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SAN DIEGO STATE UNIVERSITY

Vascular Contributions to Neurocognitive Impairment among Older Persons with HIV

A dissertation submitted in partial satisfaction of the
requirements for the degree Doctor in Philosophy

in

Clinical Psychology

by

Jessica Lynette Montoya

Committee in charge:

University of California, San Diego

Professor Igor Grant, Chair
Professor Paul J. Mills
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San Diego State University

Professor Aaron Blashill
Professor Linda Gallo

2017

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Chair

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2017

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PEER-REVIEWED PUBLICATIONS:

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1. Pasipanodya, E.C., **Montoya, J.L.**, Rooney, A., Gouaux, B., & Moore, D.J. (2017, June). Latent trajectories of ART adherence and predictors of classification in an ART intervention among methamphetamine users. Poster presentation at the *12th International Conference on HIV Treatment and Prevention Adherence,* Miami, FL.
2. **Montoya, J. L.**, Iudicello, J., Oppenheim, H. A., Fazeli, P., Potter, M., Ma, Q., Mills, P. J., Ellis, R. J., Grant, I., Letendre, S. L., Moore, D. J., & the HNRP (2016, September). Coagulation and neurocognitive functioning in older adults HIV+ adults on suppressive antiretroviral therapy. Poster presentation at the *7th International Workshop on HIV and Aging*, Washington, DC, USA.
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report of antiretroviral adherence among HIV-infected methamphetamine users. Oral presentation at the *11th International Conference on HIV Treatment and Prevention Adherence,* Fort Lauderdale, FL.

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7. **Montoya, J.L.**, Gouaux, B., Rooney, A., Casaletto, K., Grant, I., & Moore, D.J. (2015, April). Predictors of antiretroviral adherence among active methamphetamine users with HIV. Oral presentation at the *36th Annual Meeting & Scientific Sessions of the Society of Behavioral Medicine*, San Antonio, TX.
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9. Moore, D.J., Fazeli, P.L., Marquine, M.J., Dufour, C., **Montoya, J.L.**, Henry, B., Moore, R.C., Woods, S.P., Letendre, S., Jeste, D.V., Grant, I., & the HNRP Group (2014). Lower levels of moderate physical activity are associated with neurocognitive impairment among older HIV+ adults. Oral presentation at the *7th Symposium on Neuropsychiatry and HIV*, Barcelona, Spain.
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presentation at the *75th Annual Meeting of the College on Problems of Drug Dependence*, San Diego, CA.

14. **Montoya, J.L.**, Cattie, J.E., Morgan, E.E., Woods, S.P., Moore, D.J., Atkinson, J.H., Grant, I., and the TMARC Group (2013, June). Patterns of methamphetamine use vary by age and HIV serostatus. Poster presentation at the *75th Annual Meeting of the College on Problems of Drug Dependence*, San Diego, CA.
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17. **Montoya, J.L.,** Moore, D.J., Umlauf, A., Abramson, I., Duarte, N., Badiee, J., Woods, S.P., Atkinson, J.H., Grant, I., & The HNRP Group. (2012, August). The temporal association of methamphetamine use, HIV status, and affective distress. Poster presentation at the *120th Annual Convention of the American Psychological Association*, Orlando, FL.

ABSTRACT OF THE DISSERTATION

Vascular Contributions to Neurocognitive Impairment among Older Persons with HIV

by

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Doctor of Philosophy in Clinical Psychology

University of California, San Diego, 2017
San Diego State University, 2017

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HIV-associated neurocognitive impairment (NCI) is highly prevalent in the modern era of combination antiretroviral therapy, and older persons (50 years and older) are particularly vulnerable to the burden of HIV-associated NCI. In addition, cardiovascular disease is increasingly observed in HIV. Three studies were conducted to investigate the association between markers of vascular risk and NC function among persons living with HIV/AIDS.

For all three studies, participants completed standardized neurobehavioral and neuromedical assessments. NC function was evaluated using a well-validated comprehensive battery. The first study evaluated the relationships among markers of vascular remodeling, arterial stiffness (measured by pulse pressure, PP), and NC function among older HIV-seropositive (HIV+; n = 72) and HIV-seronegative (n = 36) adults. A biomarker of vascular remodeling was associated with greater PP and worse NC function. PP had a quadratic relationship with NC function, such that lower and higher PP values,

relative to the entire sample mean, were associated with worse NC function. These findings indicate that vascular remodeling may contribute to arterial stiffening and changes in PP, which, in turn, deleteriously affect NC function. The second study assessed the impact of disturbances in coagulation on NC function in the same cohort of older HIV+ and HIV-seronegative adults. Coagulation moderated the effect of HIV on NC function, such that greater coagulation imbalance was associated with poorer NC function among HIV+ participants. The moderating effect of coagulation on neurocognition was driven by procoagulant but not anticoagulant or fibrinolytic biomarkers. These findings indicate that procoagulation may exert a detrimental effect on NC function among older HIV+ adults. Lastly, the third study aimed to examine the association between visit-to-visit variability in blood pressure (BPV) and NC change in a well-characterized HIV+ cohort (N = 533). BPV was not significantly associated with rate of NC change; however, baseline PP was a significant predictor of rate of NC change. These findings suggest that arterial stiffness might be a crucial factor impacting NC function over time among HIV+ adults.

The findings of these studies indicate that vascular remodeling, arterial stiffening, and procoagulation may contribute to poorer NC outcomes among HIV+ persons. Biomarkers of vascular processes may provide valuable information regarding the prognosis and risk stratification of HIV+ adults for NCI.

INTRODUCTION

The HIV epidemic in the U.S. has experienced a notable demographic shift due to the widespread use of combination antiretroviral therapy (cART). Persons 50 years and older make up about half of the US HIV/AIDS population and account for 15% of new infections (Center for Disease Control and Prevention, 2008a; 2008b). cART-treated adults in the U.S. also have a life expectancy approaching that of the general population (Samji et al., 2013).

Given the advances of cART, HIV has transitioned from an acute, rapidly debilitating illness to a chronic medical condition in the U.S. (Stoff, 2004). Despite achievement of "undetectable" HIV RNA plasma levels (generally <50 copies/ml) following initiation of cART, persons living with HIV experience persistent immune activation (Kuller et al., 2008). Thus, the chronic nature of HIV disease is currently characterized by a dynamic interplay between viral persistence and immune response.

Long-term cART-treated patients may be vulnerable to the development of noncommunicable diseases typically associated with aging, such as cardiovascular disease (CVD) (Deeks, 2011). In addition, HIV-associated neurocognitive impairment (NCI) is still highly prevalent in the cART era (Heaton et al., 2010), and the burden of HIV-associated NCI is anticipated to increase with advancing age (Cysique, Bain, Brew, & Murray, 2011). While the advances of cART are associated with both longevity and subsequent increased risk for CVD, both increasing age and CVD risk factors likely exert an impact on neurocognitive (NC) functioning (Cysique & Brew, 2009). Thus, research regarding the role of CVD risk factors and their modification in the risk and progression of HIV-associated NCI is of growing interest (Cruse, Cysique, Markus, & Brew, 2012).

Current challenges in the health care of persons aging with HIV/AIDS are defining the factors related to neurologic morbidity and identifying an integrated approach for treating these factors. Delineating the relative contribution of CVD risk factors in the pathogenesis of HIV-associated NCI may allow for the identification of adjunct therapies aimed at improving health outcomes for persons aging with HIV/AIDS. Therefore, this dissertation project aims to evaluate the associations among markers of CVD risk and NC functioning among persons with HIV.

HIV-Associated Neurocognitive Impairment (NCI)

Despite the effectiveness of modern cART for reducing HIV-related mortality, HIV-associated neurocognitive disorders (HAND) are still highly prevalent (Heaton et al., 2010). The use of cART has effectively diminished the prevalence of HIV-associated dementia, the severest form of HAND (Price & Spudich, 2008); however, up to 50% of persons with HIV demonstrate mild-to-moderate NCI (Heaton et al., 2010). Despite the observed prevalence of largely "mild" impairments, individuals with HIV-associated NCI demonstrate difficulties on functional outcomes (Heaton et al., 2004), including medication adherence and financial management (Thames et al., 2011).

In the pre-cART era, HIV-associated NCI was characterized by difficulties in psychomotor skills, verbal fluency, and speed of information processing (Heaton et al., 2011). HIV-associated NCI during the pre-cART era occurred primarily in late stages of AIDS and correlated with HIV encephalitis, which reflected robust viral replication (Cherner et al., 2002; Wiley & Achim, 1994) and microglia activation (Glass, Fedor, Wesselingh, & McArthur, 1995) with aberrant cytokine expression (Anderson, Zink, Xiong, & Gendelman, 2002) in the brain. In contrast, HIV-associated NCI in the current

era of cART is not necessarily associated with HIV encephalitis (Everall et al., 2009; Gelman et al., 2012; Gelman et al., 2013) and may affect patients with low plasma viral loads and high CD4+ T cell counts (Brew, 2004; Cysique & Brew, 2011; Nath et al., 2008). In the cART era, HIV-associated NCI demonstrates more variability in the clinical course (Grant, 2008; Nath et al., 2008) and is most commonly characterized by deficits in learning, episodic memory, executive functions, and working memory (Heaton et al., 2011). The etiology of HIV-associated NCI in the cART era is multifactorial and may be related to both direct and indirect consequences of HIV, the immune response, and comorbid factors (Valcour, Sithinamsuwan, Letendre, & Ances, 2011c), such as subclinical CVD, cumulative exposure to antiretroviral (ART) medications (Marra et al., 2009), neurodegenerative changes (Soontornniyomkij et al., 2012), coinfection with hepatitis C virus (HCV), and substance use disorders (Cherner et al., 2005; Letendre et al., 2005).

Older Persons Living with HIV are Vulnerable to HIV-Associated NCI

Older adults appear to be particularly vulnerable to HIV-associated NCI relative to their younger counterparts (Becker, Lopez, Dew, & Aizenstein, 2004; Cherner et al., 2004; Sacktor et al., 2007; Valcour et al., 2004). At present, studies attempting to elucidate the association between age and risk for HIV-associated NCI have yielded discordant results (Valcour, Paul, Neuhaus, & Shikuma, 2011a). Some studies have observed a greater risk for adverse consequences on the central nervous system structure and function among older adults with HIV, relative to both their younger counterparts with HIV and older persons without HIV (Ernst & Chang, 2004; Green et al., 2005). Other studies, however, have revealed independent effects of HIV serostatus and age with

minimal or no evidence of a synergistic or interaction effect between these two factors (Cysique, Maruff, Bain, Wright, & Brew, 2011c; Valcour et al., 2011a; Wilkie et al., 2003).

One of the first studies examining the incidence of NCI in HIV in relation to age observed that older adults with HIV (≥ 50 years) were twice as likely to have HIV-associated dementia than their younger counterparts (Valcour et al., 2004). Age, viral burden (i.e., greater viral load in cerebrospinal fluid; CSF), and their interaction were found to be significant predictors of NCI, indicating that older adults with HIV may be at greater risk for HIV-associated NCI (Cherner et al., 2004). Similarly, in a community-based one-year longitudinal study, age was a significant risk factor for prevalence of NCI among persons with HIV, and HIV viral load at study entry was associated with development of NCI at the one-year follow-up visit (Becker et al., 2004).

At the domain level, older adults with HIV (≥ 50 years) appear particularly vulnerable to deficits in episodic memory (Sacktor et al., 2007; Scott et al., 2011; Woods, Dawson, Weber, Grant, & Group, 2010) and executive functions (Iudicello, Woods, Deutsch, Grant, & Group, 2012). In addition, several studies observed a HIV serostatus by age interaction for the domains of psychomotor speed (Vance, Wadley, Crowe, Raper, & Ball, 2011) and executive functioning (Sacktor et al., 2010). In addition to domain-specific deficits, older adults with HIV also exhibit greater dispersion in NC performance (i.e., increased intra-individual variability across test measures) across a broad battery of NC tasks (Morgan et al., 2011).

Although HIV-associated NCI confers increased risk of poor everyday functioning across the age continuum, older adults appear to be at a disproportionate risk

for poorer functional outcomes (Barclay et al., 2007; Doyle et al., 2012; Hinkin et al., 2004; Morgan et al., 2012; Thames et al., 2011; Vance, Fazeli, & Gakumo, 2013; Vance et al., 2011). Consistent with the increased incidence of NCI among older adults with HIV, aging and HIV appear to have synergistic deleterious effects on measures of everyday functioning (Morgan et al., 2012). For example, although persons with older age typically demonstrate higher rates of ART adherence, older adults with NCI evidence disproportionate difficulty with medication adherence (Hinkin et al., 2004; Thames et al., 2011). Furthermore, deficits in verbal episodic memory were independent and robust predictors of dependence on instrumental activities of daily living among older adults with HIV but not among younger adults with HIV (Fazeli et al., 2014). Given the clinical significance of HIV-associated NCI in older adults, defining risk factors contributing to neurologic morbidity and identifying adjunct therapies for persons aging with HIV may have important down-stream effects on improving functional outcomes.

Neurocognitive Change in the Era of Combination Antiretroviral Therapy

After initiation of cART, modest improvement in NC functioning is observed (Al-Khindi, Zakzanis, & van Gorp, 2011; Cole et al., 2007; Cysique et al., 2011b; Cysique et al., 2009; Sacktor et al., 2010; Tozzi et al., 2007). Clinically stable persons with HIV perform similarly to persons without HIV in terms of test-retest change over a one-year period despite a slightly higher NCI rate at baseline (Cysique et al., 2011b; Cysique et al., 2009). Meta-analysis of the extent to which ART improves NC functioning indicates modest improvements in attention (mean d = 0.17), executive function (mean d = 0.18), motor function (mean d = 0.24), and delayed verbal memory (mean d = 0.11) with no observed benefits of ART on delayed visual memory or visuospatial function (Al-Khindi

et al., 2011). The extent to which NC functioning improved with ART was associated with changes in CD4+ T cell count, a marker of immune system integrity (Al-Khindi et al., 2011); however sustained viral suppression does not appear, in itself, to preclude incidence or persistence of HIV-associated NCI (Tozzi et al., 2007).

Given that the mechanisms of NC decline in virally suppressed adults with HIV are unclear, a recent longitudinal CNS HIV Anti-Retroviral Therapy Effects Research (CHARTER) study investigated the incidence and predictors of NC change over a mean of 35 months (Heaton et al., 2015). During the study period, NC change was detected among 40% of the 436 study participants, with 23% declining and 17% improving. Time-to-decline analyses revealed combined effects of time-independent variables measured at the baseline visit (e.g., more significant non-HIV risks for NCI and Hispanic ethnicity) and time-dependent variables measured repeatedly across study visits (e.g., being off ART and more depressive symptoms). In contrast, time-to-improvement analyses revealed combined effects of one time-independent variable (i.e., higher estimated premorbid IQ) and various time-dependent variables (e.g., absence of a lifetime major depressive disorder). Of relevance to the aging HIV population, lower age was marginally ($p < 0.10$) associated with time to NC decline in the CHARTER study; however, this association appears confounded by a higher likelihood of HCV co-infection and lifetime methamphetamine use disorder among the younger study participants. Thus, defining the impact of age on NC change is difficult due to the confounding effect of participant characteristics on NC change.

In summary, despite the beneficial effects of ART on survival and immunological functioning, cART may only modestly improve NC functioning among persons with HIV

(Al-Khindi et al., 2011), and the impact of age on NC change in the context of HIV is uncertain. Thus, more research is needed to identify malleable factors, which may vary by age, that contribute to changes in NC functioning in the context of HIV. Research aimed at identifying mechanisms of HIV-associated NCI may inform novel pharmaceutical treatments and rehabilitation strategies aimed at improving neurologic burden.

Cardiovascular Risk Factors among Persons Living with HIV

As the life expectancy among people living with HIV increases, age-related diseases that affect the general population, such as CVD and its subclinical manifestations, are increasingly observed in persons with HIV (Dube et al., 2008; Giannarelli, Klein, & Badimon, 2011; Rodriguez-Penney et al., 2013) and are anticipated to increase progressively in the near future (Giannarelli et al., 2011). Growing evidence indicates that persons with HIV have higher rates of CVD than age-matched persons without HIV, although conflicting evidence exists (Currier et al., 2008). HIV disease markers, such as nadir CD4+ T cell count, predict an elevated risk for CVD independent of other factors (Baker et al., 2008; Ho et al., 2010), suggesting that HIV disease confers risk for CVD. Interestingly, "elite controllers" – persons naïve to cART with durably controlled HIV infection – have more carotid disease than age-matched persons without HIV (Hsue et al., 2009; Pereyra et al., 2012), supporting the hypothesis that HIV confers risk for CVD that is independent of the direct toxicity of cART, high viral replication, and advanced immunodeficiency.

