The Separate and Interactive Effects of HIV and APOE Genotype

on Cognition among Women

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THESIS

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Dedication

To my family: my mother, Anne, and my brother, Allen. I would not be where or who I am without your love and support. Thank you for believing in me.

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SUMMARY

Women with HIV are vulnerable to cognitive dysfunction compared to male counterparts. Genetic factors have not been widely examined as a contributor to cognitive dysfunction in HIV+ women. The goal of this study was to examine cognitive function in relation to Apolipoprotein E (APOE) genotype in HIV+ and HIV- women.

A total of 714 women from the Women's Interagency HIV Study (WIHS) (68.9% HIV+, 32.9% ε4+) had both longitudinal cognitive data over three visits and APOE genotyping available for analysis. We found there was no main effect of APOE genotype on any cognitive domain.

We found a significant interactive effect of HIV, APOE and time on global cognition, driven by small negative effects of the APOE ε4 allele in the HIV- control group. Finally, we found that in HIV+ women, there was a significant interactive effect between APOE and age on executive functioning, global cognition, motor skills, and processing speed, such that older HIV+ ε4+ women performed worse than older HIV+ ε4- women. In contrast, there was no main effect of APOE ε4 carrier status on any cognitive domain in younger HIV+ women or either age group of HIV- controls.

Overall, the current findings suggest that APOE genotype may be an age-related risk factor for cognitive dysfunction in HIV+ women.

INTRODUCTION

Anti-retroviral therapies (ART) have greatly extended the lifespan of HIV+ individuals. According to the CDC, almost half of American individuals living with HIV are 50 years of age or older (https://www.cdc.gov/hiv/group/age/olderamericans/index.html). As the number of HIV-infected individuals over 50 years old continues to rise, greater attention is being paid to the management of age-related comorbidities including cognitive decline. ART led to a reduction in the most severe cognitive comorbidity of HIV, HIV-associated dementia (HAD) (Heaton et al., 2011). However, asymptomatic neurocognitive impairment (ANI) and mild neurocognitive disorder (MND), the less severe cognitive comorbidities of HIV, remain common, affecting about 45% of HIV-infected individuals (Cohen & Gongvatana, 2010; Heaton et al., 2010; Sacktor et al., 2002).

The neuropathogenesis of HIV-related cognitive disorders is initiated when the HIV virus crosses the blood-brain barrier and replicates in the brain. HIV enters the brain within 15 days of infection (Davis et al., 1992) through a "Trojan horse" mechanism. That is, HIV infects monocytes which cross the blood-brain barrier and differentiate into macrophages, thereby increasing viral replication. In addition to macrophages, microglia and astrocytes are also principal cells that support HIV replication in the brain (Liu et al., 2004; Thompson et al., 2011). This process can result in the production of neurotoxins and neuronal loss. The mechanisms involved in neuropathogenesis are two-fold: Infected and/or immune-activated microglia and astrocytes release factors that facilitate a pro-inflammatory environment (Faissner et al., 2014; Wu et al., 2015; Zenón et al., 2015). Additionally, HIV proteins Tat and gp120 lead to direct neurotoxicity (Bachis et al., 2012; Buscemi et al., 2007; Fan & He, 2016; Fields et al., 2015; Nosheny et al.,

2006; Rahimian & He, 2016; Reddy et al., 2012; Sabatier et al., 1991; Wenzel et al., 2017; Zhou, Liu, & Xiong, 2017). Markers of inflammation remain high among individuals living with HIV, with discrepancies in virologic suppression between serum and cerebrospinal fluid levels (Anthony et al., 2005; Edén et al., 2007).

Most of the mechanistic and behavioral research on HIV-related cognitive dysfunction is based on samples of men because men comprise about 77% of HIV cases in the US (Center for Disease Control [CDC], 2015). The low representation of women in these research studies is problematic (Maki & Martin-Thormeyer, 2009; Vance et al., 2016) because of evidence that women are more vulnerable to cognitive dysfunction compared to male counterparts (Maki et al., 2018). In the largest study of cognition in HIV+ women, the Women's Interagency HIV Study (WIHS), HIV+ women showed deficits in verbal learning and memory as well as processing speed compared to HIV- women (Maki et al., 2015). In the largest study of male/female differences in HIV-related cognitive impairment, women in the WIHS were demographically-matched with men in the Multicenter AIDS Cohort Study (MACS), the longest-running study of HIV disease progression in men in the United States (Maki et al., 2018). Among the cognitive measures common to both studies—which did not include verbal learning and memory—HIV+ women were more likely than HIV+ men to score in the impaired range in psychomotor speed, attention, motor skills, and on the executive function measure Trail-Making Test B (Maki et al., 2018). The factors that give rise to women's vulnerability to cognitive impairment in HIV are unknown, but may relate to mental health symptoms and disorders (Rubin et al., 2017; Rubin, Pyra, et al., 2016; Rubin, Wu, et al., 2016), substance use disorders (Keutmann et al., 2017; Martin et al., 2016; Martin et al., 2011), immune activation (Meier et al., 2009), HIV pathogenesis (Addo & Altfeld, 2014), and/or antiretroviral pharmacokinetics (Ofotokun, Chuck, & Hitti, 2007).

With the exception of COMT (Sundermann et al., 2013), genetic factors have not been widely examined as a contributor to cognitive dysfunction in HIV+ women. The goal of this study is to examine cognitive function in relation to Apolipoprotein E (*APOE*) genotype in HIV+ and HIV- women in order to determine if the genotype may contribute to cognitive impairment, particularly among older women. Produced mainly by astrocytes, ApoE is a class of apolipoproteins that transports cholesterol to neurons via ApoE receptors (Liu et al., 2013; Mahley, 1988). The three apoE isoforms apoE2, apoE3, and apoE4 are encoded by the ε2, ε3, and ε4 alleles of the *APOE* gene, which are respectively found in 8%, 78%, and 14% of the population (Bu, 2009; Liu et al., 2013). Mahley (1988) found that approximately 28% of the population carries at least one copy of the *APOE* ε4 allele. ApoE4, encoded by the ε4 allele of the *APOE* gene, influences the clearance of soluble amyloid-Beta (Aβ) and increases amyloid deposition (Castellano et al., 2011; Mahley & Rall, 2000), a neuropathological hallmark of late-onset Alzheimer's disease (AD). ApoE4 is associated with earlier onset and a greater extent of cerebral Aβ accumulation (Morris et al., 2010). The *APOE* ε4 allele is the most robust genetic predictor of AD (E H Corder et al., 1993; Strittmatter et al., 1993). Paradoxically, the ε4 allele is associated with improved cognition in younger adults and may confer risk for cognitive decline only in older age, which has led to the antagonistic pleiotropy hypothesis of *APOE* (Tuminello & Han, 2011).

A meta-analysis of about 58,000 participants from 27 independent studies (Neu et al., 2017) found that the risk for mild cognitive impairment (MCI; a prodromal stage of AD) and AD associated with ε4 allele carrier status was greater in women compared to men, at least at certain ages. Among those aged 55-70 years, the risk of converting from normal to MCI was higher in ε4+ women compared to men, and among those aged 65-75 years, the risk of converting from MCI to AD was higher in ε4+ women compared to men. Furthermore, Altmann et al. (2014) found that

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APOE4 was associated with an increase in CSF total tau and the ratio of tau to beta-amyloid significantly in MCI women but not MCI men (Altmann et al., 2014). This suggests that APOE4 effects may be related to tau pathology in women and that tau pathology develops earlier among female ε4 carriers than male counterparts. More broadly, it demonstrates the need to study *APOE* effects in women.

There is conflicting evidence about the association between *APOE* genotype and cognition among HIV+ individuals. Several studies have found an association between cognitive impairment—defined as HAD, HAND, impairment on global cognition, or <40 T-score on at least 2 cognitive domains—and *APOE* ε4 genotype among HIV+ individuals (Panos et al., 2013; Soontornniyomkij et al., 2012; Spector et al., 2010), while other studies found no association (Becker et al., 2015; Burt et al., 2008; Joska et al., 2010; Morgan et al., 2013). Of these negative studies, a large study of HIV-infected men from The Multicenter AIDS Cohort Study (MACS), the largest longitudinal study of the natural and treated course of HIV in gay and bisexual men, found no association between *APOE* genotype and incident cognitive decline defined as T-scores lower than 40 on at least 2 cognitive domains (Becker et al., 2015). Becker et al. (2015) found that age was not a significant moderator of the relationship between *APOE* and cognitive decline. The study authors stated there was a need to replicate these analyses in women and to reserve conclusions about *APOE* ε4 carrier status effects on distinct domains of cognitive functioning. This Master's Defense aims to address that gap in knowledge.

To date, only two (Hoare et al., 2013; Morales et al., 2012) of eight studies on the interactive effects of APOE and HIV on cognitive domains included a majority of women (Table 1). As shown in Table 1 ("Studies including women that examined the separate and/or interactive effects of HIV, APOE, and age on individual cognitive domains."), sample sizes of studies that

included women ranged from n=36 to n=466. Women comprised 4% to 21.2% of the sample among larger studies (i.e., samples sizes of 76 to 466) and comprised a majority (76.74% to 100%) in the smaller studies that ranged from n=36 to n=45 (Andres et al., 2011; L. Chang et al., 2011; Chang et al., 2014; Hoare et al., 2013; Morales et al., 2012; Morgan et al., 2013; Panos et al., 2013; Wendelken et al., 2016). Four of the eight studies showed evidence of an association between *APOE* and cognition, either in a main effect of *APOE* on at least one cognitive domain in HIV+ individuals (Chang et al., 2014; Hoare et al., 2013; Morales et al., 2012; Wendelken et al., 2016) or a significant interaction between *APOE* and HIV if the study included HIV- controls (Chang et al., 2014; Morales et al., 2012). The domains affected in the larger studies were attention/working memory (Chang et al., 2014) and executive functioning (Wendelken et al., 2016), though the largest study (n=466) found that there was no interaction between HIV and *APOE* on any cognitive domain (Morgan et al., 2013). In post hoc analyses, Chang et al. (2014) found HIV+ ε4+ individuals performed significantly worse than HIV+ ε4- on executive function, fluency, verbal memory, and attention/working memory. Thus, from these eight studies it appears that HIV-infected *APOE* ε4 carriers may show select impairments in executive function, verbal fluency, verbal memory, and attention/working memory.

It is possible that age modifies the relationship between HIV and *APOE* in women. For example, Wendelken et al. (2016) showed an association between *APOE* ε4 status and executive function in a sample comprised mostly of individuals aged 60 years and older. Chang et al. (2014) found that HIV+ e4+ individuals aged 50 years and older had slower performance for TMTB, an executive function measure, compared to their younger counterparts. Panos et al. (2013) found reduced executive function and processing speed among older HIV+ ε4+ adults, independent of HIV disease severity, compared to *APOE* ε4-noncarriers. Although these results suggest that

APOE ε4 status influences executive function in HIV+ individuals, the lack of seronegative controls in these studies suggests a need for further investigation on the interactive effects of HIV, *APOE*, and aging on cognitive domains.

The mechanisms underlying the interaction between *APOE* and HIV status remain poorly understood. Clinical and basic science studies suggest that inflammatory mechanisms are likely involved. HIV+ ε4 carriers show altered levels of glial metabolites, myo-inositol (MI) and total creatine (tCR) in select brain regions, specifically the basal ganglia (BG) and the parietal cortex (Chang et al., 2014). Reduced clearance of Aβ due to ApoE4 may lead to greater inflammation, which subsequently makes individuals more cognitively vulnerable (Chang et al., 2014). ApoE4 mice have greater levels of cytokines for longer periods than ApoE2 and ApoE3 mice (Zhu et al., 2012). Wendelken et al. (2016) suggested that *APOE* may exacerbate HIV-related neuropathology. HIV+ compared to HIV- individuals have lower structural connectivity within the temporal and parietal cortex (Jahanshad et al., 2012), lower white matter volume in total cerebral and total cerebellum as well as lower grey matter in subcortical regions (Chang et al., 2011), and decreased fractional anisotropy of the corpus callosum (Hoare et al., 2013). Wendelken et al. (2016) found lower FA broadly throughout the brain in HIV+ e4+, similar to the patterns of deficits in structural connectivity found in HIV (Gongvatana et al., 2009), which may have been an exacerbation of typical HIV patterns.

