COMBINED EFFECTS OF AGE AND HIV DISEASE ON CHANGES IN EVERYDAY FUNCTIONING OVER ONE YEAR

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Abstract

Introduction: Although HIV disease has evolved into a manageable condition with increased life expectancy, HIV-associated neurocognitive disorders (HAND) still persist in roughly 30-50% of people with HIV (PWH). As the HIV population lives longer, it is imperative to understand how aging impacts the expression and trajectory of the daily impact of HAND. The current study examined the combined effects of age and HIV disease on change in everyday functioning over one year and investigated the mediating role of changes in neurocognition. **Methods:** This observational, retrospective study employed a repeated measures factorial design. A total of 183 individuals with and without HIV were enrolled into younger (ages 18 to 40) and older groups (ages 50+). Participants completed a comprehensive neurocognitive evaluation and several assessments of everyday functioning at baseline and follow-up visits approximately 14 months apart. Study questions were analyzed using repeated measures MANOVAs, GLM mediation models, and cross-lagging panel models. **Results:** While cross-sectional age by HIV interactions were observed in the expected direction, these were tempered by a three-way interaction between age, HIV, and time for ADL declines such that older PWH exhibited steeper declines across 14-months. Change in neurocognition did not mediate the relationship between age and HIV status with everyday functional outcomes. Notably, baseline ADL declines predicted subsequent change in neurocognition at follow-up within the entire sample. **Conclusions:** Synergistic effects of aging and HIV disease were observed to accelerate functional declines over one year. Everyday functional declines may occur independently of, and prior to, neurocognitive changes, emphasizing the clinical relevance for accurate assessment and tracking of everyday functioning in older PWH.

Introduction

HIV disease has evolved into a chronic medical condition. People with HIV (PWH) are increasingly living into older adulthood and the life-expectancy for those who are able to fully engage in healthcare has reached near-normal levels (CDC, 2020). This shift in the epidemic is predominately due to the introduction of combined antiretroviral therapies (cART; i.e., medications that control viral replication), which are especially effective in managing HIV with earlier initiation and proper adherence (Marcus et al., 2016; Romley et al., 2014). However, despite the immunovirological benefits of cART, neurocognitive deficits still persist as a common sequelae of HIV disease (Heaton et al., 2010, 2011). It is estimated that 30-50% of PWH evidence HIV-associated neurocognitive disorders (HAND; Heaton et al., 2010). As is true of many neurocognitive disorders (e.g., Alzheimer's disease and related dementias), age is a major risk factor for HAND (Becker et al., 2004). Thus, the prevalence of HAND is expected to increase in the coming decades, which highlights the importance of understanding how older age influences the expression and trajectory of the daily impact of this heterogeneous neurocognitive disorder.

HAND diagnoses fall along a spectrum that ranges from Asymptomatic Neurocognitive Impairment (ANI, estimated prevalence in 20-33% of PWH), to Minor Neurocognitive Disorder (MND, estimated prevalence in 9-12% of PWH), to HIV-Associated Dementia (HAD, estimated prevalence in 1-2% of PWH; Antinori et al., 2007; Heaton et al., 2010; Tierney et al., 2017). In order to appropriately classify HAND, the presence and severity of neurocognitive and functional declines must be assessed in line with the Frascati criteria (Antinori et al., 2007). The Frascati criteria is the current gold-standard for diagnosing HAND in research and clinical settings (Heaton et al., 2010; Saylor et al., 2016; Tierney et al., 2017). These criteria greatly

improved upon previous diagnostic criteria for HAND (e.g., AAN AIDS Task Force, 1991; DSM-5, APA, 2013) by outlining specific guidelines with clear language to stage functional declines (i.e., intact functioning, mild decline, and major decline) across multiple domains and modalities, including clinician-rated functional status, employment status, everyday cognitive symptoms and performance-based functional assessments (Antinori et al., 2007). The ANI diagnostic criteria require evidence of neurocognitive declines on standardized testing (≤ 1 SD below normative mean in two domains), and intact functioning for everyday activities (i.e., individuals experience minor difficulties in one or fewer domains of functioning). The MND criteria include the same cut-offs for neurocognitive deficits, but also require reduced efficiency from prior levels of functioning (i.e., mild functional decline) in two or more aspects of daily life (e.g., work, household management, social activities, transportation). Individuals with mild functional decline may require assistance or prompting from others to successfully complete instrumental activities of daily living (IADLs). The diagnostic criteria for HAD require markedly low neurocognitive functioning (≤ 2 SDs below normative mean in two domains) and severe disruptions in two or more aspects of everyday functioning (i.e., major functional decline). Individuals with major functional decline may require substantial or complete assistance with IADLs. The Frascati criteria also clearly state the observed functional declines must not be exclusively attributable to other medical or psychiatric comorbidities and are linked to the observed neurocognitive impairment. Strong associations between neurocognitive functions and everyday outcomes in the context of HAND are well established in the HIV literature (Gorman et al., 2009; Heaton et al., 2004a). Evidence suggests that domain-level impairments in executive functions, learning, attention and working memory predict deficits in everyday functioning for PWH (Cattie et al., 2012; Heaton et al., 2004a). Thus, neurocognitive functions are an important

contributing feature to HAND and everyday functional outcomes. Additional factors to consider when classifying HAND include psychiatric symptoms of depression and apathy (Matchanova et al., 2020), which may directly interfere with everyday functional activities (Gorman et al., 2009; Kamata et al., 2013) and influence self-reported functional and cognitive complaints (Blackstone et al., 2012; Rourke et al., 1999).

Older age is another potential modulating factor in the context of HAND that warrants further exploration. As the lifespan for PWH increases and the prevalence of HAND remains high, it is imperative to understand the course of normal aging processes and everyday functional outcomes in HAND. Aging is associated with a number of medical, cognitive and psychological complications that can increase risk of poorer everyday functioning in PWH. HIV disease causes weakened or disrupted immune functions, inflammation, and vascular changes (Fanales-Belasio et al., 2010), and when these conditions combine with age-associated cellular damage and physiological declines, this could increase risk for disease and illness (Izaks & Westendorp, 2003). Thus, it follows that higher rates of medical co-morbidities are observed in older PWH, such as diabetes, chronic pulmonary disease, and hepatitis-C co-infection (Hernandez & Sherman, 2011; Rodriguez-Penney et al., 2013). In combination, age and HIV may also have additive effects on brain structures and functions. For instance, HIV increases neuroinflammation and targets brain regions that are impacted by normal aging processes, which may accelerate physiological and cognitive changes (Kamkwalala & Newhouse, 2017). In turn, these neurological changes can negatively impact neurocognitive abilities. Indeed, the prevalence and severity of HAND classification increases as a function of age (Sheppard et al., 2015). Prior research suggests the combined influences of age and HIV contribute to specific deficits in executive functions, attention, and psychomotor speed (Hardy & Vance, 2009; Iudicello et al.,

2012). Lastly, older PWH may experience adverse psychological outcomes, including greater levels of depression and substance use (Kamkwalala & Newhouse, 2017; Liu et al., 2014), although other work suggests that depressive symptoms may actually decrease in older PWH (Rooney et al., 2019). Furthermore, self-perceived aging symptoms (i.e., feeling older than same-aged peers) are elevated in older PWH, which might limit vocational and social activities in daily life (Fumaz et al., 2012).

All of this combines to suggest that older PWH may be at increased risk for poorer everyday functioning outcomes. The literature reveals that older PWH consistently display impairment in IADLs (Kamata et al., 2013; Moore et al., 2017). Beyond simply avoiding functional declines, older PWH are three times less likely to experience successful functional aging outcomes (i.e., thriving in their everyday activities) than healthy older adults (Fazeli et al., 2020). Commonly observed functional difficulties in PWH include managing finances, household care, communicating, driving, maintaining employment, and managing medications (Gorman et al., 2009; Kamat et al., 2012; Mindt et al., 2003). Of note, older PWH generally have better medication adherence than younger PWH, but the increased risk of neurocognitive decline in older PWH may jeopardize their otherwise superior performance of this everyday health behavior (Gorman et al., 2009; Hinkin et al., 2004). These findings illuminate the complexities in the relationship between age and functional outcomes in HIV disease when examined cross-sectionally. Thus, it is of paramount importance to understand how these factors combine to influence the course of everyday functional change over time in order to prevent negative real-world outcomes for PWH.

The existing literature on longitudinal change in functioning for healthy older adults can help guide this investigation in PWH. Overall, competence for everyday task performance tends

to decline with age (Willis et al., 1992). Such declines may be evident over five to six-year spans for older adults (i.e., aged ≥ 65; Lin et al., 2013), and within a two-year period for the oldest old (i.e., aged ≥ 84; Zarit et al., 1995). Given what we know about the potential for HIV to accelerate processes associated with normal aging (e.g., Sheppard et al., 2017), examining functional change over time is necessary to determine the timeline of functional declines in older populations with HIV. Notably, the functional changes healthy older adults experience (e.g., navigating familiar streets, managing small sums of money) may be accompanied by neurocognitive declines as well (e.g., executive functions and memory; Farias et al., 2009; Tucker-Drob, 2011). Seeing as HAND classifications are highly prevalent in older PWH, changes in neurocognition are also an important consideration in the context of functional changes. These studies reveal the benefit of longitudinal observations for understanding the trajectory of functional changes in healthy aging and support its use to examine the synergistic effects of aging and HIV disease on everyday functioning over time.

However, the only studies that have examined the combined impact of age and HIV disease on everyday functional outcomes have used a cross-sectional design. Vance and colleagues (2011) found that older PWH scored moderately worse than seronegatives and younger PWH on performance-based IADLs (i.e., slower in finding a phone number in a telephone book, calculating change, locating ingredients on a can and items in a grocery store, and identifying directions on a pill bottle). Notably, slower performance on these five timed IADL tasks was related to worse neurocognitive functioning, but not disease severity, for PWH (Vance et al., 2011). Further work by Vance and colleagues (2013) exhibited similar findings of largely worse performance on these same five timed IADL tasks in older PWH. Interestingly, the four study groups (i.e., young HIV+, young HIV-, old HIV+, old HIV-) did not exhibit

differences in accuracy for 28 untimed performance-based reasoning tasks, which involved real-life materials relating to medication, telephone, and finance problems (Vance et al., 2013). In terms of vocational functioning, greater rates of disability and lower rates of gainful employment have been observed in older PWH relative to older seronegative and younger HIV+ peers (Kordovski et al., 2017). For those older PWH who did maintain employment, they reported moderately worse vocational functioning for efficiency, productivity, and oversight in the workplace when compared to younger seronegatives (Kordovski et al., 2017). The starkest evidence in the literature for a combined effect of HIV and age on functioning was found in a sample of 179 old and young adults with and without HIV (Morgan et al., 2012). Findings revealed moderately greater declines for instrumental (e.g., financial and medication management, shopping, and transportation) and basic (e.g., housekeeping, bathing, and dressing) ADLs in older PWH relative to their younger and seronegative counterparts.

To my knowledge there are no studies that have employed a longitudinal design to investigate relationships between HIV, aging, and declines in everyday functioning. Although one study revealed that baseline neurocognition predicted declines in medication adherence and driving over one year in 16-28% of an HIV sample, the study did not examine differences in younger versus older PWH (Thames et al., 2013). The aforementioned cross-sectional studies also only used one or two proxies to assess everyday functioning. The use of multiple types of everyday functioning measures (e.g., self-reported cognitive symptoms, clinician-rated functioning) may reduce limitations of individual measures (e.g., reporter bias, mood symptoms) and increase sensitivity to detect HAND (Blackstone et al., 2012). These studies illuminate a dearth of research examining the interactivity of age and HIV on changes in different types of everyday functioning over time.

The primary aim of the current thesis study was to employ a repeated measures approach to examine the synergistic effects of age and HIV serostatus on change in functional outcomes over a one-year period. Another goal of this study was to evaluate whether neurocognitive functioning influences the relationship between these predictors and everyday functional changes. My primary hypothesis was that HIV seropositivity and older age would be independently associated with functional declines over one-year. Additionally, I predicted an age by HIV serostatus interaction such that older PWH would be more likely to exhibit functional declines. My second hypothesis predicted that change in global neurocognitive abilities would partially mediate the influences of age and HIV serostatus on changes in everyday functioning.