The mechanisms underlying vulnerability to CVD in the context of HIV is the focus of intense investigation. People with HIV often have more traditional CVD risk

factors (e.g., hypertension, diabetes mellitus, dyslipidemia). However, traditional risk factors do not account fully for the increased risk for CVD (Grinspoon et al., 2008; Grunfeld et al., 2009; Triant, Lee, Hadigan, & Grinspoon, 2007), such that CVD risk scores like Framingham and Reynolds appear to underestimate risk levels for adults with HIV (Parra et al., 2010). HIV disease is associated with increases in markers of inflammation (e.g. C-reactive protein) (Lau et al., 2006), endothelial activation (e.g. intercellular and vascular cell adhesion molecules) (de Larranaga, Petroni, Deluchi, Alonso, & Benetucci, 2003; Wolf et al., 2002) and coagulation (e.g. D-dimer) (Kuller et al., 2008; Wolf et al., 2002), suggesting potential processes that may underlie vulnerability for CVD.

Cardiovascular Disease Risk Factors as a Key Underpinning of HAND

Recent evidence indicates that CVD risk factors may contribute to HIV-associated NCI. Persons with HIV who were untreated for cerebrovascular risk demonstrated poorer performance in the NC domains of processing speed, learning/memory, and executive functioning compared to persons with HIV who were pharmacologically treated for cerebrovascular risk (Foley et al., 2010). In the multicenter study, Strategies for Management of Antiretroviral Therapy (SMART), prior CVD and CVD risk factors (i.e., hypercholesterolemia and hypertension) were associated with poorer NC performance in a sample of patients with well-controlled viremia (Wright et al., 2010). Carotid intima-media thickness, a subclinical marker of atherosclerosis, has also been linked to reduced psychomotor speed (Becker et al., 2009) and global NC performance (Fabbiani et al., 2013) in the context of HIV. The growing body of research on the role of CVD risk factors in the pathogenesis of HIV-associated NCI supports continued research aimed at

identifying CVD risk factors that contribute to neurologic morbidity in the aging HIV population. The proposed dissertation project aims to add to this growing body of research by examining the associations among markers of CVD risk (i.e., arterial stiffness, coagulation imbalance, and visit-to-visit variability in blood pressure; BPV) and NC functioning among adults with HIV.

Arterial Stiffness and Neurocognitive Functioning. Persons with HIV may evidence greater arterial stiffness than demographically matched persons without HIV (Chan & Dart, 2011; Echeverria et al., 2014; van Wijk et al., 2006). Some studies, however, reported no differences in arterial stiffness by HIV serostatus (e.g., Papita, Albu, Fodor, Itu, & Carstina, 2011). Arterial stiffening is a complex process that may result from functional and structural changes in the arterial wall (Lakatta & Levy, 2003). With increased arterial stiffening, there are observed changes in blood pressure (BP) such that systolic BP (SBP) increases, diastolic BP (DBP) decreases, and pulse pressure (PP) – defined as the difference between SBP and DBP readings – increases (Lakatta & Levy, 2003). Elevation of PP, a surrogate marker of arterial stiffness, is associated with progression of carotid intimal media thickening (Zureik et al., 1999) and is an independent risk factor for future cardiovascular events (Blacher et al., 2000; Franklin, Khan, Wong, Larson, & Levy, 1999; Glynn, Chae, Guralnik, Taylor, & Hennekens, 2000; Sesso et al., 2000). Until about the sixth decade of life, SBP and DBP both increase linearly with age; thereafter, SBP continues to rise while DBP begins to decrease, resulting in a steep rise in PP (Franklin et al., 1997).

In regard to NC functioning, the relationship between PP and risk of Alzheimer disease (AD) and dementia appears to have a U-shared relationship, such that lower and

higher PP confers risk relative to mean PP (Qiu, Winblad, Viitanen, & Fratiglioni, 2003). A recent investigation found that PP elevation is associated with increased phosphorylated tau (P-tau) protein and decreased β-amyloid 1–42 ($A\beta_{1-42}$) in older adults without NCI, suggesting that pulsatile hemodynamics may be related to subclinical neurodegeneration (Nation et al., 2013). The associations between PP and CSF biomarkers observed in older adults without NCI were limited to persons in the fifth and sixth decades of life and were not observed among persons beyond the sixth decade. A plausible explanation for this age-dependent relationship is that PP is less relevant among older persons who may have additional factors contributing to neurodegeneration, whereas PP is among the few factors modifying cerebral amyloidosis and tau-related neurodegeneration in younger individuals.

The neurologic consequence of arterial stiffness in the context of HIV disease remains unclear and warrants investigation. In study 1, we aim to evaluate the association between NC functioning and PP. We hypothesized that PP would have a quadratic relationship with NC functioning, such that lower and higher PP values (relative to sample mean PP) will be associated with worse NC functioning.

Coagulation and Neurocognitive Functioning. In the context of HIV disease, impairment of endothelial function is observed with viral replication (Blum, Hadas, Burke, Yust, & Kessler, 2005; Ross et al., 2008). Endothelial cell activation is characterized by an increased expression of various leukocyte adhesion molecules, platelet aggregation, and blood clotting (Blake & Ridker, 2001; Blann, 2000; Pearson et al., 2003). Thus, persons with HIV may experience imbalance in coagulation given impaired endothelial function and immune activation (Funderburg, 2014; Funderburg &

Lederman, 2014; Hileman et al., 2012). Coagulation imbalance is observed in the context of viral replication (Baker et al., 2013a; de Larranaga et al., 2003). For example, in a subset of participants in the SMART trial, HIV replication was associated with complex changes in the extrinsic pathway, such as short-term increases in some procoagulants (e.g., higher FVIII) and decreases in anticoagulants [e.g., lower antithrombin (AT) and lower protein C] (Baker et al., 2013a). Some studies have found that biomarkers indicative of coagulation decrease with initiation of cART (e.g., Baker et al., 2011); however, cART-treated persons appear to be vulnerable to coagulation imbalance relative to persons without HIV (Neuhaus et al., 2010). Although untreated patients may have elevated D-dimer levels relative to treated patients on cART, both untreated and treated patients on cART are observed to have reduced platelet aggregation and clot initiation (Haugaard et al., 2013).

Coagulation imbalance is linked to increased risk for CVD among persons with HIV (Duprez et al., 2012; Ford et al., 2010; Musselwhite et al., 2011; Nordell et al., 2014; Tenorio et al., 2014). D-dimer, a fibrin degeneration product, has been the most studied biomarker indicative of coagulation in the HIV literature and demonstrates significant clinical associations with several health outcomes (e.g., venous thromboembolism, cardiovascular events, and all-cause mortality) (Duprez et al., 2012; Ford et al., 2010; Justice et al., 2012; Kuller et al., 2008; Musselwhite et al., 2011; Nordell et al., 2014; Tenorio et al., 2014). Further, older persons with HIV may be particularly vulnerable to coagulation imbalance, given that aging further exerts a strong influence on hemostatic biomarkers, such as D-dimer (Deguchi, Deguchi, Wada, & Murashima, 2000).

The clinical consequences of HIV disease on coagulation in the context of suppressive ART remains unclear. In study 2, we aimed to assess the impact of disturbances in coagulation (i.e., coagulation imbalance) on NC functioning in HIV. We hypothesized that greater coagulation imbalance would have a detrimental effect on neurocognitive functioning in HIV. A better understanding of the role of coagulation in HIV-associated NCI may lead to the utilization of specific treatments aimed at reducing coagulopathy.

Visit-to-visit Variability in Blood Pressure and Neurocognitive Change. Initiation of cART is associated with both elevations in BP and hypertension among persons with HIV (Bergersen, Sandvik, Dunlop, Birkeland, & Bruun, 2003; Chow et al., 2003; Palacios et al., 2006; Seaberg et al., 2005). Changes in BP that accompany initiation of cART appear to be associated with traditional risk factors (e.g., older age, higher body mass index) rather than HIV disease characteristics (e.g., prevalence of AIDS, duration of HIV infection, HIV RNA level, CD4+ T cell count, and cART exposure) (Palacios et al., 2006; Thiebaut et al., 2005).

Hypertension is a critical, treatable risk factor for vascular events and a leading indication for prescribed drugs (Woodwell & Cherry, 2004). The predictive value of hypertension also appears age-dependent, such that the association between BP and vascular events decreases with age despite the increased incidence of vascular events with age (Lewington et al., 2002; Rothwell et al., 2004). Another limitation of the clinical use of individual BP readings is the variability in the course of BP between visits and the occurrence of episodic hypertension (Colandrea, Friedman, Nichaman, & Lynd, 1970; Cuffe, Howard, Algra, Warlow, & Rothwell, 2006; Hypertension Detection and Follow-

Up Program Cooperative Group, 1978; Perry & Miller, 1992). Visit-to-visit variability in BP (BPV) has previously been dismissed as random and an obstacle to reliable estimate of "true" BP (Klungel et al., 2000; MacMahon et al., 1990; Turner & van Schalkwyk, 2008). However, recent research suggests that BPV may be an important risk factor for vascular events (Rothwell et al., 2010a; Rothwell et al., 2010b). Even when mean SBP was effectively lowered in medication trials, high visit-to-visit variability in SBP (SBPV) was indicative of poor prognosis (Rothwell et al., 2010a; Rothwell et al., 2010b). The benefits of antihypertensive drugs on the reduction of vascular events may be partly attributable to a reduction in BP variability (Rothwell et al., 2010a; Webb, Fischer, Mehta, & Rothwell, 2010).

The role of BPV in NC change was recently examined in prospective studies involving patients with Alzheimer's disease (AD) and patients at risk for CVD (Lattanzi, Luzzi, Provinciali, & Silvestrini, 2014; Sabayan et al., 2013). In one study involving patients affected by mild-to-moderate AD, SBPV was defined by the coefficient of variation (i.e., standard deviation x 100/mean) and found to be associated with a significant decline in NC status, as measured by the Mini Mental State Examination (Lattanzi et al., 2014). Interestingly, visit-to-visit variability in DBP (DBPV), mean SBP, and mean DBP did not demonstrate an association with the course of NC change. Thus, fluctuations in SBP over time may be a correlate of NC decline in AD patients. Additionally, in a prospective cohort study involving persons at risk for CVD, higher BPV, defined as the standard deviation of BP measurements across visits, was associated with impaired NC function in older age (>70 years) (Sabayan et al., 2013). Although the association between BPV and NC change has not been extensively studied in various

patient populations, the initial studies in AD and CVD risk indicate that variation in BP across clinical visits may be a useful prognostic marker for NC decline. To our knowledge, longitudinal cohort studies involving persons with HIV have not investigated the association between BPV and changes in NC functioning. Research examining the role of BPV in HIV-associated NCI may be particular relevant given that ART use has been associated with alterations in BP. Thus, in study 3 we examined whether BPV predicts longitudinal NC change among persons with HIV. We hypothesized that age and BPV would have an interacting effect on NC change, such that the strength of the association between BPV and NC change would decrease with older age.

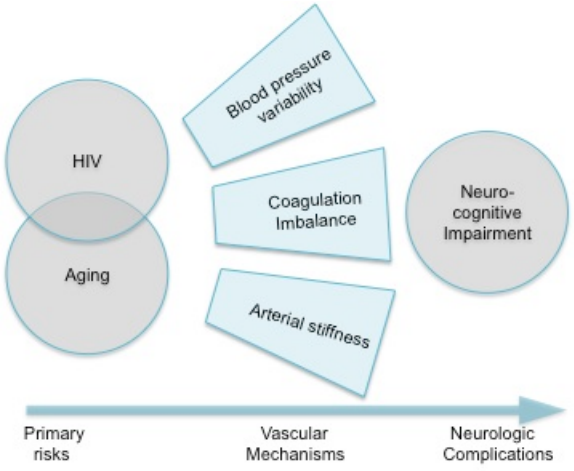

Figure 1. Proposed mechanisms underlying HIV-associated neurocognitive impairment

Study Objective

As cART treated individuals live longer, the aging HIV population is particularly vulnerable to NCI, which has downstream effects on functional outcomes. Research is needed to bolster our understanding of CVD risk factors in the risk and progression of

HIV-associated NCI. HIV is associated with chronic inflammation and endothelial dysfunction, suggesting that vascular processes may underlie vulnerability for HIV-associated NCI (figure 1). This dissertation project aims to contribute to the body of research regarding the vascular contributions of HIV-associated NCI through three studies designed to use existing data to evaluate the associations among markers of CVD risk [i.e., arterial stiffness, coagulation imbalance, and BPV] and NCI among persons living with HIV/AIDS.

CHAPTER 1.

Elevated Markers of Vascular Remodeling and Arterial Stiffness Are Associated with Neurocognitive Function in Older HIV+ Adults on Suppressive Antiretroviral Therapy

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Abstract

Background: HIV is associated with elevated markers of vascular remodeling that may contribute to arterial fibrosis and stiffening, and changes in pulse pressure (PP). These changes may, in turn, deleteriously affect autoregulation of cerebral blood flow and neurocognitive function.

Methods: To evaluate these mechanisms, we studied markers of vascular remodeling, PP, and neurocognitive function among older (≥50 years of age) HIV-infected (HIV+; n = 72) and HIV-seronegative (HIV-; n = 36) adults. Participants completed standardized neurobehavioral and neuromedical assessments. Neurocognitive functioning was evaluated using a well-validated comprehensive battery. Three plasma biomarkers of vascular remodeling (i.e., angiopoietin 2, Tie-2, and vascular endothelial growth factor; VEGF) were collected.

Results: HIV+ and HIV- participants had similar levels of plasma Ang-2 (p = .48), Tie-2 (p = .27), VEGF (p = .18), and PP (p = .98). In a multivariable regression model, HIV interacted with Tie-2 (β = .41, p < .01) and VEGF (β = -.43, p = .01) on neurocognitive function, such that lower Tie-2 and higher VEGF values were associated with worse neurocognitive function for HIV+ participants. Greater Tie-2 values were associated with increased PP (r = .31, p < .01). In turn, PP demonstrated a quadratic association with neurocognitive function (β = -.33, p = .01), such that lower and higher, relative to mean sample, PP values were associated with worse neurocognitive function.

Conclusions: These findings indicate that vascular remodeling and altered cerebral blood flow autoregulation contribute to neurocognitive function. Furthermore, HIV moderates

the association between vascular remodeling and neurocognitive function but not the association between PP and neurocognitive function.

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Key Words: aging, arterial stiffness, cognition, pulse pressure

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INTRODUCTION

HIV-associated neurocognitive impairment (NCI) remains highly prevalent in the current era of combination antiretroviral therapy (cART),[1] although the severity of impairment tends to be milder than in the pre-cART era.[1,2] Even mild forms of NCI can be associated with poor everyday functioning.[3,4] The burden of HIV-associated NCI is projected to increase as persons living with HIV (HIV+) age.[5] In addition, older age–related diseases that affect the general population, such as cardiovascular disease (CVD), are increasingly observed in HIV+ persons[6–8] and are anticipated to increase in the future.[7] With the increased incidence and prevalence of CVD, there is a growing body of evidence demonstrating the detrimental effect of CVD risk factors on neurocognitive function among HIV+ persons.[9–11]

HIV disease, which is characterized by chronic inflammation, may confer risk for increased arterial stiffness.[12–15] Arterial stiffening is a complex process involving structural and functional changes in the arterial wall that occurs with normal aging[16] and is accelerated by chronic inflammatory conditions, such as diabetes mellitus and hypertension.[17,18] Arterial remodeling is influenced by multiple biological pathways, including vascular endothelial growth factor (VEGF) and angiopoietin pathways.[19] VEGF and angiopoietins are considered to work in concert during vascular remodeling, such that VEGF is expressed during the earliest stages of vascular remodeling and the angiopoietin pathway plays a larger role in vessel maturation.[20] With increased arterial stiffening, changes in blood pressure (BP) occur such that systolic BP (SBP) increases, diastolic BP (DBP) decreases, and pulse pressure (PP)—defined as the difference between SBP and DBP readings—increases.[16] PP is a surrogate marker of arterial stiffness, and elevation of PP is an

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independent risk factor for future cardiovascular events and cerebrovascular disease.[21–25] Markers of arterial stiffness are associated with neurocognitive performance and decline in relatively healthy middle-aged adults.[26,27] On the other end of the spectrum, poor cerebral perfusion related to low PP is associated with increased risk of NCI.[28]

The neurologic consequences of vascular remodeling and arterial stiffness in the context of chronic HIV disease remain unclear and warrant investigation. The first aim of this study is to examine the relation of vascular remodeling with neurocognitive function. Angiogenic growth factors were examined because of their role in vascular remodeling.[19,29] Second, we aim to investigate the association of vascular remodeling with PP. We hypothesize that biomarkers associated with vascular remodeling will be related to greater PP. Lastly, we aim to evaluate the association between neurocognitive function and PP. We hypothesize that PP will have a quadratic relationship with neurocognitive function, such that lower and higher PP values (relative to sample mean PP) will be associated with worse neurocognitive function.