The goal of this defense is to examine the separate and interactive effects of age and APOE genotype on cognitive performance in HIV+ women and HIV-controls in the WIHS. This study will address limitations in the current literature because the WIHS has longitudinal cognitive data, and large sample of HIV+ women and seronegative controls. Furthermore, this study can be viewed as generalizable to women in the U.S. given that the participants are representative of

HIV+ women across the United States. The large sample size provides sufficient statistical power, and includes key covariates that other studies lacked, particularly reading ability (proxy for educational attainment), substance abuse, and mental health factors (e.g., depressive symptoms) which are all known to have confounding effects on cognition. As most of the women in the WIHS are Black or Hispanic, the WIHS's diversity is relevant given that the effect of *APOE* genotype on HIV disease progression has been shown to be more pronounced in Black Americans than in European Americans (Burt et al., 2008).

The aims of this study were to predict the separate and interactive effects of HIV and *APOE* ε4 carrier status on distinct cognitive domains in women. We hypothesized that: 1) HIV-infected (HIV+) women would perform worse than at-risk HIV-uninfected (HIV-) women on measures of verbal memory, executive functioning, and global cognition; 2) *APOE* ε4 carriers would perform worse than ε4 noncarriers on measures of executive functioning, attention, and global cognition; 3) There would be a significant interaction between HIV and *APOE* on executive functioning, verbal memory, fluency, and global cognition such that the negative effect of the ε4 allele would be more pronounced in HIV+ women compared to HIV- women; and 4) There would be a more pronounced negative effect of the ε4 allele in HIV+ women would be more evident with increased age. Specifically, in analyses stratified by HIV, we predicted that there would be more pronounced effects of *APOE* genotype on executive functioning in older women (aged 50+) compared to younger women (aged < 50 years).

METHODS

Study population. Established in 1994 across 6 clinical sites (Chicago, Bronx, Brooklyn, Washington DC, San Francisco, and Los Angeles), the WIHS is the largest longitudinal study of

the natural and treated history of HIV in women. A total of 2623 participants enrolled from 1994 to 1996, and 1143 enrolled from 2001 to 2002 (n=3766; 2791 HIV+ and 975 HIV- women). All participants provided informed consent through established WIHS procedures, with consent for genetic testing as an optional component. Participants completed neuropsychological testing between 2009 and 2011 and were re-evaluated every two years in conjunction with WIHS semiannual core study visits. At each of these core visits, participants also completed physical examinations, medical and psychosocial interviews, and blood draws to assess HIV status/viral load as well as immune, kidney, and liver function. WIHS participants fluent in English (n = 1,908) were targeted for baseline cognitive assessments. Exclusionary criteria were applied to this group after a core semiannual visit in order to acquire relevant information that helped determine eligibility. Of these 1,908 women, 1,595 (84%) completed cognitive assessments. Limited attendance at WIHS visits contributed to the 16% missing data; 45% of women who did not complete cognitive testing attended 2 or fewer semiannual visits during the 2-year wave compared to 3% of women who did complete cognitive testing ($p < 0.001$).

Of the 1,595 participants, 74 were excluded from the baseline cognitive on the basis of the following exclusion criteria: (1) presence of conditions that limit test validity (e.g., hearing loss, impaired vision, immediate influence of illicit substances; n=11); (2) history of stroke/cerebrovascular accident (n=13); and (3) self-reported use of antipsychotic medication in the past 6 months (n=50). Sixty-four women had self-reported dementia or dementia by medical record and completed cognitive assessments. They were included because of uncertainty of the validity of the diagnosis and to ensure representation across the range of cognitive performance.

For the purposes of this study, HIV+ and HIV- women who consented to both genetic and cognitive testing and who completed at least three neurocognitive visits were included. A total of

932 WIHS participants had complete longitudinal cognitive data across the three visits, 749 of whom (80%) also had APOE data. For this particular topic, the WIHS Executive Committee gave approval and an IRB exemption was obtained from the University of Illinois at Chicago. All participants provided written informed consent. Exclusionary criteria included: (1) missing data on *APOE* genotype, (2) conditions with potentially confounding effects on neurocognitive tests (e.g., hearing loss, impaired vision, acute intoxication); (3) history of stroke/CVA; and (4) self-reported use of antipsychotic medication in the past 6 months. A comprehensive neuropsychological battery was administered to participants at baseline and every two years for four years, for a total of three administrations.

Neuropsychological Outcome Measures. The neurocognitive test battery assesses seven cognitive domains (Maki et al. 2015): verbal memory, verbal learning, attention and concentration, executive functioning (behavioral inhibition, mental flexibility, working memory), psychomotor speed, verbal fluency, and fine motor skills. T-scores were computed for each of these cognitive domains using baseline neurocognitive scores in the original 1,521 women by averaging the derived T-scores of all individual outcomes within each domain.

Verbal learning and *verbal memory* were assessed with the Hopkins Verbal Learning Test-Revised (HVLT-R), a list-learning task in which 12 words from three semantic categories are read aloud during each of three learning trials and the participant is asked to recall the list after each trial and after a 20-25 minute delay (Brandt and Benedict 2001). *Verbal learning* was assessed with the following two indices from the HVLT-R, a 12-item list-learning task (Brandt and Benedict 2001): (1) trial 1 (single trial learning) and (2) percent retention (delayed recall/maximum score on trial 2 or 3). *Verbal memory* was assessed with the following two indices from the HVLT-R:

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(1) number of words recalled after a 20-min delay (delayed free recall) and (2) total words recalled across each of three learning trials (total learning).

Attention and concentration as well as executive functioning were assessed with the Stroop Colour-Word Test (Comalli et al. 1962), Trail-Making Test, and the Letter-Number Sequence test (LNS) from the Wechsler Adult Intelligence Scale IV (WAIS IV). The Stroop test is a measure of selective attention and cognitive flexibility (Comalli et al. 1962), comprised of three trials: 1) The individual reads aloud a series of color words printed in black ink (Word task); 2) The individual reads aloud the color of a bar of X's (Color task); and 3) The individual reads aloud the names of colors printed in conflicting ink colors (e.g., the word "green" will appear in red ink) and is asked to name the color of the ink (Color-word task). The third trial provides a measure of an individual's ability to inhibit cognitive interference, occurring when processing one attribute of a stimulus affects the processing of another attribute of the same stimulus (Stroop, 1935). The Trail-Making Test is comprised of two conditions: a part *A* in which the participant is asked to draw lines to connect numbers in circles in numerical sequence as rapidly as possible; a part *B* in which the participant is asked to draw lines to connect numbers and letters in circles in alternating numerical and alphabetical order as rapidly as possible. The total time in seconds required to complete each task on the Trail-Making Test represents the individual's scores on parts A, representing processing speed, and B, representing executive functioning (Tombaugh, 2014). The Letter-Number Sequencing task is a measure of working memory and attention (Wechsler, 1997; Crowe, 2000), in which the individual is asked to reorder a series of letters and numbers in increasing order. *Attention and concentration* was assessed with time to complete the first two trials of the Stroop Colour-Word Test (Comalli et al. 1962), time to complete Trail-Making Test part A, and number correct on the control/attention condition from the Letter-Number Sequence

test (LNS) from the Wechsler Adult Intelligence Scale IV (WAIS IV). Executive function includes the ability to plan, direct and maintain attention, organize, problem solve, reason, and self-regulate (Luria, 1966; Zelazo, Carter, Reznick, & Frye, 1997*). Executive functioning* was assessed with trial 3 of the color-word condition (the difference in reaction time between color naming in the neutral condition and color naming in the incongruent condition) of the Stroop test (Comalli et al. 1962), which measures behavioral inhibition; time to complete Trail-Making Test part B, which measures mental flexibility; and total scores from the working memory condition of the Letter-Number sequencing (LNS) task.

Psychomotor speed was assessed with the Symbol Digit Modalities Test (SDMT). The Symbol Digit Modalities Test measures attention, concentration and speed of information processing (Smith, 1982), in which the individual has 90 seconds to pair specific numbers with geometric figures from a reference key. Scores are computed based on the total number of correct responses.

Verbal fluency was assessed with the Category and Letter Fluency tasks. The Verbal Fluency test is a short test of verbal functioning, or participants' lexical access ability, consisting of two tasks: Category Fluency and Letter fluency. Individuals are given a minute to verbalize as many unique words as possible that fit under a semantic category, for Categorical Fluency (e.g., animals), or that start with a given letter, for Letter Fluency (e.g., F, A, S) (Lezak et al., 2012). As participants must select words within their mental lexicon that fall under particular criteria, all while avoiding repetition and remaining focused, it is thought that executive control is necessary (Fisk and Sharp, 2004). Scores are based on the number of unique correct words.

Fine motor skill was assessed with time to complete the Grooved Pegboard (GP) test. The Grooved Pegboard is a test of manipulative dexterity that requires visual-motor coordination (Ruff

and Parker, 1993). The individual is asked to insert pegs with keys along one side into randomly positioned slots on a board as quickly as the individual can with her non-dominant and dominant hand.

Covariates. Time-varying covariates included HIV serostatus; age; annual household income; hepatitis C virus antibody (HCV) status (indicative of HCV exposure); self-reported recent (within 6 months), former (>6 months), or no (never) use of marijuana, crack, cocaine, and/or heroin and smoking; self-reported recent (within 6 months) heavy alcohol use as defined by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) (for women, >8 drinks/week or >4 drinks in one sitting), depressive symptoms (Center for Epidemiologic Studies Depression Scale (CES-D) score ≥16); recent antidepressant use; study geographic site; and for HIV+ participants, medication use, log-transformed HIV RNA, and CD4 (per 100 cell increase), CD4 nadir <200, as well as ever having an AIDS diagnosis.

Statistical analysis. We examined differences in demographic characteristics among the four groups (HIV−/ ε4−; HIV−/ ε4+; HIV+/ ε4−; HIV+/ ε4+) by conducting a two (HIV serostatus: HIV-/HIV+) by two (*APOE* genotype: ε4-/ε4+) between-subjects analysis of variance (ANOVA) for continuous variables and Breslow-Day tests for categorical variables. Cognitive testing norms for low-income minority women were recently established using a regression approach to estimate premorbid levels of function for the total sample (Rubin et al., 2016, Maki et al. 2015; Manly et al. 2011; Rubin et al. 2015; Rubin et al. 2014; Valcour et al. 2015) based on scores of HIV- WIHS women (N= 1521; Maki et al. 2015). This was accomplished by regressing each cognitive outcome on age, years of education, race/ethnicity, and results of the reading recognition subtest from the Wide Range Achievement Test-Revised (WRAT-R) (Wilkinson 1993), as a proxy for educational

quality (Manly et al. 2002). The resulting unstandardized beta weights, constants, and standard errors were used to calculate predicted scores for each test. Predicted scores were subsequently subtracted from each woman's actual score and transformed to *z* scores (using means of 50 and standard deviations of 10), facilitating comparisons across cognitive outcomes which otherwise would be on different scales.

We used linear mixed-effects regression analyses to examine the separate and interactive effects of HIV status and *APOE* genotype on cognitive domains. We also stratified women by HIV status to examine the separate and interactive effects of *APOE* genotype, age (>50 years old = older, <50 years old = younger), and time on cognitive domains. In these analyses, we modeled a random slope and intercept for each participant's cognitive test performance over time and random intercepts for participants as well as participants nested within study geographic site. Using the lme4 package in R to conduct linear mixed-effects regression analyses (Bates, Mächler, Bolker, & Walker, 2015), Satterthwaite approximations for degrees of freedom were used via the lmerTest package to obtain p-values (Kuznetsova, Brockhoff, & Christensen, 2017).