Methods

Participants

The retrospective sample included 183 individuals in the San Diego area who were recruited through HIV clinics, word-of-mouth, and community-based organizations. Participants were enrolled at baseline into either the younger (ages 18 to 40) or older (ages ≥ 50) groups. The age cutoff of 50 was used for inclusion in the older group because 1) HIV disease may accelerate cognitive changes associated with aging processes (Kamkwalala & Newhouse, 2017), and 2) the largest percentage (43%) of older adults with HIV fall between ages 50 and 54 (CDC, 2018). A maximum age of 40 for membership in the younger group was used to ensure sufficient differentiation in age between the groups in the spirit of traditional discrepant age-group designs in the cognitive aging literature. HIV serostatus was determined using a Western blot/ELISA or a MedMira rapid test. Exclusion criteria were an estimated verbal IQ score less than 70 on the Wechsler Test of Adult Reading (WTAR; Wechsler, 2001) and a history of psychotic disorders, intellectual disability, or neurological conditions (e.g., active central nervous system

opportunistic infections, seizure disorders, head injury with loss of consciousness > 30 minutes, stroke with neurological sequelae, non-HIV-related dementias). Additionally, participants were excluded if criteria for a substance use disorder was met within 1 month of baseline testing or if a toxicology screen for illicit drugs (except marijuana) was positive on the day of baseline testing. The sociodemographic and clinical characteristics for the sample are shown in Table 1. All participants provided written, informed consent.

Design

This observational, retrospective study employed a longitudinal, factorial design to examine changes in everyday functions over one year based on HIV serostatus and age. Comparisons were conducted between four groups that were split across two levels of each independent variable (i.e., younger HIV-, younger HIV+, older HIV-, older HIV+). All participants in the retrospective sample completed a baseline and one-year follow-up visit that were on average 14 months (*SD* = 2.63) apart. Neurocognitive abilities, everyday functioning, and health-related quality of life were evaluated at both visits. Participants were part of a larger parent study cohort that originally enrolled and evaluated 373 eligible participants at baseline. The 183 participants who returned for follow-up evaluations were compared to those who were not retained. Note that the present sample overlaps with that described in Kordovski et al. (2019) and the reported differences are extracted from that study. HIV serostatus, level of education, estimated IQ, racial/ethnic group membership, current affective distress, lifetime substance dependence and anxiety disorder rates were similar between retained and lost participants (*ps* > .05; Kordovski et al., 2019). The only notable group differences were significantly younger age and higher frequency of lifetime Major Depressive Disorders for retained participants (*ps* < .05), which will be considered interpretively in the Discussion of the thesis results.

Materials and Procedure

Everyday Functioning

All participants completed a comprehensive neuropsychological evaluation at baseline and follow-up visits from which several measures of everyday functioning were derived for this thesis. The Lawton and Brody Activities of Daily Living Questionnaire – Heaton Revision (ADL; see Heaton et al., 2004a, b; Woods et al., 2004) assessed self-reported functioning on 16 IADL items at "best" and "now." Each item was either scored "1" if any decline occurred from "best" to "now," or "0" if no decline occurred. Continuous ADL decline scores were calculated by summing the decline scores across the 16 items, whereby higher scores indicated greater declines (maximum possible score = 16). Cronbach's alpha was .73 at baseline and .77 at follow-up. The test-retest correlation for total ADL decline between visits was .71 ($p < .001$, 95% CI = .63, .77) and total ADL declines did not significantly change between visits (W = -132.5, $p = .82$, $d = .02$).

The Prospective and Retrospective Memory Questionnaire (PRMQ; Smith et al., 2000) is a 16-item instrument that was used to assess frequency of memory symptoms in daily life on a scale from 1 (never) to 5 (very often). The Cronbach's alpha was .94 at both baseline and follow-up visits, respectively. Test-retest correlation was .75 ($p = < .001$, 95% CI = .68, .81) and average PRMQ scores did not vary significantly between visits (W = -638.5, $p = .36$, $d = .06$). The Confusion and Bewilderment Scale from the Profile of Mood States assessment (POMS; McNair et al., 1981) includes 7-items that measure subjective cognitive symptoms (e.g., confused, unable to concentrate) over the past week on a scale from 0 (not at all) to 4 (extremely). Cronbach's alpha for the 7-items at baseline and follow-up visits was .86 and .82, respectively. The test-retest correlation was .64 ($p < .001$, 95% CI = .55, .72) and scores on the

POMS Confusion/Bewilderment scale did not differ significantly between visits (W = -1025.0, p = .14, d = .12). POMS and PRMQ scores were both converted into demographically adjusted T-scores based on available norms (Crawford et al., 2003; Nyenhuis et al., 1999). A continuous everyday cognitive symptoms variable was calculated by generating the average of the T-scores on the POMS and the PRMQ for each participant.

The Karnofsky Performance Status Scale (KPSS; Karnofsky & Burchenal, 1949) recorded clinician ratings of participant functional status on a scale from 0 (dead) to 100 (normal activity, no care needed). From baseline to follow-up evaluation, KPSS ratings declined (W = -1767.5, p = .004, d = .20) and the Spearman's rho test-retest correlation was .62 (p < .001). Employment status was gathered via semi-structured interview and coded into four levels (i.e., employed, unemployed, disabled, retired). Employment status varied significantly within the sample from baseline to follow-up visits (p < .001) such that the proportion of participants "employed" increased from 38% to 44%, respectively, and the proportion of "unemployed" subjects decreased from 32% to 26% of the sample, respectively. The proportion of "disabled" (22%) and "retired" (8%) participants remained consistent from baseline to follow-up visits.

Operationalization of Functional Status

Functional status was determined for every participant at each study visit by applying the Frascati diagnostic scheme for HAND (Antinori et al., 2007), as operationalized by Matchanova and colleagues (2020). The Frascati criteria provide specific guidelines for categorizing functional status based on the measures described above into three stages: intact functioning (i.e., no decline), mild decline, or major decline. Notably, the functional declines collected via the study measures were not exclusively due to medical symptoms or comorbidities. The criteria for each stage of functional decline using the measures in the current study are outlined below.

Intact Functioning. Individuals with KPSS scores ≥ 90 or who self-reported mild decline on fewer than two items on the ADL questionnaire were classified with intact IADL functioning. For employment, individuals who reported being "employed" or "retired," or who reported "I am efficient at work" on the work item of the ADL questionnaire were categorized with intact functioning. Lastly, individuals with scores less than one standard deviation (<1.0 SD) above the mean score for either the PRMQ or the POMS Confusion/Bewilderment scale were considered functionally intact for everyday cognitive symptoms.

Mild Functional Decline. Individuals were classified with mild functional decline in IADLs if KPSS scores fell between 70 and 89, or if individuals reported mild decline from "best" to "now" on two or more items on the ADL questionnaire. For example, a decline on the transportation item would be coded for a participant if at "best" they reported "I drive my own car or take public transportation on my own" and "now" they reported "I arrange my own travel using taxis, but do not drive or use public transportation." Mild decline in employment status was determined by identifying individuals who reported a decline from "best" to "now" on the work item from the ADL scale (e.g., at "best" they reported "I am efficient at work" and "now" they reported "I am not very efficient at work and have difficulty maintaining attention or finishing tasks"). Individuals who scored ≥ 1.0 (and < 2.0) standard deviations above the mean for either the PRMQ or POMS, and who did not meet full criteria for either major depressive or generalized anxiety disorders according to the Composite International Diagnostic Interview (CIDI version 2.1; WHO, 1998), were categorized with mild functional decline for everyday cognitive symptoms.

Major Functional Decline. Participants were classified with major functional decline in IADLs if their KPSS clinician rating was less than 70 or if participants, or their knowledgeable

informant, indicated greater than mild decline in functioning from "best" to "now" on two or more ADL items. For example, a participant was coded with major decline if on the transportation item at "best" they reported "I drive my own car or take public transportation on my own" and "now" they reported "I can travel on public transportation or use taxis if I am assisted by another." Participants who reported their vocational status as "unemployed" or "disabled," or who reported "I am no longer able to work" on the ADL work item were classified with major functional decline in employment. Individuals who scored ≥ 2.0 SDs above the mean on the PRMQ or POMS, and who did not meet criteria for depressive or generalized anxiety disorders, were categorized as major decline for everyday cognitive symptoms.

Global functional status was assessed at baseline and follow-up visits separately. According to the Frascati criteria, a global classification of mild or major functional decline requires declines in two or more domains of functioning. Thus, classifications in IADLs, employment, and everyday cognitive symptoms were examined to determine global functional status (e.g., mild decline in IADLs, mild decline in employment, and intact functioning in cognitive symptoms would constitute a global functional classification of "Mild Decline").

Neurocognitive Functioning

Each participant was administered a full battery of neurocognitive tests at baseline and follow-up visits which evaluated six domains of cognition commonly implicated in HAND (Antinori et al., 2007). Two assessments were used to evaluate each domain of neurocognition per Frascati criteria recommendations. Attention was assessed using the Digit Span subtest from the Wechsler Memory Scale, third edition (WMS-III; Wechsler, 1997) and Trial 1 from the California Verbal Learning Test, second edition (CVLT-II; Delis et al., 2000). Executive functions were assessed using the Total Moves score from the Tower of London Test (ToL,

Drexel Version; Culbertson & Zillmer, 1999), and the Total Time score from the Trail Making Test, Part B (TMT; Army Individual Test Battery, 1944; Heaton et al., 2004b). Learning was assessed using the Logical Memory I subtest from the WMS-III and Total Trials 1-5 from the CVLT-II. Delayed memory was assessed using the Logical Memory II subtest from the WMS-III and the Long Delay Free Recall trial from the CVLT-II. Information processing speed was assessed using the Total Time score from the TMT, Part A (Heaton et al., 2004b) and the Total Execution Time from the ToL Test. Motor skills were assessed using the completion times for dominant and nondominant hand trials on the Grooved Pegboard Test (Heaton et al., 2004b; Kløve, 1963).

Raw scores from each neurocognitive measure were converted to sample-based z-scores. A global sample-based neurocognitive z-score was calculated for each participant by taking the average z-scores across all tests at each respective study visit. Global neurocognitive z-score change was calculated by subtracting the baseline global neurocognitive z-score from the follow-up global neurocognitive z-score. Positive global neurocognitive change scores indicated an improvement in neurocognition from baseline to follow-up, whereas negative global neurocognitive change scores indicated a decline in neurocognition. A Global Deficit Score (GDS) approach was also used to determine normatively based neurocognitive deficits at baseline and follow-up evaluations, separately. Demographically adjusted T-scores were calculated for each test based on available normative data. Then, each T-score was converted into a deficit score for each measure (see Carey et al., 2004). Finally, a GDS was calculated by taking the average of all deficit scores across the test battery for each participant, where GDS ≥ .50 were categorized as neurocognitively impaired.

Determining Change in Frascati HAND Classifications

HAND classifications were determined at baseline and follow-up visits separately (see Woods et al., 2004). First, GDS scores were examined to determine the presence of neurocognitive impairment. Individuals with no neurocognitive impairment were labeled "normal." Then, if GDS scores indicated neurocognitive impairment, global functional status was examined. Individuals who exhibited neurocognitive impairment accompanied by intact functioning were classified with "subsyndromic neurocognitive disorder." Finally, individuals who exhibited both neurocognitive impairment and functional decline (either mild or major) were labeled with "syndromic neurocognitive disorder." Next, HAND classifications at baseline and follow-up visits were compared to determine whether change occurred and the direction of change over one year. This process resulted in three mutually exclusive categories of HAND changes: improve, stable, and decline. The "improve" classification included change from lower to higher levels over time (e.g., "subsyndromic" to "normal"). HAND classifications were considered "stable" when they remained the same between visits (e.g., "subsyndromic" at both baseline and follow-up). Participants were classified with "decline" if they exhibited changes from higher to lower levels over time (e.g., "subsyndromic" to "syndromic").