METHODS

Participants and Procedure

The present study included 72 HIV+ and 36 HIV− community-dwelling older (ie, aged 50 and above) adults who participated in the California HIV/AIDS Research Program Successfully Aging Seniors with HIV study at the UCSD HIV Neurobehavioral Research Program. The study protocol was approved by the UCSD Institutional Review Board, and all participants provided written informed consent to participate. Inclusion criteria were (1) being at least 50 years of age, (2) being on cART (for HIV+ participants), and (3) having an undetectable plasma HIV viral load (<48 copies per milliliter for HIV+ participants). Exclusion criteria included a history of non–HIV-related neurologic disorders or any other known condition that might account for impaired neurocognitive function (eg, seizure disorder). Each participant underwent standardized neuropsychological, neuromedical, and psychiatric assessments.

Neurocognitive Assessment

Participants completed a comprehensive neurocognitive test battery (administration time: 2–2.5 hours) that assesses 7 neurocognitive domains consistent with Frascati recommendations for neuroAIDS research.[30] The 7 neurocognitive domains were speed of information processing (SIP), learning, memory, executive functioning, verbal fluency, working memory, and fine motor functioning (see Heaton et al[1] for details on the specific test battery). Raw scores from the neurocognitive tasks were converted to demographically adjusted T-scores (mean = 50, SD = 10 in healthy subjects) using the best available normative standards, which correct for the effects of age, education, sex, and ethnicity, as appropriate.[3,31,32] T-scores were further corrected for exposure to previous neurocognitive assessment, as needed. The demographically adjusted T-scores were averaged to derive a global T-score, the main outcome of interest in statistical analyses.

Neuromedical Assessment

Medical characterization of study participants included measurement of vital signs, anthropometrics, medical comorbidities, and current prescription medications. Blood was collected by venipuncture, and aliquots were stored at −80°C until assayed. BP was measured in the seated position with an automated sphygmomanometer. PP was calculated as the difference between SBP and DBP. Body mass index (BMI) was calculated from measured height and weight. Medical comorbidities and prescribed and over-the-counter medications were determined by interview.

For the HIV+ group, the following HIV disease characteristics were collected: AIDS diagnosis, estimated duration of HIV infection, current and nadir cluster of differentiation 4 $(CD4)^+$ T-cell counts, and duration of cART. HIV RNA level was measured in plasma by reverse transcriptase polymerase chain reaction (Abbott Diagnostics; lower limit of quantitation 48 copies per milliliter).

Biomarkers Related to Vascular Remodeling

Vascular remodeling–related biomarkers were measured in plasma by immunoassay: Angiopoietin 2 (Ang-2) (R&D Systems, Minneapolis, MN), VEGF, and endothelium-specific receptor tyrosine kinase (Tie-2) (Meso Scale Discovery, Rockville, MD). Assays were performed in duplicate, and assays for the samples with coefficients of variation greater than 20% or outliers that were more than 4 SDs from the mean were repeated. Assays for 10% of the samples were also repeated to ensure operator and batch consistencies.

Psychiatric Assessments

Study participants underwent a comprehensive psychiatric research evaluation. The Composite International Diagnostic Interview,[33] a computer-assisted clinical interview, was administered. The Composite International Diagnostic Interview assesses the presence of lifetime and current affective disorders [eg, major depressive disorder (MDD)] and substance-use disorders using diagnostic criteria based on the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*.[34] The Medical Outcome Study 36-Item Short-Form version 1.0[35] was used to assess physical functioning and emotional well-being.

Statistical Analyses

Comparison of demographic, medical, biomarker, psychiatric, and neuropsychological data across HIV+ and HIV− groups was performed with 2-tailed *t* test or Pearson χ^2 test, as appropriate. Biomarkers were $\log_{10}$ transformed to reduce skewness as is standard practice. Pearson correlations for continuous variables and *t* tests for categorical variables were conducted between the dependent variables (DV) and

explanatory variables (listed in Tables 1 and 2) to identify covariates to include in subsequent multivariable linear regression models (critical $\alpha = 0.10$).

Three multivariable linear regression tests were conducted to examine the association between (1) biomarkers of vascular remodeling (independent variables, IV) and neurocognitive function (DV), (2) biomarkers of vascular remodeling (IV) and PP (DV), and (3) PP (IV) and neurocognitive function (DV). Given our objective to examine whether HIV moderates these relations, all multivariable linear regression analyses tested for HIV by IV interactions. Before final model selection, the variable inflation factor was used to check for multicollinearity among predictor variables, and model selection was rerun to include only one of the correlated variables at a time. To achieve parsimonious models, variables were only retained in the final models if they had P values <0.10. All statistical tests were performed with JMP 11.0.0 (SAS, 2013).

RESULTS

Participants

The sample consisted of 108 participants who were predominantly middle-aged [mean 58.5 (SD 6.3) years] non-Hispanic white (77.8%) men (76.9%) with some college education [mean 14.5 (SD 2.6) years]. Demographic, medical, and psychiatric characteristics of the sample are presented in

TABLE 1. Demographic and Clinical Characteristics of Sample (N = 108)

	All (N = 108)	HIV+ (n = 72)	HIV− (n = 36)	*P*
Descriptive demographics				
Age, mean (SD)	58.5 (6.3)	58.2 (6.5)	59.0 (5.9)	0.53
Education, mean (SD)	14.5 (2.6)	14.6 (2.6)	14.3 (2.7)	0.57
Male, n (%)	83 (76.9)	61 (84.7)	22 (61.1)	0.006
Non-Hispanic white, n (%)	84 (77.8)	61 (84.7)	23 (63.9)	0.01
Vital signs and anthropometrics				
PP, mean (SD)	58.8 (17.8)	58.8 (17.6)	58.7 (18.5)	0.98
SBP, mean (SD)	134.4 (20.9)	133.4 (20.7)	136.4 (21.7)	0.49
DBP, mean (SD)	75.6 (11.1)	74.6 (10.0)	77.7 (12.8)	0.17
MAP, mean (SD)	95.0 (12.5)	94.0 (11.8)	97.0 (13.7)	0.23
Pulse, mean (SD)	65.2 (10.9)	65.5 (11.5)	64.7 (9.8)	0.70
BMI, mean (SD)*	27.4 (5.7)	27.5 (5.8)	27.3 (5.4)	0.87
Medical comorbidities				
Hyperlipidemia, n (%)	54 (50.0)	43 (59.7)	11 (30.6)	0.004
Hypertension, n (%)	45 (41.7)	32 (44.4)	13 (36.1)	0.41
Ever smoker, n (%)	45 (41.7)	30 (41.7)	15 (41.7)	1.00
Current smoker, n (%)	37 (34.3)	27 (37.5)	10 (27.8)	0.32
Diabetes mellitus, n (%)	27 (25.0)	20 (27.8)	7 (19.4)	0.35
Hepatitis C virus, n (%)	22 (20.4)	16 (22.2)	6 (16.7)	0.50
Current medications				
NSAID, n (%)	33 (30.6)	25 (34.7)	8 (22.2)	0.18
Antihypertensive drug, n (%)	34 (31.5)	26 (36.1)	8 (22.2)	0.14
Lipid-lowering drug, n (%)	40 (37.0)	32 (44.4)	8 (22.2)	0.02
Antidepressant drug, n (%)	35 (32.4)	32 (44.4)	3 (8.3)	<0.001
Psychiatric characteristics/diagnoses				
Current MDD, n (%)*	9 (8.4)	8 (11.3)	1 (2.8)	0.13
LT MDD, n (%)	50 (46.3)	40 (55.6)	10 (27.8)	0.006
LT alcohol-use disorder, n (%)	52 (48.6)	36 (50.0)	16 (45.7)	0.68
LT cannabis-use disorder, n (%)	30 (28.0)	23 (31.9)	7 (20.0)	0.20
LT meth-use disorder, n (%)	29 (27.1)	21 (29.2)	8 (22.9)	0.49
LT cocaine-use disorder, n (%)	23 (21.5)	17 (23.6)	6 (17.1)	0.44
MOS physical health, mean (SD)	70.3 (22.7)	65.2 (23.2)	80.3 (18.1)	<0.001
MOS mental health, mean (SD)	70.7 (23.1)	65.2 (22.9)	81.7 (19.5)	<0.001
Biomarkers of vascular injury and remodeling				
Ang-2, pg/mL, median (IQR)	4073 (2865–5359)	4030 (3002–5443)	4144 (2110–5427)	0.48
Tie-2, pg/mL, median (IQR)	7307 (6088–8484)	7568 (6184–8386)	7041 (5540–8529)	0.27
VEGF, pg/mL, median (IQR)	115 (80–178)	126 (87–206)	107 (73–159)	0.18

*n = 107.
IQR; interquartile range; LT, lifetime; MAP, mean arterial pressure; meth, methamphetamine; MOS, Medical Outcome Study; NSAID, nonsteroidal anti-inflammatory drug.

TABLE 2. HIV+ Group Characteristics

HIV Disease–Related Characteristic	HIV+ (n = 72)
AIDS, n (%)*	43 (60.6)
Duration of HIV infection, yrs, mean (SD)*	17.3 (8.1)
Current CD4+ T-cell count, median (IQR)†	654 (487–843)
Nadir CD4+ T-cell count, median (IQR)	180 (49–308)
Duration of exposure to ARVs, yrs, mean (SD)*	11.9 (7.1)
Undetectable plasma HIV RNA, n (%)	70 (100.0)
Prescribed protease inhibitor, n (%)	36 (50.0)

*n = 71.
†n = 70.
AIDS, acquired immunodeficiency syndrome; ARV, antiretroviral; IQR; interquartile range.

Table 1. In general, HIV serostatus groups were largely comparable (ie, P values for group differences > 0.05) across many characteristics, including age, education, vital signs, anthropometrics, medical comorbidities, medical prescriptions, and proportion of current MDD and lifetime substance-use disorders. About 44 vs. 36% of HIV+ and HIV− groups were hypertensive, respectively, and of whom 81% vs. 62% were taking antihypertensive medications. The HIV+ group had more non-Hispanic white participants (84.7% vs. 63.9%, $P = 0.01$), men (84.7% vs. 61.1%, $P = 0.006$), hyperlipidemia (59.7% vs. 30.6%, $P = 0.004$), and lifetime MDD (55.6% vs. 27.8%, $P = 0.006$).

Among the HIV+ participants (n = 72), the mean estimated duration of HIV infection was 17.3 years, the mean duration of exposure to cART was 11.9 years, the median current CD4+ T-cell count was 654 cells per cubic millimeter, and the median nadir CD4+ T-cell count was 180 cells per cubic millimeter. HIV disease–related characteristics of the HIV+ sample are presented in Table 2.

HIV+ participants had worse neurocognitive function [global T-score = 45.8 (SD 7.0)] than HIV− participants [global T-score = 49.9 (SD 6.4)] ($P = 0.004$). HIV+ and HIV− participants had similar levels of plasma VEGF, Ang-2, and Tie-2 (P values for group differences > 0.05; Table 1). PP values did not differ between the HIV+ [mean (SD) = 58.8 (17.6)] and HIV− [mean (SD) = 58.7 (18.5)] participants ($P = 0.98$).

Vascular Remodeling and Neurocognitive Function

At the univariable level, global T-scores did not have statistically significant correlations with the biomarkers of vascular remodeling: Ang-2 ($r = -0.03$, $P = 0.77$), Tie-2 ($r < 0.01$, $P = 0.99$), and VEGF ($r = -0.10$, $P = 0.32$). Multivariable linear regression analyses were conducted to test for potential interacting effects of HIV and biomarkers of vascular remodeling on neurocognitive function. Of the covariates listed in Tables 1 and 2, pulse, diabetes, antidepressant prescription, current MDD, lifetime MDD, and the Medical Outcome Study physical health composite were associated with global T-scores (P values < 0.10). The best fitting model of neurocognitive function (model adjusted $R^2 = 0.13$, $P < 0.01$; Table 3, model 1) identified a statistically significant interaction between HIV and Tie-2 ($\beta = 0.32$, $P = 0.03$), such that lower Tie-2 values were associated with lower global T-scores (ie, worse neurocognitive function) for HIV+ participants. For HIV− participants, higher Tie-2 values were associated with lower global T-scores. The interaction between HIV and VEGF was retained in the final model ($\beta = -0.33$, $P = 0.05$). Neither the interaction term between HIV and Ang-2 nor the main effect of Ang-2 met statistical significance (P values > 0.10) and were not retained in the final model.

Vascular Remodeling and PP

To examine empirically whether vascular remodeling was related to elevated PP, correlational analyses were performed in the entire sample (Table 4). Higher PP correlated with higher values of Tie-2 ($r = 0.31$, $P < 0.01$), but not VEGF ($r = 0.10$, $P = 0.32$) or Ang-2 ($r = 0.03$, $P = 0.76$). Multivariable linear regression analysis was performed to test for interacting effects of HIV and biomarkers of vascular remodeling on PP. Of the covariates listed in Tables 1 and 2, age, BMI, dyslipidemia, hypertension, current smoker status, and nonsteroidal anti-inflammatory drug, antihypertensive, and lipid-lowering drug use were associated with PP (P values < 0.10). In the best fitting model (model adjusted $R^2 = 0.24$, $P < 0.01$; Table 3, model 2), Tie-2 ($\beta =$

TABLE 3. Multivariable Linear Regression Models (N = 108)

	Adjusted R^2	F	β	P
Model 1. Association between vascular injury (IV) and neurocognitive functioning (DV)				
Overall model	0.13	3.53		<0.01
HIV serostatus (ref: HIV−)			−0.28	<0.01
HIV × Tie-2 interaction			0.32	0.03
HIV × VEGF interaction			−0.33	0.05
Tie-2			−0.22	0.15
VEGF			0.24	0.16
Diabetes mellitus			−0.21	0.03
Model 2. Association between vascular injury (IV) and PP (DV)				
Overall model	0.24	11.44		<0.01
BMI			0.32	<0.01
Tie-2			0.31	<0.01
Age			0.22	0.01
Model 3. Association between PP (IV) and neurocognitive functioning (DV)				
Overall model	0.22	4.57		<0.01
HIV serostatus (ref: HIV−)			−0.29	<0.01
PP			0.41	<0.01
PP^2			−0.33	0.01
HIV × Tie-2 interaction			0.41	<0.01
HIV × VEGF interaction			−0.43	0.01
Tie-2			−0.38	0.02
VEGF			0.38	0.03
Diabetes mellitus			−0.19	0.04

Tie-2, log transformed, and VEGF, log transformed.
PP^2, quadratic term.

TABLE 4. Correlations Between Vascular Biomarkers and Vital Signs (N = 108)

	Ang-2	Tie-2	VEGF
Tie-2	0.11		
VEGF	0.28*	0.29*	
SBP	−0.06	0.36†	0.09
DBP	−0.16	0.19	0.00
MAP	−0.13	0.31*	0.05
PP	0.03	0.31*	0.10

*$P < 0.01$.
†$P < 0.001$.
MAP, mean arterial pressure.

0.31, $P < 0.01$), age ($\beta = 0.22$, $P = 0.01$), and BMI ($\beta = 0.32$, $P < 0.01$) were statistically significant predictors of PP. Neither the interactions between HIV and biomarkers of vascular remodeling nor the main effects of Ang-2 and VEGF (P values > 0.10) were statistically significant.

