)			1095/2278 (48%)	0.031
	B (HIV+ symptomatic)	61/115 (53%)	1011/2163 (47%)			1072/2278 (47%)	
	C (AIDS)	10/115 (9%)	101/2163 (5%)			111/2278 (5%)	
CD4 Cell Nadir ¹ by Visits		435.2 (241.7)	404.2 (237.1)			409.0 (238.1)	<.0001
CD4 Cell Count ¹ by Visits		530.2 (283.4)	492.1 (286.5)			497.9 (286.3)	<.0001
Plasma HIV RNA by Visits	No	1587/3125 (51%)	6892/17352 (40%)			8479/20477 (41%)	<.0001
	Yes	1365/3125 (44%)	7623/17352 (44%)			8988/20477 (44%)	
	Missing	173/3125 (6%)	2837/17352 (16%)			3010/20477 (15%)	
Diagnosis of Diabetes by Visits	No	2904/3125 (93%)	16787/17352 (97%)	6590/6832 (96%)	20014/20577 (97%)	46295/47886 (97%)	<.0001
	Yes	179/3125 (6%)	171/17352 (1%)	169/6832 (2%)	135/20577 (1%)	654/47886 (1%)	
	Missing	42/3125 (1%)	394/17352 (2%)	73/6832 (1%)	428/20577 (2%)	937/47886 (2%)	
Diagnosis of Hypertension by Visits	No	1453/3125 (46%)	10998/17352 (63%)	3135/6832 (46%)	12790/20577 (62%)	28376/47886 (59%)	<.0001
	Yes	1614/3125 (52%)	4083/17352 (24%)	3587/6832 (53%)	5523/20577 (27%)	14807/47886 (31%)	
	Missing	58/3125 (2%)	2271/17352 (13%)	110/6832 (2%)	2264/20577 (11%)	4703/47886 (10%)	
Psychotropic Medication Use by Visits	No	2572/3125 (82%)	15190/17352 (88%)	5809/6832 (85%)	18115/20577 (88%)	41686/47886 (87%)	<.0001
	Yes	553/3125 (18%)	2161/17352 (12%)	1023/6832 (15%)	2462/20577 (12%)	6199/47886 (13%)	
	Missing	–	1/17352 (0.01%)	–	–	1/47886 (0.002%)	
History of HBV Infection by Visits	No	2806/3125 (90%)	15973/17352 (92%)	6575/6832 (96%)	19860/20577 (97%)	45214/47886 (94%)	<.0001
	Yes	319/3125 (10%)	1379/17352 (8%)	257/6832 (4%)	717/20577 (3%)	2672/47886 (6%)	
History of HCV Infection by Visits	No	2681/3125 (86%)	15671/17352 (90%)	6482/6832 (95%)	19853/20577 (96%)	44687/47886 (93%)	<.0001
	Yes	444/3125 (14%)	1681/17352 (10%)	350/6832 (5%)	724/20577 (4%)	3199/47886 (7%)	
Pain (present/absent) by Visits	No	2404/3125 (77%)	14889/17352 (86%)	5542/6832 (81%)	18725/20577 (91%)	41560/47886 (87%)	<.0001
	Yes	721/3125 (23%)	2463/17352 (14%)	1290/6832 (19%)	1852/20577 (9%)	6326/47886 (13%)	
Fatigue (present/absent) by Visits	No	2715/3125 (87%)	15323/17352 (88%)	6451/6832 (94%)	19722/20577 (96%)	44211/47886 (92%)	<.0001
	Yes	399/3125 (13%)	2001/17352 (12%)	371/6832 (5%)	843/20577 (4%)	3614/47886 (8%)	