RESULTS

Study population. The sample included 492 HIV+ and 222 HIV- women (total n = 714), 32.9% of whom were APOE ε4+. The mean age was 45.71 +/- 9.25. For key covariates, 45.4% had income > \$12,000/year, 26.1% had elevated depression, 40.9% were recent smokers, 18.6% were recent marijuana users, 6.7% were recent crack, cocaine, and/or heroin users; 16.4% were recent heavy drinkers, and 18.8% were HCV+. Most participants were Black (68.1%) and/or Hispanic (16.5%).

HIV and sociodemographic factors. To examine potential differences in sociodemographic factors between HIV+ and HIV- women, independent t-tests were conducted for continuous variables and Chi-square tests for categorical variables (Table 2). There was no significant group difference in *APOE* ε4 carrier status by HIV status. On average, the HIV+ sample was older (M=46.72, SD=8.66) than the HIV- group (M=43.50, SD=10.13) at the initial cognitive visit, t(712)=4.36, p<0.001. Compared to HIV- women, HIV+ women were significantly less likely to have recently used marijuana, X^2 (1) = 3.71, p < 0.001, or crack, cocaine, and/or heroin (X^2 (1) = 5.98, p < 0.05), less likely to report heavy drinking. X^2 (1) = 9.51, p < 0.01, and more likely to be HCV+, X^2 (1) = 6.34, p < 0.05. The groups differed significantly in race, X^2 (3) = 7.86, p < 0.05, with more white (12.8%) and fewer Hispanic participants (14.8%) in the HIV+ group compared to the HIV- group (6.8% and 20.3%, respectively). There were no significant differences in the other sociodemographic factors.

APOE and sociodemographic factors. To examine potential differences in sociodemographic factors between ε4 carriers and noncarriers, independent t-tests were conducted for continuous variables and Chi-square tests for categorical variables (Table 2). There were no significant differences by *APOE* ε4 carrier status in any of the sociodemographic factors except race as ε4+ women were more likely to be Black (74.9%) compared to ε4- women (64.7%), X^2 (3) = 9.80, p < 0.05.

HIV, APOE, and sociodemographic factors. We tested the homogeneity of the odds-ratio between HIV status and *APOE* ε4 carrier status for categorical variables with the Breslow-Day

test, while between subjects ANOVA's were conducted for continuous variables (Table 2). There were no significant differences across groups in any of the sociodemographic factors.

Age and sociodemographic factors. To examine potential differences in sociodemographic factors between older (>50 years old) and younger (<50 years old) women, independent t-tests were conducted for continuous variables and Chi-square tests for categorical variables (Table 2). The mean age of the older group was 55.4 years (SD = 5.06) compared with 40.42 years in the younger group (SD = 6.27), t(712)=32.56, $p < 0.001$. Compared to older women, younger women were significantly more likely to have income > \$12,000/year, X^2 (1) = 4.28, $p < 0.05$, and less likely to be HCV+, X^2 (1) = 97.39, $p < 0.001$. There were no other significant differences.

HIV, APOE, and clinical characteristics of HIV. To examine potential differences in clinical characteristics factors between HIV+/ε4+ and HIV+/ε4- women, independent t-tests were conducted for continuous variables and Chi-square tests for categorical variables (Table 2). There were no significant differences HIV+/ε4+ and HIV+/ε4- women in any of the clinical characteristics of HIV.

HIV, Age, and clinical characteristics of HIV. To examine potential differences in clinical characteristics factors between older HIV+ and younger HIV+ women, independent t-tests were conducted for continuous variables and Chi-square tests for categorical variables (Table 2). Older HIV+ were significantly more likely than younger HIV+ women to ever have been diagnosed with AIDS, X^2 (1) = 13.29, $p < 0.001$. More specifically 53.3% of older HIV+ women were ever

diagnosed with AIDS, compared to 36% of younger HIV+ women. There were no other significant differences between groups on clinical characteristics of HIV.

Cognitive Domains. Linear mixed models were conducted to examine separate and/or interactive effects of HIV and *APOE* genotype on cognitive domains for all aims. All analyses controlled for HCV, substance abuse, alcohol use, smoking, depressive symptoms, age, and income. When applicable, covariates included clinical characteristics of HIV (Table 3).

Hypothesis 1: For Hypothesis 1, we investigated the main effect of HIV on cognition as well as the effects of HIV on cognition over the three longitudinal assessments in the full sample. We hypothesized that HIV+ women would perform worse than at-risk HIV- women on measures of verbal memory, executive functioning, and global cognition. In line with our hypothesis, HIV+ women performed worse than HIV- controls on verbal memory (t = -2.19, *P* < 0.001) and global cognition (t = -1.06, *P* = 0.017; Figures 1-2), but not on executive functioning (t = -0.91, *P* = 0.181). HIV+ women also performed significantly worse than HIV- controls on verbal learning (t = -2.194, *P* < 0.001; Figure 3). There were no significant interactions between HIV and time in these analyses (Table 3).

Hypothesis 2: In the second set of linear mixed models, we investigated the main effects of *APOE* genotype on cognition as well as the effect of *APOE* on cognition over the three longitudinal assessments. We hypothesized that *APOE* ε4 carriers would perform worse than ε4 noncarriers on measures of executive functioning, attention, and global cognition. Contrary to our

hypotheses, there was no main effect of *APOE* genotype and no significant interaction between *APOE* and time on any cognitive domain (Table 3).

Hypothesis 3A: In the third set of linear mixed models, we investigated the interactive effects of HIV and *APOE* genotype on cognition as well as the interactive effects of HIV and *APOE* on cognition over the three longitudinal assessments. We hypothesized that there would be a significant interaction between HIV and *APOE* on executive functioning, verbal memory, fluency, and global cognition such that the negative effect of the ε4 allele would be more pronounced in HIV+ women compared to HIV- women. There was no interactive effect of HIV and *APOE* on cognition. The interactive effect of HIV and *APOE* on global cognition over time was significant (t = 1.15, *P* = 0.008; Figure 4), such that HIV- ε4+ performed worse over time than HIV- ε4- women. The other 3-way interactions approached significance in a similar direction (Table 3).

Hypothesis 3B-C: In analyses stratified by HIV status, we investigated the main effect of *APOE* genotype on cognition as well as the effect of *APOE* on cognition over three longitudinal assessments. In HIV+ women, there was no main effect of *APOE* genotype on any cognitive domain. There was a significant interaction between *APOE* and time on attention (t = 1.16, *P* = 0.022) such that HIV+ ε4+ women performed worse than HIV+ ε4- women (Figure 5). In HIV-controls, there was no main effect of *APOE* genotype on any cognitive domain. There was a significant interaction between *APOE* and time on global cognition (t = -0.71, *P* = 0.045), such that HIV- ε4+ women performed worse over time than HIV- ε4- women (Figure 4), which drove the significant interaction between HIV, *APOE*, and time on global cognition in Hypothesis 3A.

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Surprisingly, there was also a significant interaction between *APOE* and time on motor skills (t = -1.36, *P* = 0.032), such that HIV- ε4+ performed worse over time than HIV- ε4- women (Figure 6).

Hypothesis 4A-B: In analyses stratified by HIV serostatus, we investigated the interactive effects of *APOE* and age on cognition as well as the interactive effects of APOE and age (>50 years old = older, <50 years old = younger) on cognition over three longitudinal assessments. We predicted that there would be more pronounced effects of *APOE* genotype on executive functioning in older women (aged 50+) compared to younger women (aged < 50 years). In line with our predictions, in HIV+ women, we found a significant interactive effect between *APOE* and age on executive functioning (t = 4.64, *P* = 0.007; Figure 7), such that older HIV+ ε4+ women performed worse than older HIV+ ε4- women. In the same direction, we also found a significant interactive effect between *APOE* and age on global cognition (t = 2.93, *P* = 0.007), motor skills (t = 3.76, *P* = 0.045), and processing speed (t = 3.74, *P* = 0.019; Figures 8-10). In HIV+ women, there was no significant interaction between *APOE* and age on any cognitive domain *over time* (Table 3), indicating that the interactions were reliable across the three study visits. In contrast to HIV+ women, in HIV- controls, we did not find a significant interactive effect between *APOE* and age on any cognitive domain (Figures 9-12, Table 3). Additionally, in HIV+ controls, there was no significant interaction between *APOE* and age on any cognitive domain *over time* (Table 3).

Hypothesis 4C-D: In stratified analyses, we investigated the main effect of *APOE* on cognition as well as the main effects of APOE on cognition over three longitudinal assessments in a subset of older HIV+ women and younger HIV+ women. In support of our hypothesis, we found

a significant main effect of *APOE* on executive functioning (t = -2.83, *P* = 0.033) and global cognition (t = -2.01, *P* = 0.012) in older HIV+ women, such that older HIV+ ε4+ women performed worse than older HIV+ ε4- women. However, there no main effect of *APOE* on any cognitive domain in younger HIV+ women.

DISCUSSION

Here we examined the separate and interactive effects of HIV and *APOE* ε4 carrier status on cognitive performance in women (n = 714). First, we hypothesized that *APOE* ε4 carriers would perform worse than ε4 noncarriers on measures of executive functioning, attention, and global cognition. Contrary to those hypotheses, there was no main effect of *APOE* genotype on any cognitive domain. Second, we predicted that HIV serostatus would interact with *APOE* to influence cognition, with worse effects in HIV+ women. Although we found a significant interactive effect of HIV, *APOE,* and time on global cognition, contrary to our hypothesis, the *APOE* ε4 allele had small negative effects only in the HIV- control group. Third, we predicted that there would be more pronounced effects of *APOE* genotype on executive functioning in older women (aged > 50 years) compared to younger women (aged < 50 years). That hypothesis was supported in analyses stratified by HIV status. Specifically, in HIV+ women, we found a significant interactive effect between *APOE* and age on executive functioning, global cognition, motor skills, and processing speed, such that older HIV+ ε4+ women performed worse than older HIV+ ε4- women. In contrast, there was no main effect of *APOE* ε4 carrier status on any cognitive domain in younger HIV+ women or either age group of HIV- controls. Overall, the current findings suggest that *APOE* genotype may be an age-related risk factor for cognitive dysfunction in HIV+ women.

These findings are in agreement with each of three other HIV studies on individual domains of cognition and examined the effects of age (Chang et al., 2014; Panos et al., 2013; Wendelken et al., 2016). Wendelken et al. (2016) showed an association between *APOE* ε4 carrier status and executive function in a sample comprised mostly of HIV+ individuals aged 60 years and older. Chang et al. (2014) found that HIV+ ε4 carriers aged 50 years and older had slower performance for TMTB, an executive function measure, compared to their younger counterparts. Panos et al. (2013) found reduced executive function and processing speed among older HIV+ ε4+ adults, independent of HIV disease severity, compared to *APOE* ε4-noncarriers. The current finding that *APOE* ε4 negatively affects cognition in older HIV+ women contrasts with findings from a large cohort of HIV+ and HIV- men (n = 2846), where *APOE* genotype did not interact with HIV or age on any cognitive outcomes (Becker et al., 2015). Most of the previous research studies on individual cognitive domains were conducted using samples comprised mostly of men. With a large sample size of HIV+ women and seronegative controls we extend this work here by showing that older HIV+ women who are ε4 carriers have increased cognitive vulnerability in executive functioning, global cognition, motor skills, and processing speed.

The apparently stronger association between *APOE* ε4 carrier status and cognition in HIV+ women compared to HIV+ men resembles findings in AD. *APOE* genotype is the strongest genetic risk factor for late-onset AD (Corder et al., 1993; Strittmatter et al., 1993). A meta-analysis of about 58,000 participants from 27 independent studies (Neu et al., 2017) found that the risk for mild cognitive impairment (MCI; a prodromal stage of AD) and AD associated with ε4 allele carrier status was greater in women compared to men, at least at certain ages. Among those aged 55-70 years with the ε4 allele, the risk of converting from normal to MCI was higher in women compared to men, and among those aged 65-75 years with the ε4 allele, the risk of converting from

MCI to AD was higher in women compared to men. The ε4 allele has more pronounced effects on hippocampal pathology (Fleisher et al., 2005), default mode network functional connectivity (Damoiseaux et al., 2012), and cortical thickness and volume (Liu et al., 2010) in women compared to men. There is also some evidence suggesting that ε4+ women are accumulate more brain amyloid over time compared to ε4+ men (Corder et al., 2004; Li et al., 2017), though other evidence suggests no sex differences (Jack et al., 2015).