PP and Neurocognitive Function

Multivariable linear regression with polynomial terms was used to determine the association between PP and neurocognitive function. The best model identified that both the linear ($\beta = 0.41$, $P < 0.01$) and quadratic ($\beta = -0.33$, $P = 0.01$) terms for PP were statistically significant in the model for neurocognitive function (model adjusted $R^2 = 0.22$, $P < 0.001$; Table 3, model 3). HIV interacted with Tie-2 ($\beta = 0.41$, $P < 0.01$) and VEGF ($\beta = -0.43$, $P = 0.01$) in relation to neurocognitive function. As illustrated in Figure 1, lower Tie-2 and higher VEGF values were associated with worse neurocognitive function for HIV+ participants. For HIV− participants, higher Tie-2 and lower VEGF values were associated with worse neurocognitive function. Diabetes mellitus was associated with worse neurocognitive function in the multivariable model ($\beta = -0.19$, $P = 0.04$). The interaction between HIV and PP was not statistically significant ($P < 0.10$) and thus not retained in the final model.

To explore whether other vital signs (SBP, DBP, and mean arterial pressure) demonstrate a similar association with neurocognitive function, additional multivariable linear regression models were conducted. Only SBP had a significant quadratic association ($\beta = -0.24$, $P = 0.03$) with neurocognitive function (model adjusted $R^2 = 0.17$, $P = 0.001$). The other vital signs (DBP and mean arterial pressure) did not have significant associations (linear or a quadratic) with neurocognitive function (P values > 0.05).

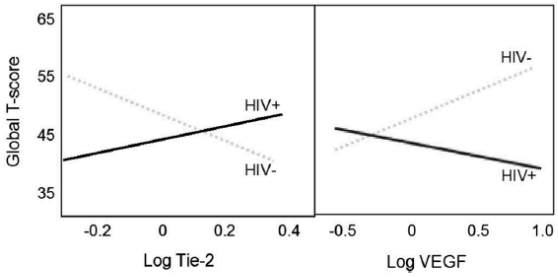

FIGURE 1. HIV interacts with biomarkers of vascular remodeling on neurocognitive function.

It should be noted that although age was univariably associated with PP, it was not included in model 3 described above because we used demographically adjusted T-scores in our analyses. In post hoc analyses using non–age-adjusted global T-scores, age and both the linear and quadratic terms of PP were independently associated with neurocognitive function (data not presented).

In post hoc analyses, we examined the associations between vascular remodeling, PP, and neurocognitive function at the domain level by conducting multivariable linear regression analyses. Statistically significant models were obtained for fine motor functioning (model adjusted $R^2 = 0.28$, $P < 0.001$), SIP (model adjusted $R^2 = 0.23$, $P = 0.001$), executive functioning (model adjusted $R^2 = 0.19$, $P = 0.01$), and learning (model adjusted $R^2 = 0.19$, $P = 0.01$). The interaction of HIV and Tie-2 on neurocognitive function was statistically significant (P values < 0.05) in the models for fine motor functioning, SIP, and learning. The interaction of HIV and VEGF on neurocognitive function was statistically significant (P values < 0.05) in the models for fine motor functioning, SIP, and learning. Lastly, a statistically significant quadratic association between PP and neurocognitive function (P values < 0.05) was observed in the models for fine motor functioning, SIP, and executive functioning.

DISCUSSION

In our cohort of older HIV+ and HIV− adults, markers of vascular remodeling and arterial stiffness were associated with neurocognitive function. HIV interacted with biomarkers of vascular remodeling (ie, Tie-2 and VEGF) on neurocognitive function. For HIV+ adults, lower Tie-2 values and higher VEGF values were associated with worse neurocognitive function. Vascular remodeling, as measured by higher Tie-2 values, was associated with greater PP values. In turn, PP had a quadratic relationship with neurocognitive function. Relative to the sample mean, lower and higher values of PP were associated with worse neurocognitive function. Together, these findings indicate that both vascular remodeling and altered cerebral blood flow autoregulation contribute to neurocognitive function. These effects seem to be driven by the neurocognitive domains of fine motor functioning, SIP, executive functioning, and learning.

Our investigation explored the association of angiogenic growth factors with both PP and neurocognitive function given their crucial role in vascular remodeling.[19,29] A complex interplay of the angiopoietins, Tie-2, VEGF, and other pro- or antiangiogenic factors contribute to angiogenesis and vascular remodeling.[36] Angiopoietins bind to the endothelial tyrosine kinase receptor Tie-2 to exert context-dependent biological functions,[36] and circulating levels of Ang-2 and Tie-2 have been associated with CVD risk factors (eg, hypertension, diabetes mellitus, and abdominal obesity).[37] Ang-2 has previously been found to have a positive

association with PP.[36] Our study did not find an association between PP and Ang-2; however, we found a positive association between PP and Tie-2. Given the cross-sectional design of this study, we are unable to infer whether this association reflects a dysregulation of VEGFs that contribute to microvascular rarefaction (ie, a deficiency in mature small vessels)[36] or PP-induced vascular remodeling.[36] Future research, particularly studies employing longitudinal designs, may tease apart the temporal association between vascular remodeling, PP, and cerebrovascular disease in the context of HIV disease.

The interactions between vascular remodeling (ie, Tie-2 and VEGF) and HIV on neurocognitive function suggest that HIV is interacting with the aging brain to affect neurologic function. VEGF is generally considered to have neuroprotective effects,[38] whereas upregulated levels of Tie-2 may reflect pathological angiogenesis.[39] For HIV− adults, we found that higher Tie-2 and lower VEGF values were associated with worse neurocognitive function. Counterintuitively, lower Tie-2 values and higher VEGF values were associated with worse neurocognitive function for HIV+ adults. One potential interpretation of these counterintuitive associations is that the neuroprotective effect of VEGF is attenuated within our HIV+ sample, given that they demonstrate good immunologic and virologic status. Emerging evidence indicates that the neuroprotective effect of VEGF may be the most robust among adults with greater risk factors for Alzheimer disease (AD).[38] It is possible that our HIV serostatus groups differ in regard to AD risk factors that, in turn, may be influencing the effect of VEGF on neurocognitive function. Alternatively, the association between lower Tie-2 values and worse neurocognitive function observed among the HIV+ sample may reflect pathological angiogenesis. Pathological angiogenesis shares many cellular and molecular processes with physiological angiogenesis (eg, sprouting of new blood vessels and recruitment of inflammatory cells to sites of inflammation); however, pathological angiogenesis is characterized by a highly disorganized vascular network.[39] Given that HIV is characterized by chronic inflammation, HIV+ adults may be particularly vulnerable to pathological angiogenic processes.

Despite not finding an interacting effect of HIV and PP on neurocognitive function, our results show an association between PP and neurocognitive function that holds in the overall sample. Arterial stiffness may lead to neurocognitive decline because of augmented pressure pulses that penetrate and cause damage to the smaller blood vessels of the brain.[40] Previous research indicates that cerebrovascular disease may be a key underpinning in HIV-associated NCI.[41] We found a quadratic association between PP and neurocognitive function. This is consistent with literature demonstrating a U-shaped relationship between PP and risk of AD and dementia, whereby both lower and higher ends of the PP spectrum confer risk.[28] Alternatively, the association between PP and neurocognitive function may reflect normal brain arterial aging. A recent histopathologic study showed that with age, the arteries of the brain undergo degenerative changes characterized by arterial thickening, even in the absence of atherosclerosis.[42] These degenerative changes are hypothesized to be the downstream effect of mechanical forces of blood flow.[42] Thus, it is possible that PP is indexing arterial stiffening that may be occurring in the periphery and brain.

Our sample of older HIV+ adults did not demonstrate different levels of arterial stiffness relative to older HIV− adults. This finding is in agreement with studies finding no differences in arterial stiffness by HIV serostatus,[12] although there have been reports of increased arterial stiffness in the context of HIV.[43] Divergent results among studies may be related to differences in cohort characteristics. For example, among HIV+ persons, commonly reported determinants of arterial stiffness are low nadir CD4 T-cell counts (eg, <350 cells per microliter), age, hypertension, and high cholesterol levels.[43–51] Given that our HIV+ sample demonstrated good immunologic and virologic status, potential effects of HIV-related characteristics on PP may be greatly diminished. Discerning differences in PP among HIV+ adults on suppressive cART as compared with HIV− adults requires careful selection of the appropriate HIV− comparison group.[52] Our HIV+ and HIV− samples were largely comparable across many characteristics (eg, age and prevalence of medical comorbidities and lifetime substance-use disorders). Thus, our failure to detect differences in PP may indicate that HIV+ persons do not have greater arterial stiffening when compared with an HIV− sample with a comparable prevalence of comorbidities.

Consistent with previous studies involving older HIV+ adults,[10,53] we found that diabetes mellitus emerged as an independent predictor of neurocognitive function. Diabetes mellitus has shown an association with NCI in HIV+ adults older than 55 years.[10] Likely mechanisms for the effect of diabetes mellitus on neurocognitive function may include direct damage to the brain from hyperglycemia, brain exposure to higher levels of glucose given disruption of the blood–brain barrier by HIV,[54] and/or increased risk for cerebral atherosclerosis. Imaging studies demonstrate an association between diabetes mellitus and morphological changes in the brain that are predominantly subcortical, which is similar to the subcortical effects of HIV.[55–57]

Limitations of the study include its cross-sectional design and the high likelihood of selection bias, given that the parent study aimed to investigate “successful aging” with HIV and thus may have biased our sample toward a group of HIV+ patients demonstrating good immunologic and virologic profiles. Given our small sample size, we did not test whether the effect of vascular remodeling on neurocognitive function is mediated by PP given the likelihood of type II error. Our study collected resting BP rather than ambulatory BP, which may potentially demonstrate a different association with neurocognitive function or reveal differing BP profiles between HIV+ and HIV− individuals. Our study used a proxy measure of arterial stiffness, whereas pulse wave analysis is a more direct and noninvasive method of assessing large artery or aortic stiffness.[58] Although vascular remodeling and PP were found to have associations with neurocognitive function, the clinical utility of these markers depends on the availability of efficacious treatments to reduce pathological angiogenesis and arterial stiffness and whether treatment-induced reductions

of these processes translate to improved neurocognitive outcomes.[58]

The etiology of HIV-associated NCI in the cART era is multifactorial and may be related to both direct and indirect consequences of HIV, the immune response, and comorbid factors,[59] such as subclinical CVD. Delineating the relative contribution of CVD risk factors, such as vascular remodeling and PP, in the pathogenesis of HIV-associated NCI may allow for the identification of adjunct therapies aimed at improving health outcomes for persons aging with HIV/AIDS.

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CHAPTER 2.

Coagulation Imbalance and Neurocognitive Functioning in Older HIV+ Adults on Suppressive Antiretroviral Therapy

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Abstract

Objectives: To compare plasma biomarkers of coagulation between HIV-infected individuals and HIV-uninfected controls and to assess the impact of disturbances in coagulation on neurocognitive functioning in HIV.

Design: Cross-sectional study of 66 antiretroviral therapy-treated virally suppressed HIV-infected and 34 HIV-uninfected older (≥50 years of age) adults.

Methods: Participants completed standardized neurobehavioral and neuromedical assessments. Neurocognitive functioning was evaluated using a well-validated comprehensive neuropsychological battery. Plasma biomarkers associated with procoagulation (fibrinogen, p-selectin, tissue factor, and von Willebrand factor), anticoagulation (antithrombin, protein C, and thrombomodulin), fibrinolysis (d-dimer, plasminogen activator inhibitor-1, and plasminogen) were collected. Multivariable linear regression was used to test the interaction of HIV and coagulation on neurocognitive functioning.

Results: Most participants were male (78.0%) and non-Hispanic white (73.0%) with a mean age of 57.8 years. Among HIV-infected participants, mean estimated duration of HIV infection was 19.4 years and median current $CD4^+$ cell count was 654 cells/mm^3. Levels of soluble biomarkers of procoagulation, anticoagulation, and fibrinolysis were comparable between the HIV serostatus groups. Coagulation moderated the effect of HIV on neurocognitive functioning, such that greater coagulation imbalance was associated with poorer neurocognitive functioning among the HIV-infected participants. The moderating effect of coagulation on neurocognition was driven by procoagulant but not anticoagulant or fibrinolytic biomarkers.

Conclusions: Elevated levels of procoagulants may exert a particularly detrimental effect on neurocognitive functioning among older HIV-infected persons. A better understanding of the specific role of coagulation in the etiology of HIV-associated neurocognitive disorders may lead to treatments aimed at reducing coagulopathy, thereby improving neurocognitive outcomes.

Coagulation imbalance and neurocognitive functioning in older HIV-positive adults on suppressive antiretroviral therapy

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Objectives: The aim of this study was to compare plasma biomarkers of coagulation between HIV-infected individuals and HIV-uninfected controls and to assess the impact of disturbances in coagulation on neurocognitive functioning in HIV.

Design: A cross-sectional study of 66 antiretroviral therapy treated, virally suppressed, HIV-infected and 34 HIV-uninfected older (≥50 years of age) adults.

Methods: Participants completed standardized neurobehavioral and neuromedical assessments. Neurocognitive functioning was evaluated using a well validated comprehensive neuropsychological battery. Plasma biomarkers associated with procoagulation (fibrinogen, p-selectin, tissue factor and von Willebrand factor), anticoagulation (antithrombin, protein C and thrombomodulin), fibrinolysis (d-dimer, plasminogen activator inhibitor-1 and plasminogen) were collected. Multivariable linear regression was used to test the interaction of HIV and coagulation on neurocognitive functioning.

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Keywords: ageing, coagulopathy, cognition, endothelial dysfunction, haemostasis, HIV/AIDS, inflammation

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Introduction

HIV-associated neurocognitive impairment (NCI) is highly prevalent in the modern era of combination antiretroviral therapy (ART) [1], and older adults appear to be particularly vulnerable to HIV-associated NCI [2–5]. Persons living with HIV (HIV-positive) who are untreated for cerebrovascular risk demonstrate poorer performance in the neurocognitive domains of processing speed, learning/memory and executive functioning than HIV-positive persons who are pharmacologically treated for cerebrovascular risk [6].

HIV-positive persons may experience imbalance in coagulation given impaired endothelial function and immune activation [7–9]. In a subset of participants in the Strategies for Management of Antiretroviral Therapy (SMART) trial, HIV replication was associated with complex changes in the extrinsic pathway, such as short-term increases in some procoagulants and decreases in anticoagulants [e.g. lower antithrombin (AT) and lower protein C] [10]. Some studies have found that biomarkers indicative of coagulation decrease with initiation of ART [11]; however, relative to HIV-uninfected (HIV-negative) persons, ART-treated persons appear to be vulnerable to coagulation imbalance [12]. Although untreated patients may have elevated levels of d-dimer (i.e. a fibrin degradation product frequently used as a marker of coagulation disturbances) relative to treated patients on ART, both untreated and treated patients on ART are observed to have impairments in platelet aggregation and clot initiation [13]. Furthermore, older HIV-positive persons may be particularly vulnerable to coagulation imbalance, given that ageing further exerts a strong influence on haemostatic biomarkers, such as d-dimer [14].

The clinical consequences of HIV disease on coagulation in the context of suppressive ART remain unclear. We aimed to assess the impact of disturbances in coagulation (i.e. coagulation imbalance) on neurocognitive functioning in HIV. We hypothesized that greater coagulation imbalance would have a detrimental effect on neurocognitive functioning in HIV.

Materials and methods

Participants and procedure

The present study examined 100 community-dwelling older (i.e. aged 50 years and above) HIV-positive ($n = 66$) and HIV-negative adults ($n = 34$) who participated in the California HIV/AIDS Research Program Successfully Aging Seniors with HIV study at the UCSD HIV Neurobehavioral Research Program. Specific inclusion criteria for HIV-positive participants were being on ART and having an undetectable plasma HIV viral load (<48 copies/ml). General exclusion criteria included use of an anticoagulant medication, history of non-HIV related neurologic disorders or other known conditions that may be associated with impaired neurocognitive performance (e.g. seizure disorder). The study protocol was approved by the UCSD Institutional Review Board. After providing written, informed consent, each participant underwent a standardized neuropsychological, neuromedical and psychiatric evaluation.

