Associations of cardiovascular variables and HAART with cognition in middle-aged HIV-infected and uninfected women

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Abstract

Despite use of HAART, cognitive impairment remains prevalent in HIV. Indeed, a recent study suggested that in certain instances, stopping HAART was associated with improved cognitive function (Robertson et al. 2010). HAART is occasionally associated with cardiovascular pathology and such pathology may be associated with cognitive impairment. To explore these associations, we assessed the relative contributions of cardiovascular variables such as hypertension and atherosclerosis, of HIV and HAART to cognition. Participants were members of the Women's Interagency HIV Study (WIHS). In analysis of cross-sectional data using general linear models we assessed the relationship between each cardiovascular variable and Stroop interference time and symbol digit modalities test while adjusting for age, HIV, education, depression, and race/ethnicity. We also analyzed the association of summary measures of HAART use with cognition. In multivariate models significance was limited to carotid lesions and carotid intima-medial thickness quintile (CIMT) Stroop interference time (for carotid lesions, coefficient = 10.5, CI: 3.5 to 17.5, p = 0.003, N = 1130; for CIMT quintile, coefficient = 8.6, CI =

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1.7 to 15.4, p = 0.025, N = 1130). Summary measures of protease inhibitor use and other HAART measures were in most cases not associated with cognitive score in multivariate models. We conclude that in the HAART era among middle-aged women with HIV, carotid disease may be significantly associated with some measures of cognitive impairment. In this cross-sectional study, we could detect neither positive nor negative effects of HAART on cognition.

Keywords

Cognition; HIV; Women; Hypertension; Atherosclerosis; Middle-Aged

INTRODUCTION

In many countries, the advent of HAART has also led to a dramatic decrease in the incidence and prevalence of HIV-associated dementia, but most studies suggest that despite HAART the prevalence of less severe forms of cognitive impairment ranges from 15 to 50% with estimates that this will worsen as the HIV population continues to age (McArthur et al. 2010; Heaton et al. 2010, 2011; Cohen and Gongvatana 2010). HAART may accelerate atherosclerosis (Bozzette et al. 2003; Currier et al. 2007, Mary-Krause et al. 2003), and Robertson et al (2010) showed that *discontinuing* HAART was associated with *improved* performance on some cognitive tests. This report is particularly troubling because 2 recent publications suggested that similar to persons without HIV, cardiovascular risk factors are associated with worse cognition in persons with HIV (Becker et al 2009; Wright et al. 2010). A similar study in women has not been reported and the effects of HIV and AIDS on cognition may differ between men and women (Maki and Martin-Thormeyer, 2009). We utilized neuropsychological and cardiovascular data collected on women in the Women's Interagency HIV Study (WIHS) (Bacon et al. 2005; Barkan et al. 1998) to determine: 1) whether cardiovascular risk factors are associated with cognitive performance in middle-aged women with HIV; 2) the relative effects of HIV, AIDS, and vascular disease on cognition; 3) the association of HAART-use with cognitive function.

METHODS

Cohort

The Women's Interagency HIV Study (WIHS) (Bacon et al. 2005) is an ongoing prospective study of HIV in women. The WIHS began in 1994 and has enrolled a total of 3766 women across six sites in SF, LA, Chicago, Washington, DC, Brooklyn and the Bronx (New York). WIHS initially recruited 2054 HIV-infected and 569 HIV-uninfected women in 1994–95, and an additional 737 HIV-infected and 406-HIV uninfected women in 2001–2002. Participants are evaluated every six months with an extensive interview that includes history of interval illnesses and interval substance abuse, current medications and medication adherence, physical exam, and blood and gynecological specimen collection. In 2005, the "Genetic Predictors of Substance Abuse in HIV" sub-study (Crystal et al. 2011) was started. This cross-sectional study was nested within the WIHS. All WIHS participants were eligible for the study and over 98% agreed to participate. Data presented in this report come from this substudy as well as from the WIHS core assessments.

Predictor variables

1. Cardiovascular variables

    a. Carotid lesions and carotid intima-media thickness (CIMT). Details of measurement of CIMT were previously described in Kaplan et al. 2008). Briefly, high-resolution B-mode carotid artery ultrasound was used to

image the far wall of the right common carotid artery (CCA), internal carotid artery (ICA), and carotid bulb according to the procedure of Hodis et al. (2001). For the analyses presented here, the far wall of the right common carotid artery was used to measure CIMT as a continuous variable. Standardization procedures across the 6 clinical sites have been previously described (Kaplan et al. 2008). Carotid lesions were defined as focal intimal-medial thickness more than 1.5 mm in any of the imaged segments. This cut-point has been used in several previous studies of atherosclerosis (Naqvi et al, 2010; Toubol et al, 2007). Carotid ultrasound data were collected during visits 20 to 23, April 2004 through March 2006.