		HIV+ 50	HIV+ <50	HIV- 50	HIV- <50	Overall	p Value
	Missing	11/3125 (0.35%)	28/17352 (0.16%)	10/6832 (0.15%)	12/20577 (0.06%)	61/47886 (0.13%)	
Alcohol Use Frequency by Visits	None or occasional	1090/3125 (35%)	5385/17352 (31%)	1881/6832 (28%)	4876/20577 (24%)	13232/47886 (28%)	<.0001
	Used	2005/3125 (64%)	11893/17352 (69%)	4899/6832 (72%)	15627/20577 (76%)	34424/47886 (72%)	
	Missing	30/3125 (1%)	74/17352 (0.43%)	52/6832 (1%)	74/20577 (0.36%)	230/47886 (0.48%)	
Cannabis Use Frequency by Visits	None or occasional	2383/3125 (76%)	12291/17352 (71%)	5928/6832 (87%)	16365/20577 (80%)	36967/47886 (77%)	<.0001
	Used	670/3125 (21%)	4605/17352 (27%)	834/6832 (12%)	3932/20577 (19%)	10041/47886 (21%)	
	Missing	72/3125 (2%)	456/17352 (3%)	70/6832 (1%)	280/20577 (1%)	878/47886 (2%)	
Nirtrite Inhalant Use Frequency by Visits	None or occasional	2443/3125 (78%)	13890/17352 (80%)	5846/6832 (86%)	17403/20577 (85%)	39582/47886 (83%)	<.0001
	Used	604/3125 (19%)	2906/17352 (17%)	902/6832 (13%)	2720/20577 (13%)	7132/47886 (15%)	
	Missing	78/3125 (2%)	556/17352 (3%)	84/6832 (1%)	454/20577 (2%)	1172/47886 (2%)	

Categorical variables are presented as n or n (%); continuous variables are presented as mean (SD). Percentages are based on n at baseline or number of visits, as indicated. We used χ^2 analysis to compare categorical variables, and ANOVA tests to compare continuous variables.

/ CD4 cell counts are expressed as cells per μL .

Table 2**Baseline Status of Cognitive Function by Neurocognitive Domain**

	Information Processing Speed	Episodic Memory	Executive Function	Motor Function	Working Memory
Overall	47.4 (9.2)	47.3 (9.2)	47.7 (10.3)	46.5 (12.0)	48.3 (10.6)
HIV-Seronegative	47.9 (9.1)	47.4 (9.3)	48.4 (10.2)	46.8 (11.9)	48.3 (10.6)
HIV-Seropositive	46.8 (9.4)	47.1 (9.1)	46.9 (10.5)	46.4 (12.0)	48.4 (10.5)
Asymptomatic	48.5 (9.4)	47.9 (9.0)	47.7 (10.2)	48.0 (11.1)	50.0 (11.0)
Early Symptomatic	46.0 (9.1)	46.5 (9.1)	46.5 (10.6)	45.4 (12.4)	47.7 (10.2)
Late Symptomatic/AIDS	42.4 (9.0)	45.5 (8.8)	43.3 (10.6)	40.9 (13.7)	44.3 (10.2)
HIV-Seropositive vs. HIV-Seronegative	.0005 <i>f</i>	.42	<.0001	.62	.92
HIV-Seropositive by Clinical Disease Stage	<.0001	.04	.0002	.0001	.02

Data are neurocognitive domains scores adjusted to T scores (with mean of 50 and SD of 10). We also shifted the valence such that higher scores always reflected higher performance. Tests for significance between HIV-seropositive vs HIV-seronegative subsamples and tests among the HIV seropositive subsamples by clinical disease stage (including the HIV seronegative subsample) were done with Kruskal-Wallis ANOVAs.

Adjusted domain score (standard deviation)

f
p value

Table 3

Linear model analyses for full sample and full model sample plus time since seroconversion on a subsample