Health-Related Quality of Life

The RAND 36-Item Short-Form Health Survey (SF-36) is a self-report questionnaire used to assess health-related QoL (HRQoL; Ware & Sherbourne, 1992). The response format varies by item and includes 5-point Likert type scales (e.g., rating "During the past 4 weeks, how much did pain interfere with your normal work?" from 1 = "Not at all" to 5 = "Extremely"), 3-point Likert type scales (e.g., rating "Does your health now limit you in these activities? If so, how much?" for various activities from 1 = "Yes, Limited A Lot" to 3 = "No, Not Limited At All"), and dichotomous yes/no responses (e.g., "During the past 4 weeks, have you had any of

the following problems with your…regular daily activities as a result of your physical health?" where 1 = "Yes" and 2 = "No"). Cronbach's alpha for all 36 items was .95 at both baseline and follow-up evaluations. The SF-36 assesses health concepts on eight different subscales: physical functioning, role limitations due to physical health, bodily pain, social functioning, mental health, role limitations due to emotional problems, energy and fatigue, and general health perceptions. Each of the eight subscales receives a score from 0 to 100, whereby higher scores indicate better HRQoL. These eight subscales load onto two component summary measures of physical HRQoL (i.e., physical functioning, role limits-physical, bodily pain, and general health subscales) and mental HRQoL (i.e., mental health, role limits-emotional, social functioning, and vitality subscales; Ware et al., 1994). The physical and mental HRQoL components are linked to separable outcomes (e.g., chronic medical conditions and psychiatric disorder severity, respectively) in different clinical populations (McHorney et al., 1993), which supports the rationale to examine these component scores separately in relation to the variables of interest in the current study. The physical and mental health component scores were generated by calculating the average of the four respective subscale scores for each component, which provided a summary score between 0 and 100 whereby higher scores indicated better physical and mental HRQoL. Test-retest correlation between visits was strong for both physical HRQoL (ICC = .72, $p < .001$, 95% CI = .64, .79) and mental HRQoL (ICC = .66, $p < .001$, 95% CI = .57, .73). Sample scores did not vary for physical HRQoL (W = 101.0, $p = .89$, $d = .04$) or mental HRQoL (W = 849.0, $p = .23$, $d = .04$) between baseline and follow-up evaluations.

Medical and Psychiatric Evaluation

A medical evaluation for all participants was conducted by a research nurse. The evaluation included a review of systems (e.g., nadir CD4 cells/μL), medical comorbidities (e.g.,

Hepatitis C virus co-infection), duration of HIV infection, a blood draw to assess current CD4 cells/μL and HIV RNA plasma viral load, current medications (e.g., cART), and a urine toxicology screening.

Psychiatric conditions were assessed using the Composite International Diagnostic Interview (CIDI, version 2.1; WHO, 1998). The CIDI is a semi-structured interview that was conducted by certified research assistants to determine the presence of current (i.e., within the last 30 days) and lifetime diagnoses of Major Depressive Disorder, Generalized Anxiety Disorder, and Substance Use Disorder according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (APA, 1994). Sample information for all medical and psychiatric variables are displayed in Table 1.

Data Analysis

First, I visually inspected the data to check for outliers, coding consistency and quality assurance purposes. Then, I conducted Little's Missing Completely At Random (MCAR) test in SPSS (version 26) to assess whether the data was missing completely at random to ensure this would not influence my analyses and results. The missing data were shown to be missing completely at random (Little's MCAR test, all *ps* > .05) and thus missing data points did not skew my results. Power analyses were conducted using the G*Power software (version 3.1.9.6; Faul et al., 2009). Statistical analyses were conducted using JMP Pro (14.0.0), Jamovi (The Jamovi Project, 2020), and MPlus (Muthén & Muthén, 1998-2017).

To test my first hypothesis, I conducted four parallel repeated measures multivariate analysis of variance (MANOVA) models to examine how group membership based on age and HIV serostatus related to repeated measures outcomes for ADL decline scores, everyday cognitive symptoms (i.e., mean T-score from POMS and PRMQ), and raw scores on the physical

and mental HRQoL scales. Covariates for this model were identified using a data driven approach (e.g., Field-Fote, 2019), whereby any sociodemographic or clinical variable listed in Table 1 (e.g., gender, psychiatric diagnoses) that significantly differed between the four study groups (i.e., old HIV+, old HIV-, young HIV+, young HIV-) and related to both baseline and follow-up scores for each respective functional variable at a significance of $p < .05$ was included as a covariate. Simple chi-square, ANOVA, and correlational analyses were conducted to test differences for categorical and continuous sociodemographic variables between the four age-HIV groups and in relation to the continuous functional variables. A power analysis revealed the sample (N=183) had adequate power (1-B = .88) to detect a medium effect size with a critical alpha of .05 for my primary analysis.

For my second hypothesis, I conducted a series of general linear model (GLM) mediation analyses in Jamovi to investigate whether change in neurocognition mediated the relationship between age and HIV status with everyday functioning outcomes. Covariates were selected for inclusion in the mediation models if they differed by study group and significantly related to both the neurocognitive change and everyday functioning change variables at $p < .05$. For all mediation models, the predictor was study group membership based on age and HIV status. Separate models were conducted to examine each of the functional outcomes, which included change in ADL declines, change in everyday cognitive symptoms, and change in physical and mental HRQoL scores. The first set of mediation models entered continuous sample-based neurocognitive z-score change as the mediator. The second set of mediation models entered categorical change in Frascati-defined HAND classifications as the mediator, which was an ordinal variable (i.e., decline, stable, improve). I used 95th percentile bootstrap confidence intervals to determine whether the mediation effects were statistically significant. Additionally,

cross-lagged panel models were conducted using MPlus to examine ways in which age and HIV serostatus interactions, change in global neurocognitive z-score, and change in the various functional measures related to one another. Specifically, these models allowed me to examine how group status related to baseline and follow-up changes in neurocognitive and functional outcomes, as well as to examine whether baseline neurocognition predicted residualized change in functional outcomes, and vice versa. Using young HIV-s as the comparison group, dummy coded variables were generated for the remaining three study groups. Regression coefficients were examined for pathways between repeated neurocognitive measures, repeated functional measures, baseline neurocognition and follow-up everyday functioning, baseline everyday functioning and follow-up neurocognition, and group effects on each baseline and follow-up measure of neurocognition and everyday functioning.

Results

Activities of Daily Living

A repeated measures MANOVA was conducted to examine differences in baseline and follow-up ADL decline scores among the four study groups. The only sociodemographic variables that differed by study group and were related to ADL decline scores were lifetime GAD and HCV (ps < .05), which were included as covariates in the model. The overall between-subjects model was significant ($F(5,176)=8.34$, $p<.001$, $\eta^2=.24$) and a main between-subjects effect was observed for HIV serostatus ($F(1,176)=5.13$, $p=.025$, $\eta^2=.03$) such that PWH had greater ADL decline scores at both visits. However, no main effect was observed for age group ($p=.49$, $\eta^2=.003$). Main effects were also observed for covariates of lifetime GAD ($F(1,176)=7.82$, $p=.006$, $\eta^2=.04$), such that individuals with GAD exhibited greater ADL decline scores at both visits, and HCV ($F(1,176)=4.61$, $p=.033$, $\eta^2=.03$) such that participants with HCV

exhibited greater ADL declines. A significant between-subjects interaction of HIV serostatus and age group was observed ($F(1,176)=4.15$, $p=.043$, $\eta^2=.02$). Follow-up pairwise comparisons with Tukey-Kramer HSD corrections revealed that older PWH exhibited greater ADL decline scores than old and young seronegative groups at baseline ($ps<.03$, mean Cohen's $d=.69$) and greater ADL decline scores than the other three study groups at follow-up ($ps<.02$, mean $d=.70$). However, the interpretations of the main effects and cross-sectional between-subjects interaction were tempered by a significant three-way interaction between HIV serostatus, age group, and time ($F(1,176)=4.05$, $p=.046$, $\eta^2=.02$). The post-hoc ANOVA model examining study group differences in magnitude of ADL decline score change was significant ($F(3,178)=2.67$, $p=.049$, $\eta^2=.04$). Omnibus group differences were driven by reductions in ADL problems for younger PWH relative to increased ADL problems in older PWH over one year ($p=.03$, $d=.51$). No other significant group differences were observed for ADL declines ($ps>.20$, $ds < .62$). Results are displayed in Figure 1.

Everyday Cognitive Symptoms

A second repeated measures MANOVA was employed to investigate changes in everyday cognitive symptoms (i.e., POMS and PRMQ) from baseline to follow-up between the four study groups. Based on the data-driven approach to select covariates, lifetime GAD and HCV were also included in this model. The overall between-subjects model was significant ($F(5,176)=8.28$, $p<.001$, $\eta^2=.24$) and main effects emerged for lifetime GAD ($F(1,176)=6.53$, $p=.012$, $\eta^2=.04$), such that those with GAD reported greater cognitive symptoms at both study visits, and HCV ($F(1,176)=7.26$, $p=.008$, $\eta^2=.04$), whereby those with HCV reported greater cognitive symptoms at both study visits. A main between-subjects effect was observed for HIV serostatus ($F(1,176)=4.27$, $p=.040$, $\eta^2=.02$), in the expected direction whereby PWH reported

greater cognitive symptoms. However, no main effect of age group was observed (p=.63, η^2=.001). The MANOVA model revealed a significant between-subjects interaction of age group and HIV serostatus on everyday cognitive symptoms (F(1,176)=3.95, p=.049, η^2=.02). Follow-up pairwise comparisons revealed greater cognitive symptoms for older PWH relative to older HIV- and younger HIV+ groups at baseline (ps<.009, mean d=.70). At follow-up, older PWH reported greater cognitive symptoms than older and younger seronegative groups (ps<.01, mean d=.73). These results were tempered by a significant three-way interaction between HIV serostatus, age group, and time (F(1,176)=4.62, p=.033, η^2=.03). A planned post-hoc analysis was conducted using a one-way ANOVA to probe the significant three-way interaction between HIV, age, and time on everyday cognitive symptoms. However, the model did not reveal significant omnibus differences between study groups on change in everyday cognitive symptoms (F(3,178)=1.58, p=.195, η^2=.03). Results are displayed in Figure 2.

Health-Related Quality of Life

Two parallel repeated measures MANOVAs were conducted to examine change in HRQoL between the four study groups from baseline to follow-up. The overall model examining change in physical HRQoL, which included lifetime GAD and HCV as covariates, was significant (F(5,175)=12.06, p<.001, η^2=.34). Main effects were observed for HIV serostatus (F(1,175)=10.34, p=.002, η^2 = .06), such that PWH reported lower physical HRQoL at both visits, age group (F(1,175)=12.98, p<.001, η^2=.07), such that older participants reported lower physical HRQoL, and lifetime GAD (F(1,175)=5.24, p=.023, η^2=.03), such that individuals with GAD reported lower physical HRQoL at both visits. The within-subjects results revealed no significant main effects or interactions (all ps>.54). Results are displayed in Figure 3.

The model examining change in mental HRQoL between the study groups only included lifetime GAD as a covariate. The overall model was significant ($F(4,175)=8.31$, $p<.001$, $\eta^2=.19$), and main effects emerged for HIV serostatus ($F(1,175)=8.87$, $p=.003$, $\eta^2=.05$), such that PWH had lower mental HRQoL at both visits, and lifetime GAD ($F(1,175)=10.13$, $p=.002$, $\eta^2=.06$), such that individuals with GAD reported lower mental HRQoL at both visits. There was no main effect of age group on mental HRQoL ($p=.34$, $\eta^2=.005$). Interestingly, a within-subjects interaction between time and age group was observed ($F(1,175)=5.40$, $p=.021$, $\eta^2=.03$) and a three-way interaction between HIV serostatus, age group, and time fell just above the *a priori* level of significance with a small effect size ($p=.061$, $\eta^2=.02$). A post-hoc one-way ANOVA was conducted to probe the possible three-way interaction to identify study group differences in mental HRQoL change over one year. The model revealed significant omnibus HIV-age group differences ($F(3,176)=3.27$, $p=.023$, $\eta^2=.05$). Follow-up pairwise comparisons revealed these omnibus differences were driven by an increase in mental HRQoL for young HIV- participants over one year relative to slight declines for older adults with ($p=.02$, $d=.64$) and without ($p=.03$, $d=.72$) HIV. Results are displayed in Figure 4.

Mediation Models with Neurocognitive Change

A series of GLM mediation models were analyzed to examine whether change in global neurocognitive z-scores or change in HAND status mediated the relationship between age-HIV group membership and change in the four everyday functioning measures. Using the data-driven confound approach, no sociodemographic variables significantly related to all three variables in each mediation model (all *p*s>.05) and thus no covariates were included in the following analyses. The mediation results are displayed in Tables 2-5.