   b. HDL and LDL. Beginning in 1997, participants were instructed to fast for at least 8 h prior to blood draws. Methods of collection and measurement of HDL and LDL have been described previously (Hodis et al. 2001).

   c. Glomerular filtration rate (eGFR) was calculated following previously described methods (Tsui et al 2009).

   d. Blood pressure was recorded using a standardized protocol as previously described (Mansoor et al. 2009). Hypertension was defined as either average measured systolic BP >140 mm Hg, or diastolic BP >90 mm Hg, or a self-reported diagnosis of hypertension with use of antihypertensive medications.

   Data concerning previous myocardial infarction (MI) and diabetes were collected as described previously (Bacon et al. 2005; Barkan et al. 1998).

2. <u>HIV-related variables.</u> Methods for determining HIV-status, AIDS, CD4, viral load, and duration of HAART were described previously (Bacon et al. 2005; Barkan et al. 1998; Kaplan et al. 2008). Viral load:.0=undetectable (< 80 copies/ml); 1 = 81–3000, 2 > 3000.

At every visit, the number of different protease inhibitors (PIs), nucleotide reverse transcriptase inhibitors (NRTIs), and non-nucleotide reverse transcriptase inhibitors (NNRTIs) a subject was using in the past 6 months was recorded. We then totaled these scores for the first 25 visits (the Stroop was administered starting at visit 25) creating the variables total-PI, total-NRTI, and total- NNRTI. Because we were concerned that taking PIs might have negative consequences on cognition, we also counted the number of NRTIs and NNRTIs taken at each visit without concomitant PIs and then summed this variable to create the variable total-ARV-noPI (ARV – anti-retroviral).

3. Ethnicity was self-reported as described previously (Bacon et al. 2005; Barkan et al. 1998). 96.1% of participants described themselves as white, Hispanic, or African-American. The remaining subjects were combined with the Hispanic subjects.

4. Education was divided into 3 levels: 1) did not complete high school; 2) completed high school, but no further schooling; and 3) completed high school and had some further schooling.

5. <u>Depression.</u> Symptoms of depression were recorded with the Center for Epidemiological Studies – Depression scale (CES-D) at every visit (Radloff, 1977) and participants were divided into 2 groups: CES-D <= 15, and CES-D >= 16.

Outcomes/neuropsychological tests

  a. The symbol-digit test (SDMT) (Smith 1982; Lezak et al. 2004) was administered to all English-speaking WIHS participants during visits 21 to 24 (October 2004 to September 2006) as part of the core assessment. Some participants completed the testing on all 4 visits. Only the 1st score is used for each subject.

  b. We administered the Comalli-Kaplan Stroop (Stroop 1935; Comalli et al. 1962) during visits 25–28, October 2006 to September 2008 as part of the Genetic Predictors Study. Women who spoke Spanish, but not English, did not take the Stroop test. We report condition 3, the Stroop interference task. Times greater than 240 seconds were coded as 240 seconds (9 out of 1426 participants had scores greater than 240 seconds). Errors were recorded, but were not used to adjust interference times. For both neuropsychological tests SDMT, and Stroop) we used raw scores rather than normalized data.

Inclusion criteria—Data presented in this report include all data collected by wave 28, concluding in September 2008 on participants enrolled in the genetic predictors of substance abuse in HIV substudy. 1426 participants (472 uninfected and 954 HIV-infected) completed the Stroop and 1450 (467 uninfected and 983 infected) completed the symbol digit test. For the Stroop test carotid imaging was available on 1183 (386 uninfected and 797 infected). For the SDMT, carotid imaging was available on 1216 (391 uninfected, 891 infected). Our methods of assessing the effects of missing data on analytic results are discussed below.

Time intervals between predictor and outcome vatriables—The median interval between the date of carotid imaging and the dates when the Stroop was administered was 23.5 months before (range 36 months before to 7 months before). The median interval between the date of carotid imaging and the dates of symbol-digit testing was 5.5 months before (range 23 months before to 8 months after).

