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Cognitive Function and Health-Related Quality of Life in Older Adults with HIV

by

Hannah Jin Sun Jang

DISSERTATION

Submitted in partial satisfaction of the requirements for the degree of

DOCTOR OF PHILOSOPHY

in

Nursing

in the

**Copyright 2016
By
Hannah Jin Sun Jang**

DEDICATION

To my mother, Myong Sun Jang

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First and foremost, I would like to give all glory and honor to God for this amazing opportunity to pursue higher education in the beautiful, compassionate world of nursing that no one in my “family” could have fathomed.

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As Florence Nightingale, statistician and founder of modern nursing, once said: “So never lose an opportunity of urging a practical beginning, however small, for it is wonderful how often in such matters the mustard-seed germinates and roots itself.”

My nursing research career will continue.

ABSTRACT

Combination antiretroviral therapy has dramatically decreased AIDS-related mortality, allowing Persons Living with the Human Immunodeficiency Virus (PLWH) to live into advanced ages and, by virtue of older age, become at heightened risk for the same comorbidities experienced by healthy older adults. Data suggest that both increased age and HIV are independent risk factors for cognitive impairment and cognitive impairment directly affects Health-Related Quality of Life (HRQOL). This dissertation contributes to the science of caring for older PLWH. It explores the presence of cognitive function as measured by two tools. The Patient's Assessment of Own Function Inventory (PAOFI) is a self-report measure of cognitive function and the Neuropsychological Test Battery (NTB) is a more time intensive clinical measure of cognitive function. This cross-sectional study was a secondary data analysis that determined if PAOFI is predictive of NTB performance and to determine cognitive and depressive symptom correlates to HRQOL in a cohort of PLWH age 60 and older. This sample included a total of 73 older PLWH in the San Francisco Bay Area. Self-report of cognitive function had no correlations with clinical measures of cognitive function in older PLWH. Depression explained more of the variance in PAOFI, controlling for the NTB. Older PLWH who reported better physical HRQOL also reported better cognitive function. Furthermore, those who reported better mental HRQOL scores reported less self-report of cognitive impairment, less depression, and scored better on the NTB. This study determined that self-report alone is not enough to detect cognitive impairment in older PLWH. Instead, the mental health summary score of the HRQOL was a better measure of cognitive function as assessed by the NTB. This work has broad implications for clinical care of older PLWH. A more comprehensive understanding of an older PLWH's HRQOL has significant implications to improve the quality of care in older PLWH with cognitive impairment.

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Chapter 1: Introduction

Problem statement

Older persons living with the Human Immunodeficiency Virus (PLWH) comprise one of the fastest growing groups in the nation (Centers for Disease Control and Prevention, 2013). CDC (2011) reports the proportion of PLWH who progressed to AIDS within one year of diagnosis was greater among persons older than 60 years of age (52%) compared to persons younger than 25 years of age (16%). The population of PLWH are growing older and the prevalence of HIV-associated neurocognitive disorders (HAND) remain as high as rates reported in the pre- combination antiretroviral therapy (cART) era (Heaton et al., 2010c). Although cART has dramatically decreased AIDS-related mortality, allowing those diagnosed with HIV to live into advanced ages (Gebo & Justice, 2009), older PLWH are at risk for the same problems experienced by healthy older adults, likely at an accelerated rate (Centers for Disease Control and Prevention, 2011).

Those experiencing the “graying of HIV” have unique needs in order to have or maintain a positive health-related quality of life (HRQOL). Both increased age and a positive HIV status are independent risk factors for impairment in cognitive function and it is well-established that increased age amplifies risk for neurodegenerative diseases such as Alzheimer’s disease (AD) (Rourke, Halman, & Bassel, 1999; Wagner, Sweet, Butt, Lai, & Cella, 2009). The aging of PLWH and their HRQOL affects their adherence to care and can exacerbate mental health conditions, including impairment in cognitive function and depression (Rourke et al., 1999; Thames et al., 2011).