Analytic Models	Predictors (below)	Full Model/Full Sample					Full Model with Sub-Sample Adding "Time Since Seroconversion" to the Model				
		Cognitive Domain Dependent Variables					Cognitive Domain Dependent Variables				
Independent Variables:		Information Processing Speed	Episodic Memory	Executive Function	Motor Function	Working Memory	Information Processing Speed	Episodic Memory	Executive Function	Motor Function	Working Memory
Age		-0.20 (0.01) (-0.23,-0.18) p<.0001	-0.18 (0.02) (-0.21,-0.15) p<.0001	-0.16 (0.01) (-0.19,-0.14) p<.0001	-0.40 (0.02) (-0.44,-0.35) p<.0001	-0.13 (0.02) (-0.17,-0.08) p<.0001	-0.20 (0.01) (-0.23,-0.18) p<.0001	-0.17 (0.02) (-0.20,-0.14) p<.0001	-0.15 (0.01) (-0.18,-0.13) p<.0001	-0.40 (0.02) (-0.44,-0.35) p<.0001	-0.13 (0.02) (-0.17,-0.08) p<.0001
HIV Clinical Disease Stage ²											
AIDS		-0.61 (0.37) (-1.34,0.13) p=0.10	-0.64 (0.45) (-1.51,0.24) p=0.15	-0.80 (0.39) (-1.57,-0.03) p=0.042	-3.40 (0.64) (-4.66,-2.14) p<.0001	-2.45 (0.62) (-3.66,-1.24) p<.0001	-1.39 (0.46) (-2.28,-0.49) p=0.002	-0.99 (0.55) (-2.07,0.09) p=0.07	-2.41 (0.47) (-3.33,-1.50) p<.0001	-3.46 (0.81) (-5.05,-1.88) p<.0001	-2.49 (0.76) (-3.98,-1.00) p=0.001
Early symptomatic		0.38 (0.23) (-0.06,0.82) p=0.09	0.35 (0.28) (-0.20,0.90) p=0.21	0.38 (0.24) (-0.09,0.85) p=0.12	0.35 (0.40) (-0.43,1.14) p=0.38	-0.85 (0.38) (-1.59,-0.11) p=0.025	0.22 (0.29) (-0.35,0.78) p=0.45	-0.01 (0.38) (-0.75,0.74) p=0.99	-0.42 (0.30) (-1.00,0.16) p=0.16	0.73 (0.56) (-0.36,1.82) p=0.19	-0.87 (0.50) (-1.86,0.11) p=0.08
Asymptomatic		0.43 (0.23) (-0.02,0.87) p=0.060	-0.05 (0.28) (-0.61,0.50) p=0.86	0.51 (0.24) (0.04,0.98) p=0.034	-0.02 (0.40) (-0.81,0.77) p=0.96	-0.98 (0.38) (-1.73,-0.24) p=0.010	0.24 (0.28) (-0.32,0.80) p=0.39	-0.52 (0.37) (-1.26,0.21) p=0.16	-0.21 (0.29) (-0.79,0.36) p=0.47	0.32 (0.55) (-0.75,1.39) p=0.56	-0.86 (0.50) (-1.84,0.12) p=0.09
Age × HIV Disease Stage Interactions:											
Age × AIDS		0.11 (0.04) (0.03,0.18) p=0.004	0.03 (0.05) (-0.06,0.13) p=0.51	0.18 (0.04) (0.10,0.25) p<.0001	-0.03 (0.07) (-0.17,0.12) p=0.70	0.002 (0.07) (-0.13,0.14) p=0.98	0.06 (0.04) (-0.03,0.15) p=0.17	-0.08 (0.06) (-0.20,0.03) p=0.13	-0.02 (0.05) (-0.11,0.07) p=0.63	-0.03 (0.08) (-0.20,0.13) p=0.70	0.05 (0.08) (-0.11,0.20) p=0.54
Age × Symptomatic		0.05 (0.02) (0.01,0.08) p=0.007	0.03 (0.02) (-0.01,0.08) p=0.14	0.17 (0.02) (0.14,0.20) p<.0001	-0.08 (0.03) (-0.14,-0.01) p=0.019	0.08 (0.03) (0.02,0.14) p=0.013	-0.02 (0.03) (-0.08,0.03) p=0.42	-0.06 (0.03) (-0.13,0.01) p=0.09	-0.03 (0.03) (-0.09,0.02) p=0.28	-0.07 (0.05) (-0.17,0.03) p=0.18	0.15 (0.05) (0.06,0.25) p=0.001
Age × Asymptomatic		0.07 (0.02) (0.04,0.10) p<.0001	0.05 (0.02) (0.01,0.10) p=0.018	0.17 (0.02) (0.14,0.20) p<.0001	-0.01 (0.03) (-0.08,0.05) p=0.73	0.12 (0.03) (0.06,0.18) p=0.0001	0.01 (0.03) (-0.04,0.06) p=0.70	0.001 (0.03) (-0.07,0.07) p=0.98	-0.05 (0.03) (-0.11,0.003) p=0.07	0.04 (0.05) (-0.06,0.14) p=0.47	0.20 (0.05) (0.10,0.29) p<.0001
Overall Test for Interaction Effect		<.0001	.13	<.0001	.052	.002	.10	.03	.28	.02	.0004
Time since Seroconversion (yrs)							0.11 (0.03) (0.05,0.16) p<.0001	0.14 (0.03) (0.08,0.21) p<.0001	0.30 (0.03) (0.24,0.35) p<.0001	0.01 (0.05) (-0.09,0.11) p=0.84	-0.02 (0.05) (-0.11,0.07) p=0.68
Control Variables:											
Race and Ethnicity ³		-4.27 (0.30) (-4.87,-3.68) p<.0001	-5.29 (0.36) (-6.00,-4.59) p<.0001	-6.75 (0.33) (-7.40,-6.10) p<.0001	-6.47 (0.51) (-7.46,-5.47) p<.0001	-2.17 (0.49) (-3.13,-1.22) p<.0001	-3.79 (0.36) (-4.51,-3.08) p<.0001	-4.26 (0.43) (-5.11,-3.42) p<.0001	-6.15 (0.39) (-6.91,-5.39) p<.0001	-5.71 (0.61) (-6.91,-4.50) p<.0001	-2.27 (0.60) (-3.45,-1.09) p=0.0002