Global neurocognitive functioning

Participants completed a standardized neurocognitive test battery (administration time: 2–2.5 h) that assesses seven neurocognitive domains commonly affected by HIV, including speed of information processing, learning, memory, executive functions, verbal fluency, working memory and fine motor function [1]. Raw scores from the neurocognitive tasks were converted to demographically adjusted T-scores ($M = 50$, $SD = 10$ in neurological normal individuals) using the best available normative standards [15–17]. The demographically adjusted T-scores were then averaged to derive neurocognitive domain T-scores and a global T-score, the latter of which was used in statistical analyses as the primary dependent variable. Global T-scores were chosen over other approaches (e.g. deficit scores) given their normal distribution that matches the assumptions of parametric statistical analyses and their wider use across the neuropsychological literature [18]. Higher global T-scores represent better neurocognitive functioning with scores between 35 and 40 reflecting mild impairment.

Plasma biomarkers of coagulation

Biomarker assays were measured by immunoassay in duplicate in EDTA-treated plasma derived from peripheral blood samples collected by routine phlebotomy. Commercial immunoassay suppliers were Millipore (fibrinogen, tissue factor, thrombomodulin; Darmstadt, Germany), R&D Systems [AT, plasminogen activator-inhibitor-1 (PAI-1), protein C, p-selectin, von Willebrand factor (vWF); Minneapolis, Minnesota, USA], SEKISUI (d-dimer; Lexington, Massachusetts, USA) and Cell Biolabs (plasminogen; San Diego, California, USA). Measurements were repeated if the coefficient of variation was greater than 20% or if the measurement was greater than four standard deviations from the mean.

Coagulation imbalance

Coagulation imbalance was operationalized in a similar fashion to other composite indices representing physiological systems [19]. The selected biomarkers represent three physiological systems: procoagulation (fibrinogen, p-selectin, tissue factor, vWF), anticoagulation (AT, protein C, thrombomodulin) and fibrinolysis (d-dimer, PAI-1, and plasminogen). Coagulation imbalance was constructed first by dichotomizing the 10 individual biomarkers on the basis of median splits of the entire sample (i.e. assigning a score of '1' to values in the upper 50th percentile and a score of '0' to values in the lower

50th percentile). The individual binary variables were summed to create summary scores for each of the three physiological systems: procoagulation (values ranging from 0 to 4), anticoagulation (values ranging from 0 to 3) and fibrinolysis (values ranging from 0 to 3). A coagulation imbalance score (values ranging from 0 to 10) was calculated on the basis of summation of the 10 individual biomarker binary variables, with a higher coagulation imbalance score representing more activation/turnover of haemostatic factors.

Plasma biomarkers of inflammation

Biomarkers representing inflammatory processes [i.e. soluble CD163 (sCD163), soluble CD14 (sCD14) and complement C3] [20] were available for a subset of participants ($n = 93$). Biomarker assays were measured by immunoassay in duplicate in EDTA-treated plasma. The commercial immunoassay suppliers were R&D Systems (sCD163 and sCD14; Minneapolis, Minnesota, USA) and Assaypro (complement C3; St Charles, Missouri, USA). As with the biomarkers of coagulation, measurements were repeated if the coefficient of variation was greater than 20% or the measurement was greater than four standard deviations from the mean.

Covariates

Neuromedical assessment

Medical characterization of study participants included medical comorbidities (e.g. dyslipidemia, diabetes mellitus and hypertension) and current prescription medications [i.e. lipid-lowering drug, nonsteroidal anti-inflammatory drug (NSAID), antihypertensive and antidepressant drugs]. Medical comorbidities were defined by the presence of self-reported diagnosis and/or specific drug treatment for the condition (e.g. metformin for diabetes mellitus).

HIV disease characteristics

All HIV-positive participants were on suppressive ART. The following information was obtained for our HIV-positive sample: estimated duration of HIV infection, AIDS diagnosis, current and nadir $CD4^+$ T-cell counts, and whether or not the participant was on a protease inhibitor based regimen.

Psychiatric assessment

All study participants administered the Composite International Diagnostic Interview [21] to assess for the presence of lifetime and current affective and substance use disorders using diagnostic criteria on the basis of the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders [22]. The Beck Depression Inventory-II (BDI-II) [23] was administered to assess current depressive symptoms.

Statistical analyses

The distributions of residuals were visually inspected when performing statistical tests to determine whether transforming individual variables was appropriate to meet statistical assumptions of parametric tests. When appropriate, variables were $\log_{10}$ transformed. Comparison of demographic, neuromedical and psychiatric data between the HIV-positive and HIV-negative groups was performed with two-tailed *t*-test or Pearson's chi-squared test, as appropriate. Two-tailed *t*-tests were conducted to compare individual biomarkers and coagulation composite scores by HIV serostatus. When the assumption of equal variances was not met, Welch's *t*-test was used. Hedge's g statistic for continuous variables and odds ratios for binary variables were used to generate effect sizes for group comparisons. Next, correlates of coagulation imbalance were explored to identify both personal and inflammatory factors related to coagulation.

To test whether coagulation and HIV have an interacting effect on neurocognitive functioning, four multivariable linear regression models were conducted. Each multivariable model included an HIV by coagulation (i.e. coagulation imbalance, procoagulation, anticoagulation or fibrinolysis) interaction term. Models were run with and without statistical adjustment for relevant covariates. Covariates were selected on the basis of which variables in Table 1 demonstrated univariable associations (i.e. Pearson's correlations for continuous variables and *t*-tests for categorical variables) with the primary dependent variable (neurocognitive functioning, i.e. global T-score) at a critical $\alpha = 0.10$. The following covariates were identified as having met our criterion for inclusion in the multivariable analyses: BMI, diabetes mellitus, use of an antidepressant, current major depressive disorder (MDD), lifetime MDD and self-reported depression scores. For analyses only involving the HIV-positive participants, the following HIV disease-specific variables met our criterion for inclusion in the multivariable analyses: current $CD4^+$ and AIDS status. The variable inflation factor was used to identify multicollinearity among predictor variables prior to final model selection. Final models included only one of the correlated variables. All statistical tests were performed with JMP 11.0.0 (SAS Institute Inc., Cary, North Carolina, USA).

Results

Participants

The sample consisted of 100 participants who were predominantly middle-aged [mean 57.8 (SD 6.0) years], non-Hispanic white (73.0%) men (78.0%) with some college education [mean 14.3 (SD 2.7) years]. Demographic, medical and psychiatric characteristics of the sample are presented in Table 1.

In general, HIV-positive and HIV-negative groups were largely comparable (i.e. *P* values for group differences >0.05) across many of the characteristics, including age, education, medical comorbidities (i.e. hypertension, tobacco smoking, diabetes mellitus and hepatitis C), medical prescriptions (i.e. NSAID, antihypertensive and

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Table 1. Demographic and clinical characteristics of sample ($N = 100$).

Variable	All ($N = 100$)	HIV-positive ($n = 66$)	HIV-negative ($n = 34$)	P	Effect size
Descriptive demographics					
Age, mean (SD)	57.8 (6.0)	57.3 (6.1)	58.8 (5.9)	0.26	−0.25
Education, mean (SD)	14.3 (2.7)	14.3 (2.7)	14.2 (2.7)	0.80	0.04
Male, *n* (%)	78 (78.0%)	56 (84.8%)	22 (64.7%)	0.02	3.05
Non-Hispanic white, *n* (%)	73 (73.0%)	52 (78.8%)	21 (61.8%)	0.07	0.43
Medical comorbidities and anthropometric measurement					
Hyperlipidemia, *n* (%)	43 (44.3%)	33 (52.4%)	10 (29.4%)	0.03	2.64
Ever smoker, *n* (%)	40 (41.2%)	26 (41.3%)	14 (41.2%)	0.99	1.00
Hypertension, *n* (%)	37 (38.1%)	24 (38.1%)	13 (38.2%)	0.99	0.99
Current smoker, *n* (%)	32 (33.0%)	23 (36.5%)	9 (26.5%)	0.32	1.60
Diabetes, *n* (%)	19 (19.6%)	13 (20.6%)	6 (17.6%)	0.72	1.21
Hepatitis C virus, *n* (%)	18 (18.6%)	12 (19.0%)	6 (17.6%)	0.87	1.10
BMI, mean (SD)	27.2 (5.3)	26.9 (5.4)	27.7 (5.1)	0.45	−0.15
Current medications					
Lipid-lowering drug, *n* (%)	30 (30.0%)	23 (34.8%)	7 (20.6%)	0.14	2.06
NSAID, *n* (%)	28 (28.0%)	20 (30.3%)	8 (23.5%)	0.47	1.41
Antihypertensive, *n* (%)	27 (27.0%)	19 (28.8%)	8 (23.5%)	0.57	1.31
Antidepressant, *n* (%)	32 (32.0%)	28 (42.4%)	4 (11.8%)	<0.01	5.52
Psychiatric characteristics/diagnoses					
BDI-II total, median [IQR]	6.0 [0.3–14.8]	9.5 [2.8–16.3]	1.5 [0.0–5.3]	<0.01	0.86
Current MDD, *n* (%)	11 (11.1%)	10 (15.4%)	1 (2.9%)	0.06	6.00
LT MDD, *n* (%)	48 (48.0%)	38 (57.6%)	10 (29.4%)	<0.01	3.26
LT alcohol use disorder, *n* (%)	50 (50.0%)	33 (50.0%)	17 (51.5%)	0.89	0.94
LT cannabis use disorder, *n* (%)	25 (25.3%)	18 (27.3%)	7 (21.2%)	0.51	1.39
LT meth use disorder, n (%)	28 (28.3%)	20 (30.3%)	8 (24.2%)	0.53	1.36
HIV disease characteristics					
Years of infection, median [IQR][a]	–	19.4 [11.3–25.5]	–	–	–
AIDS, *n* (%)	–	41 (62.1%)	–	–	–
Current $CD4^+$ T-cell count, median [IQR][b]	–	654 [476–865]	–	–	–
Nadir $CD4^+$ T-cell count, median [IQR][a]	–	180 [41–300]	–	–	–
Current PI use, *n* (%)[c]	–	31 (47.7%)	–	–	–

Effect sizes are based on Hedge's g statistic for continuous variables and odds ratios for binary variables. Note: BDI-II, Beck Depression Inventory – II; LT, lifetime; MDD, major depressive disorder; PI, protease inhibitor.
[a]$n = 64$.
[b]$n = 62$.
[c]$n = 65$.

lipid-lowering drug use) and proportion of current MDD and lifetime substance use disorders. The HIV-positive group had more men (84.8% vs. 64.7%, $P = 0.02$), cases of hyperlipidemia (52.4% vs. 29.4%, $P = 0.03$), cases of lifetime MDD (57.6% vs. 29.4%, $P < 0.01$) and a higher proportion on an antidepressant medication (42.4% vs. 11.8%, $P < 0.01$). The HIV-positive group also had higher scores on a self-report measure of depression symptoms (9.5 vs. 1.5, $P < 0.01$).

Among the HIV-positive participants ($n = 66$), the mean estimated duration of HIV infection was 19.4 years, the median current $CD4^+$ T-cell count was 654 cells/μl and the median nadir $CD4^+$ T-cell count was 180 cells/μl.

Comparison of coagulation biomarkers between HIV serostatus groups

Of the 10 individual coagulation biomarkers, the HIV serostatus groups only differed on fibrinogen, which was higher in the HIV-negative group ($P = 0.04$, hedges $g = -0.45$; Table 2). No significant differences were found between the HIV-negative and HIV-positive groups for the coagulation imbalance composite score or the three individual coagulation indices (i.e. procoagulation, anticoagulation and fibrinolysis; $P > 0.05$). The procoagulant, anticoagulant and fibrinolytic factor indices were not univariably associated with each other ($P > 0.05$; Table 3).

Personal factors and inflammatory biomarkers are associated with coagulation

Higher coagulation imbalance scores were univariably associated with higher BMI ($r = 0.23$, $P = 0.02$), being on lipid-lowering drug, having a dyslipidemia diagnosis and having a current MDD diagnosis ($P < 0.05$). Higher coagulation imbalance scores were univariably associated with higher levels of inflammatory biomarkers complement C3 ($r = 0.25$, $P = 0.01$), sCD163 ($r = 0.24$, $P = 0.02$) and sCD14 ($r = 0.22$, $P = 0.03$). Higher procoagulant scores were univariably associated with higher BDI-II scores and both current and lifetime MDD diagnoses ($P < 0.05$). Higher anticoagulant score was only univariably associated with being on a lipid-lowering drug ($P = 0.01$), whereas higher fibrinolytic score was univariably associated with higher BMI ($r = 0.21$, $P = 0.03$) and complement C3 ($r = 0.25$, $P = 0.02$). None of the HIV disease characteristics were univariably associated with any of the coagulation indices within the HIV-positive group ($P > 0.05$).

Table 2. Plasma biomarkers related to coagulation and inflammation by HIV serostatus.

Biomarker	HIV-positive ($n=66$) Median (IQR)	HIV-negative ($n=34$) Median (IQR)	*P*	Effect size
Procoagulants				
Fibrinogen (mg/dl)	180.5 (131.9–214.8)	195.6 (164.1–231.0)	0.04	−0.45
P-Selectin (ng/ml)	37.2 (29.9–46.7)	38.2 (29.4–48.4)	0.74	−0.12
Tissue factor (pg/ml)	1150 (490–1723)	1175 (680–1583)	0.87	0.09
vWF (pg/ml)	97.1 (97.1–152.5)	97.1 (97.1–112.5)	0.06	0.36
Anticoagulants				
Antithrombin (μg/ml)	0.67 (.50–1.36)	0.81 (0.57–1.73)	0.99	0.22
Protein-C (μg/ml)	0.05 (0.03–0.06)	0.05 (0.04–0.06)	0.97	0.01
Thrombomodulin (ng/ml)	4.00 (2.69–5.24)	3.77 (3.41–4.84)	0.34	0.16
Fibrinolytic factors				
D-dimer (μg/ml)	0.41 (0.31–0.64)	0.50 (0.33–0.70)	0.46	−0.16
PAI-1 (μg/ml)	0.03 (0.02–0.05)	0.02 (0.02–0.04)	0.11	0.42
Plasminogen (mg/dl)	11.55 (8.92–13.71)	12.54 (9.12–16.68)	0.30	−0.24
Inflammation				
Soluble CD163 (ng/ml)	1225 (888–1798)[a]	832 (594–1341)	0.03	0.41
Soluble CD14 (pg/ml)	2106 (1842–2338)[a]	1639 (1484–2020)	<0.001	0.97
Complement C3 (mg/dl)	1010 (760–1476)[a]	998 (693–1356)	0.87	0.03

Effect size based on Hedge's g statistic. PAI-1, plasminogen activator inhibitor-1; vWF, Von Willebrand factor.
[a]$n=59$.

Coagulation moderates the association between HIV serostatus and neurocognitive functioning

HIV-positive participants had worse neurocognitive functioning [mean global *T*-score = 46.2 (SD 6.9)] than HIV-negative participants [mean global T-score = 49.5 (SD 6.6)] ($P=0.02$; Hedge's g = −0.48). Four separate multivariable linear regression models were used to test whether HIV and the coagulation imbalance composite scores have an interacting effect on neurocognitive functioning. The first model of neurocognitive functioning (Model-adjusted $R^2=0.10$, $P=0.005$; Fig. 1) identified a statistically significant interaction between coagulation imbalance composite score and HIV ($\beta=-0.39$, $P=0.01$). Follow-up analyses indicated that coagulation imbalance composite score had a statistically significant positive association with neurocognitive functioning among the HIV-positive group ($r=-0.30$, $P=0.01$) but not the HIV-negative group ($r=0.22$, $P=0.22$). The second model of neurocognitive functioning (Model adjusted $R^2=.10$, $P=.005$) identified a statistically significant interaction between the procoagulant index score and HIV ($\beta=-0.38$, $P=0.02$). Similar to the coagulation imbalance composite score, the procoagulant index score had a statistically significant positive association with neurocognitive functioning among the HIV-positive group ($r=-0.31$, $P=0.01$) but not the HIV-negative group ($r=0.18$, $P=0.30$). Models 1 and 2 and their respective interaction terms remained statistically significant ($P<0.05$) after adjusting for relevant covariates (i.e. BMI, diabetes, antidepressant use and current MDD diagnosis). In posthoc analyses, variables associated with coagulation imbalance (i.e. BMI, lipid-lowering drug use, dyslipidemia diagnosis, current MDD diagnosis and inflammatory biomarkers C3, sCD163 and sCD14) were added to Models 1 and 2 to examine whether inflammation, rather than coagulation

Table 3. Correlation matrix among coagulation factors and neurocognitive function.