Statistical analysis—Cardiovascular variables were the predictors of primary interest in this study. The dependent variables were the earliest valid time to completion of the Stroop interference test or SDMT score. Linear regression models were constructed that included *all* of the following variables: age, education group, ethnicity group, depression group, HIV-seropositive or HIV-seronegative as well as *one* of the following cardiovascular predictors: hypertension, diabetes mellitus, LDL-cholesterol, HDL-cholesterol, history of MI, CIMT, carotid lesion, and eGFR. Analyses were then repeated with age as a covariate. A separate analysis was conducted for each CV predictor, to avoid undue multicollinearity. In a separate analysis to assess the relative effects of AIDS and cardiovascular predictors on cognition we used a 3 level HIV-clinical group factor: 1) HIV-seronegative, 2) HIV-seropositive but not AIDS, and 3)AIDS), or SN HIV-seronegative),

Continuous predictors were categorized into quintiles, in order to avoid the implicit assumption that their association with the dependent variable takes a linear form. For analyses confined to HIV-patients, continuous variables such as CD4 count and viral load were divided into tertiles. Drug use variables were divided into 3 groups. Non-users comprised the lowest group; participants having used these drugs were divided equally into low and high-use groups.

Tests of interaction between the CV predictor and other covariates were conducted. Variance inflation factors were examined as a check for excessive multicollinearity. Model residuals were examined for normality and for outliers; no observations were excluded as outliers.

Since up to 30% of subjects would be excluded in a standard casewise-deletion analysis due to missing values, sensitivity of results to missing data was approached using two alternative analysis strategies: multiple imputation (MI) with 10 imputations, using Markov chain Monte Carlo imputation and assuming normality of distributions, as implemented in SAS Release 9.2 PROC MI/MIANALYZE (SAS Institute, Cary NC); and maximum likelihood (ML) estimation using the method of weighted EM (Ibrahim 1990) as implemented in LogXact for SAS PROCs Release 7 PROC XMISS (Cytel Corp, Cambridge, MA). As indicated in the methods, we used 3 analysis methods to evaluate the effects of missing data on our results. Prediction of Stroop and SDMT did not differ substantially among the 3 analysis methods: 1) complete-case; 2) multiple imputation; and 3) weighted EM. For conciseness, we report below only the conventional complete-case analyses for each individual cardiovascular variable. Significance was set at $p < 0.05$ and we did not correct for multiple comparisons.

RESULTS

The demographic, neuropsychological, and cardiovascular profiles of the HIV-seropositive (hereafter referred to as HIV+ and seronegative participants (SN)) in this study are shown in table 1. Over 90% of participants completed both the SDMT and the Stroop interference test.

Association of vascular markers with Stroop an SDMT

In general linear models before age adjustment, participants with carotid lesions scored on average 17.6 seconds slower on the Stroop interference test (10.8 to 24.4, $p < 0.001$) than participants without carotid lesions (table 2). The coefficient was decreased to 10.5 seconds (3.5 to 17.5, $p = 0.003$) when age-quintile was included as a cofactor. Before age adjustment, the top CIMT quintile, history of MI, diabetes, hypertension, and the lowest eGFR quintile were also associated with significantly worse Stroop score. Carotid lesions, the top CIMT quintile, and history of MI had the largest effects, hypertension and eGFR had moderate effects, and diabetes had the smallest significant effect. With age adjustments, the coefficients were attenuated by 40 to 109% and statistical significance for diabetes, hypertension, history of MI, and eGFR was lost. HDL and LDL quintiles were not significantly associated with Stroop score before or after age adjustment (data not shown).

We repeated these analyses with SDMT as the outcome variable. Before age adjustment, the top CIMT quintile, carotid lesions, hypertension, diabetes, and eGFR (bottom quintile) but not history of MI were associated with significantly worse symbol digit score. However, with age adjustments the coefficients were markedly attenuated, and no cardiovascular variable remained significantly associated with symbol digit score. LDL quintiles were not significantly associated with symbol digit score before or after age adjustment.

Relative effects of cardiovascular variables and HIV/AIDS on cognition

Persons with HIV+ performed significantly worse than SN persons on the Stroop and SDMT before age adjustment. After age-adjustment, HIV+ was significantly associated with worse SDMT score, but not with worse Stroop score. The comparative effects of HIV and cardiovascular variables depended in part on the neuropsychological test. The Stroop test appeared more sensitive to the cardiovascular measures, and statistical significance remained after age-adjustment for carotid lesions, but not for HIV. The opposite was true of the SDMT. With age correction, significance remained for HIV but was lost for carotid lesions. This last association was mostly due to participants with AIDS. When analyses were confined to HIV+ persons without AIDS, significance was lost (coefficient = 1.3, −.3 to 2.8, $p = 0.109$).

Relationship between between HAART use and cognitive score

In general linear models confined to HIV+ participants and controlling for ethnicity, depression, age, and site, summary measures of PI, NRTI, NNRTI, and non-PI anti-retroviral use, the group with highest NRTI use had a significantly lower score on the SDMT than non-users (B = −3.5, −6.3 to −.62, p = 0.017). However, no other anti-retroviral group was associated with cognitive score on the SDMT, and no anti-retroviral group was associated with score on the Stroop.