Activities of Daily Living

The model investigating neurocognitive z-score change as a mediator in the relationship between study group and change in ADL declines confirmed the direct effect of group on ADL changes, which was driven by greater declines in older PWH relative to younger PWH (95% CI=-1.87, -.28, *p*=.011). However, there was no indication of a significant indirect pathway through neurocognitive z-score change (95% CI =-.20, .05, *p*=.430), indicating that neurocognitive change did not mediate this relationship. Similarly, a parallel model examining change in HAND classification as a mediator confirmed the direct group effect on ADL change, driven again by differences in old versus young PWH (95% CI=-1.83, -.30, *p*=.006). There were no indirect effects of HAND status change in this relationship (95% CI=-.15, .09, *p*=.840), suggesting that it was not a significant mediator. The model results are displayed in Table 2.

Everyday Cognitive Symptoms

Another GLM model was conducted to examine whether neurocognitive z-score differences mediated the relationship between age-HIV group status and change in everyday cognitive symptoms. A direct group effect was observed (i.e., young vs. old HIV+) on everyday cognitive symptom change (95% CI=.33, 5.94, *p*=.028). However, the indirect relationship of study group on change in cognitive symptoms through neurocognitive z-score change as a mediator was not significant (95% CI=-1.21, .17, *p*=.272). A parallel model examining change in HAND status as a mediator revealed the same direct effect of group on everyday cognitive symptom change (95% CI=.19, 5.75, *p*=.046), but the mediating effect of HAND status change failed to reach significance (95% CI=-1.06, .76, *p*=.700). Model results are displayed in Table 3.

Health-Related Quality of Life

Two sets of mediation models were conducted to examine whether neurocognitive z-score change mediated the relationship between study group as the predictor and change in

physical or mental HRQoL as the outcomes. The model examining physical HRQoL failed to observe significant direct or indirect effects (*ps*>.05). These findings were confirmed with parallel mediation models including change in HAND status as the mediator between study group and physical HRQoL outcomes (*ps*>.26). The model results are displayed in Table 4. The second set of models examined neurocognitive z-score change as the mediator first, and mental HRQoL as the outcome of interest. Findings confirmed the direct effect of study group (i.e., young HIV- vs. old HIV+) on change in mental HRQoL (95% CI=3.09, 19.82, *p*=.008). However, the mediating effect of change in neurocognitive z-scores was not significant (95% CI=-.34, 2.54, *p*=.254). The parallel model examining change in HAND status as the mediator also revealed the direct effect of study group (young HIV- vs. old HIV+) on change in mental HRQoL (95% CI=4.11, 19.27, *p*=.003), but did not reveal a significant mediating effect through change in HAND status (95% CI=-.64, 2.35, *p*=.625). These results are displayed in Table 5.

Cross-Lagged Models with Neurocognitive Change

In order to investigate the cross-sectional and prospective associations between neurocognitive performance and the three functional outcomes, a series of cross-lagged panel models were fit to the data where each functional outcome was analyzed separately. Within each model, study groups were dummy coded using young HIV-s as the comparison group to evaluate how age and HIV interactions may be related to changes in neurocognitive and functional variables over 14 months. There was no information about fit because the following models were just identified. The critical alpha was set at .01 due to the large number of analyses.

Activities of Daily Living

A cross-lagged panel model was analyzed to examine how HIV status and age interact to predict change in ADL decline after accounting for change in neurocognitive functioning over a

14-month interval (see Figure 5). Neurocognition was stable over time, β = .83, SE = .04, β*=.79, $p < .001$. ADL decline scores also exhibited stability across 14-months, β = .74, SE = .06, β*=.67, $p < .001$. Neurocognition and ADL declines were not correlated with one another at either baseline or follow-up visits (ψ*s < .-.19, *ps* > .01). Interestingly, the cross-lagged effect of baseline ADL declines predicting follow-up neurocognitive performance was significant, β = -.03, SE = .01, β*= -.12, $p < .003$. However, baseline neurocognitive scores did not predict ADL declines at follow-up, β = -.16, SE = .22, β*= -.04, $p = .47$. These findings indicate the possibility of a causal effect for baseline ADLs predicting neurocognitive outcomes over a 14-month period. Predictors accounted for approximately 73% of the variance in neurocognitive scores, $R^2 = .73$, and 53% of the variance in ADL declines, $R^2 = .53$. The only significant group effect was observed for old HIV+ on baseline neurocognition, β = -.65, SE = .14, β*= -.50, $p < .001$, and baseline ADL declines, β = 1.44, SE = .50, β*= .30, $p = .004$. There were no other group effects on neurocognition or ADL declines at baseline or follow-up visits (*ps* > .01).

Everyday Cognitive Symptoms

A parallel cross-lagged panel model was conducted to examine everyday cognitive symptoms as the functional outcome of interest (see Figure 6). Both neurocognition, β = .84, SE = .05, β*=.80, $p < .001$, and everyday cognitive symptoms, β = .68, SE = .05, β*= .73, $p < .001$, were stable over time. Neurocognitive performance and everyday cognitive symptoms were not significantly correlated at baseline, ψ* = -.12, $p = .095$. Although residualized change in these measures were significantly negatively correlated at follow-up, ψ* = -.25, $p < .001$, there were no significant cross-lagged effects. Specifically, neurocognitive performance at baseline did not predict everyday cognitive symptoms 14-months later, β = -1.34, SE = .85, β*= -.08, $p = .12$, and baseline cognitive symptoms did not predict neurocognitive performance at follow-up, β = -.002,

SE = .002, β*= -.03, p = .48. Predictors accounted for approximately 72% of the variance in neurocognitive scores, R^2 = .718, and 59% of the variance in everyday cognitive symptoms, R^2 = .589. The only significant group effect was observed for old HIV+ on baseline neurocognition, β = -.65, SE = .14, β*= -.50, p < .001. Group status did not significantly predict baseline everyday cognitive symptoms or residualized change in neurocognition and everyday cognitive symptoms after 14-months (*ps* > .01).

Health-Related Quality of Life

A cross-lagged panel model examining the relationship between group status with change in neurocognition and physical HRQoL revealed high stability across 14-months for both neurocognitive performance, β = .82, SE = .05, β*= .78, p < .001, and physical HRQoL, β = .65, SE = .06, β*= .63, p < .001, (see Figure 7). Although these measures were significantly correlated at baseline (ψ* = .27, p < .001) and residualized change in neurocognition and physical HRQoL were correlated at follow-up (ψ* = .22, p = .002), no significant cross-lagged effects were observed (*ps* > .03). Group effects were present for old HIV+s in relation to neurocognitive performance, β = -.65, SE = .14, β*= -.50, p < .001, and physical HRQoL scores, β = -24.43, SE = 4.74, β*= -.52, p < .001, at baseline. No group effects were observed for residualized change in neurocognition and physical HRQoL after 14-months (*ps* > .03).

A cross-lagged panel model examining the relationship between group status with change in neurocognition and mental HRQoL revealed high stability across 14-months for both neurocognitive performance, β = .83, SE = .04, β*= .79, p < .001, and mental HRQoL, β = .62, SE = .06, β*= .62, p < .001, (see Figure 8). Residualized change in neurocognition and mental HRQoL were correlated at follow-up (ψ* = .20, p = .005) but the two measures were not significantly correlated at baseline (p = .035). Moreover, no significant cross-lagged effects were

observed (*ps* > .10). A group effect was observed for old HIV+s on baseline neurocognitive performance, β = -.65, SE = .14, β*= -.50, $p < .001$, and on residualized change in mental HRQoL scores at follow-up, β = -14.84, SE = 3.79, β*= -.33, $p < .001$. The only other significant group effect emerged for young HIV+s on follow-up mental HRQoL, β = -10.85, SE = 4.16, β*= -.19, $p = .009$. No other group effects were observed (*ps* > .01).

Discussion

Everyday functioning declines are crucial to understand in the context of aging and HIV disease, as these two factors independently increase risk of functional dependence. Though numerous studies exhibit evidence that older PWH fare worse cognitively and functionally relative to their older seronegative counterparts, there is a dearth of research exploring how age and HIV disease synergistically impact declines in these domains over time. The current thesis study examined the interactive effects of older age and HIV disease on change in ADLs, everyday cognitive symptoms, and HRQoL across 14-months, and investigated whether neurocognitive change played a mediating role in these relationships.

Cross-Sectional Age and HIV Interaction

Before discussing the repeated measures aspects of the study, it is important to note that I observed the expected combined adverse effects of HIV and aging on ADL functions and everyday cognitive symptoms cross-sectionally, after controlling for anxiety and HCV infection. Specifically, at each study visit older PWH exhibited poorer functioning in these domains compared to seronegatives and younger PWH. The observed differences revealed older PWH scored worse on these two functional outcomes at medium-to-large effect sizes. The interaction was not confounded by demographic (e.g., gender or education), psychiatric, or medical variables based on the approach utilized to select relevant covariates for the model. My findings

align with previous work which found poorer self-reported and performance-based ADL capacity in older PWH (Morgan et al., 2012; Vance et al., 2011, 2013). Given that older adults with HIV may carry greater load of age-associated conditions (e.g., incontinence, frailty; Hosaka et al., 2019), we can understand how the combined burden of HIV disease with these conditions may lead to increased dependence in everyday activities and at earlier ages of onset (i.e., 50 years old; Kamkwalala & Newhouse, 2017). Interestingly, the current results failed to reveal synergistic effects of HIV and aging on HRQoL. Although older PWH may exhibit poorer quality of life (Liu et al., 2014), alternate findings indicate that medical co-morbidities and depression, but not age, impact HRQoL in HIV populations (Rodriguez-Penney et al., 2013). Indeed, it appears that across the lifespan PWH and seronegatives show comparable levels of HRQoL, grit, and resilience in the absence of depression (Rooney et al., 2019). In this context, the current findings suggest that as PWH age, their capacity for resilience in the face of adverse health and social conditions may allow them to maintain adequate physical and mental HRQoL.

Repeated Measures for Main Effects of Age and HIV

Models adjusting for anxiety and HCV infection revealed a main effect of age on mental HRQoL over time such that younger individuals increased relative to small decreases for older adults at a small-to-medium effect size. The literature reveals mixed findings of both increases and declines in mental HRQoL for older adult populations (Barile et al., 2013; Choi et al., 2020). Factors linked to declines in mental HRQoL include greater co-morbid health conditions, depression, and sedentary behaviors, all of which tend to increase in older age (Balboa-Castillo et al., 2011; Chan et al., 2009). As such, this may explain the observed declines in mental HRQoL for older adults. No other main effects of HIV or age were found to impact the rate or direction of change in functional measures across 14-months. Although there is sufficient

evidence to support higher levels of everyday functioning problems in PWH relative to seronegatives and other chronic disease populations, very small proportions of PWH exhibit detectable declines in clinically significant functional impairment across one year (Hays et al., 2000; Laverick et al., 2017; Thames et al., 2013). Annual stability is observed for everyday functioning in cognitively healthy older adults as well (Farias et al., 2009). Thus, it may be difficult to detect meaningful changes in everyday functioning across one year for older adult and HIV populations.

Repeated Measures Age, HIV, and Time Interaction

The most notable finding from the current study was the observed interaction of age and HIV with change in ADL declines across 14-months. This supported my primary hypothesis of a combined adverse effect of aging and HIV on rate of everyday functional declines. Specifically, analyses revealed older PWH exhibited worsening ADL dependence over time as compared to younger PWH, who showed moderate improvements. This difference was accompanied by a medium effect size, after controlling for anxiety and HCV, and was independent of potential confounding sociodemographic or clinical variables based on my approach to select covariates. Both young and old seronegatives experienced relative stability in ADL functioning across the 14-month time span. Essentially, my findings revealed unexpected functional improvements in younger PWH, which may be driven by greater cognitive and behavioral resilience (McGowan et al., 2018). On the other hand, older PWH became notably worse at managing daily activities over the same time period. Similarly, Thames and colleagues (2013) were able to detect declines in medication management and driving across one year for 16% and 28%, respectively, of an older HIV sample. Although the average participant in that study was approximately 50 years old, the investigators did not stratify the sample by age. The current study therefore affirms the

existence of functional declines across one year in PWH and provides novel evidence that older PWH may be at risk for steeper declines. Looking to studies in healthy aging samples, functional declines in everyday task competence exist across longer periods of time (i.e., up to seven years) and are driven by poorer cognitive and physical health factors (Willis et al., 1992). For PWH, risk factors such as increased fatigue, neuropsychiatric and medical disorders, lower premorbid functioning, and nadir CD4 counts can impact ADL capacity (Barroso et al., 2014; Lin et al., 2013; Morgan et al., 2012). In this context, the current study provides support that HIV disease can combine with older age to have negative synergistic impacts on functional declines over shorter spans of time than are observed in the healthy aging process.