	Coagulation imbalance score	Procoagulants	Anticoagulants	Fibrinolytic factors
Procoagulants				
All ($N=100$)	0.73***			
HIV-positive ($n=66$)	0.71***			
HIV-negative ($n=34$)	0.76***			
Anticoagulants				
All ($N=100$)	0.62***	0.12		
HIV-positive ($n=66$)	0.58***	0.05		
HIV-negative ($n=34$)	0.68***	0.34		
Fibrinolytic factors				
All ($N=100$)	0.53***	0.13	−0.01	
HIV-positive ($n=66$)	0.57***	0.19	−0.01	
HIV-negative ($n=34$)	0.48**	0.04	−0.02	
Global *t* score				
All ($N=100$)	−0.10	−0.14	−0.06	0.03
HIV-positive ($n=66$)	−0.30*	−0.31*	0.17	0.05
HIV-negative ($n=34$)	0.22	0.18	0.05	0.18

*$P<0.05$.
**$P<0.01$.
***$P<0.001$.

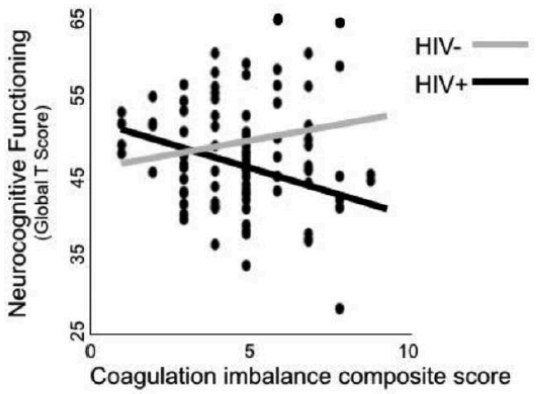

Fig. 1. HIV serostatus and coagulation imbalance interact on neurocognitive functioning.

imbalance, was uniquely associated with neurocognitive functioning. Both models 1 and 2 and their respective interaction terms remained statistically significant ($P < 0.05$). The inflammatory biomarkers were not statistically significant predictors of neurocognitive functioning in the multivariable models ($P > 0.05$).

Models 3 and 4 separately tested the interaction between the anticoagulant index score and HIV and the interaction between the fibrinolytic factor score and HIV. Neither model 3 nor 4 was statistically significant with or without adjustment of relevant covariates (overall model $P > 0.05$).

Procoagulant biomarkers, and not HIV-disease characteristics, are uniquely associated with neurocognitive functioning in older HIV-positive adults on suppressive antiretroviral therapy

A series of multivariable models were run that included only the HIV-positive cases in order to adjust for HIV-disease related variables associated with neurocognitive functioning (i.e. AIDS status and current $CD4^+$ cell count). The procoagulant index remained a statistically significant predictor of neurocognition ($\beta = -0.27$, $P = 0.03$) in a multivariable model adjusting for the effects of BMI, diabetes antidepressant use, current MDD diagnosis, AIDS status and current $CD4^+$ cell count. None of the covariates included in this multivariable model were statistically significant ($P > 0.05$). The coagulation imbalance composite score ($\beta = -0.19$, $P = 0.18$) did not remain statistically significant in the multivariable model adjusting for these same covariates. In addition, neither the anticoagulant ($\beta = -0.04$, $P = 0.76$) or fibrinolytic factor ($\beta = 0.01$, $P = 0.93$) indices achieved statistical significance in analogous multivariable models involving only the HIV-positive sample.

Discussion

In our cross-sectional study, levels of soluble biomarkers of procoagulation, anticoagulation and fibrinolysis were comparable between ART-treated virally suppressed HIV-positive older adults and the HIV-negative comparison group. Elevated markers of coagulation were associated with traditional cardiovascular risk factors (e.g. higher BMI and diagnosis and treatment of dyslipidemia) and depressed mood. HIV and coagulation imbalance had an interacting effect on neurocognitive functioning, such that greater coagulation imbalance was associated with poorer neurocognitive functioning among the HIV-positive, but not the HIV-negative, group. The moderating effect of coagulation imbalance appeared to be driven by procoagulant factors, rather than anticoagulant or fibrinolytic markers. These findings indicate that elevated levels of procoagulant markers may exert a particularly detrimental effect on neurocognitive functioning among ART-treated, virally suppressed, HIV-positive older adults.

HIV was not found to confer risk for coagulation imbalance in our study sample consisting of ART-treated, virally suppressed, HIV-positive older adults and an HIV-negative comparison group. Although ART-naive HIV-positive persons show elevated levels of various coagulation-related biomarkers (e.g. fibrinogen, d-dimer and vWF) [24,25], it remains unclear whether initiation and long-term use of ART produces a normal coagulation profile. With the initiation of ART, biomarkers of coagulation may decrease (e.g. fibrinogen, d-dimer, vWF and P-selectin) or increase (e.g. protein C and AT), such that levels may be comparable to those among HIV-negative comparison groups [24–27]. Not all biomarkers, however, may travel with ART status, as was the case of fibrinogen in the SMART study [10]. When comparing HIV-positive adults on vs. off ART, ART does appear to alter coagulation biomarkers, resulting in lower levels of d-dimer [28–31], vWF [10,28,30,32], fibrinogen [33] and PAI-1 [31], and higher levels of AT [10] and protein C [10,30]. Comparison between ART-treated HIV-positive persons and HIV-negative comparison groups has yielded mixed results, with some studies reporting differences in levels of coagulation biomarkers (e.g. elevations of d-dimer, thrombomodulin, AT, fibrinogen and PAI-1 among HIV-positive adults) [34–38] and others finding no differences among the same biomarkers (e.g. comparable levels of thrombomodulin and d-dimer between HIV serostatus groups) [39,40].

The profile of coagulation in HIV disease is clearly complex. Discrepant findings in the existing literature are likely an artefact of unique features of individual study cohorts. For example, studies differ on whether participants are in the early and acute infection period vs. long-term survivors of HIV disease. Our study, in particular, enrolled a HIV-positive cohort which was on

suppressive ART, and our HIV-negative cohort was recruited to be medically and behaviourally similar to our HIV-positive cohort (e.g. similar prevalence of substance use disorders, diabetes mellitus, hepatitis C). Thus, the results of this study should be interpreted with consideration of our cohort's unique demographic and clinical characteristics.

Specific HIV disease characteristics, such as current $CD4^+$ T cell count, do not appear to be associated with coagulation indices among older HIV-positive persons. In older HIV-positive persons with virologic suppression on ART, the effect of HIV disease parameters on coagulation may be eclipsed by other factors exerting an influence on hemostasis factors, such as BMI, presence and treatment of dyslipidemia and inflammatory biomarkers. Our failure to detect an association between the coagulation indices and HIV disease characteristics may reflect that this association is weak or absent in the context of ART, viral suppression, chronic HIV disease, older age and/or presence of medical comorbidity burden.

In our study, coagulation biomarkers were related to several inflammatory biomarkers. Specifically, higher coagulation imbalance scores had positive associations with sCD163, sCD14 and complement C3. Monocyte/macrophage activation is hypothesized to be a source of inflammatory cells in the central nervous system (CNS) and a key mechanism for CNS pathogenesis [41]. Persistent monocyte/macrophage activation, measured by plasma sCD163, has been previously observed in neurophysiologically impaired, HIV-positive individuals on virally suppressive ART [42]. Among chronically infected HIV-positive adults, sCD163 levels appear to decrease with decreasing HIV RNA levels but may not return to seronegative levels, indicating residual monocyte/macrophage activation [43]. Similarly, sCD14, a marker of systemic immune activation, appears to interact with a marker of abdominal obesity on NCI [44]. Complement C3, a primary mechanism of innate immunity, may also be a marker of cardiometabolic risk among persons ageing with HIV [20]. Likely, the relationship between coagulation imbalance and inflammation is bidirectional, with coagulation imbalance being both a consequence of inflammation and an amplifier of the inflammatory response [8].

Chronic inflammation can lead to disruption of the endothelium, which has been reported in HIV disease [45–47]. Endothelial dysfunction may play a pivotal role in the pathogenesis of cerebral small vessel disease [48] via the breakdown of the blood–brain barrier [49] and impairment of cerebral reactivity and autoregulation [50]. Haemostatic changes are hypothesized to play a secondary role to endothelial activation, such that damaged endothelial cells can act as a substrate for the initiation of coagulation [51]. The procoagulant index employed in this study was based on values of fibrinogen, p-selectin, tissue factor and vWF. Thus, the procoagulant index may represent both endothelial dysfunction and coagulation imbalance. When accompanied by endothelial dysfunction, elevation in plasma fibrinogen levels has been found to increase the risk of subclinical white matter lesions [52]. Elevation in procoagulant factors, such as fibrinogen, is hypothesized to influence cerebral hypoperfusion and the development of white matter lesions, thereby contributing to neurocognitive decline [52].

Several limitations of this study should be noted. This study used a cross-sectional, observational design and thus causality from the observed associations among HIV, coagulation imbalance and neurocognitive functioning cannot be inferred. Furthermore, both HIV infection and ART likely exert an influence on neurocognitive functioning, and without an ART-naive comparison sample, we cannot disentangle the effect of ART on neurocognitive functioning. Given that the parent study aimed to investigate 'successful aging' with HIV, there is a high likelihood of selection bias such that we recruited a sample of HIV-positive patients demonstrating good immunologic and virologic profiles, and these older HIV-infected individuals mostly represent a long-term 'survivor' cohort. Lastly, we operationalized the coagulation biomarkers into three theorized physiological systems that have not been previously validated; however, a large panel of biomarkers as utilized in the present study has not been previously used in relation to both HIV and neurocognition. These three physiological systems are likely dynamic and complex, and future research is needed to determine the most optimal method for modelling biomarkers of coagulation.

Endothelial activation and coagulation imbalance likely play mechanistic roles leading to poorer neurocognitive functioning outcomes in HIV-positive adults. Thus, biomarkers of endothelial activation and coagulation may provide valuable information regarding the prognosis and/or risk stratification of HIV-positive adults. Although greater procoagulant values were found to have an association with neurocognitive functioning for ART-treated, virally suppressed, HIV-positive older adults, the clinical utility of coagulation imbalance as a predictor of neurocognitive functioning depends on whether treatment-induced reductions in procoagulant levels translate to improved neurocognitive outcomes. A better understanding of the specific role of coagulation in the cause of HIV-associated neurocognitive disorders may lead to specific treatments aimed at reducing coagulopathy, thereby improving neurocognitive outcomes.

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data for the work. M.P. performed biomarker assays. J.L.M. performed statistical analysis and wrote the first draft of the manuscript. All authors critically revised and provided final approval of the manuscript.

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Conflicts of interest

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CHAPTER 3.

Rate of neurocognitive change is not related to visit-to-visit variability in blood pressure among persons with HIV

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Abstract

Background: Visit-to-visit variability in blood pressure (BPV) is associated with neurocognitive decline in various clinical populations vulnerable to central nervous system injury. The present study examined whether visit-to-visit variability in blood pressure (BPV) predicts longitudinal neurocognitive change among HIV-infected (HIV+) persons.

Methods: Participants included 533 HIV-infected persons followed for up to twelve years in cohort studies at the UCSD HIV Neurobehavioral Research Program (at baseline: Mean age=42.8; 81.6% male; 61.5% non-Hispanic white; AIDS=68.8%; Median current CD4=362; Median duration of HIV infection=9.2 years). Participants completed a comprehensive neurocognitive battery at each study visit. Neurocognitive status was plotted over time to derive a rate of neurocognitive change using practice-adjusted global scaled scores. Visit-to-visit variability for systolic blood pressure (SBPV) and diastolic blood pressure (DBPV) were defined through the coefficient of variation (SD x 100/mean).

Results: Baseline age was a significant predictor of rate of change in scaled scores ($\beta = -0.19$, $p < 0.001$). Neither SBPV ($\beta = -0.04$, $p = 0.38$) or DBPV ($\beta = 0.01$, $p = 0.74$) were shown to be significant predictors of rate of change in scaled scores. Neither SBPV or DBPV interacted with age to predict rate of change in scaled scores (*p-values* < .05). In multivariable model, hepatitis C co-infection (diagnosed during study visit vs. no diagnosis) ($\beta = -0.14$, $p = 0.001$) and diabetes status (diagnosed at baseline vs. no diagnosis) ($\beta = -0.12$, $p = 0.04$) were statistically significant predictors of rate of change in global scaled scores.

Conclusions: These results suggest that BPV may not be a strong predictor of subsequent neurocognitive change in a well-characterized HIV+ cohort. The mechanisms of NC change in HIV+ patients in the current era of ART remains largely unknown, and thus, additional research is warranted.

Key words: HIV, hypertension, blood pressure, cognitive impairment, cardiovascular

Introduction

HIV-associated neurocognitive impairment (NCI) remains prevalent in the current era of antiretroviral therapy (ART) (Heaton et al., 2010). The burden of HIV-associated NCI is projected to increase as HIV-infected (HIV+) persons age (Cysique et al., 2011). The etiology of HIV-associated NCI in the current ART era is multifactorial and may be related to comorbid factors, such as subclinical cardiovascular disease (CVD) (Valcour et al., 2011b).

Antiretroviral therapy (ART) use is associated with a higher prevalence of hypertension, which appears to be driven by elevations in systolic blood pressure (SBP) (Seaberg et al., 2005). Increased blood pressure (BP) among HIV+ persons on ART appears to be associated with traditional CVD risk factors (e.g., older age and higher body mass index) rather than HIV disease characteristics (e.g., prevalence of AIDS, duration of HIV infection, HIV RNA level, and CD4+ T cell count) (Palacios et al., 2006; Thiebaut et al., 2005).

Hypertension is a critical, treatable risk factor for vascular events (Woodwell & Cherry, 2004). However, the predictive value of incident hypertension is limited for various reasons. First, the strength of the association between higher BP and increased incidence of vascular events decreases with older age (Lewington et al., 2002; Rothwell et al., 2004). Second, the variability in the course of BP between assessment visits, including the occurrence of episodic hypertension, limits the reliability of BP as a vascular risk factor (Colandrea et al., 1970; Cuffe et al., 2006; Hypertension Detection and Follow-up Program Cooperative Group, 1978; Perry & Miller, 1992). Visit-to-visit variability in BP (BPV) has previously been dismissed as random and an obstacle to

reliable estimate of "true" BP (Klungel et al., 2000; MacMahon et al., 1990; Turner & van Schalkwyk, 2008). However, recent research suggests that BPV may be an important risk factor for vascular events (Rothwell et al., 2010a; Rothwell et al., 2010b). Even when mean systolic SBP was effectively lowered in medication trials, higher visit-to-visit variability in SBP (SBPV) was indicative of poorer prognosis (Rothwell et al., 2010a; Rothwell et al., 2010b).

The role of BPV in neurocognitive (NC) change was recently examined in prospective studies involving patients with Alzheimer's disease (AD) and patients at risk for CVD (Lattanzi et al., 2014; Sabayan et al., 2013). Among patients affected by mild-to-moderate AD, greater SBPV was associated with a significant decline in NC status, as measured by the Mini Mental State Examination (Lattanzi et al., 2014). Interestingly, visit-to-visit variability in diastolic BP (DBPV), mean SBP, and mean DBP did not demonstrate an association with the course of NC change. Thus, fluctuations in SBP over time may be a correlate of NC decline in AD patients. Additionally, in a prospective cohort study involving persons at risk for CVD, greater BPV was associated with impaired NC functioning in older age (>70 years) (Sabayan et al., 2013). Although the association between SBPV and NC change has not been extensively studied in various patient populations, the initial studies involving AD patients or patients at risk for CVD indicate that variation in BP across visits may be a useful prognostic marker for NC decline.

To our knowledge, longitudinal cohort studies involving HIV+ persons have not investigated the association between BPV and changes in NC functioning. Research examining the role of BPV in NC functioning among HIV+ persons may be particular

relevant given that ART use has been associated with alterations in BP. We hypothesized that age and BPV would have an interacting effect on NC change, such that the strength of the association between BPV and NC change would decrease with older age.