Given the relatively young age of our older sample (mean age = 55 years) and the exclusion of women with dementia from the core WIHS neurocognitive evaluation, the cognitive deficits in older HIV+ ε4+ women in our study are not indicative of a current AD diagnosis. An examination of the pattern of effects across cognitive domains, however, may provide insights into whether *APOE* ε4 -related accumulation of Aβ. We hypothesized that we would see ε4 effects on verbal memory, but effects were observed in executive function and global cognition. Elevated Aβ has been associated with longitudinal cognitive decline in verbal memory and cognitive status but not executive function in clinically normal elderly individuals (Bilgel et al., 2018; Farrell et al., 2017). The association between *APOE* genotype and longitudinal cognitive decline, either defined as time to impairment or decline in verbal memory or verbal fluency, was stronger in women than in men (Beydoun et al., 2012). Elevated Aβ with co-occurring neurodegeneration defined by hippocampal volume loss and/or glucose hypometabolism has been associated with verbal memory declines among clinically normal elderly individuals (Bilgel et al., 2018; Papp et al., 2017; Wirth et al., 2013) or both verbal memory declines and executive functioning declines (Petersen et al., 2016). The current pattern of results indicate that HIV and *APOE* genotype interact to affect executive functions but not verbal memory, suggesting that amyloidosis alone may not be a key mechanistic factor in these older HIV+ adults.

APOE4 effects in this study might reflect tau-related mechanisms. *APOE* ε4 is associated with higher levels of CSF tau (Toledo et al., 2015) as well as tau at autopsy (Farfel, Yu, De Jager, Schneider, & Bennett, 2016) but only in the presence of Aβ. In several studies, the association between *APOE* ε4 and tau was greater in women (Altmann et al., 2014; Corder et al., 2004; Jack et al., 2015; Toledo et al., 2015), while two found no sex differences in tau accumulation (Damoiseaux et al., 2012; Sampedro et al., 2015). For example, Altmann et al. (2014) found that *APOE* ε4 was associated with an increase in CSF total tau and the ratio of tau to beta-amyloid significantly in MCI women but not MCI men. Cognitive decline is observed among cognitively normal elderly individuals in the presence of both Aβ and tau, but there is no association between cognitive decline and tau among those with low Aβ (Sperling et al., 2018). Again, however, these pathological changes are associated with longitudinal declines in memory, not executive function (Sperling et al., 2018), suggesting that the combined effects of *APOE* ε4 on amyloid and tau are not a likely mechanism.

Given the mean age of 55.4 years in the older group, it is important to consider whether menopause-related decreases in estrogen and progesterone as mechanisms contributing to APOE effects in this study. Estrogen and progesterone have a number of protective roles against APOE-related pathogenesis, such as the inhibition of Aβ accumulation and tau hyperphosphorylation (Pike et al., 2009). Transgenic mouse models of AD show that females have earlier accumulation of Aβ compared to men (Callahan et al., 2001; Lee, Cole, Palmiter, Suh, & Koh, 2002). In animal models, ovariectomy leads to increased Aβ levels which are offset by estradiol treatment (Petanceska et al., 2000). Gonadal hormones can alter APP processing, which in turn can lead to a reduction in Aβ production (Amtul, Wang, Westaway, & Rozmahel, 2010; Desdouits-Magnen et al., 1998; Jaffe, Toran-Allerand, Greengard, & Gandy, 1994; Manthey, Heck, Engert, & Behl,

2001; Thakur & Mani, 2005). Additionally, estradiol may promote the clearance of Aβ by increasing levels of Aβ-degrading enzymes such as neprilysin (Liang et al., 2010; Xiao, Sun, Liu, Zhang, & Huang, 2009) or prevent the aggregation of plaques by increasing transthyretin expression (Amtul et al., 2010; Oliveira, Ribeiro, Cardoso, & Saraiva, 2011; Quintela et al., 2009; Schwarzman et al., 1994).

Early postmenopausal HIV+ women may be more likely than similarly aged men to show cognitive deficits due to hormonal changes and/or the presence of menopausal symptoms such as sleep disruption. Menopause itself appears to affect select cognitive domains including verbal memory and processing speed (Greendale et al., 2009), though there appears to be a rebound in the postmenopausal period. It is unknown how *APOE* ε4 might moderate those menopause-related changes. In both men and women, sleep deprivation is associated with deficits in verbal memory, attention, and executive functioning (Gervais et al., 2017; Walker, 2009), but biological sex is largely ignored in these studies (Gervais et al., 2017). Sleep disruption is a common complaint in midlife women, as 40-60% of women undergoing the menopausal transition report sleep problems (Kravitz et al., 2003; Polo-Kantola, 2011), including ethnically diverse women (Kravitz et al., 2008). The most common complaint during the menopausal transition is sleep difficulties due to frequent awakenings (Kravitz et al., 2008). Frequent awakenings may disrupt brain clearance of Aβ, which may play a causal role in the development of AD (Mander et al., 2016; Musiek & Holtzman, 2016). In mice, intact slow-wave sleep leads to a two-fold increase in the rate of Aβ clearance. Future studies are needed to determine if menopause-related sleep disruptions may contribute to the effects of HIV and *APOE* on cognition in HIV+ women.

The negative effects of *APOE* ε4 in older HIV+ women but not older HIV- women suggests that HIV-related factors may exacerbate the effects of APOE4 on the brain. HIV proteins interfere

with neuronal autophagy which can increase tau and Aβ accumulation (Campbell, Rawat, Bruckman, & Spector, 2015; Fields et al., 2015; Fields et al., 2013). HIV proteins can also indirectly interfere with Aβ degradation (Daily, Nath, & Hersh, 2006; Rempel & Pulliam, 2005) and promote Aβ fibrillation, misfolding, and aggregation; Aβ and tat form multifibrillar structures in double-transgenic Tat and APP mice (Hategan et al., 2017). In the presence of HIV, APOE4 leads to more pronounced downregulation in the expression of genes involved in neurogenesis compared to APOE3 (Geffin et al., 2017). APO4 has also been found to interact with HIV proteins or infected cells. Tat enters all CNS cells by endocytosis and competes with APOE as it binds to low-density lipoprotein receptor-related protein 1 (LRP1) (Khan et al., 2018). By inhibiting the uptake and clearance of APOE4, Tat binding prolongs the circulation of APOE4. APOE4 can enhance HIV infectivity and potentially increase HIV/AIDS progression (Debaisieux, Rayne, Yezid, & Beaumelle, 2012; Liu et al., 2000; Vendeville et al., 2004). Additionally, gp120 may compete with APOE4 on the neuronal surface and increase susceptibility to HIV infection (Burt et al. 2008). Cells exposed to HIV proteins (eg, Tat or gp120) were three times more susceptible to neurotoxic effects in APOE ε4/ε4 cells (Turchan-Cholewo et al., 2006). APOE4 is particularly less potent in preventing HIV-1 Tat internalization and Tat-mediated HIV-1 long terminal repeat (LTR) transactivation, in contrast with APOE2 and APOE3 (Khan et al., 2018). Tat is essential for viral replication, and APOE4 is worse than APOE2 and APOE3 at preventing the Tat from activating HIV-1 replication. Further, modifying the structure of APOE4 into an APOE3-like phenotype enhanced the effect of APOE4 in blocking Tat-mediated HIV-1 LTR transactivation (Khan et al., 2018).

There is evidence to suggest that Aβ deposition is greater in HIV (Achim et al., 2009; Green et al., 2005; Soontornniyomkij et al., 2012) and HIV may also increase tau deposition in the

hippocampus (Anthony et al., 2006). As aging-associated cognitive impairments in HIV are thought to reflect pathological cellular mechanisms of the virus (Geffin & McCarthy, 2018), future studies should examine the separate and interactive effects of Aβ, tau, and neurodegeneration on cognition over time among HIV+ ε4+ individuals. Given our clinical findings that older HIV+ ε4+ women have worse executive functioning and global cognition, it is possible that this group of aging women are accumulating more Aβ in their prefrontal cortices. It remains unclear if worse cognitive performance in older HIV+ women who carry the ε4 allele is mediated by Aβ burden, and it is important that future neuroimaging studies track the progression of Aβ and tau burden by brain region and compare the rates of pathological protein accumulation as a function of HIV status. Such clinical studies are warranted, as prefrontal cortex neurons that were previously exposed to HIV proteins were more susceptible to the direct neurotoxic effects of APOE4 circulating in the central nervous system (Turchan-Cholewo et al., 2006). Lastly, longitudinal studies across the menopausal transition would provide insights into the extent to which menopause-related factors influence the interactive associations between APOE4 and HIV on cognitive performance.

This study had many strengths compared to other eight studies of the interactive effects of HIV and *APOE* on cognition. This was a large, longitudinal study of HIV+ women versus HIV-controls while the prior eight studies were cross-sectional, with limited female representation, and few control participants. Of the eight prior studies, only half included HIV- controls with sample sizes ranging from n=36 to n=177. We also included a comprehensive neuropsychological battery, with multiple measures of executive function including Trial 3 of the Stroop, TMTB, and the working memory condition of the LNS. Seven of the clinical studies used the TMTB, seven studies used Trial 3 of the Stroop, and none used LNS. We also had a sample that was racially

representative of the female HIV cases in the United States. The WIHS also included comprehensive questionnaires and measures that other studies did not control for, including key covariates such as reading ability, substance abuse, and mental health factors—which are all known to have confounding effects on cognition (Maki et al., 2015). The interaction between HIV and *APOE* persisted above and beyond these covariates.

Despite those strengths, our study had certain limitations. Our main limitation was that participants in our study were not old enough to assess the effects of age as a continuous variable, and stratifying participants with a cut-off of 50 years yielded a low mean age of 55.4 years (SD = 5.06). Our age analyses were limited by the small number of women over age 60 (n=35) as well as survival bias. Another limitation of this study is the exclusion of women who were missing data. Out of 1,595 WIHS Participants who completed baseline cognition, only 932 WIHS participants had complete longitudinal cognitive data across the three visits and 749 of these 932 (80%) also had *APOE* data. Most of the drop-out was due to the closing of the Los Angeles site of the WIHS.

In sum, these findings suggest that *APOE* genotype is a cognitive risk factor in HIV+ women age 50 and older. These results differ from results in the MACS, raising the possibility of a sex-related vulnerability to cognitive impairment, a pattern similar to AD. The mechanisms are unknown but the pattern of results may be indicative of direct effects of HIV proteins and APOE4 to frontal regions, neuroinflammation, early signs of Aβ-induced damage, or menopause-related factors such as hormonal declines or sleep disturbances. Future studies should assess these sex differences as well as the mechanisms underlying this apparently sex-related cognitive risk factor among older HIV+ women.

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Table 1

Studies including women that examined the separate and/or interactive effects of HIV, APOE, and age on individual cognitive domains.