Analytic Models	Full Model/Full Sample					Full Model with Sub-Sample Adding „Time Since Seroconversion” to the Model				
	Cognitive Domain Dependent Variables					Cognitive Domain Dependent Variables				
Predictors (below)	Information Processing Speed	Episodic Memory	Executive Function	Motor Function	Working Memory	Information Processing Speed	Episodic Memory	Executive Function	Motor Function	Working Memory
Education ⁴										
Some College Experience	4.16 (0.39) (3.39,4.92) p<.0001	4.06 (0.46) (3.16,4.95) p<.0001	5.19 (0.43) (4.36,6.03) p<.0001	3.15 (0.64) (1.90,4.41) p<.0001	0.54 (0.62) (-0.66,1.75) p=0.38	3.60 (0.46) (2.70,4.49) p<.0001	3.64 (0.54) (2.58,4.69) p<.0001	4.58 (0.49) (3.63,5.54) p<.0001	2.74 (0.76) (1.25,4.23) p=0.0003	1.13 (0.75) (-0.35,2.61) p=0.13
College Degree	5.21 (0.41) (4.40,6.03) p<.0001	5.69 (0.49) (4.72,6.65) p<.0001	6.15 (0.45) (5.27,7.04) p<.0001	4.06 (0.69) (2.71,5.41) p<.0001	1.04 (0.67) (-0.27,2.34) p=0.12	4.79 (0.47) (3.87,5.71) p<.0001	5.34 (0.55) (4.26,6.42) p<.0001	5.93 (0.50) (4.96,6.91) p<.0001	3.99 (0.78) (2.47,5.52) p<.0001	1.42 (0.77) (-0.09,2.94) p=0.06
Some Post-Graduate Experience or Degree	5.69 (0.40) (4.90,6.48) p<.0001	6.44 (0.49) (5.48,7.40) p<.0001	6.13 (0.44) (5.27,7.00) p<.0001	4.19 (0.69) (2.84,5.53) p<.0001	1.14 (0.66) (-0.16,2.45) p=0.09	5.54 (0.46) (4.65,6.44) p<.0001	6.18 (0.55) (5.10,7.26) p<.0001	6.19 (0.49) (5.24,7.14) p<.0001	3.68 (0.78) (2.15,5.21) p<.0001	1.57 (0.77) (0.06,3.09) p=0.042
Income (Annual) ⁵										
\$20,000 –\$40,000	0.32 (0.13) (0.07,0.58) p=0.014	0.50 (0.17) (0.17,0.83) p=0.003	0.48 (0.13) (0.22,0.74) p=0.0003	0.72 (0.25) (0.23,1.21) p=0.004	0.42 (0.23) (-0.02,0.87) p=0.06	0.25 (0.14) (-0.03,0.53) p=0.08	0.39 (0.18) (0.04,0.75) p=0.029	0.32 (0.15) (0.03,0.60) p=0.030	0.49 (0.27) (-0.04,1.02) p=0.07	0.40 (0.24) (-0.08,0.87) p=0.10
\$40,000	0.70 (0.15) (0.40,1.00) p<.0001	0.80 (0.20) (0.40,1.19) p<.0001	1.20 (0.16) (0.90,1.51) p<.0001	1.75 (0.29) (1.17,2.33) p<.0001	0.71 (0.27) (0.18,1.23) p=0.008	0.63 (0.16) (0.31,0.95) p<.0001	0.69 (0.21) (0.28,1.10) p=0.0009	1.08 (0.17) (0.75,1.41) p<.0001	1.56 (0.31) (0.95,2.17) p<.0001	0.60 (0.28) (0.06,1.15) p=0.031