Methods

Participants

Participants included 533 HIV+ individuals followed for up to twelve years (median follow-up time = 5.2 years) in NIH-funded cohort studies at the University of California, San Diego (UCSD) HIV Neurobehavioral Research Program. Study visits occurred every 6 months to 1 year [median number of study visits = 6) between May 5, 1999 to April 5, 2012. Studies were approved by the UCSD Institutional Review Board. All participants provided informed consent for participation in these cohort studies and agreed for their data to be used for future studies assessing the impact of HIV on the nervous system. Exclusion criteria included history of neurological (e.g., seizure disorders) or severe psychiatric (e.g., schizophrenia) conditions. Inclusion criteria were: being HIV+ (based on enzyme-linked immunosorbent assay with Western blot confirmation), having at least three study visits with valid global NC scores, having laboratory data (i.e., vital sign data) available within one month of NC data, and being primarily English-speaking. Forty-nine percent of the sample had previously undergone NC testing.

Materials and Procedures

Participants completed comprehensive NC and neuromedical evaluations every 6 months to 1 year.

Neurocognitive Evaluation

The NC battery comprised 15 measures covering seven NC domains (see Cysique et al., 2011b for a list of tests by domain). Raw test scores were transformed into scaled scores adjusted for repeated testing (Cysique et al., 2011b). The scaled scores were then averaged to provide a global scaled score, which was used for analyses. Scaled scores are standard scores with a mean of 10 and a standard deviation of 3. Assuming a normal distribution of scores, two-thirds of the population are expected to obtain scaled scores between 7 and 13 (i.e., the "within normal limits"). Global scaled scores of 7 and above were characterized as being "within normal limits," and global scaled scores less than 7 were considered to be in the "impaired" range.

To characterize the trajectory of NC change, a NC change status from baseline was generated for each follow-up visit (i.e., changes in global scaled score from "within normal limits" to "impaired" and vice versa). The individual visit change status for each participant was then merged into an overall change status: (1) stably normal: if a participant's global scaled score was "within normal limits" at baseline and at all following study visits, (2) stably impaired: if a participant's global scaled score was in the "impaired" range at baseline and at all following study visits, (3) improved: if a participant's global scaled score was in the "impaired" range at baseline and then changed and remained "within normal limits" at subsequent visits, (4) declined: if a participant's global scaled score was "within normal limits" at baseline and then changed and remained in the "impaired" range at subsequent visits, and (5) fluctuated: if a participant's global scaled score fluctuated over time (i.e., the global scaled score was within normal limits at some study visits and in the impaired range at other visits with no stable pattern).

Neuromedical Evaluation

Medical characterization of study participants included measurement of vital signs and medical comorbidities. BP was measured in the seated position with an automated sphygmomanometer. Pulse pressure (PP), a surrogate marker of arterial stiffness, was calculated as the difference between SBP and DBP. Visit-to-visit variability for SBP, DBP, and PP (PPV) were defined by the coefficient of variation (SD x 100/mean), which is consistent with previous investigations of BPV (e.g., (Lattanzi et al., 2014)). Medical comorbidities were determined by interview.

Routine clinical chemistry panels, complete blood counts, rapid plasma reagin, hepatitis C (HCV) antibody, and CD4+ T cells (flow cytometry) were performed at a Clinical Laboratory Improvement Amendments (CLIA)-certified, or CLIA equivalent, laboratory. HIV RNA levels in plasma were measured by reverse transcriptase polymerase chain reaction (Roche Amplicor, v. 1.5; lower limit of quantitation, 50 copies per milliliter). Self-reported data was gathered on duration of HIV infection, nadir CD4+ T cell count, and ART status (on/off).

Statistical Methods

A series of one-way ANOVAs were conducted with age and individual BPV variables (i.e., SBPV, DBPV, and PPV) as the dependent variables and NC change status (i.e., stably normal, stably impaired, improved, declined, and fluctuated) as the primary independent variable. Pairwise comparisons utilizing a Tukey-Kramer adjustment for multiple testing were conducted on any significant omnibus effects in order to further examine between-group differences. Hedge's g statistic for continuous variables was used to generate effect sizes for group comparisons.

To evaluate the effects of baseline age and BPV on rate of NC change, we used a mixed effects linear regression with subject-specific random intercepts and slopes. This statistical model assumes participants have different baseline global scaled scores (intercepts) and varying trajectories of change in global scaled scores over time (slopes). The model regressed mean global scaled scores on time (in years). Individual slopes were obtained from the model and used as outcomes in a linear regression. The slopes estimated the average changes in global scaled scores with every year passed. Baseline age and individual BPV variables were considered the primary predictor variables. We also evaluated the impact of potential HIV-disease related and medical comorbidity covariates (presented in table 8). Covariates were included in the multivariable model if univariable analyses showed that they were univariably associated with the outcome variable (random slopes) at 0.10 significance level. Backward model selection process was applied and the final multivariable model kept only those covariates that had *p*-values less than 0.05.

Statistical significance was determined using two-sided tests at a critical α level of 0.05. Analyses were performed in the statistical software R v3.1.1 and JMP 11.0.0 (SAS, 2013).

Results

Study participants

Demographic, HIV disease characteristics, and medical comorbidity data are presented in Table 8. The cohort consisted of mostly non-Hispanic white men, with ages ranging from 18 to 70 years of age. The mean duration of HIV infection was 9.2 years, and majority of the participants had an AIDS diagnosis at their baseline visit (68.8%).

The vital sign data, including BPV variables, are presented in Table 9. Comparisons between baseline and last visit data showed that SBP increased, DBP decreased, and PP increased over the course of the study (*p values* < 0.05).

Characterization of neurocognitive change

On average, global scaled scores of the study sample were "within normal limits" at baseline [mean = 8.8 (SD 2.3)]. In regard to trajectories of NC functioning with time, 64.7% of the sample was classified as "stably normal," 2.5% as "improved," 11.8% as "stably impaired," 5.8% as "declined," and 15.2% as "fluctuated" (Table 10; Figure 4).

Association between baseline age, BPV, and trajectories of NC change

The groups based on NC change status differed by age [$F(4, 528) = 4.15$, $p = 0.03$]. *Post-hoc* Tukey test ($p = 0.001$, hedges g = 0.52) indicated that the "stably impaired" group [mean age = 46.4 (SD 7.1)] differed in age from the "stably normal" group [mean age = 41.9 (SD = 8.8)]. The NC change groups did not differ by baseline SBP [$F(4, 528) = 0.62$, $p = 0.65$], baseline DBP [$F(4, 528) = 1.26$, $p = 0.28$], baseline PP [$F(4, 528) = 1.30$, $p = 0.27$], SBPV [$F(4, 528) = 1.68$, $p = 0.15$] or DBPV [$F(4, 528) = 0.24$, $p = 0.92$]. A one-way omnibus test indicated a trend towards group differences on PPV [$F(4, 528) = 2.23$, $p = 0.06$], though this omnibus model did not reach statistical significance at $\alpha = 0.05$. *Post-hoc* Tukey test ($p = 0.07$, hedges g = 0.87) indicated a trend towards greater PPV among the "fluctuated" group [mean age = 22.5 (SD 10.5)] compared to the "improved" group [mean age = 14.5 (SD 8.9)].

Association between baseline age, BPV, and rate of NC change

A univariable model predicting rate of NC change (as measured by random slopes) from baseline age was significant ($\beta = -0.19$, $p < 0.001$). Based on univariable

models, baseline SBP (β = -0.08, p = 0.06) and baseline DBP (β = 0.00, p = 1.00) were not statistically significant predictors of rate of NC change. Baseline PP (β = -0.10, p = 0.03) was a statistically significant predictor of rate of NC change. Based on univariable models predicting rate of NC change, none of the BPV variables were shown to be significant predictors: SBPV (β = -0.04, p = 0.38), DBPV (β = 0.01, p = 0.74), and PPV (β = -0.01, p = 0.86). Separate multivariable models were run to test the interaction between age and the various BP variables (i.e., baseline SBP, baseline DBP, baseline PP, SBPV, DBPV, and PPV). None of the interaction terms involving age and the individual BP variables were statistically significant (p *values* > 0.05).

Rate of neurocognitive change: Clinical correlates

None of the HIV disease characteristics presented in Table 8 were statistically significant predictors of rate of NC change (p *values* > 0.10). Among the medical comorbidities presented in Table 8, HCV [F(2, 530) = 8.4, p = 0.001], hypertension [F(2, 530) = 3.6, p = 0.03], and diabetes mellitus [F(2, 530) = 7.3, p < 0.001] were statistically significant predictors of rate of NC change. *Post-hoc* Tukey tests (p *values* < 0.05) indicated that study participants diagnosed with HCV during the study had the greatest negative rate of change [mean slope = -0.12 (SD 0.13)], followed by those with a diagnosis at baseline [mean slope = -0.04 (SD 0.06)], and then those without an HCV diagnosis [mean slope = -0.02 (SD 0.07)]. *Post-hoc* Tukey test (p = 0.02) indicated statistically significant differences in rate of change in scaled scores between those without a hypertension diagnosis [mean slope = -0.02 (SD 0.06)] and those diagnosed with hypertension at baseline [mean slope = -0.04 (SD 0.07)]. *Post-hoc* Tukey tests indicated that study participants without a diabetes mellitus diagnosis [mean slope = -

0.03 (SD 0.07)] had a statistically significant lower negative rate of NC change than study participants diagnosed with diabetes mellitus at baseline [mean slope = -0.06 (SD 0.06); $p = 0.01$] and study participants diagnosed with diabetes during the study [mean slope = -0.06 (SD 0.07); $p = 0.02$].

Multivariable model: Rate of NC change

A multivariable model of rate of NC change was run with our primary predictor variables and covariates that were univariably associated with random slopes (i.e., HCV status, hypertension status, and diabetes mellitus status). In the best fitting model [Model adjusted $R^2 = 0.07$, $F(5, 527) = 9.1$ $p < 0.001$], age at baseline ($\beta = -0.15$, $p = 0.001$), HCV status [diagnosed at baseline vs. no diagnosis ($\beta = -0.10$, $p = 0.02$) and diagnosed during study vs. diagnosed at baseline ($\beta = -0.12$, $p = 0.004$)], and diabetes status [diagnosed at baseline vs. no diagnosis] ($\beta = -0.13$, $p = 0.03$) were statistically significant predictors of rate of NC change. None of the BP variables were retained in the best fitting model.

Discussion

The aim of the present longitudinal study was to examine the role of BPV in NC change among a well-characterized HIV+ cohort. Variability in BP measurements over time was not significantly associated with trajectories or rate of NC change in this cohort. Of the various BP measurements examined in the current study, only baseline PP was univariably associated with rate of NC change. This significant univariable association, however, was not retained as an independent predictor of NC change in a model adjusting for the effect of potential covariates. These results suggest that BP measurements,

including baseline and visit-to-visit variability values, might not be strong predictors of subsequent NC change among HIV+ persons.

Our mostly null findings are in contrast to previous studies showing associations between NC decline and BPV. Studies involving non-demented elderly patients have found an association between greater BPV and worse NC outcomes (Bellelli et al., 2004; Kilander, Nyman, Boberg, Hansson, & Lithell, 1998; Ohya et al., 2001) while other studies found an association between greater BPV and better NC performance (Keary et al., 2007; Okonkwo, Cohen, Gunstad, & Poppas, 2011). Furthermore, SBPV was associated with a NC decline (as measure by MMSE scores) among patients with mild-to-moderate AD (Lattanzi et al., 2014). Fluctuations in BP over time are hypothesized to exert an effect on NC decline via impairment of cerebral hemodynamics, which has downstream effects on cerebral microvasculature (Alrawi, Panerai, Myint, & Potter, 2013; Katsogridakis et al., 2013). In support of this hypothesis, previous studies have shown that greater BPV is related to endothelial injury and impaired functioning of smooth muscle cells that line blood vessels (Diaz et al., 2012; Diaz et al., 2013). Thus, arterial stiffness might be a crucial factor underlying the association between BPV and NC functioning (Nagai, Hoshide, Ishikawa, Shimada, & Kario, 2012). Interestingly, the current study detected a univariable association between PP, a surrogate marker of arterial stiffness, and rate of NC change. Thus, it may be that the direct effect of BPV on neurocognition is muted in the context of HIV but that the downstream effect of BPV (i.e., arterial stiffness) is a significant predictor of NC decline. BPV is also hypothesized to exert a detrimental impact on neurocognition via cerebral hypoperfusion, which then leads to neuronal injury and cell death, particularly in vulnerable brain regions (e.g., the

hippocampus) (Brickman et al., 2010). In support of this mechanism, greater BPV was found to be related to lower hippocampal volume and the presence of cerebral microbleeds and cortical infarcts (Sabayan et al., 2013). Alternatively, the observed association between BPV and NC change in previous longitudinal studies may simply be a byproduct of a shared common factor(s), and BPV and NC change may not be causally related. Thus, our null findings may reflect the true absence of an association between BPV and NC change.

HCV co-infection was among the independent predictors of rate of NC change observed in the present study. Similar to HIV, HCV crosses the blood-brain barrier via infected leukocytes (Forton, Thomas, & Taylor-Robinson, 2004) and is able to replicate in brain tissue (Letendre et al., 2007). Modulation of cytokines and neurotoxicity are likely mechanisms by which HCV contributes to NCI among HIV+ patients (Schuster & Gonzalez, 2012). In a previous longitudinal study, treatment of HCV with pegylated interferon and ribavirin was associated with persistent NC decline (Cattie et al., 2014). Furthermore, the observed NC deficits persisted for months after treatment cessation (i.e., 42.5% remained neurocognitively impaired), even among individuals who had achieved virologic suppression of HCV (Cattie et al., 2014). The observed association between HCV and rate of NC change in the current study should be interpreted with consideration of the study period given that most baseline assessments in the present study were completed in the early 2000s. More recently, rapid progress in the development of treatments for HCV has occurred. Thus, the effect of HCV co-infection on NC change observed in this present study may be specific to HIV+ cohorts who received treatment prior to the era of direct-acting antivirals.

Consistent with previous cross-sectional studies in HIV (McCutchan et al., 2012; Valcour et al., 2005), we found that diabetes mellitus emerged as an independent predictor in our multivariable model of rate of NC change. Diabetes mellitus may impact NC functioning over time via direct damage to the brain from hyperglycemia, higher exposure of glucose in the brain given disruption of the blood-brain barrier by HIV (Leibson et al., 1997), and/or increased vulnerability for cerebral atherosclerosis. In addition, both vascular and metabolic factors may directly lead to the deposition of β-amyloid (Aβ) in the brain (de la Torre, 2002; Fotuhi, Hachinski, & Whitehouse, 2009; Sperling et al., 2011). Cerebral Aβ plaque deposition may compromise the functions of cerebral endothelial cells and blood vessels, thereby limiting the brain's capability to maintain adequate cerebral brain flow (Iadecola, 2004). In a clinico-pathological study of HIV+ adults, cerebral Aβ plaque deposition was associated with HIV-associated NCI among *APOE* ε4 carriers (Soontornniyomkij et al., 2012).

There were several limitations to our study to consider while interpreting the results. A major limitation of the current study is that it is observational in nature, limiting our ability to infer causation. On average, our study sample was relatively young (mean age = 42.8 years old). Cohort studies involving a greater representation of older participants might yield different correlates of NC change. Most baseline assessments in the present study were completed in the early 2000s, and the median duration of HIV infection was 9.2 years. Findings might differ in cohorts based on when they were infected and how quickly they initiated ART. Additionally, we had incomplete data on individual specific prescription medications that target BP, and thus, we are unable to control for the effects of specific antihypertensive drugs regimens on BPV. Lastly, the

frequency of BP readings and the interval between BP readings (e.g., days, months or years) may greatly impact the estimation of BPV. The frequency by which we collected BP readings in our observational study may therefore greatly limit our ability to detect potential associations between BPV and NC change. Our limitations are countered by various strengths, such as the use of a comprehensive NC battery that has been validated in HIV and the relatively long study follow-up time.

Overall, BPV may not be a good predictor of NC change trajectory or rate of NC change in the long term. These findings support other risk factors (i.e., HCV and diabetes mellitus diagnoses) as independent predictors of rate of NC change in HIV+ patients. The mechanisms of NC change in HIV+ patients in the current era of ART remains largely unknown, and thus, additional research is warranted in order to inform the development of therapeutic techniques aimed at preserving central nervous system functioning in this vulnerable population.