Study (author, year)	Sample size (HIV+/HIV-)	Percent female	Cross sectional or longitudinal	Verbal Learning	Verbal memory	Executive function	Attention	Working Memory	Attention and Working Memory	Psychomotor speed/Speed of information processing	Visuospatial	Motor	Fluency	Main effect HIV	Main effect of APOE	Interactive effects of HIV and A...
Andres et al. (2011)	HIV+ n = 48 with HAND; ε4+ n = 15, age 48.7 years; ε4− n = 33, Age = 45.8 years; HIV- n = 39; ε4+ n = 11, age 47.2 years ε4− n = 28, age 47.0 years	6.90%	Cross-sectional	WAIS-III Digit Span (forward), AVLT trials 1 and 5	Rey Osterreith Complex Figure test (immediate and delayed), AVLT trial 7	Controlled Oral Word Association Test, RFFT, Animal Naming Test, Stroop Color Word Interference Test, TMTB	N/A	N/A	Paced Auditory Serial Addition Test trial 1; WAIS-III Digit Span (backward), WAIS-III Letter-number Sequencing, Arithmetic, CalCAP sequential reaction time (1-back, true positives only, and 2-back, true positives only)	TMTA, Symbol Digit Test, Stroop Color and Word naming	N/A	Grooved Pegboard (dominant and non-dominant hands), Timed Gait	N/A	N/A	N/A	HIV+ ε4+ subjects with HAND had poorer performance...; HIV+ ε4- subjects with HAND on verbal learning, verbal memory, fluency, attention and global cognition.
Chang et al. (2011)	HIV+ n =69; ε4− <50 years n =31; ε4− ≥ 50 years n =16; ε4+ <50 years n =11; ε4+ ≥50 years n =11; HIV- n =70; ε4− <50 years n =32; ε4− ≥ 50 years n =22; ε4+ < 50 years n =9; ε4+ ≥ 50 years n =7	10.10%	Cross-sectional	AVLT Trial 5 and Rey-Osterreith Complex Figure Test (Immediate Recall)	AVLT Delayed Recall (Trial 7) and Rey Complex Figure Delayed Recall	Stroop Interference and TMTB	N/A	N/A	WAIS-III Digit Span Backward, Letter-Number Sequencing, Arithmetic and Paced Auditory Serial Addition Test 1	Symbol Digit, TMTA, Stroop Color Naming, and CalCAP Simple Reaction Time	N/A	Grooved Pegboard dominant and non-dominant hands	RFFT and Verbal Fluency (with letters FAS)	N/A	N/A	HIV+ ε4+ subjects had poorer performance...Animal fluency, FAS fluency, TMTB, and in verbal fluency, executive function, learning and memory compared to...ε4- subjects and HIV- controls
Morales et al. (2012)	HIV+ n = 20, HIV- n = 16	100%	Cross-sectional	N/A	AVLT (Trial 5, Memory Recall, Delayed Memory)	Stroop Color Word Test, TMTB	N/A	N/A	N/A	Symbol Digit Modality Test, Visual Reaction Time non-dominant hand, Auditory Reaction Time non-dominant hand	N/A	TMTA, Grooved Pegboard (non-dominant and dominant hand)	NS	NS	ε4+ HIV- performed worse in executive functioning and on Trial 5 of the RAVLT, but ε4+ HIV+ did not perform worse in these domains.	N/A
Hoare et al. (2013)	HIV+ n = 45, ε4+ n = 24, ε4- n = 19	76.74%	Cross-sectional	HVLT-Revised Learning Trials total, BVMT-Revised Learning trials total	HVLT-Revised Free Recall, BVMT-Revised Free Recall, Rey-Osterrieth Complex Figure	WCST-64 Perseverative Responses, Stroop Interference Ratio	N/A	N/A	N/A	Symbol Digit Modality Test, Symbol Search	Brief Visuospatial Memory Test	Grooved Pegboard Test Finger Tapping Test	Verbal fluency	HVLT-Revised Learning Trials total, BVMT-Revised Learning trials total	Participants who were ε4+ performed worse in HVLT-R immediate and delayed recall, but not in Verbal fluency, Digit Symbol, Symbol Search, Brief Visuospatial Memory Test, Wisconsin Card Sorting Test, Stroop Colour and Word Test, Grooved Pegboard Test, Finger Tapping Test, Rey-Osterrieth Complex Figure, Wechsler memory scale, and Mental Alternation Test.	N/A
Panos et al. (2013)	HIV+ n = 259; ε4+ > 50 years n = 18; ε4+ < 50 years n = 59; ε4- > 50 years n = 39; ε4- < 50 years n = 143	15%	Cross-sectional	HVLT-Revised Learning Trials total, BVMT-Revised Learning trials total	HVLT-Revised Free Recall, BVMT-Revised Free Recall	TMTB, Wisconsin Card Sorting Test	N/A	PASAT Trial 1, WAIS-III letter-number sequencing	Digit Symbol, TMTA, Symbol Search	N/A	N/A	N/A	N/A	NS	N/A
Morgan et al. (2013)	HIV+ n =466; ε4+ n = 144, age 44.3 years; ε4- n = 322, age 44 years	21.20%	Cross-sectional	HVLT-Revised Learning Trials total, BVMT-Revised Learning trials total and delayed recall	HVLT-Revised Delayed Recall, BVMT-Revised Delayed Recall	Halstead Category Test, WCST-64 Perseverative Responses, TMTB, Stroop Interference Ratio	N/A	N/A	PASAT, WAIS-III LNS	TMTA, WAIS-III Digit Symbol and Symbol Search, Stroop Color-Word Test	N/A	Grooved Pegboard, (non-dominant and dominant hand)	Controlled Oral Word Association Test and Semantic Fluency (animals)	N/A	NS	NS
Chang et al. (2014)	HIV+ n = 80 (28.8% ε4+), HIV- n = 97 (28.9% ε4+)	10.70%	Cross-sectional	AVLT Trial 5 and Rey-Osterreith Complex Figure Test (Immediate Recall)	AVLT Delayed Recall (Trial 7) and Rey Complex Figure Delayed Recall	Stroop Interference and TMTB	N/A	N/A	WAIS-III Digit Span Backward, Letter-Number Sequencing, Arithmetic, and Paced Auditory Serial Addition Test 1	Symbol Digit, TMTA, Stroop Color Naming, and CalCAP Simple Reaction Time	N/A	Grooved Pegboard dominant and nondominant hands	RFFT and Verbal Fluency (with Letters Fluency and Verbal Fluency)	HIV+ individuals performed worse in Fluency, Speed of information processing, Attention/working memory, verbal learning, verbal memory	APOE ε4+ subjects had poorer attention/working memory than ε4- subjects	Trends toward significance observed comparing HIV+ ε4+ individuals to HIV+ ε4- on executive function, fluency, verbal memory, attention/working memory
Wendelken et al. (2016)	HIV+ n = 76, ages 60 and older (median = 64 years)	4%	Cross-sectional	N/A	Delayed and immediate recall trials of the CVLT-II,	Modified Trails TMTB, Stroop Interference, Lexical	CVLT-II Trial 1, Digit Span Forward	N/A		TMTA, WAIS-III Digit Symbol Modalities Test, Stroop	VOSP, Benson Figure Copy, pentagon copy	Grooved Pegboard, Finger Tapping		N/A	ε4 carriers demonstrated greater deficits in cognitive performance in the executive domain	N/A

	ε4+ n = 19				Story Recall, and Benson Figure delayed recall	Fluency (D words), Digit Span Backward				Color Naming						
	ε4- n = 57															

Table 2

*Key Sociodemographics by HIV status, APOE status, HIV*APOE, and age.*

	ε4- HIV- (n=141)	ε4+ HIV- (n=81)	ε4- HIV+ (n=338)	ε4+ HIV+ (n=154)	Younger (n=462)	Older (n=252)
HIV+, n (%)	-	-	-	-	308 (66.7)	184 (73.0)
APOE ε4+, n (%)	-	-	-	-	155 (33.5)	80 (31.7)
Age at first visit, mean (SD)[H, HxA, Ag]	43.33 (10.30)	43.78 (9.87)	46.96 (8.67)	46.18 (8.63)	40.43 (6.27)	55.40 (5.06)
Annual household income > $12,000/y, n (%)[Ag]	55 (39.0)	41 (50.6)	155 (45.9)	73 (47.4)	196 (42.4)	128 (50.8)
Currently depressed, n (%)	36 (25.5)	27 (33.3)	85 (25.1)	38 (24.7)	116 (25.1)	70 (27.8)
Current smoker, n (%)	63 (44.7)	40 (49.4)	131 (38.8)	58 (37.7)	182 (39.4)	110 (43.7)
Recent marijuana use, n (%)[H, HxA]	36 (25.5)	23 (28.4)	52 (15.4)	22 (14.3)	93 (20.1)	40 (15.9)
Recent CCHCAT use, n (%)[H, HxA]	9 (6.4)	14 (17.3)	17 (5.0)	8 (5.2)	30 (6.5)	18 (7.1)
Recent heavy alcohol use, n (%)[H, HxA]	27 (19.1)	24 (29.6)	44 (13.0)	22 (14.3)	85 (18.4)	32 (12.7)
Hepatitis C RNA positive, n (%)[H, HxA, Ag]	18 (12.8)	11 (13.6)	67 (19.8)	38 (24.7)	37 (8.0)	97 (38.5)
WRAT-3 reading subtest standard score, mean (SD)	88.64 (19.52)	90.23 (16.86)	91.92 (17.23)	91.53 (18.50)	91.03 (18.32)	90.94 (17.28)
Race, n (%) H, A, HxA						
White non-Hispanic	14 (9.9)	1 (1.2)	45 (13.3)	18 (11.7)	49 (10.6)	29 (11.5)
Black non-Hispanic	92 (65.2)	60 (74.1)	218 (64.5)	116 (75.3)	315 (68.2)	171 (67.9)
Hispanic	29 (20.6)	16 (19.8)	61 (18.0)	12 (7.8)	75 (16.2)	43 (17.1)
Other	6 (4.3)	4 (4.9)	14 (4.1)	8 (5.2)	23 (5.0)	9 (3.6)
CD4N > 200, n (%)	-	-	308 (91.1)	142 (92.2	279 (90.9)	158 (85.9)
CD4 nadir, mean (SD)	-	-	206.39 (120.6)	201.08 (121.5	209.57 (119.47)	196.64 (122.87)
Ever AIDS, n (%)[Ag]	-	-	140 (41.4)	62 (40.3	111 (36.0)	98 (53.3)
Years on ART, mean (SD)	-	-	10.73 (4.7)	10.58 (5.0	12.23 (5.15)	13.08 (5.34)
Viral load, mean (SD)	-	-	313.8 (111.0)	298.3 (115.4	249.63 (111.75)	250.99 (114.49)
Proportion of visits virally suppressed, mean (SD)	-	-	54.54 (29.0)	52.53 (29.4	56.34 (29.08)	58.05 (24.78)

Note.

[H]Main effect of HIV status significant at p<.05;

[A]Main effect of *APOE* genotype significant at p<.05;

[HxA]HIV × *APOE* interaction significant at p<.05;

[Ag]Main effect of age dichotomized by > 50 years old significant at p<.05;

"Recent" refers to within 6 months of the most recent WIHS visit.

cART = combination antiretroviral therapy; ART = antiretroviral therapy.

Table 3

The separate and interactive effects of APOE, HIV, age, and time on cognitive domains.