ART Era (before versus after 1/1/96)	0.58 (0.12) (0.35,0.82) p<.0001	0.97 (0.15) (0.68,1.27) p<.0001	1.81 (0.12) (1.56,2.05) p<.0001	0.43 (0.22) (-0.01,0.87) p=0.055	1.46 (0.20) (1.06,1.86) p<.0001	0.60 (0.13) (0.35,0.85) p<.0001	0.82 (0.16) (0.50,1.13) p<.0001	1.62 (0.13) (1.36,1.88) p<.0001	0.35 (0.24) (-0.12,0.83) p=0.15	1.48 (0.22) (1.05,1.90) p<.0001
Diabetes Diagnosis	-0.09 (0.36) (-0.80,0.62) p=0.80	-0.30 (0.59) (-1.45,0.86) p=0.62	0.05 (0.37) (-0.68,0.79) p=0.88	-4.08 (0.89) (-5.83,-2.34) p<.0001	1.46 (0.78) (-0.07,3.00) p=0.06	-0.41 (0.42) (-1.23,0.41) p=0.33	-0.37 (0.66) (-1.66,0.92) p=0.57	-0.56 (0.43) (-1.40,0.28) p=0.19	-3.89 (1.00) (-5.86,-1.92) p=0.0001	1.95 (0.87) (0.26,3.65) p=0.024
Hypertension Diagnosis	0.01 (0.14) (-0.27,0.29) p=0.92	-0.45 (0.20) (-0.85,-0.06) p=0.025	0.03 (0.15) (-0.26,0.32) p=0.83	-0.84 (0.29) (-1.42,-0.27) p=0.004	0.05 (0.27) (-0.48,0.57) p=0.85	-0.11 (0.15) (-0.41,0.19) p=0.47	-0.47 (0.21) (-0.89,-0.05) p=0.028	-0.28 (0.16) (-0.59,0.03) p=0.08	-0.72 (0.31) (-1.34,-0.11) p=0.022	0.09 (0.28) (-0.47,0.64) p=0.76
Fatigue Level	-0.65 (0.15) (-0.95,-0.35) p<.0001	-0.07 (0.19) (-0.44,0.30) p=0.72	-0.74 (0.16) (-1.05,-0.44) p<.0001	-0.33 (0.28) (-0.88,0.22) p=0.24	0.20 (0.26) (-0.31,0.71) p=0.45	-0.76 (0.17) (-1.09,-0.43) p<.0001	-0.13 (0.20) (-0.52,0.26) p=0.52	-0.72 (0.17) (-1.05,-0.38) p<.0001	-0.22 (0.30) (-0.81,0.38) p=0.48	0.19 (0.27) (-0.34,0.73) p=0.48
Pain	0.03 (0.11) (-0.19,0.26) p=0.78	-0.36 (0.17) (-0.69,-0.03) p=0.032	-0.22 (0.12) (-0.45,0.01) p=0.06	-0.32 (0.25) (-0.82,0.17) p=0.20	-0.12 (0.23) (-0.57,0.32) p=0.59	0.07 (0.13) (-0.18,0.32) p=0.58	-0.43 (0.18) (-0.79,-0.08) p=0.018	-0.19 (0.13) (-0.45,0.06) p=0.14	-0.09 (0.28) (-0.64,0.46) p=0.74	-0.23 (0.25) (-0.72,0.26) p=0.36
Psychotropic Medication Use	0.20 (0.10) (0.005,0.39) p=0.045	-0.11 (0.14) (-0.37,0.16) p=0.43	-0.05 (0.10) (-0.24,0.15) p=0.66	-0.43 (0.20) (-0.83,-0.03) p=0.034	0.002 (0.18) (-0.36,0.36) p=0.99	0.31 (0.11) (0.10,0.52) p=0.004	-0.23 (0.15) (-0.51,0.06) p=0.12	-0.06 (0.11) (-0.27,0.15) p=0.58	-0.41 (0.22) (-0.84,0.02) p=0.06	0.03 (0.19) (-0.35,0.41) p=0.88