Discussion

Our major findings are: 1) carotid lesions and top CIMT quintile were significantly associated with Stroop interference time but not with SDMT. 2) The magnitude of these associations were comparable to the effect of AIDS on these tests and larger than the effect of HIV without AIDS. 3) On all but one analysis, there was no association between HAART use and cognitive score.

There are only 2 previous studies of the association of carotid lesions and cognition in persons with HIV. The first included only 47 patients with HIV (Yaldizi et al. 2006). The second had substantial numbers of subjects but only examined men (Becker et al. 2009). Thus our study extends the work of Becker et al (2009) by demonstrating that cardiovascular variables are associated with cognitive function in women with HIV. Whereas Becker et al. (2009) found that the associations were not longer significant when age was included as a covariate, we found significance for carotid lesions with Stroop interference time even when age was included as a covariate.

At least one other study has investigated the influence of cardiovascular variables on cognitive function in HIV. Wright et al. (2010) showed an association between prior cardiovascular disease, hypertension, and hypercholesterolemia on measures of motor speed in 292 participants from the SMART study. However, only 122 women were studied, carotid measures were not available, and the neuropsychological evaluation was limited to the color trails test.

This is the largest study of the association of cardiovascular markers with cognition in women with HIV. The association of carotid lesions with cognitive impairment has not been demonstrated in such a young cohort; indeed the mean age of our participants is 9 years less than in the study of Becker et al. (2009) and 15 years younger than the youngest non-HIV study. Very few studies have investigated the prevalence of carotid lesions in persons under 40 years of age. If subclinical carotid disease proves to be prevalent in early middle age in patients with and/or without HIV, as suggested by these data, it could have substantial public health significance.

We recognize that a limitation of our finding is that only 2 neuropsychological tests were included in our analyses, and a significant result in the fully controlled models, was found for the Stroop interference tests but not for SDMT. Although multiple brain regions are involved in solving any neuropsychological test, the interference part of the Stroop test requires persistence of concentration and is a sensitive measure of frontal lobe function. In contrast, the DSMT is more a test of complex scanning and visual tracking and may be less sensitive to some types of frontal lobe dysfunction. As the frontal lobes appear to be the major site of brain dysfunction associated with vascular disease, it is not surprising to see a dissociation in the effect of cardiovascular variables on test score. Future studies assessing the effects of cardiovascular variables on cognition will need to include an array of sensitive neuropsychological tests that probe function in multiple brain regions.

The recent report of Robertson et al. (2010) has forced a reconsideration of the benefits and risks of HAART in relation to cognitive function. Analysis of the effects of HAART on cognition is extremely challenging as even within drug classes some drugs may occasionally be associated with deleterious effects on cognition whereas other drugs in the same class are less likely to have such an effect (see the possible deleterious effects of efavirenz (Ciccarelli et al, 2011)). Future longitudinal studies are needed to replicate and extend the findings of Robertson et al (2010) on whether certain HAART regimens have deleterious effects on cognition. If true, one possible explanation is that certain anti-retroviral drugs exacerbate atherosclerosis and that atherosclerosis somehow leads to cognitive impairment. Our cross-sectional study in general did not show an association between ARVs and worse cognitive score.

Our finding of no association of HIV-serostatus with score on at least one neuropsychological test is consistent with two studies from the Men's AIDS Cohort Study (MACS) that showed no difference in cognitive scores either cross-sectionally (Cole et al. 2007; Becker et al. 2009) or longitudinally (Cole et al. 2007) between HIV+ patients and SN participants. Several earlier studies, most with small numbers of subjects, had showed no difference in cognitive scores between asymptomatic participants in the early stages of HIV and SN participants (Mason et al. 1998; Damos et al. 1997; Odiase et al. 2007; Stern et al. 1998).

What is the mechanism by which carotid lesions might influence cognition? Although hypertension and other cardiovascular risk factors might lead to increased numbers of strokes and thus to cognitive impairment, we do not believe this is likely mechanism. Clinically-recognized strokes occurred in only 37 of our subjects. MRI data were not available to determine whether silent infarcts may have occurred. A previous study of the relationship between carotid stenosis and cognitive impairment in elderly patients without HIV found that strokes on MRI did not account for the cognitive impairment (Mathiesen et al. 2004). Although cardiovascular risk factors increase the risk for Alzheimer's disease and Alzheimer pathology can predate clinical symptoms by years (Craft et al. 2009), we believe that it is unlikely that preclinical Alzheimer disease would account for measurable psychological differences among early middle-aged subjects. We believe that the mechanism by which hypertension and other cardiovascular factors may impair brain function has not yet been identified.