Importantly, the current findings build upon prior cross-sectional studies of everyday functioning in older HIV populations. Methods typically used to measure functional decline do not measure actual declines across time points per se, but rather record declines relative to perceived premorbid levels (Heaton et al., 2004a; Woods et al., 2004). Although a number of studies have examined everyday functioning problems in older PWH, I am not aware of any studies which explicitly investigate change in everyday functioning across two time points using multiple functional measures in this population. In this way, the current study contributes greatly to the literature by providing evidence of accelerated ADL declines by using a baseline measure of functioning as an anchor against which to assess actual change over one year. The findings also reveal exceptional clinical relevance in that older PWH on average reported significant increases in ADL dependence at a rate of 0.4 domains across 14-months. This trajectory indicates two to three years may be a sufficient span of time for older PWH to become dependent in a full domain of functioning. For patients who fall out of care or who do not receive a comprehensive neurocognitive evaluation, these functional problems may be missed. This rate of

decline has serious implications for downstream influences on patient safety, independent living, and HIV management. Thus, it may be clinically useful to assess and monitor functional declines for older PWH on an annual basis in order to manage medical and social care for these potentially vulnerable individuals.

Although the omnibus interaction between age, HIV, and time was observed for everyday cognitive symptoms over one year, it was accompanied by a small-to-medium effect size and the follow-up analyses did not reveal meaningful group differences. Prior longitudinal work in the pre-cART era found that cognitive symptoms increased across an 18-month span for younger adults with and without HIV (Saykin et al., 1991). More recently, Kordovski et al. (2019) found that although elevated everyday cognitive symptoms were present in older PWH, they exhibited relative stability in these symptoms over one-year. Additionally, older populations without neurocognitive impairment show stable and comparable levels of cognitive complaints relative to younger adults across four-year intervals (Hohman et al., 2011; Smith et al., 2000). These prior findings taken together with the current null results indicate that changes in everyday cognitive symptoms are not accelerated over one year in the context of aging in PWH. To adequately detect changes in this domain for HIV populations, longer periods of data collection beyond one year may be necessary. Larger sample sizes may also increase the ability to detect group level changes in everyday cognitive symptoms, although the current study revealed adequate power in that I was able to detect meaningful changes in ADLs within older and younger PWH.

The current results revealed the absence of additional burdens due to HIV and age on changes in HRQoL, which was observed to be stable in PWH and older adults. An exploratory post-hoc investigation of the trend-level interaction revealed improvements in mental health functioning for young seronegative individuals across one year. As such, my hypothesis did not

find support for accelerated declines in mental HRQoL for older PWH. While older HIV populations report lower mental HRQoL than elderly persons with other chronic conditions, changes across one year are relatively unremarkable in both samples (Ronel et al., 2018). In sum, the current findings align with the literature regarding stability for mental health functioning over time in older PWH. Prior research also indicates that positive psychology factors including resilience, greater social supports, and perceived self-efficacy can buffer against declines in HRQoL, despite the fact that older PWH may carry greater burdens of cognitive impairments, disability, and medical co-morbidities (Emlet et al., 2013).

Role of Neurocognitive Change

Neurocognitive changes, as measured by both sample-based z-scores and Frascati-defined clinical impairments, were not found to influence the relationship between age and HIV serostatus with declines in any of the everyday functional outcomes. This was surprising given prior research showing that baseline neurocognitive performance can predict longitudinal functional declines for driving and medication management in PWH; although it has also been shown that changes in employment activities appear to be independent of neurocognitive abilities (Chernoff et al., 2010; Thames et al., 2013). Thus, although poorer baseline neurocognition can be associated with declines in everyday functioning for PWH, the current study aligns with mixed results in the literature which indicate that changes in neurocognition and everyday functioning may not be closely linked in this population. It is possible that 14 months is not sufficient to detect notable changes in neurocognition, reducing the robustness of this variable as a mediator. Indeed, neurocognitive performance and classifications remain relatively stable in HIV samples across 14-month to 4-year time spans (Casaletto et al., 2014; Elicer et al., 2018). On the contrary, some longitudinal studies have observed accelerated motor functioning declines

in gait speed and grip strength for older PWH relative to their seronegative peers (Schrack et al., 2015, 2016). Becker and colleagues (2011) detected neurocognitive declines across six months in PWH, which were associated with accelerated declines in medication adherence. However, their method to determine neurocognitive change was sensitive to normative deficits in neurocognitive functions for clinical samples. Changes in both global sample-based neurocognitive scores and objective Frascati classifications for HAND, which are cross-sectionally related to everyday functional impairments (Shirazi et al., 2017), did not influence changes in everyday functioning in the current sample.

More complex cross-lagged panel models which examined how HIV status and age relate to ADL declines over one-year, accounting for change in neurocognition, aligned with the mediation models and revealed no relationship between change in neurocognition with ADL declines for any of the study groups. Intriguingly, baseline ADL declines were associated with change in neurocognition across 14-months, but the opposite relationship was not significant. The cross-lagged model uncovered this prospective relationship between everyday functioning and neurocognition which could not be measured in the mediation models. While neurocognitive change over one year did not mediate ADL declines over the same time period, this finding makes sense in light of the fact that baseline ADLs predicted follow-up changes in neurocognition. Initially this relationship may seem counterintuitive, seeing as neuropsychological research in both aging and HIV populations is heavily focused on initial neurocognitive deficits and the subsequent impact on functional dependence (Thames et al., 2013; Willis et al., 1992). However, functional problems may exist in the absence of neurocognitive deficits for up to 50% of HIV+ samples (Heaton et al., 2004a). Moreover, Ettenhofer and colleagues (2010) established a reciprocal relationship such that baseline

neurocognition predicted medication adherence, which in turn predicted global neurocognitive and executive functions six months later. Indeed, recent findings suggest that lower functional reserve (i.e., observed functioning lower than expected given neural, cognitive, and demographic factors) can predict clinically significant cognitive declines up to 7 years later (Kraal et al., 2021). Thus, problems with everyday functioning may reduce independence in ADLs and engagement in cognitively stimulating activities, which together can have downstream impacts on neurocognitive declines. Future work might examine causal effects of everyday functioning on neurocognition, and potential mediating factors within this relationship, across longer spans of time to understand how to prevent these negative outcomes in aging populations with HIV.

The remaining cross-lagged panel models found no notable prospective relationships with neurocognition and everyday cognitive symptoms or HRQoL. In line with the mediation findings, change in neurocognition does not appear to be related to these two proxies of everyday functioning in older PWH. For everyday cognitive symptoms, this could be due to the aforementioned stability in this domain across time for PWH (Kordovski et al., 2019). Interestingly, prior work found that baseline neurocognition could predict HRQoL at later time points, which does not align with the current findings (Jones et al., 2019). However, Jones and colleagues (2019) also found that declines in neurocognitive functions correlated with declines in HRQoL over an average span of 7 years in PWH. Indeed, HRQoL and cognitive declines may be difficult to detect in this population during time spans less than four years (Casaletto et al., 2014; Elicer et al., 2018; cf. Becker et al., 2011). As such, after accounting for neurocognitive changes, subjective experience of cognitive symptoms in daily life and perceived quality of life appear to remain relatively stable across 14-months, regardless of HIV serostatus or age. Meaningful

changes in everyday cognitive symptoms and HRQoL may require observation over much longer durations of time, which could inform the aims of future research.

Final Remarks

There are a few limitations in the data analysis of the current study which warrant attention. First, the large number of analyses requires mention of Type I error risk. Although my power analysis revealed I could detect medium effect sizes, some of my data analyses revealed small effect sizes. Conducting multiple primary and follow-up data analyses increased my risk of detecting small, statistically significant effects which may be false positive findings. When applicable, I utilized corrections (e.g., Tukey-Kramer HSD, stricter p-values) to reduce my risk of false positive errors across multiple analyses. Despite the implemented corrections, the risk of Type I error is not completely eliminated and thus interpretation of these small effect sizes does warrant caution in the context of my study power. Alternatively, detecting the medium effect size I was powered for in the ADL change analyses suggests greater confidence that this is a robust effect. Second, there may be limitations to interpreting main effects in the context of significant interactions in my MANOVA models. Specifically, interpreting the significant, independent main effects of HIV and age on everyday functioning may fail to fully address how these variables combine to ultimately impact the outcome of interest. In this way, the interaction tempers these main effects because to say HIV serostatus impacts everyday functioning overall may not accurately account for the nuanced impact of aging on poorer functional outcomes within the context of HIV disease.

The current study also possesses some methodological limitations which might inform future research. Use of global neurocognition to understand associations with change in everyday functioning may lack sensitivity to domain-specific cognitive declines which relate to functional

problems. Indeed, greater declines in episodic memory and executive functions relate to greater IADL declines in aging and HIV samples (Farias et al., 2009). Future studies could investigate associations between domain-specific cognitive changes and functional declines longitudinally for older PWH. The current study also assessed self-reported everyday functions, which are subject to reporter bias. More objective, performance-based functional assessments can detect ADL declines that parallel neurocognitive declines for healthy older individuals (Tucker-Drob, 2011). Future longitudinal use of objective functional measures may further illuminate these associations in aging PWH. Furthermore, my repeated measures design precludes interpretation of true longitudinal changes, which require at least three time points (Shahar, 2009). Subsequent studies may utilize a true longitudinal design to understand the trajectory of everyday functional changes in older PWH. Finally, there is potential sample bias in that participants lost to follow-up were older and had lower rates of depression than retained participants. It is possible that older individuals did not return due to cognitive (e.g., forgetting appointments) or functional (e.g., transportation challenges) problems. Perhaps retained participants had greater stability in these domains or generally exhibited better functioning than the older individuals who did not return. Higher rates of depression in the retained sample could also bias self-reported everyday functioning, which further supports use of performance-based measures in future studies.

The major takeaway from the current thesis study is that older PWH are at risk for greater dependence and steeper declines in ADLs in the span of one year. This suggests negative, compounding effects of age and HIV on everyday functioning. Moreover, self-reported ADL declines at baseline predicted changes in neurocognition over time across the entire sample. These findings are clinically relevant, especially due to the fact that older PWH exhibited greater problems with independently managing ADLs at baseline. The presence of everyday functional

problems before the emergence of neurocognitive deficits can inform the importance of accurately assessing and monitoring everyday functioning problems, in addition to neurocognition, in clinical practice for older adults with HIV disease. Diagnostic classification schemes, such as the one used to determine HAND in the current study, often focus primarily on identifying the presence of neurocognitive deficits, then subsequently assessing everyday functional declines to determine whether individuals are symptomatic (i.e., neurocognitive symptoms impact everyday functioning) or not (Antinori et al., 2007; Woods et al., 2004). The current findings support clinical practice that emphasizes the equal and independent assessment of ADL problems and neurocognitive deficits for aging populations with HIV disease to ensure well-rounded patient care.

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Table 1. Demographic and clinical information for the study groups at baseline.

Variable	Younger HIV+ (*n* = 35)	Older HIV+ (*n* = 77)	Younger HIV- (*n* = 27)	Older HIV- (*n* = 44)	*p*
Sociodemographic					
Age (years)	32.3 (5.2)	56.4 (5.9)	30.0 (6.5)	56.0 (4.8)	**<.001**
Gender (% men)	82.9	85.7	63.0	68.2	**.032**
Education (years)	12.6 (1.5)	14.4 (2.5)	13.5 (1.8)	14.5 (2.3)	**<.001**
WTAR VIQ	99.5 (11.4)	102.0 (10.7)	102.2 (10.1)	104.9 (9.9)	.154
GDS (% impaired)	25.7	28.6	14.8	11.4	.096
Race/ethnicity (%)					.066
Caucasian	45.7	66.2	40.7	70.5	
African American	28.6	20.8	25.9	11.4	
Hispanic	20.0	11.7	29.6	15.9	
Other	5.7	1.3	3.8	2.2	
Psychiatric					
Major depressive disorder (%)					
Current	11.4	7.8	3.7	4.6	.580
Lifetime	60.0	61.0	48.2	50.0	.506
Generalized anxiety disorder (%)					
Current	5.7	3.9	0.0	0.0	.159
Lifetime	11.4	20.8	3.7	4.6	**.019**
Lifetime substance use disorder (%)	60.0	77.9	70.4	70.5	.283
Medical					
Hepatitis C Virus (%)	5.7	33.8	3.7	15.9	**< .001**
HIV Duration (months)	49.7 (53.8)	135.9 (98.5)	–	–	**< .001**
Plasma RNA Detectable (%)	31.3	19.7	–	–	.204
Current CD4 count (cells/μL)	552.7 (241.6)	580.8 (309.9)	–	–	.605
Nadir CD4 count (cells/μL)	260.5 (182.3)	178.4 (159.0)	–	–	**.025**
AIDS (%)	37.1	63.6	–	–	**.009**
Prescribed cART (%)	85.7	90.9	–	–	.420

Note. Values are Means (Standard Deviation) or valid sample % values. Younger ≤ 40 years old; Older ≥ 50 years old; WTAR VIQ = Wechsler Test of Adult Reading Verbal IQ estimate; GDS = Global Deficit Score; RNA = Ribonucleic acid; CD4 = Cluster of Differentiation 4; AIDS = Acquired Immune Deficiency Syndrome; cART = Combination antiretroviral therapy. **Bold** indicates $p < .05$.