Analytic Models	Full Model/Full Sample						Full Model with Sub-Sample Adding "Time Since Seroconversion" to the Model					
	Cognitive Domain Dependent Variables						Cognitive Domain Dependent Variables					
Predictors (below)	Information Processing Speed	Episodic Memory	Executive Function	Motor Function	Working Memory		Information Processing Speed	Episodic Memory	Executive Function	Motor Function	Working Memory	
History of HBV Infection	-0.20 (0.43) (-1.04,0.63) p=0.63	-0.48 (0.57) (-1.61,0.64) p=0.40	0.53 (0.46) (-0.36,1.43) p=0.24	-0.98 (0.81) (-2.56,0.60) p=0.23	0.12 (0.77) (-1.38,1.62) p=0.88		-0.04 (0.48) (-0.99,0.91) p=0.94	-0.06 (0.65) (-1.34,1.22) p=0.93	0.04 (0.51) (-0.95,1.04) p=0.93	-0.30 (0.93) (-2.12,1.53) p=0.75	0.09 (0.89) (-1.65,1.82) p=0.92	
History of HCV Infection	-1.25 (0.38) (-1.99,-0.50) p=0.001	-1.36 (0.49) (-2.31,-0.40) p=0.005	-1.36 (0.41) (-2.16,-0.56) p=0.0008	-3.05 (0.69) (-4.41,-1.69) p<.0001	-1.84 (0.67) (-3.15,-0.53) p=0.006		-1.06 (0.45) (-1.95,-0.16) p=0.020	-1.50 (0.56) (-2.60,-0.39) p=0.008	-1.39 (0.48) (-2.32,-0.45) p=0.004	-2.17 (0.82) (-3.77,-0.57) p=0.008	-2.46 (0.79) (-4.02,-0.90) p=0.002	
Cannabis Use ⁶	0.13 (0.14) (-0.15,0.41) p=0.36	-0.07 (0.19) (-0.44,0.30) p=0.72	0.22 (0.15) (-0.07,0.51) p=0.13	0.25 (0.28) (-0.29,0.79) p=0.36	0.45 (0.25) (-0.04,0.95) p=0.07		0.07 (0.15) (-0.23,0.37) p=0.65	0.04 (0.20) (-0.35,0.44) p=0.82	0.11 (0.16) (-0.20,0.42) p=0.49	0.28 (0.30) (-0.30,0.86) p=0.34	0.45 (0.27) (-0.08,0.97) p=0.09	
Nitrite Inhalant Use ⁶	0.48 (0.14) (0.21,0.75) p=0.0006	0.25 (0.19) (-0.12,0.63) p=0.19	0.14 (0.14) (-0.14,0.42) p=0.34	-0.07 (0.28) (-0.61,0.48) p=0.81	0.07 (0.26) (-0.43,0.58) p=0.77		0.45 (0.15) (0.16,0.74) p=0.002	0.17 (0.20) (-0.22,0.56) p=0.39	0.14 (0.15) (-0.16,0.43) p=0.35	-0.09 (0.29) (-0.67,0.48) p=0.76	0.08 (0.27) (-0.45,0.60) p=0.77	
Total Body Weight (% change from prior visit)	-0.01 (0.01) (-0.02,0.0001) p=0.051	-0.01 (0.01) (-0.03,0.002) p=0.09	-0.01 (0.01) (-0.02,0.01) p=0.27	-0.002 (0.01) (-0.03,0.02) p=0.86	0.02 (0.01) (0.001,0.04) p=0.045		-0.01 (0.01) (-0.02,0.003) p=0.12	-0.01 (0.01) (-0.03,0.01) p=0.16	-0.01 (0.01) (-0.02,0.004) p=0.15	-0.005 (0.01) (-0.03,0.02) p=0.73	0.03 (0.01) (0.01,0.05) p=0.010	
Body Mass Index (BMI)	0.10 (0.02) (0.07,0.14) p<.0001	-0.01 (0.02) (-0.06,0.04) p=0.59	0.05 (0.02) (0.01,0.09) p=0.009	0.03 (0.04) (-0.04,0.11) p=0.34	0.02 (0.03) (-0.05,0.08) p=0.65		0.11 (0.02) (0.07,0.15) p<.0001	-0.002 (0.03) (-0.05,0.05) p=0.94	0.06 (0.02) (0.02,0.11) p=0.004	0.03 (0.04) (-0.04,0.11) p=0.40	0.02 (0.04) (-0.05,0.09) p=0.58	