This is the largest study of the association of cardiovascular markers with cognition in women with HIV. Strengths include the large number of women with carotid ultrasonography and the well matched control group without HIV. Weaknesses include the limited battery of neuropsychological tests, the cross sectional analyses, and the lack of brain imaging. We are now administering every two years a more complete neuropsychological battery so that we will be able to study the association of the cardiovascular variables with change in neuropsychological function over time. Comparison of the women's data with a men's cohort would also be desirable. A hypothesis proposing a mechanism by which these cardiovascular risk factors leads to brain dysfunction might also suggest cardiovascular measures that are more proximate to the mechanism of cognitive impairment than the measures used in this study.

Acknowledgments

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Table 1

Demographic, cardiovascular, and neuropsychological characteristics of study participants.

	HIV-seropositive	**HIV-seronegative**	**p**
Age when took Stroop N=920, 443	43.1±8.8	38.5±10.1	<0.001
Age when took SDMT N = 983, 464	41.7±8.8	37.2±10.0	< 0.001
CESD depression score N = 915, 438	13.7±12.4	12.8±11.9	< 0.225
WRAT number correct N = 776, 366	29.1±7.7	29.0±7.4	0.605
Interference time N = 920, 467	132.7±37.7	124.9±3.1	<0.001
Symbol digit # correct N = 983, 467	41.5±12.6	44.4±11.8	<0.001
HDL Cholesterol N = 881, 418	49.9±16.9	54.6±13.5	<0.001
LDL cholesterol N = 805, 392	101.7±34.7	100.8±31.8	0.861
CIMT N = 774, 371	0.73±0.12	0.72±0.12	0.020
Estimated GFR N = 914, 439	95.3±27.4	99.5±23.3	0.005
Ethnicity			0.051
White N = 120, 43	9.7%	13.0%	
Hispanic N = 163/99	17.7%	22.3%	
African-American N = 607, 281	66.0 %	63.4%	
Other N = 30, 20	3.3%	4.5%	
Diabetes mellitus present N = 152, 71	17.2%	18.6%	0.558
Diabetes mellitus not present N = 730, 346			
Any carotid lesion present N = 80, 26	10.3%	7.0%	0.081
No carotid lesion present N = 694,395			
History of MI N = 16, 13	1.7%	2.9%	0.165
No History of MI N = 904,433			
Hypertensive or on meds N = 282, 117	31.3%	27.7%	0.199
Not hypertensive nor on meds N = 620,306			

The number of participants with available data for each variable are listed in the cells in the left-most column. The first value is for HIV-seropositive, the second for HIV-seronegative. Except for percentages, values are means ± standard deviation.

Table 2

Regression coefficients of cardiovascular variables for predicting Stroop interference time after controlling for age, HIV, depression group, education group, site, and ethnic group. Regression coefficients are listed for HIV when carotid lesions were the cardiovascular variable of interest, but varied little when other cardiovascular variables were included. The Ns vary between cardiovascular variables and are in noted in parentheses. For variables divided into quintiles, Ns listed are for the number of participants in the 5 combined quintiles.

	Coefficient	CI	P
HIV	3.5	−.86 to 7.8	0.116
Carotid lesion (N = 1130)	10.5	3.5 to 17.5	0.003
Carotid – top quintile to bottom	8.6	1/7 to 15.4	0.025
Hypertension (N = 1102)	3.0	−1.7 to 7.7	0.21
History of MI (N = 1130)	9.3	−4.2 to 22.9	0.178
Diabetes Mellitus (N = 1088)	2.1	−3.2 to 7.5	0.437
GFR 5th N = 1122; bottom quintile vs. top	−0.80	−8.0 to 6.94	0.828

Table 3

Regression coefficients of cardiovascular variables for predicting SDMT. Covariates are the same as listed for table 2. For variables divided into quintiles, Ns listed are for the number of participants in the 5 combined quintiles.

	Coefficient	CI	P
HIV	−1.5	−2.9 to −0.10	0.036
Carotid lesion (N = 1130)	−1.4	−3.7 to 0.85	0.217
Carotid quintile	−1.8	−4.2 to 0.61	.144
Hypertension (N = 1102)	−.62	−2.1 to 0.9	0.909
History of MI (N = 1130)	0.26	−4.2 to 4.7	0.857
Diabetes Mellitus (N = 1088)	−0.30	−2.0 to 1.4	0.739
GFR 5th (N = 1122) bottom quintile vs. top	0.52	−1.8 to 2.8	.659