Table 2. Neuropsychological change mediation models with study group and ADL change.

Model	Path A (Group-NP Change)	Path B (NP Change-ADL Change)	Path C' (direct: Group-ADL Change)	Path C (indirect: NP Change mediation)
Group (O- v. O+) – ***NP Z Change*** – ADL change	B = -.03 CI [-.17, .10]	B = -.49 CI [-1.31, .28]	B = -.34 CI [-.98, .26]	B = .01 CI [-.07, .12]
Group (Y+ v. O+) – ***NP Z Change*** – ADL change	B = .10 CI [-.05, .25]	B = -.49 CI [-1.31, .28]	**B = -1.03** **CI [-1.87, -.28]***	B = -.05 CI [-.20, .05]
Group (Y- v. O+) – ***NP Z Change*** – ADL change	B = .13 CI [-.05, .298	B = -.49 CI [-1.31, .248]	B = -.07 CI [-.97, .79]	B = -.06 CI [-.25, .05]
Group (O- v. O+) – **NP Frascati Change** – ADL change	B < -.01 CI [-.14, .14]	B = -.40 CI [-1.42, .44]	B = -.33 CI [-.89, .24]	B < .01 CI [-.09, .10]
Group (Y+ v. O+) – **NP Frascati Change** – ADL change	B = .03 CI [-.15, .22]	B = -.40 CI [-1.42, .44]	**B = -1.07** **CI [-1.83, -.30]****	B = -.01 CI [-.15, .09]
Group (Y- v. O+) – **NP Frascati Change** – ADL change	B = .11 CI [-.13, .33]	B = -.40 CI [-1.42, .44]	B = -.09 CI [-.91, .75]	B = -.05 CI [-.24, .09]

Note. Values are fully standardized effect sizes (B) and 95% confidence intervals. *ADL* activities of daily living questionnaire, *O-* Old HIV-, *O+* Old HIV+, *Y-* Young HIV-, *Y+* Young HIV+, *NP Z Change* neuropsychological z-score change, *NP Frascati Change* neuropsychological Frascati HAND classification change. *p<.05; **p < .01

Table 3. Neuropsychological change mediation models with study group and everyday cognitive symptom change.

Model	Path A (Group-NP Change)	Path B (NP Change-Cognitive Sx Change)	Path C' (direct: Group-Cognitive Sx Change)	Path C (indirect: NP Change mediation)
Group (O- v. O+) – ***NP Z Change*** – Cog. Sx change	B = -.03 CI [-.16, .11]	**B = -3.84** **CI [-7.38, -.31]***	B = .88 CI [-1.55, 3.29]	B = .11 CI [-.43, .76]
Group (Y+ v. O+) – ***NP Z Change*** – Cog. Sx change	B = .10 CI [-.04, .26]	**B = -3.84** **CI [-7.38, -.31]***	**B = 3.14** **CI [.33, 5.94]***	B = -.38 CI [-1.21, .17]
Group (Y- v. O+) – ***NP Z Change*** – Cog. Sx change	B = .13 CI [-.04, .29]	**B = -3.84** **CI [-7.38, -.31]***	B = -.76 CI [-4.67, 3.34]	B = -.49 CI [-1.39, .16]
Group (O- v. O+) – **NP Frascati Change** – Cog. Sx change	B < -.01 CI [-.14, .14]	**B = -3.92** **CI [-7.57, -.79]***	B = .99 CI [-1.32, 3.78]	B < -.01 CI [-.69, .61]
Group (Y+ v. O+) – **NP Frascati Change** – Cog. Sx change	B = .03 CI [-.16, .23]	**B = -3.92** **CI [-7.57, -.79]***	**B = 2.87** **CI [.19, 5.75]***	B = -.11 CI [-1.06, .76]
Group (Y- v. O+) – **NP Frascati Change** – Cog. Sx change	B = .11 CI [-.11, .33]	**B = -3.92** **CI [-7.57, -.79]***	B = -.81 CI [-4.89, 3.15]	B = -.44 CI [-1.87, .35]

Note. Values are fully standardized effect sizes (B) and 95% confidence intervals. *Cog. Sx* everyday cognitive symptoms measured by mean score from Profile of Mood States and Prospective and Retrospective Memory Questionnaires, *O-* Old HIV-, *O+* Old HIV+, *Y-* Young HIV-, *Y+* Young HIV+, *NP Z Change* neuropsychological z-score change, *NP Frascati Change* neuropsychological Frascati HAND classification change. ***$p < .05$

Table 4. Neuropsychological change mediation models with study group and physical health-related quality of life.

Model	Path A (Group-NP Change)	Path B (NP Change-Phys. HRQoL Change)	Path C' (direct: Group-Phys. HRQoL Change)	Path C (indirect: NP Change mediation)
Group (O- v. O+) – ***NP Z Change*** – Phys. HRQoL change	B = -.03 CI [-.17, .11]	B = 6.35 CI [-.27, 12.74]	B = 1.99 CI [-4.68, 8.37]	B = -.18 CI [-1.55, .69]
Group (Y+ v. O+) – ***NP Z Change*** – Phys. HRQoL change	B = .12 CI [-.03, .28]	B = 6.35 CI [-.27, 12.74]	B = 1.88 CI [-5.33, 8.61]	B = .78 CI [-.25, 2.38]
Group (Y- v. O+) – ***NP Z Change*** – Phys. HRQoL change	B = .13 CI [-.03, .29]	B = 6.35 CI [-.27, 12.74]	B = 1.19 CI [-6.47, 8.94]	B = .81 CI [-.36, 2.11]
Group (O- v. O+) – **NP Frascati Change** – Phys. HRQoL change	B < -.01 CI [-.14, .15]	B = 4.28 CI [-3.43, 12.17]	B = 1.81 CI [-4.18, 7.67]	B < -.01 CI [-1.10, .78]
Group (Y+ v. O+) – **NP Frascati Change** – Phys. HRQoL change	B = .06 CI [-.12, .23]	B = 4.28 CI [-3.43, 12.17]	B = 2.41 CI [-4.66, 9.09]	B = .25 CI [-.69, 1.66]
Group (Y- v. O+) – **NP Frascati Change** – Phys. HRQoL change	B = .11 CI [-.12, .32]	B = 4.28 CI [-3.43, 12.17]	B = 1.52 CI [-6.46, 9.91]	B = .48 CI [-.84, 2.19]

Note. Values are fully standardized effect sizes (B) and 95% confidence intervals. *Phys. HRQoL* physical health-related quality of life, *O-* Old HIV-, *O+* Old HIV+, *Y-* Young HIV-, *Y+* Young HIV+, *NP Z Change* neuropsychological z-score change, *NP Frascati Change* neuropsychological Frascati HAND classification change.

Table 5. Neuropsychological change mediation models with study group and mental health-related quality of life.

Model	Path A (Group-NP Change)	Path B (NP Change-Mental HRQoL Change)	Path C' (direct: Group-Mental HRQoL Change)	Path C (indirect: NP Change mediation)
Group (O- v. O+) – ***NP Z Change*** – Mental HRQoL change	B = -.03 CI [-.16, .11]	B = 6.41 CI [-.36, 13.80]	B = -.21 CI [-7.08, 6.89]	B = -.15 CI [-1.54, .78]
Group (Y+ v. O+) – ***NP Z Change*** – Mental HRQoL change	B = .12 CI [-.03, .27]	B = 6.41 CI [-.36, 13.80]	B = .76 CI [-6.84, 8.45]	B = .79 CI [-.26, 2.22]
Group (Y- v. O+) – ***NP Z Change*** – Mental HRQoL change	B = .13 CI [-.05, .29]	B = 6.41 CI [-.36, 13.80]	**B = 11.03** **CI [3.09, 19.82]***	B = .82 CI [-.34, 2.54]
Group (O- v. O+) – **NP Frascati Change** – Mental HRQoL change	B < -.01 CI [-.14, .15]	B = 3.61 CI [-4.06, 11.15]	B = -.36 CI [-7.63, 5.71]	B < -.01 CI [-.83, .90]
Group (Y+ v. O+) – **NP Frascati Change** – Mental HRQoL change	B = .06 CI [-.12, .25]	B = 3.61 CI [-4.06, 11.15]	B = 1.34 CI [-5.80, 8.65]	B = .21 CI [-.86, 1.53]
Group (Y- v. O+) – **NP Frascati Change** – Mental HRQoL change	B = .11 CI [-.11, .33]	B = 3.61 CI [-4.06, 11.15]	**B = 11.45** **CI [4.01, 18.91]***	B = .40 CI [-.66, 2.53]

Note. Values are fully standardized effect sizes (B) and 95% confidence intervals. *Mental HRQoL* mental health-related quality of life, *O-* Old HIV-, *O+* Old HIV+, *Y-* Young HIV-, *Y+* Young HIV+, *NP Z Change* neuropsychological z-score change, *NP Frascati Change* neuropsychological Frascati HAND classification change. *$p < .01$

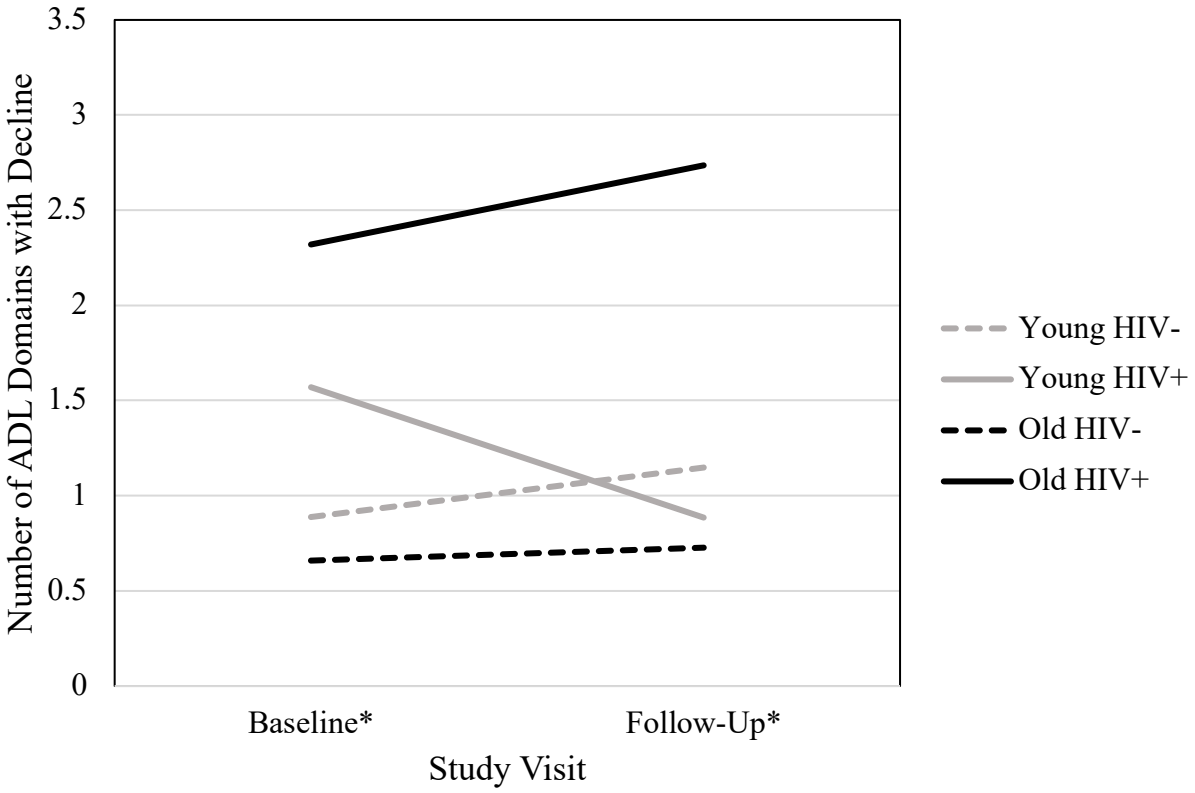

Figure 1. A line chart displaying number of ADL domains out of 16 total where participants indicated a decline from premorbid abilities. Thus, higher scores indicate worse daily functioning. (Mean standard error for Young HIV- = .45, Young HIV+ = .40, Old HIV- = .36, Old HIV+ = .27). *$p < .001$