Depressed Mood Level	-0.03 (0.01) (-0.04,-0.02) p<.0001	-0.03 (0.01) (-0.04,-0.01) p=0.0002	-0.03 (0.01) (-0.04,-0.02) p<.0001	-0.004 (0.01) (-0.02,0.02) p=0.72	-0.03 (0.01) (-0.05,-0.01) p=0.002		-0.03 (0.01) (-0.04,-0.02) p<.0001	-0.03 (0.01) (-0.04,-0.02) p<.0001	-0.03 (0.01) (-0.04,-0.02) p<.0001	-0.01 (0.01) (-0.03,0.01) p=0.36	-0.02 (0.01) (-0.04,-0.01) p=0.012	
Alcohol Use ⁷ Weekly	-0.04 (0.14) (-0.31,0.23) p=0.79	-0.60 (0.20) (-0.99,-0.21) p=0.002	-0.11 (0.14) (-0.39,0.17) p=0.43	0.36 (0.29) (-0.21,0.93) p=0.22	0.30 (0.27) (-0.23,0.83) p=0.27		-0.03 (0.15) (-0.32,0.25) p=0.82	-0.49 (0.20) (-0.89,-0.08) p=0.018	-0.07 (0.15) (-0.36,0.22) p=0.64	0.57 (0.30) (-0.03,1.17) p=0.06	0.16 (0.28) (-0.39,0.70) p=0.57	
Monthly	-0.13 (0.16) (-0.45,0.19) p=0.43	-0.41 (0.23) (-0.85,0.03) p=0.07	-0.08 (0.17) (-0.41,0.25) p=0.64	0.37 (0.33) (-0.28,1.03) p=0.26	0.45 (0.31) (-0.15,1.05) p=0.14		-0.13 (0.17) (-0.47,0.21) p=0.46	-0.39 (0.24) (-0.85,0.07) p=0.10	-0.01 (0.18) (-0.36,0.33) p=0.94	0.56 (0.35) (-0.13,1.24) p=0.11	0.24 (0.32) (-0.39,0.86) p=0.45	
< Monthly	-0.38 (0.17) (-0.72,-0.04) p=0.027	-0.82 (0.24) (-1.29,-0.35) p=0.0007	-0.21 (0.18) (-0.56,0.14) p=0.24	-0.63 (0.35) (-1.32,0.06) p=0.07	-0.39 (0.32) (-1.03,0.24) p=0.23		-0.43 (0.19) (-0.79,-0.06) p=0.021	-0.69 (0.25) (-1.18,-0.19) p=0.006	-0.09 (0.19) (-0.46,0.29) p=0.65	-0.43 (0.37) (-1.16,0.30) p=0.25	-0.53 (0.34) (-1.20,0.14) p=0.12	
Cigarette Smoking Pack- Years	-0.02 (0.01) (-0.03,-0.01) p=0.001	-0.02 (0.01) (-0.03,-0.002) p=0.031	-0.04 (0.01) (-0.05,-0.03) p<.0001	-0.03 (0.01) (-0.05,-0.01) p=0.015	-0.01 (0.01) (-0.03,0.01) p=0.28		-0.02 (0.01) (-0.03,-0.003) p=0.016	-0.02 (0.01) (-0.03,-0.001) p=0.039	-0.04 (0.01) (-0.05,-0.02) p<.0001	-0.02 (0.01) (-0.05,-0.001) p=0.044	-0.01 (0.01) (-0.03,0.01) p=0.43	

¹ Cell Information [Line 1: Estimated regression coefficient (standard error); Line 2: 95% confidence interval; Line 3: p value]

² By the CDC staging system adding parameterization vs. HIV-seronegative participants

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Predictors: All other participants vs. White, Non-Hispanic participants

The reference group was the combined categories from Table 1 of those with HS education or less than high school education.

The reference group was those with annual income of < \$20,000

The reference group was those with "no or rare use"

The reference group was those with "daily use"