Hypothesis	Sample	Independent Variable(s)		Verbal Learning	Verbal Memory	Executive Functioning	Attention	Verbal Fluency	Motor Skills	Processing Speed	Global Cognition
Aim 1	Whole sample	HIV	T	**t = -2.194**	**t = -2.194**	t = -0.906	t = -1.014	t = -0.466	t = -0.894	t = -0.737	**t = -1.062**
			P	**p < 0.001*****	**p < 0.001*****	p = 0.181	p = 0.134	p = 0.469	p = 0.228	p = 0.274	**p = 0.017***
Aim 1	Whole sample	HIV*Time	T	t = 0.494	t = 0.694	t = -0.182	t = -0.028	t = 0.272	t = -0.624	t = -0.354	t = 0.097
			P	p = 0.243	p = 0.105	p = 0.615	p = 0.946	p = 0.396	p = 0.078[t]	p = 0.258	p = 0.637
Aim 2	Whole sample	APOE	T	t = -0.067	t = -0.41	t = -0.017	t = -0.578	t = -0.293	t = -0.864	t = -0.048	t = -0.321
			P	p = 0.916	p = 0.521	p = 0.979	p = 0.377	p = 0.637	p = 0.229	p = 0.942	p = 0.455
Aim 2	Whole sample	APOE*Time	T	t = 0.281	t = -0.00003	t = 0.198	t = 0.654	t = 0.329	t = -0.529	t = 0.015	t = 0.07
			P	p = 0.500	p = 1.000	p = 0.577	p = 0.103	p = 0.297	p = 0.129	p = 0.961	p = 0.728
Aim 3A	Whole sample	APOE*HIV	T	t = 0.15	t = -0.646	t = -0.197	t = 0.745	t = 1.945	t = 0.718	t = 1.323	t = 0.483
			P	p = 0.910	p = 0.633	p = 0.888	p = 0.594	p = 0.141	p = 0.639	p = 0.339	p = 0.597
Aim 3A	Whole sample	APOE*HIV*Time	T	t = 1.672	t = 1.583	t = 1.409	t = 1.578	t = 0.043	t = 1.311	t = 1.081	**t = 1.15**
			P	p = 0.059[t]	p = 0.078[t]	p = 0.064[t]	p = 0.067[t]	p = 0.949	p = 0.077[t]	p = 0.099[t]	**p = 0.008****
Aim 3B	HIV+	APOE	T	t = -0.114	t = -0.694	t = -0.178	t = -0.424	t = 0.339	t = -0.754	t = 0.316	t = -0.184
			P	p = 0.883	p = 0.365	p = 0.828	p = 0.602	p = 0.665	p = 0.403	p = 0.680	p = 0.722
Aim 3B	HIV+	APOE*Time	T	t = 0.846	t = 0.556	t = 0.633	**t = 1.158**	t = 0.369	t = -0.091	t = 0.336	t = 0.45
			P	p = 0.094[t]	p = 0.279	p = 0.155	**p = 0.022***	p = 0.328	p = 0.826	p = 0.354	p = 0.067[t]
Aim 3C	HIV-	APOE	T	t = -0.497	t = -0.413	t = 0.097	t = -0.755	t = -1.209	t = -1.372	t = -0.893	t = -0.653
			P	p = 0.653	p = 0.720	p = 0.929	p = 0.493	p = 0.207	p = 0.248	p = 0.458	p = 0.395
Aim 3C	HIV-	APOE*Time	T	t = -0.919	t = -1.045	t = -0.773	t = -0.531	t = 0.325	**t = -1.359**	t = -0.703	**t = -0.711**
			P	p = 0.227	p = 0.155	p = 0.187	p = 0.403	p = 0.582	**p = 0.032****	p = 0.224	**p = 0.045***
Aim 4A	HIV+	APOE*Age	T	t = 1.636	t = 2.089	**t = 4.635**	t = 2.534	t = 2.152	**t = 3.757**	**t = 3.735**	**t = 2.931**
			P	p = 0.306	p = 0.191	**p = 0.007****	p = 0.135	p = 0.186	**p = 0.045***	**p = 0.019***	**p = 0.007****
Aim 4A	HIV+	APOE*Age*Time	T	t = 0.272	t = 0.283	t = 1.321	t = -0.289	t = 0.183	t = 0.954	t = 1.149	t = 0.649
			P	p = 0.795	p = 0.790	p = 0.152	p = 0.783	p = 0.815	p = 0.268	p = 0.126	p = 0.202
Aim 4B	HIV-	APOE*Age	T	t = -2.578	t = -2.624	t = 1.738	t = -3.082	t = -1.805	t = 4.522	t = 2.607	t = 0.185
			P	p = 0.280	p = 0.293	p = 0.456	p = 0.192	p = 0.379	p = 0.078[t]	p = 0.317	p = 0.912
Aim 4B	HIV-	APOE*Age*Time	T	t = 1.153	t = 1.635	t = -0.984	t = 0.01	t = -0.091	t = -2.207	t = -1.228	t = -0.384
			P	p = 0.487	p = 0.308	p = 0.443	p = 0.995	p = 0.944	p = 0.111	p = 0.332	p = 0.620
Aim 4C	HIV+ (>50 years old)	APOE	T	t = -0.959	t = -2.125	**t = -2.834**	t = -1.584	t = -1.082	t = -2.887	t = -1.914	**t = -2.011**
			P	p = 0.468	p = 0.108	**p = 0.033***	p = 0.234	p = 0.319	p = 0.094[t]	p = 0.095[t]	**p = 0.012***
Aim 4D	HIV+ (<50 years old)	APOE	T	t = 0.4	t = -0.073	t = 1.561	t = 0.521	t = 1.251	t = 0.713	t = 1.9	t = 0.962
			P	p = 0.673	p = 0.940	p = 0.127	p = 0.616	p = 0.238	p = 0.476	p = 0.059[t]	p = 0.155
Aim 4F	HIV- (>50 years old)	APOE	T	t = 1.328	t = 1.38	t = -0.062	t = 0.932	t = 0.483	t = -4.026	t = -2.288	t = -0.276
			P	p = 0.492	p = 0.510	p = 0.974	p = 0.624	p = 0.779	p = 0.103	p = 0.307	p = 0.836
Aim 4G	HIV- (<50 years old)	APOE	T	t = -1.371	t = -1.344	t = 0.251	t = -1.89	t = -2.049	t = 0.449	t = -0.022	t = -0.688
			P	p = 0.302	p = 0.312	p = 0.849	p = 0.145	p = 0.061[t]	p = 0.729	p = 0.988	p = 0.450

[t] p<0.1; * p<0.05; ** p<0.01, *** p<0.001

All models controlled for HCV, substance abuse, alcohol use, smoking, depressive symptoms, age, and income. Clinical characteristics of HIV included medication use, log-transformed HIV RNA (i.e., viral load), and CD4 (per 100 cell increase), CD4 nadir <200, as well as ever having an AIDS diagnosis.

Hypothesis 1: Main Effect of
HIV on Verbal Memory

***P<0.001, main effect of HIV on verbal memory.
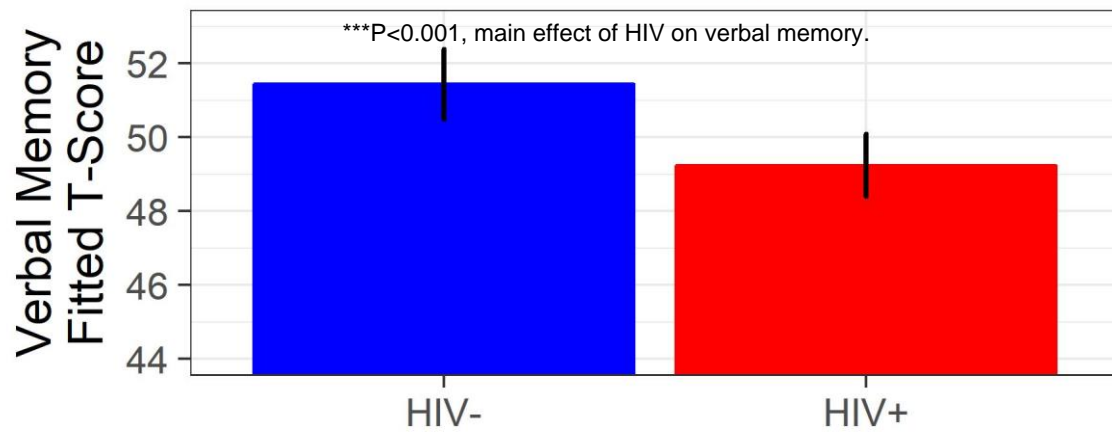
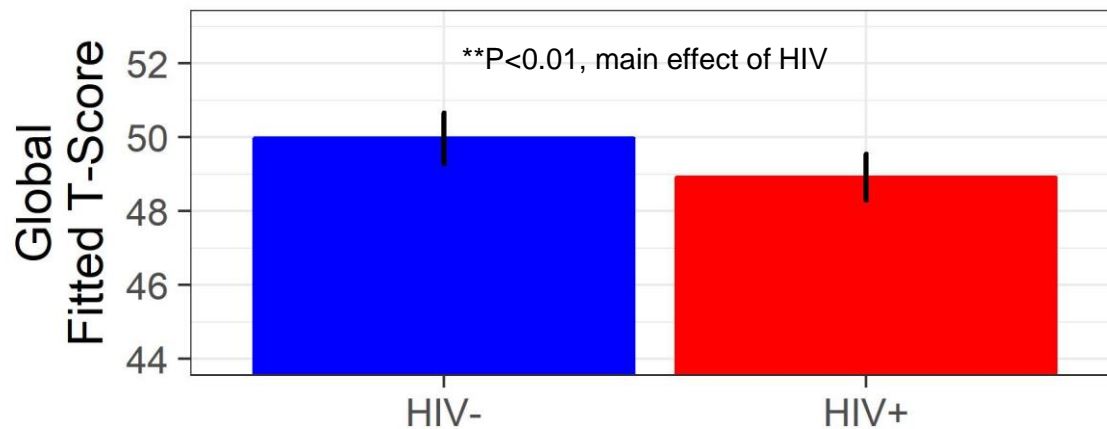*Figure 1*. Error bars represent standard error of the mean.

Figure 2. Error bars represent standard error of the mean.

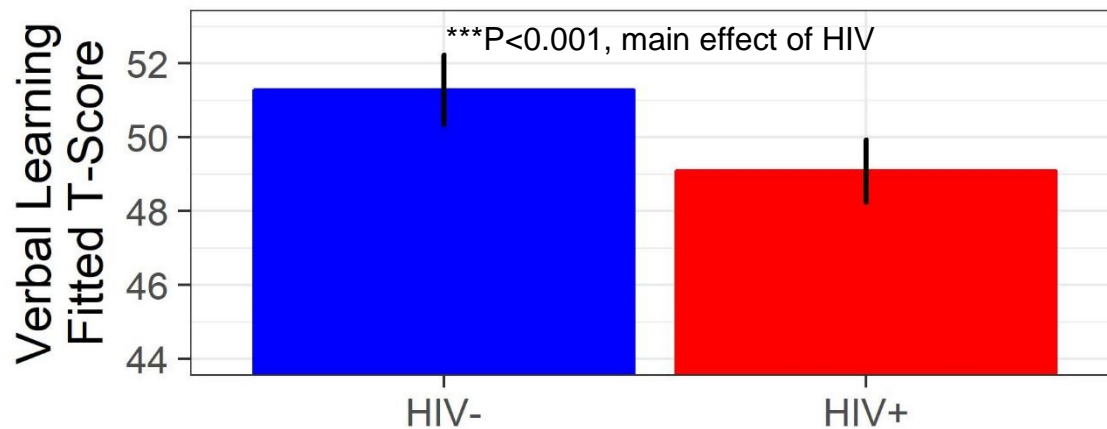Hypothesis 1: Main Effect of HIV on Verbal Learning

Figure 3. Error bars represent standard error of the mean.

Hypothesis 3A:
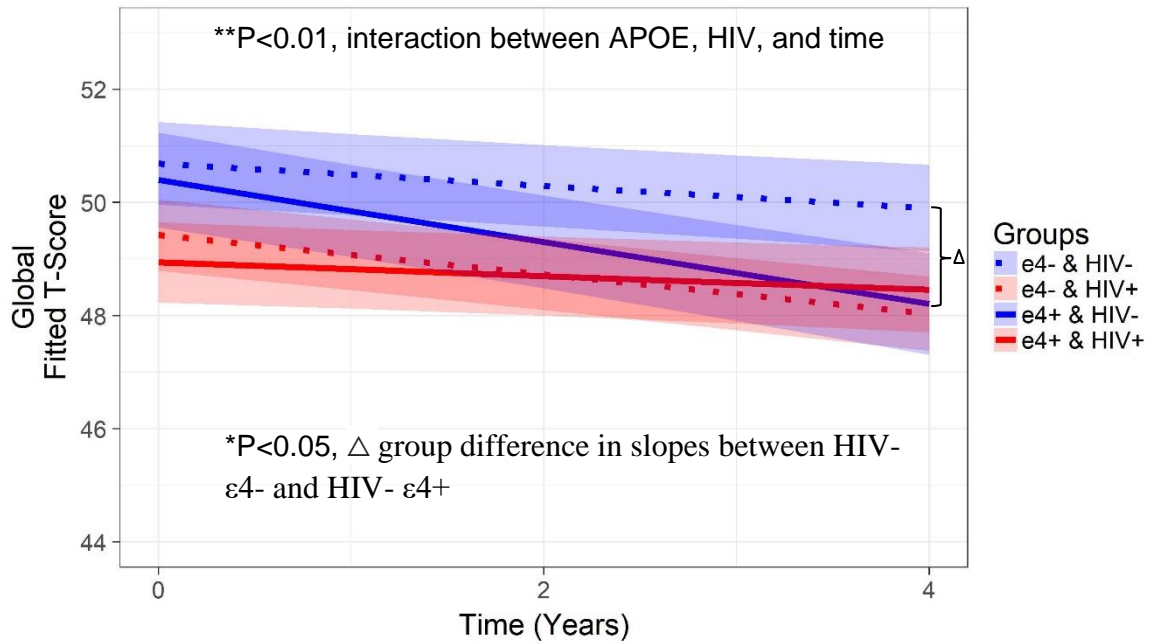Interactive effects of APOE, HIV, and time on Global Cognition

Figure 4. Shaded areas represent standard error of the mean.