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Table 8. Demographic, HIV disease, and medical comorbidity characteristics of the study cohort (N = 533)

Characteristic	Mean (SD), Median (IQR) or %
Age (years), mean (SD)	42.8 (8.8)
Sex, male	81.6%
Race	
Non-Hispanic white	61.5%
Non-Hispanic black	21.0%
Hispanic	12.8%
Other	4.7%
Education (years), mean (SD)	13.1 (2.7)
Years of HIV infection at baseline, median (IQR) [1]	9.2 (5.0 - 13.7)
AIDS [2]	
Diagnosed at/prior to baseline	68.8%
No diagnosis	24.9%
Diagnosed during study	6.4%
Plasma HIV viral load	
Stably undetectable during study	32.6%
Became undetectable during study	29.1%
Stably detectable during study	28.9%
Became detectable during study	9.4%
CD4+ T cell count at baseline, median (IQR) [3]	362 (179 - 536)
Nadir CD4+ T cell count at baseline, median (IQR) [3]	117 (21 - 270)
ART status [4]	
Stably on ART during study	44.1%
Initiated ART during study	39.9%
Stably off ART during study	12.0%
Discontinued ART during study	4.0%
Smoker status	
Never smoked	59.7%
Only smoked prior to study	3.2%
Quit smoking during study	1.3%
Initiated smoking during study	3.4%
Sustained smoker	32.5%

Notes. [1]n = 476, [2]n = 519, [3]unit = cells/μL, [4]n = 524

Table 8 continued. Demographic, HIV disease, and medical comorbidity characteristics of the study cohort (N = 533)

Characteristic	Mean (SD), Median (IQR) or %
Hepatitis C Virus	
No diagnosis	64.4%
Diagnosis at baseline	34.5%
Diagnosed during study	1.1%
Hypertension	
No diagnosis	55.2%
Diagnosis at baseline	24.4%
Diagnosed during study	20.5%
Hyperlipidemia	
No diagnosis	64.4%
Diagnosis at baseline	14.6%
Diagnosed during study	21.0%
Diabetes	
No diagnosis	86.7%
Diagnosis at baseline	6.8%
Diagnosed during study	6.6%

Table 9. Vital signs and medical co-morbidity characteristics of the full study cohort (N = 533)

Variable	Variability	Reading at baseline visit	Reading at last visit	t-ratio, *p* value
Systolic blood pressure	8.8 (3.8)	124.9 (13.4)	129.4 (17.9)	t = 5.7, $p < 0.001$
Diastolic blood pressure	11.4 (5.4)	79.9 (10.7)	76.8 (12.2)	t = -4.8, $p < 0.001$
Pulse pressure (PP)	21.4 (10.3)	45.0 (11.5)	52.6 (14.0)	t = 10.9, $p < 0.001$

Notes: Variability measured as the coefficient of the mean; t-ratio corresponds to paired-sample t-test for blood pressure reading at baseline visit versus reading at the last study visit

Table 10. Neurocognitive functioning of the full study cohort (*N*=533)

Groups defined by NC change	n (% of sample)	Random slope (rate of NC change)	Global Scaled Score		
			Baseline visit	Last visit	t-ratio, *p* value
Entire sample	533 (100%)	-0.03 (0.07)	8.8 (2.3)	8.6 (2.4)	t = -4.7, $p < 0.001$
Stably normal	345 (64.7%)	-0.02 (0.06)	10.0 (1.6)	9.9 (1.5)	t = -2.5, $p = 0.01$
Fluctuated	81 (15.2%)	-0.04 (0.08)	7.4 (1.3)	7.1 (1.3)	t = -2.3, $p = 0.03$
Stably impaired	63 (11.8%)	-0.04 (0.06)	5.0 (1.3)	4.9 (1.3)	t = -1.0, $p = 0.30$
Declined	31 (5.8%)	-0.13 (0.06)	7.9 (0.7)	5.7 (1.0)	t = -11.4, $p < 0.001$
Improved	13 (2.5%)	0.03 (0.05)	6.3 (0.6)	7.7 (0.7)	t = 6.3, $p < 0.001$

Notes: t-ratio corresponds to paired-sample t-test for global scaled scores at baseline visit versus global scaled scores at the last study visit

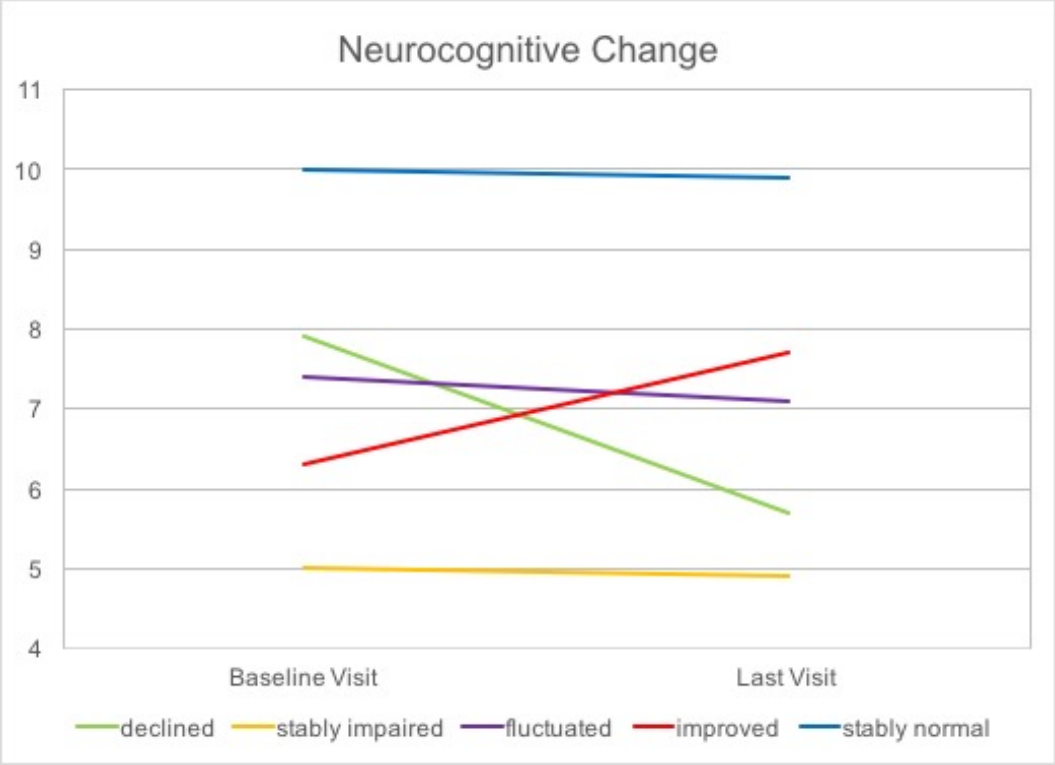

Figure 4. Trajectories of neurocognitive change of the study cohort (N = 533)

DISCUSSION

This study aimed to evaluate the contribution of CVD risk factors in NC functioning among persons with HIV. The three separate studies were designed to evaluate the associations among markers of CVD risk (i.e., arterial stiffness, coagulation imbalance, and BPV) and NC functioning among persons living with HIV/AIDS. The vascular markers (i.e., PP and biomarkers of vascular injury and coagulation) were generally comparable between ART-treated virally suppressed HIV+ older adults and the HIV-seronegative comparison group. Thus, HIV disease does not appear to confer risk for greater arterial stiffening or disturbances in coagulation imbalance in our observational studies. In the first study, a marker of vascular injury and arterial stiffness were associated with NC function, indicating that vascular remodeling may contribute to arterial stiffening and changes in PP, which, in turn, deleteriously affect NC functioning. The second study found that coagulation moderated the effect of HIV on NC functioning, such that greater coagulation imbalance was associated with poorer NC functioning among HIV+ participants. The moderating effect of coagulation on neurocognition was driven by procoagulant but not anticoagulant or fibrinolytic biomarkers, indicating that procoagulation may exert a detrimental effect on NC functioning among older HIV+ adults. Lastly, the third study did not detect a statistically significant association between BPV and trajectory or rate of NC change; however, baseline PP was a significant predictor of rate of NC change. These findings suggest that arterial stiffness might be a crucial factor impacting NC functioning over time among HIV+ adults. Together, the findings of these studies indicate that vascular remodeling, arterial stiffening, and procoagulation may contribute to poorer NC outcomes among HIV+ persons.

Cardiovascular Risk by HIV Serostatus

CVD and its subclinical manifestations are increasingly observed among long-term cART-treated HIV+ patients (Deeks, 2011). Thus, we hypothesized that our older HIV+ cohort in studies 1 and 2 would demonstrate greater arterial stiffening and disturbances in coagulation imbalance than the HIV-seronegative comparison group. Contrary to our hypothesis, HIV did not appear to confer risk for greater arterial stiffening or disturbances in coagulation imbalance in our observational studies. Delineating whether HIV confers greater risk for the development of CVD is complicated by the appropriate identification and recruitment of an HIV-seronegative comparison group. Mixed findings across published studies on the increased incidence and prevalence of CVD among HIV+ persons may be due to differences in cohort characteristics. For example, in regard to arterial stiffness, commonly reported determinants of greater arterial stiffness in HIV+ persons are low nadir CD4 T-cell counts (e.g., <350 cells per microliter), age, hypertension, and high cholesterol levels (Ferraioli et al., 2011; Ho et al., 2010; Kaplan et al., 2008; Lekakis et al., 2009; Monteiro et al., 2012; Seaberg et al., 2010; Strategies for Management of Antiretroviral Therapy Study et al., 2006; van Vonderen et al., 2009; Zeng et al., 2010). Thus, HIV+ cohorts who demonstrate good immunologic and virologic status may not show the same CVD risk profile as HIV+ cohorts with greater HIV disease and medical comorbidity burden. Overall, the failure to detect an association between the vascular risk factors (i.e., PP and biomarkers of vascular injury and coagulation) and HIV may reflect that this association is weak or absent in the context of ART, viral suppression, chronic HIV disease, older age, and/or presence of medical comorbidity burden.

CVD risk and HIV interact on neurocognitive functioning

The three studies' results indicate that vascular remodeling, arterial stiffening, and procoagulation may contribute to poorer NC outcomes among HIV+ persons. In study 1, HIV interacted with biomarkers of vascular remodeling (i.e., Tie-2 and VEGF) on NC functioning. For HIV+ adults, lower Tie-2 values and higher VEGF values were associated with worse NC functioning. The relationship between lower Tie-2 values and greater VEGF values with worse NC functioning in the HIV+ sample may reflect pathological angiogenesis, which is characterized by a highly disorganized vascular network (Fagiani & Christofori, 2013). In study 2, coagulation imbalance was found to moderate the effect of HIV on NC functioning, such that greater coagulation imbalance was found to be associated with poorer NC functioning among the HIV+, but not the HIV-, group. These findings indicate that greater coagulation imbalance may exert a particularly detrimental effect on NC functioning among older HIV+ adults. Given that HIV is characterized by chronic inflammation, older HIV+ adults may be particularly vulnerable to the detrimental effects of coagulation and angiogenic processes.

Inflammation, endothelial disruption, and hemostatic changes

HIV disease is associated with chronic inflammation, which can lead to disruption of the endothelium (Huang & Vita, 2006; Lopez et al., 2012; Solages et al., 2006). Endothelial dysfunction may contribute to a breakdown of the blood-brain barrier (Tomimoto et al., 1996) and impairment of cerebral reactivity and autoregulation (Bakker et al., 1999), thereby contributing to the pathogenesis of cerebral small vessel disease (CSVD) (Hassan et al., 2003).

Study 1 investigated the association of angiogenic growth factors with both PP and NC functioning given the crucial role of angiogenic growth factors in vascular remodeling (Marketou et al., 2010; Zachariah et al., 2012). A complex interplay of the angiopoietins, Tie-2, VEGF, and other pro- or antiangiogenic factors contribute to angiogenesis and vascular remodeling (Lieb et al., 2010). Study 1 found a positive association between vascular remodeling and arterial stiffness. Arterial stiffness may lead to NC decline due to augmented pressure pulses that penetrate and cause damage to the smaller blood vessels of the brain (O'Rourke & Safar, 2005). Previous research indicates that cerebrovascular disease may be a key underpinning in HIV-associated NCI (Soontornniyomkij et al., 2014). We found a quadratic association between PP and NC functioning. This is consistent with literature demonstrating a U-shaped relationship between PP and risk of AD and dementia, whereby both lower and higher end of the PP spectrum confers risk (Qiu et al., 2003). A recent histopathologic study showed that with older age, the arteries of the brain undergo degenerative changes characterized by arterial thickening, even in the absence of atherosclerosis (Gutierrez et al., 2016). These degenerative changes are hypothesized to be the downstream effect of mechanical forces of blood flow (Gutierrez et al., 2016). Thus, it is possible that PP is indexing arterial stiffening that may be occurring in the periphery and brain.

Hemostatic changes are hypothesized to play a secondary role to endothelial activation, such that damaged endothelial cells can act as a substrate for the initiation of coagulation (Markus et al., 2005). In study 2, coagulation biomarkers were related to several inflammatory biomarkers, including sCD163, sCD14 and complement C3. Monocyte and macrophage activation is hypothesized to be a source of inflammatory

cells in the central nervous system (CNS) and a key mechanism for CNS pathogenesis (Burdo et al., 2013a). Likely, the relationship between coagulation imbalance and inflammation is bidirectional, with coagulation imbalance being both a consequence of inflammation and an amplifier of the inflammatory response (Funderburg & Lederman, 2014). In study 2, the procoagulant composite was based on values of fibrinogen, p-selectin, tissue factor, and von Willebrand factor. Thus, the procoagulant composite represented both endothelial dysfunction and coagulation imbalance. Future investigations are needed to further elucidate the unique and combined contribution of endothelial dysfunction and coagulation to HIV-associated NCI.

Overall limitations

Several limitations of this dissertation study should be noted. The three studies used an observational design and thus causality from the observed associations cannot be directly inferred. Studies 1 and 2 utilized data from a parent study aimed at investigating "successful aging" with HIV, so there is a high likelihood of selection bias such that we recruited a sample of HIV+ patients demonstrating good immunologic and virologic profiles. Thus, the results of studies 1 and 2 should be interpreted with consideration of our cohort's unique demographic and clinical characteristics. Studies 1 and 3 collected resting BP rather than ambulatory BP, which may potentially demonstrate a different association with NC functioning. The physiological systems we investigated in the three studies are likely dynamic and complex, and future research is needed to determine the most optimal method for modeling biomarkers of CVD risk.

Treatment implications and future research

These three studies indicate that vascular remodeling/injury, arterial stiffening, and coagulation imbalance likely play mechanistic roles leading to poorer NC functioning outcomes in HIV+ adults. Thus, biomarkers of vascular remodeling/injury, arterial stiffening, and coagulation may provide valuable information regarding the prognosis and/or risk stratification of HIV+ adults. Although we observed associations between vascular remodeling/injury, arterial stiffening, and coagulation imbalance with NC functioning for older HIV+ persons, the clinical utility of these vascular risk factors as predictors of NC functioning depends on whether treatment-induced reductions in these factors translate to improved NC outcomes. A better understanding of the specific role of these vascular risk factors in the etiology of HIV-associated NCI may lead to specific treatments aimed at reducing these factors, thereby improving NC outcomes.

Future studies are needed to further elucidate the unique and combined contribution of vascular remodeling/injury and coagulation in neurocognition. Future research, particularly studies employing longitudinal designs, may tease apart the temporal association between vascular remodeling/injury, arterial stiffening, coagulation and neurocognition in the context of HIV disease. In addition, studies involving neuroimaging assessments may allow us to determine whether these vascular markers are associated with structural changes in the brain, including white matter lesions.

Conclusion

The etiology of HIV-associated NCI in the cART era is multifactorial and may be related to both direct and indirect consequences of HIV, the immune response, and comorbid factors (Valcour et al., 2011b), such as CVD and its subclinical manifestations. Delineating the relative contribution of CVD risk factors, such as arterial stiffening and

coagulation, in the pathogenesis of HIV-associated NCI may allow for the identification of adjunct therapies aimed at improving health outcomes for persons aging with HIV/AIDS.

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