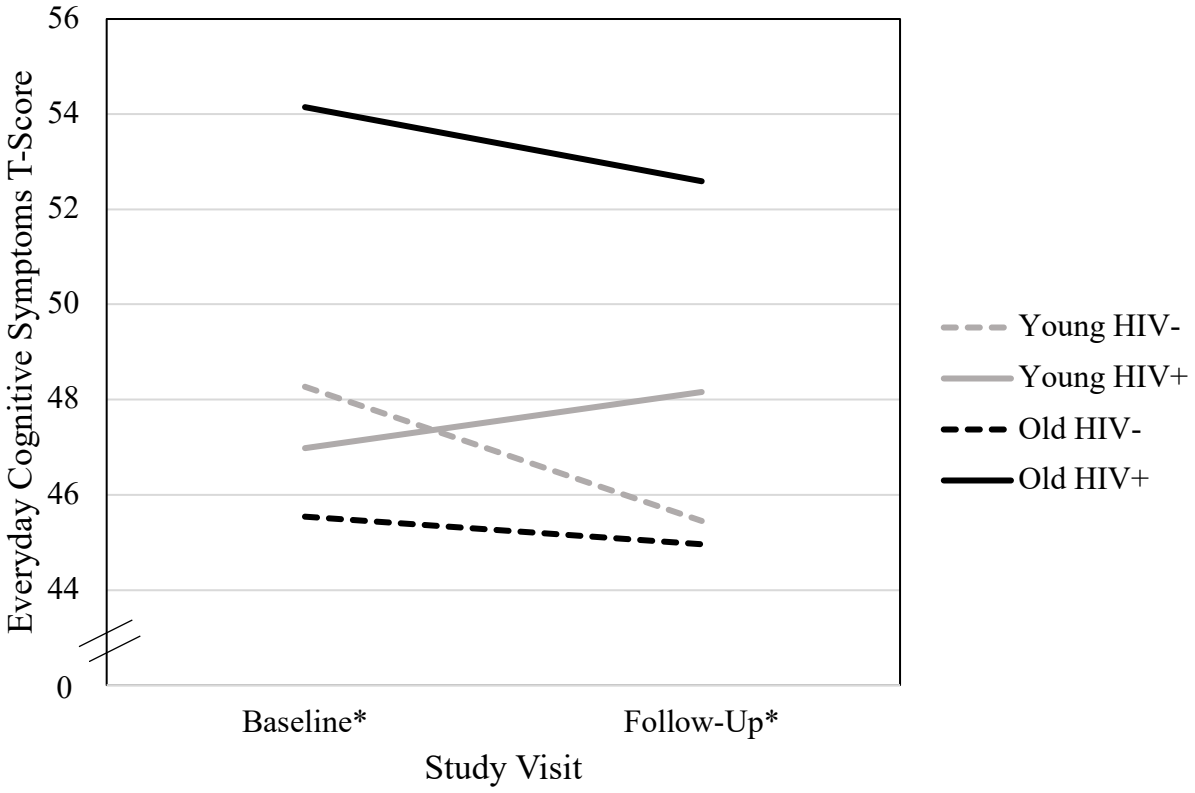

Figure 2. A line chart displaying change in everyday cognitive symptoms over one year as measured by T-scores derived from the Profile of Mood States and the Prospective and Retrospective Memory Questionnaire. Note that higher T-scores indicate greater number of everyday cognitive symptoms and worse functioning. (Mean standard error for Young HIV- = 1.58, Young HIV+ = 1.91, Old HIV- = 1.29, Old HIV+ = 1.38). * $p < .001$

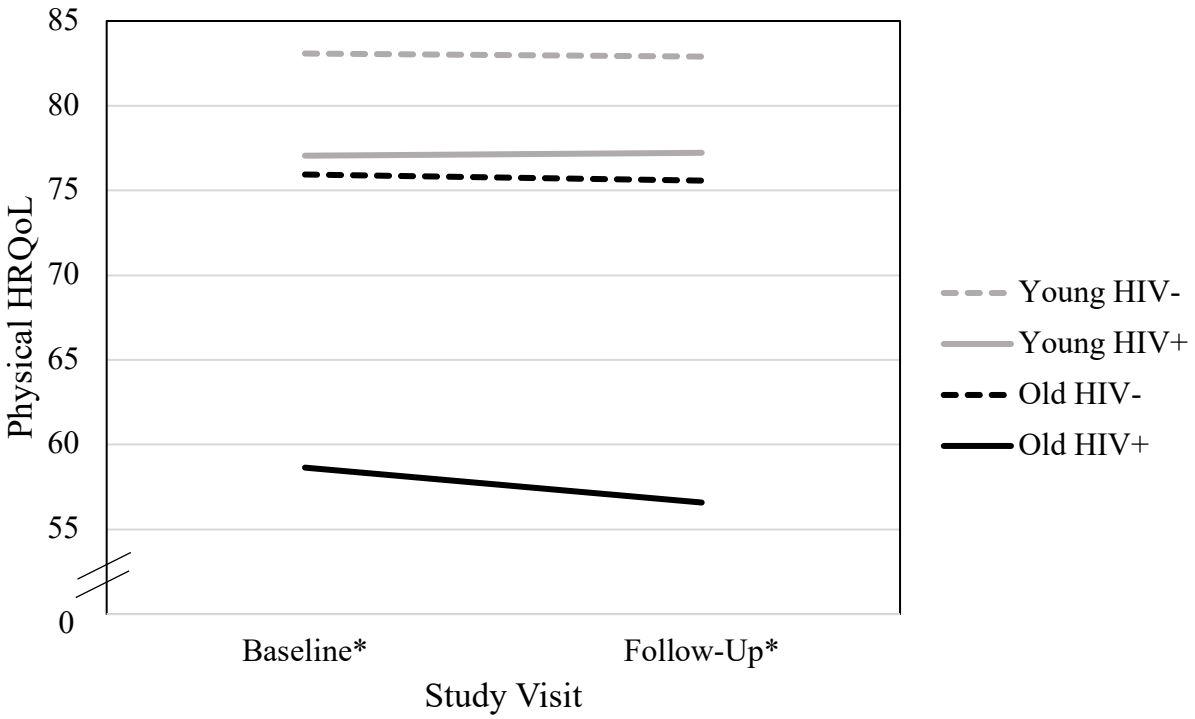

Figure 3. Line chart displaying physical health-related quality of life (HRQoL) ratings at baseline and follow-up visits. Note that higher scores indicate better physical HRQoL (maximum possible score = 100). (Mean standard error for Young HIV- = 4.16, Young HIV+ = 3.68, Old HIV- = 3.26, Old HIV+ = 2.48). *$p < .001$

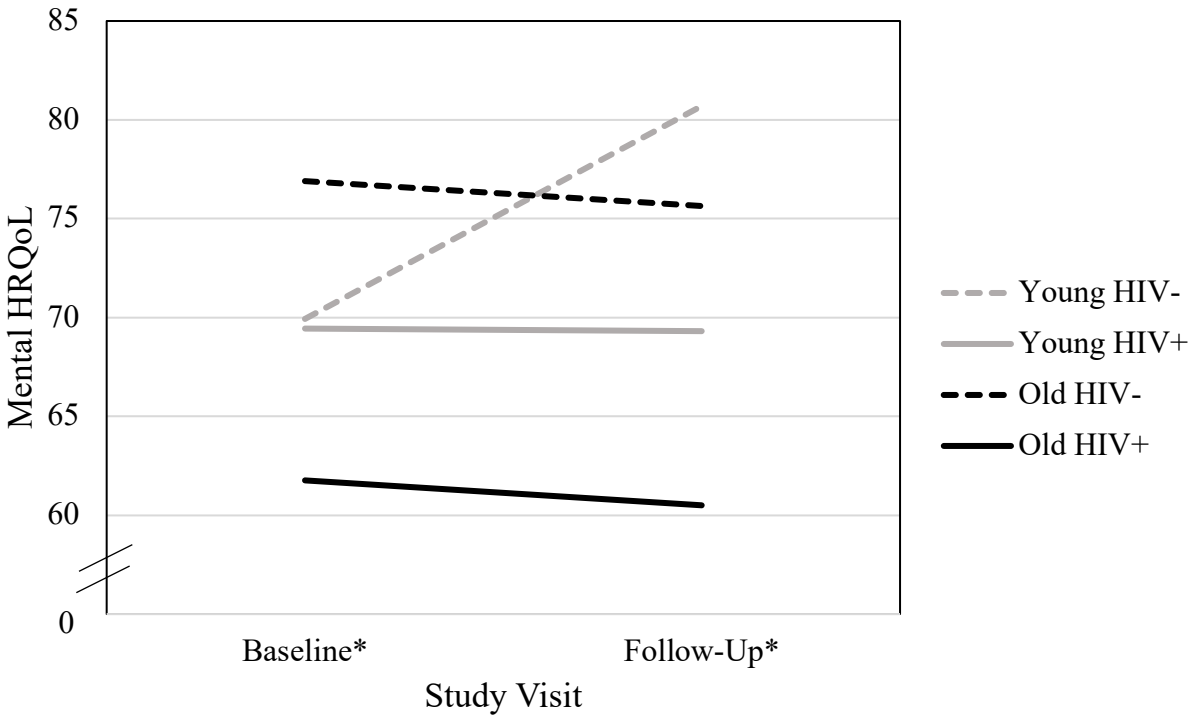

Figure 4. Line chart displaying mental health-related quality of life (HRQoL) ratings at baseline and follow-up visits. Note that higher scores indicate better mental HRQoL (maximum possible score = 100). (Mean standard error for Young HIV- = 2.85, Young HIV+ = 3.92, Old HIV- = 2.72, Old HIV+ = 2.69). *$p < .001$

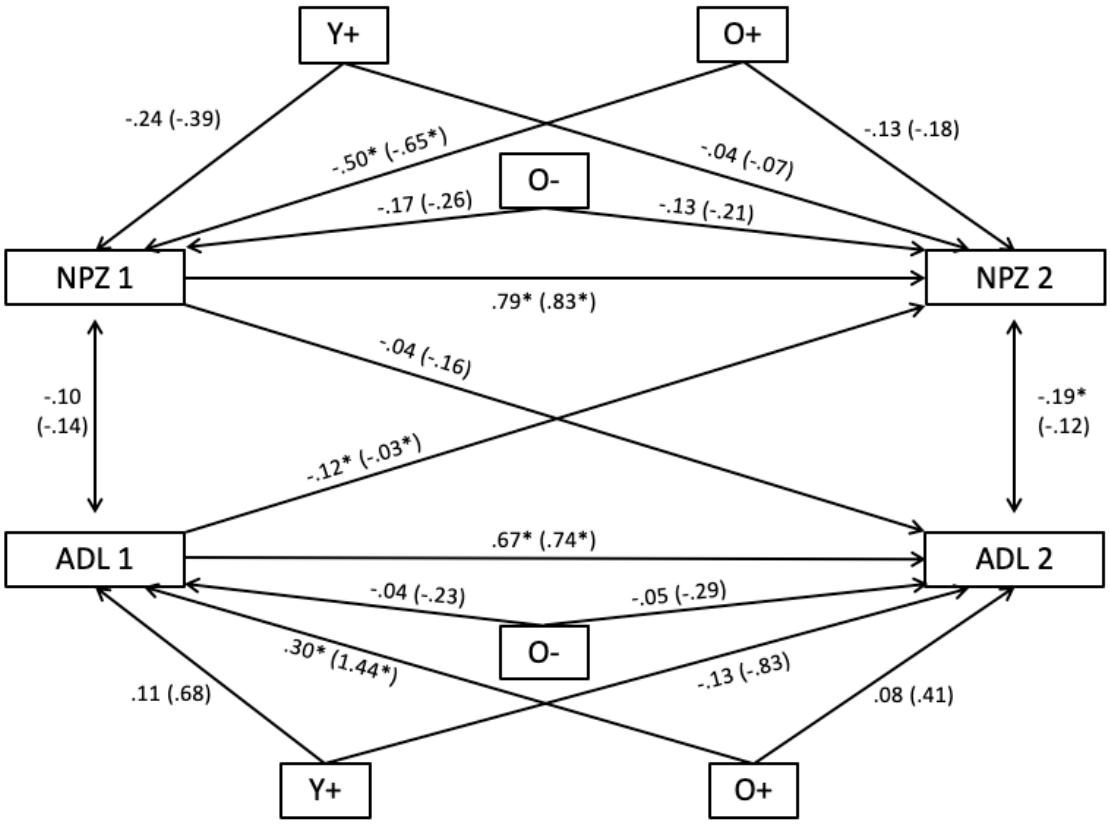

Figure 5. Cross-lagged panel model diagram displaying cross-sectional and prospective relationships between study group, global neurocognitive z-scores (NPZ) and self-reported activities of daily living (ADL) declines at baseline (time 1) and follow-up (time 2) visits across 14-months. Path estimates are standardized Beta coefficients and unstandardized Beta coefficients in parentheses. Note *O*- Old HIV-, *O*+ Old HIV+, *Y*+ Young HIV+. *$p < .01$.