Figure 5. Shaded areas represent standard error of the mean.

Hypothesis 3C:
Interactive Effects of APOE and Time
on Motor Skills in HIV- women
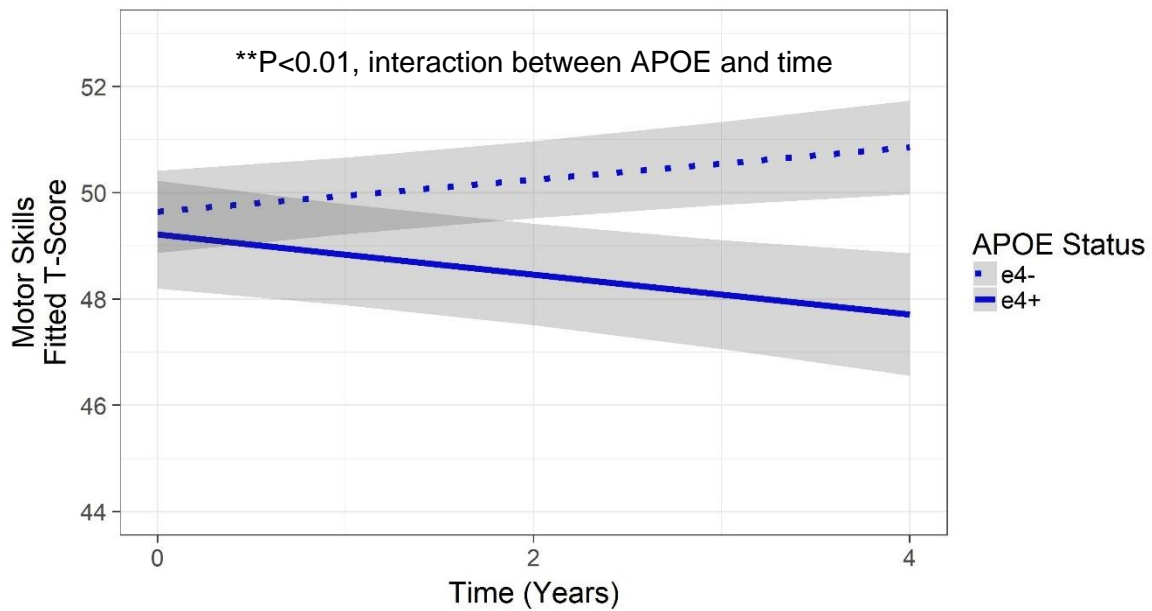
Figure 6. Shaded areas represent standard error of the mean.
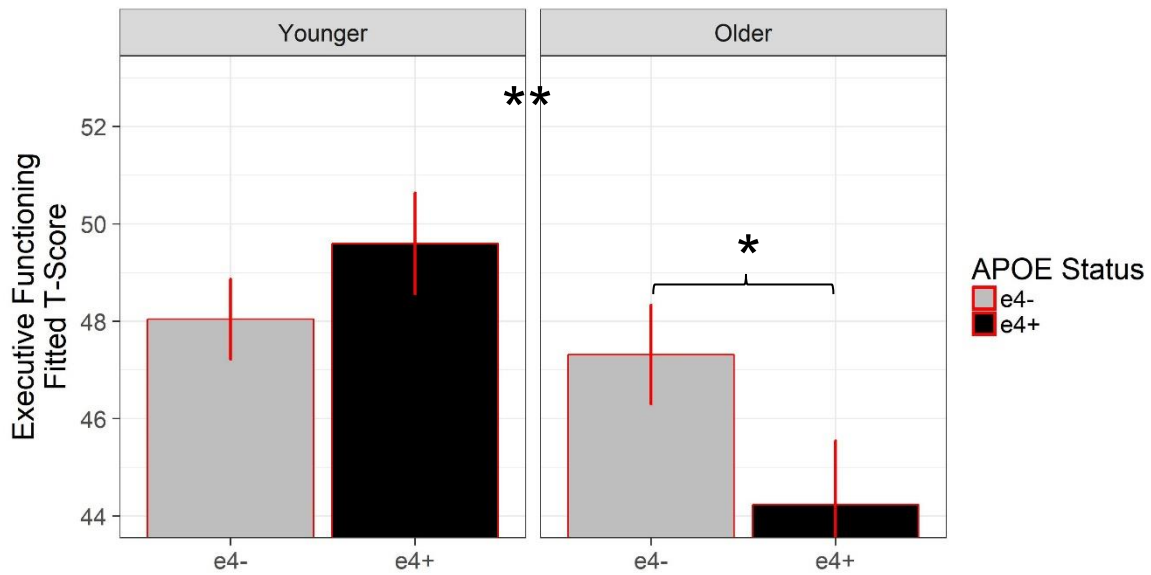
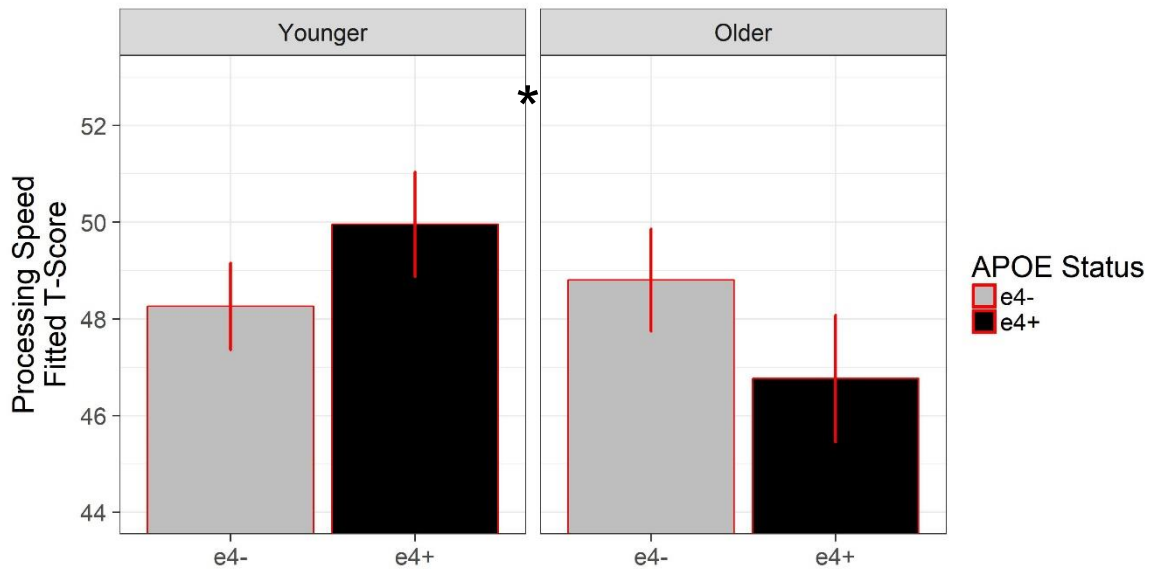*Figure 7.* Error bars represent standard error of the mean. ***p < 0.001; **p < 0.01; *p < 0.05.
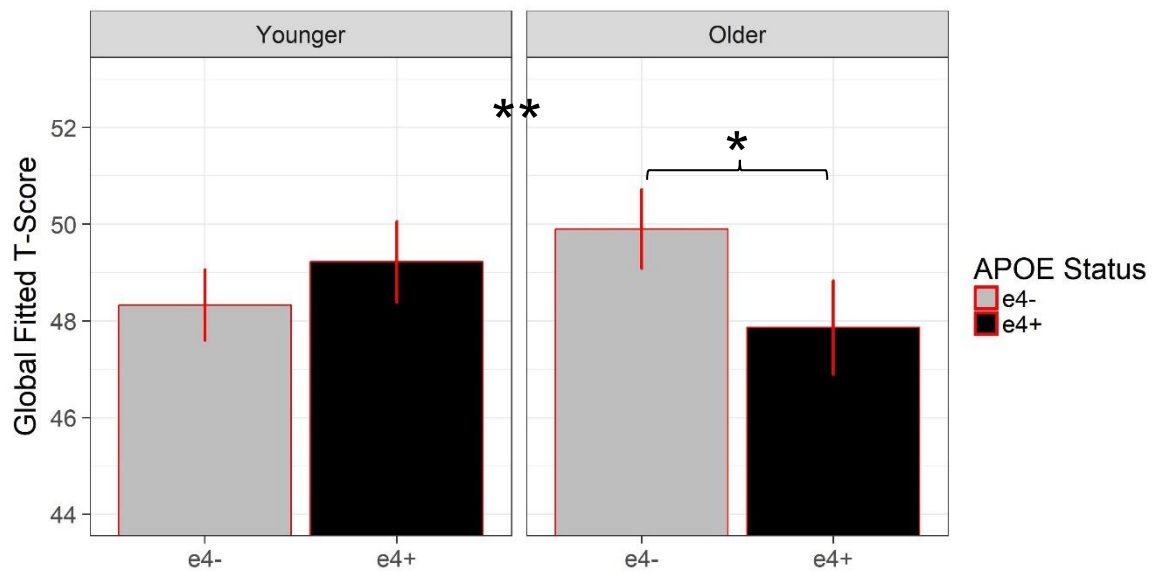
Figure 8. Error bars represent standard error of the mean. ***$p < 0.001$; **$p < 0.01$; *$p < 0.05$.

Hypothesis 4A:
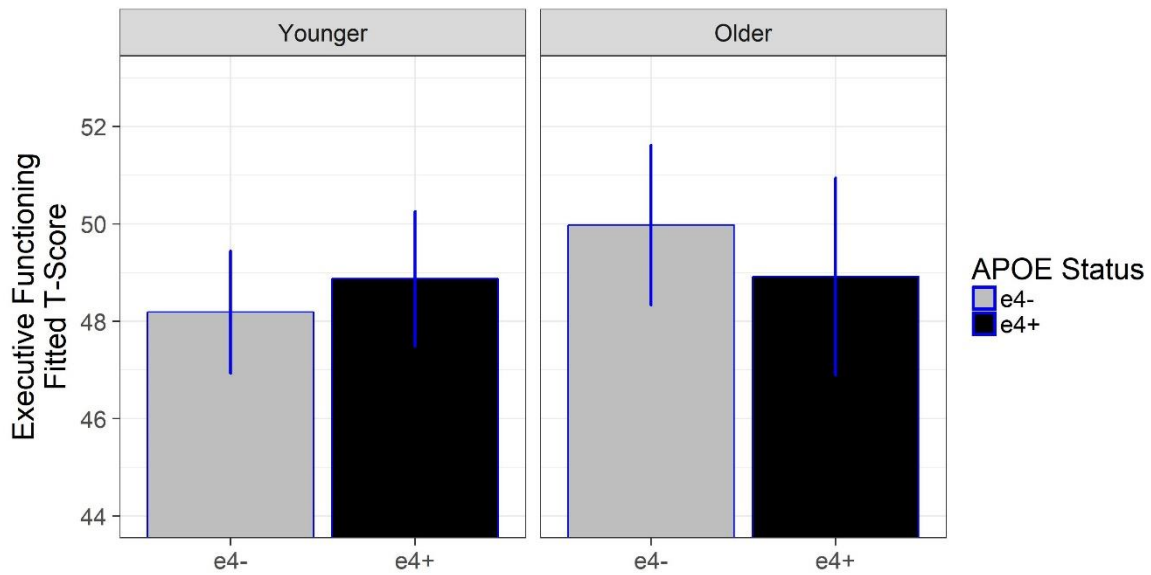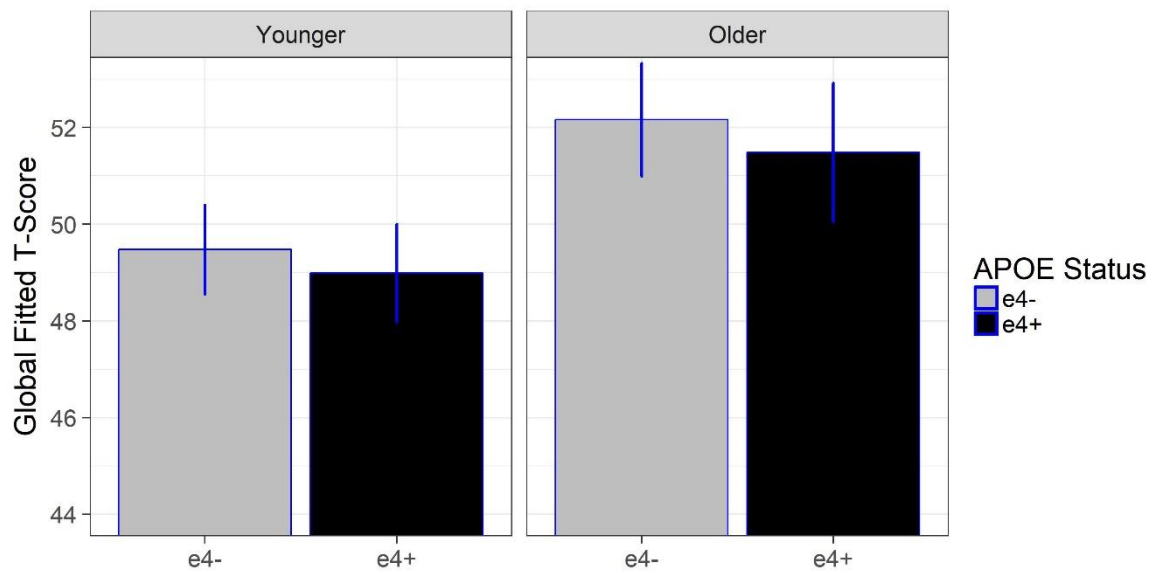Interactive Effects of APOE and Age
on Motor Skills in HIV+ women
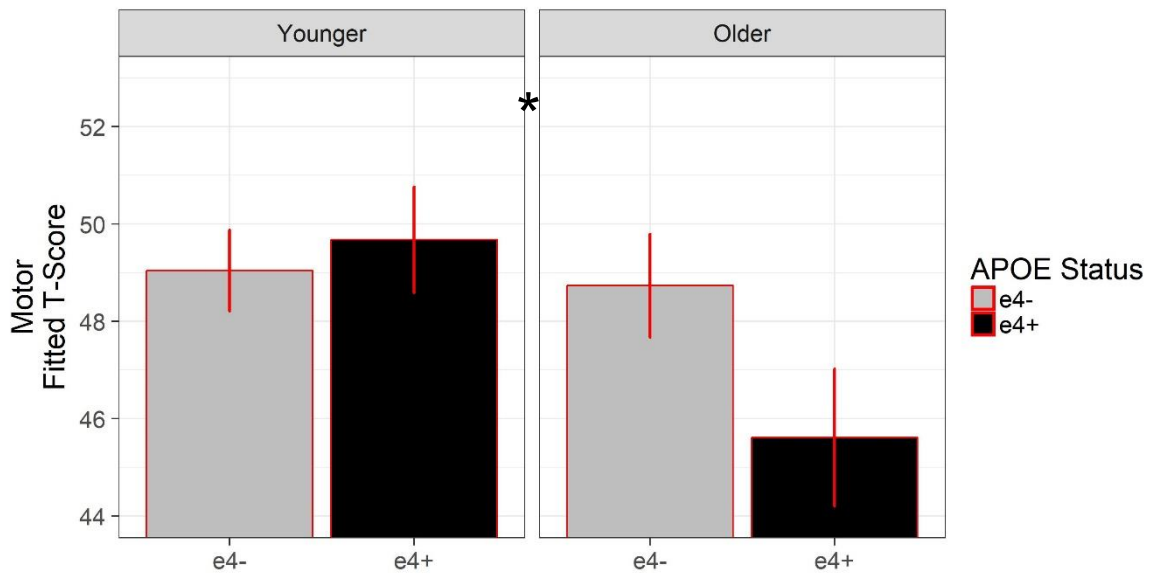
Figure 9. Error bars represent standard error of the mean. ***$p < 0.001$; **$p < 0.01$; *$p < 0.05$.

Hypothesis 4A:
Interactive Effects of APOE and Age
on Processing Speed in HIV+ women

Figure 10. Error bars represent standard error of the mean. ***$p < 0.001$; **$p < 0.01$; *$p < 0.05$.

Hypothesis 4B:
Interactive Effects of APOE and Age
on Executive Function in HIV- women

Figure 11. Error bars represent standard error of the mean.

Figure 12. Error bars represent standard error of the mean.

Hypothesis 4B:
Interactive Effects of APOE and Age
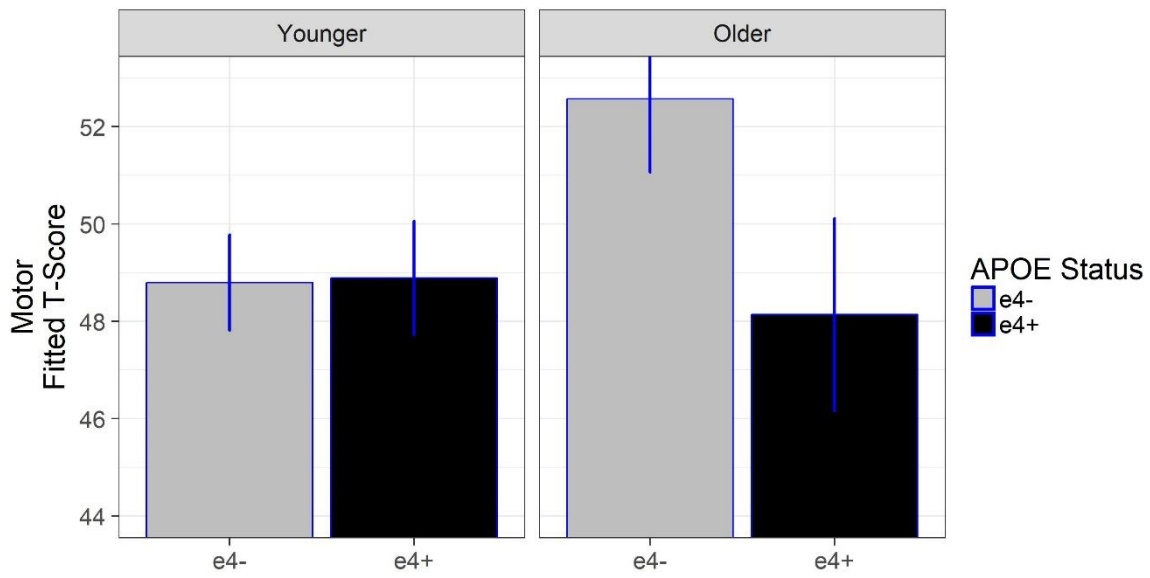on Motor Skills in HIV- women

Figure 13. Error bars represent standard error of the mean.

Hypothesis 4B:
Interactive Effects of APOE and Age
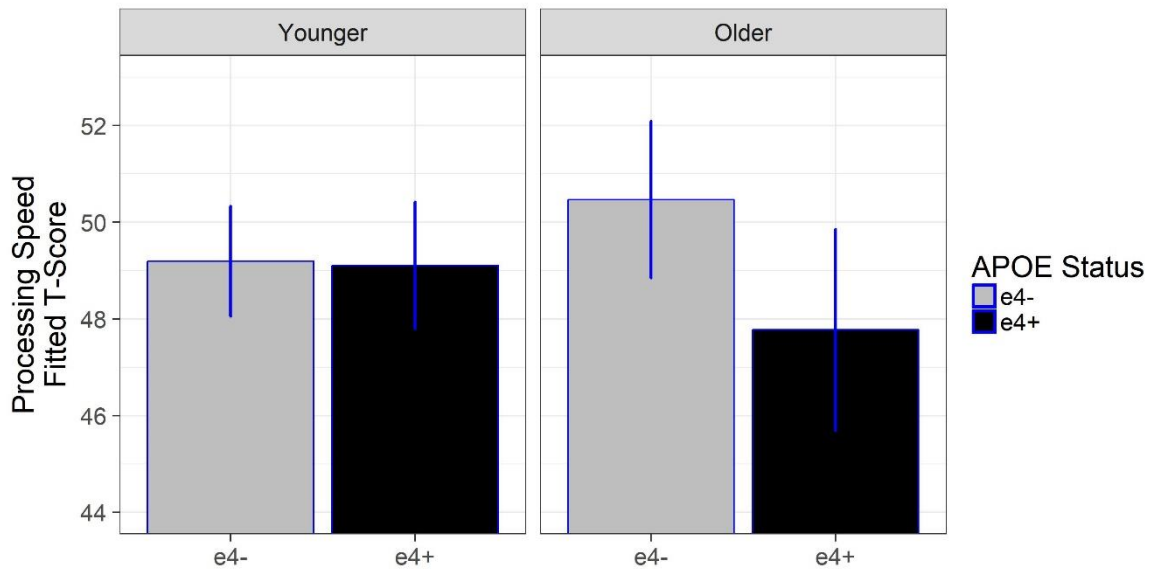on Processing Speed in HIV- women

Figure 14. Error bars represent standard error of the mean.

Notice of Determination of Human Subject Research

December 13, 2017 **(Revised February 15, 2018, February 5, 2019)**

20171338-109076-1

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RE: **Protocol # 2017-1338**
Predictors of Neurocognitive Function and HAND in HIV-infected Women

Sponsor: NIH
PAF#: 2014-00036
Grant/Contract No: 5U01AI034993
Grant/Contract Title: Chicago Consortium for the Women's Interagency HIV Study
(sub-contract with the Hektoen Institute of Medicine)
UIC Student(s): John Bark **(**rev 02/15/2018), Rachel Schroeder, Elizabeth
Wenzel

(**rev 02/05/2019**)

Dear Dr. Maki:

> The UIC Office for the Protection of Research Subjects received your "Determination of
> Whether an Activity Represents Human Subjects Research" application, and has
> determined that this activity **DOES <u>NOT</u> engage UIC.**
>
> Specifically, all data has been collected at clinical WIHS study sites around the
> country. You will regularly review neurocognitive study related outcomes, as
> prepared by the WIHS Data Management and Analysis Center (WDMAC).
> WDMAC will provide analyzed data sets, some of which will include Study

Participant ID numbers as the only identifier. You will have no access to the code linking Study Participant ID numbers with PII/PHI. You will use this data to prepare manuscripts for publication and submission to scientific conferences for abstract/poster presentation. You will also prepare reports for the sponsor (NIH) and the WIHS Executive Committee.

You may conduct your activity without further submission to the IRB. Although UIC IRB approval is not required, you must obtain prospective UIC departmental approval prior to conducting the activity at UIC.

If this activity is used in conjunction with any other research involving human subjects or if it is modified in any way, it must be re-reviewed by OPRS staff.