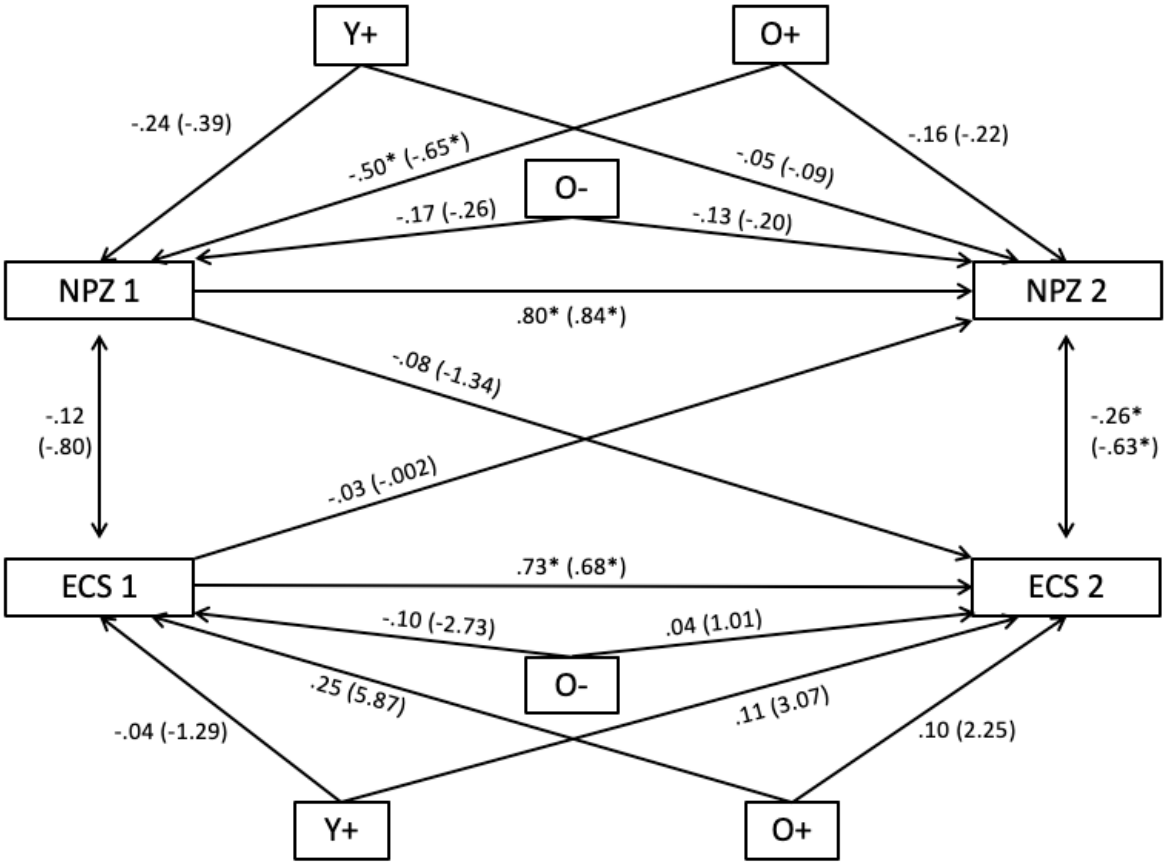

Figure 6. Cross-lagged panel model diagram displaying cross-sectional and prospective relationships between study group, global neurocognitive z-scores (NPZ) and self-reported everyday cognitive symptoms (ECS) at baseline (time 1) and follow-up (time 2) visits across 14-months. Path estimates are standardized Beta coefficients and unstandardized Beta coefficients in parentheses. Note *O*- Old HIV-, *O*+ Old HIV+, *Y*+ Young HIV+. *$p < .01$.

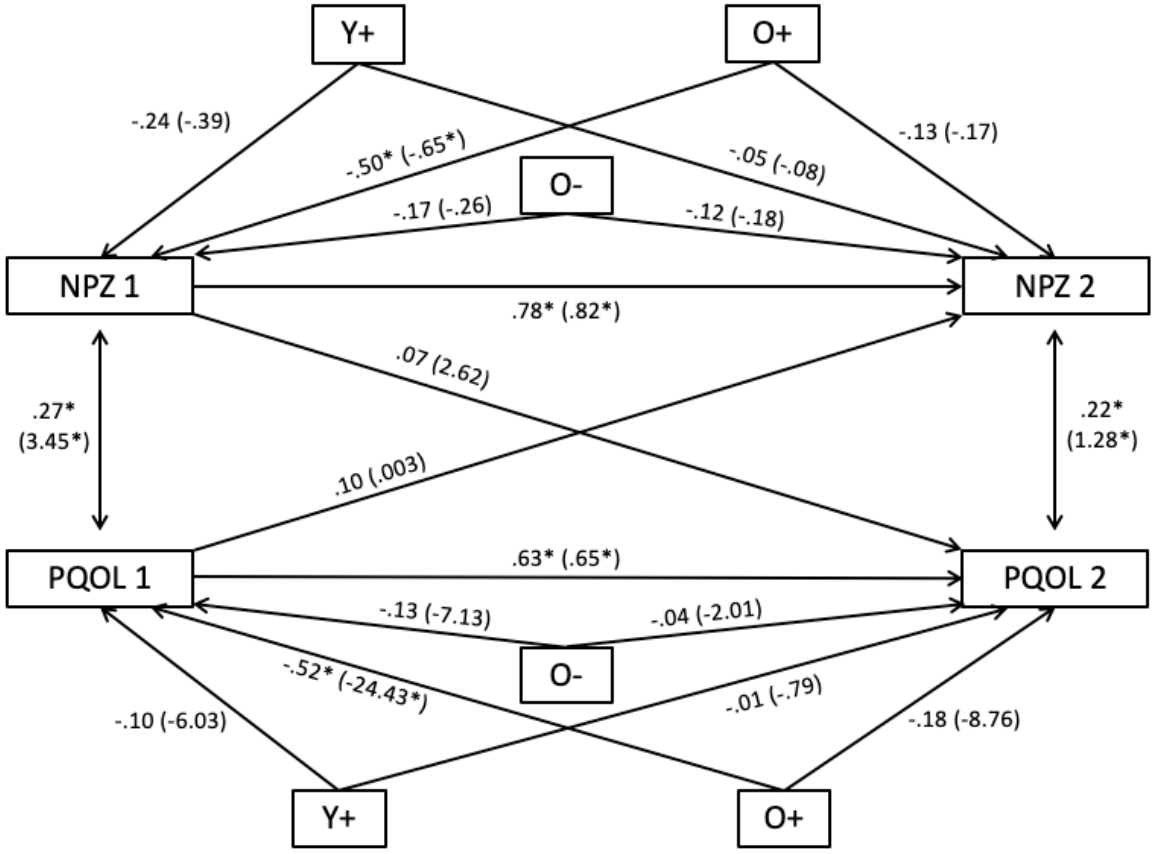

Figure 7. Cross-lagged panel model diagram displaying cross-sectional and prospective relationships between study group, global neurocognitive z-scores (NPZ) and physical health-related quality of life (PQOL) at baseline (time 1) and follow-up (time 2) visits across 14-months. Path estimates are standardized Beta coefficients and unstandardized Beta coefficients in parentheses. Note *O*- Old HIV-, *O*+ Old HIV+, *Y*+ Young HIV+. *$p < .01$.

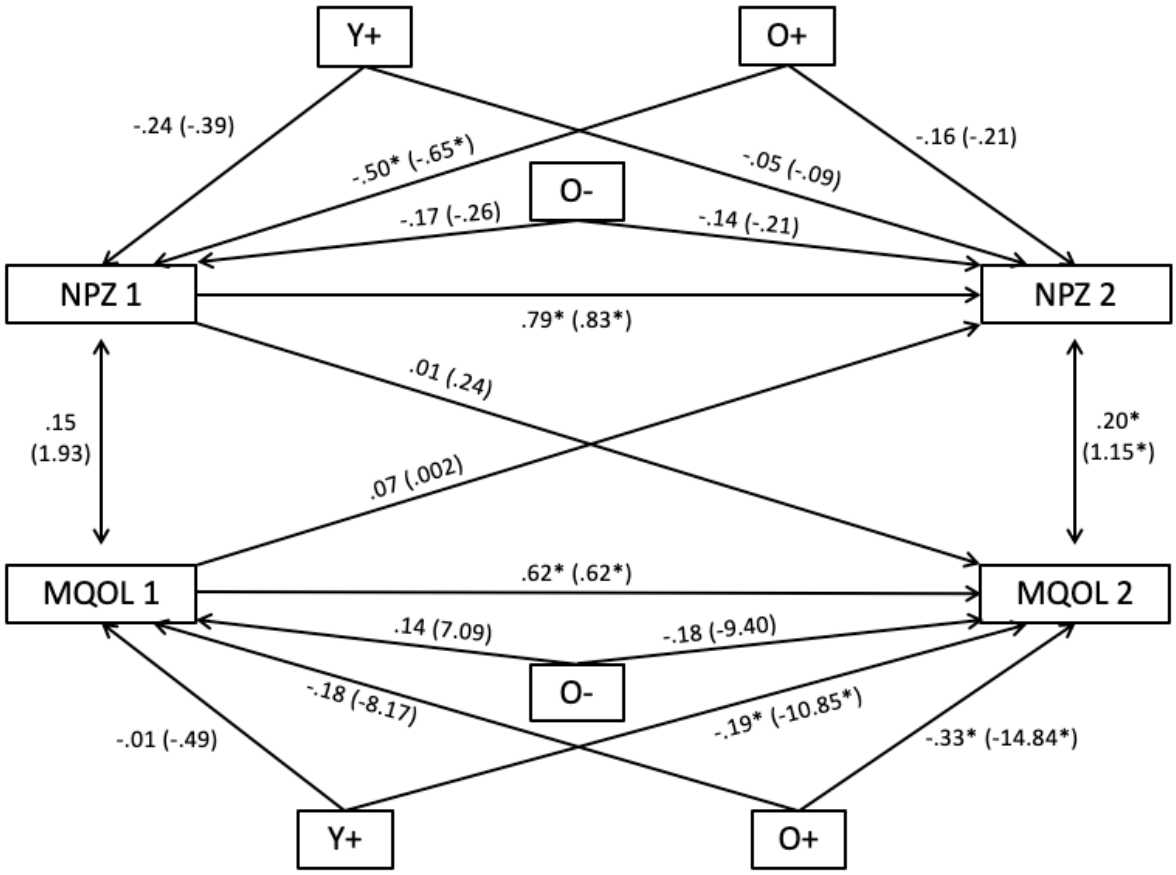

Figure 8. Cross-lagged panel model diagram displaying cross-sectional and prospective relationships between study group, global neurocognitive z-scores (NPZ) and mental health-related quality of life (MQOL) at baseline (time 1) and follow-up (time 2) visits across 14-months. Path estimates are standardized Beta coefficients and unstandardized Beta coefficients in parentheses. Note *O*- Old HIV-, *O*+ Old HIV+, *Y*+ Young HIV+. *$p < .01$.