While the data are replete with correlations between age and cognition in PLWH under the age of 50 (Coon, Lipman, & Ory, 2003; Ellis et al., 2013; Heaton et al., 2004), few studies

have addressed the risk of cognitive impairment in older PLWH (Carstensen & Fredrickson, 1998; Scott et al., 2011). The United Nations Acquired Immunodeficiency Syndrome (UNAIDS) defines adults with HIV as those between the ages of 15 to 49 years of age (United Nations Acquired Immunodeficiency Syndrome, 2010), which excludes older PLWH. Previous studies regarding PLWH typically categorize the aged as those over 50 years old. However, the research presented in this dissertation fills a gap in our understanding of the oldest group of PLWH. For the purpose of this dissertation, older PLWH will be defined as those aged 60 and older. A physician who had a study cohort established in the San Francisco Bay Area set this criterion and this dissertation is a secondary analysis of this cohort.

HRQOL is also discussed within the context of mental health and physical health functioning (Clayson et al., 2006; Revicki, Sorensen, & Wu, 1998). HRQOL is described as the functional ability or the ability to perform activities of daily living, defined within the domain of Physical Health, and the degree to which a person feels satisfaction about his or her life, defined within the domain of Mental Health (Doyle et al., 2012; Trepanier et al., 2005). This dissertation focuses on PLWH in the United States, particularly in the San Francisco Bay area.

Background

There is a strong stigma attached to HIV diagnosis in those of advanced age (Emlet, 2006a; Emlet, 2007) and there is limited data that differentiates the population of those aging with HIV and those being diagnosed at a later stage in life. Furthermore, the CDC encourages HIV testing in younger populations but not in older adults, because rates for contracting HIV in adolescence is higher than the rates for contracting HIV in later life (Centers for Disease Control, 2010; Centers for Disease Control and Prevention, 2013). Furthermore, the general public

assumes that older adults do not practice risky behavior and does not encourage HIV testing in the older adult population (Emlet, Tozay, & Raveis, 2011; Girardi, Sabin, & Monforte, 2007).

In older PLWH, a deficit in cognitive function affects HRQOL, which relates to life satisfaction (Trepanier et al., 2005), positive affect (the extent in which an individual experiences positive moods such as joy, alertness, and interest), and valued activities (Odiase, Ogunrin, & Ogunniyi, 2007; Pereira & Canavarro, 2011). Older PLWH also frequently struggle with other comorbid conditions, in addition to impairment in cognitive function that impacts their HRQOL. Impairment in cognitive function is defined as an impairment in focused attention, executive control, information processing, psychomotor speed, and/or learning efficiency (Osowiecki et al., 2000). A neuropsychological test battery (NTB) is used to assess these attributes of cognitive function and is also referred to as a clinical measure of cognitive function.

Health-related quality of life in PLWH. Comprehensive measure of HRQOL include items that assess the physical, mental, and social domains of life (Hays, Hahn, & Marshall, 2002), and for the purpose of this dissertation, physical and mental domains of HRQOL will be the main focus. The well-being aspect of HRQOL is more subjective than the functional component of HRQOL in that well-being relies on the patient's internal perceptions or self-perceptions (Hays et al., 2002). Well-being items in HRQOL tools include the person's self-perception of happiness, sadness, depression, anxiety, feelings of pain, and whether they felt energetic or lethargic (Hays et al., 2002). In the literature, asymptomatic PLWH have similar physical function HRQOL scores to the population without HIV, whereas symptomatic PLWH report worse physical function HRQOL scores (Hays et al., 2002). There are conflicting results regarding mental HRQOL scores. Some studies find mental HRQOL scores are comparable

across the various stages of HIV with PLWH reporting significantly worse mental HRQOL scores than the general population and those with other chronic diseases (Hays et al., 2002).

Neurological complications and comorbid conditions in HIV. Older PLWH often experience neurological complications and comorbid conditions such as mental health issues and functional impairment at a higher incidence than older persons without HIV (Hardy & Vance, 2009). There are more severe neurological complications in the older PLWH population than in the younger PLWH (Hardy & Vance, 2009; Valcour, Shikuma, Watters, & Sacktor, 2004b). Older PLWH who have HIV-associated impairment in cognitive function report lower HRQOL scores and poorer ability to adhere to medications and financial management skills compared to younger PLWH. Older PLWH with detectable viral loads are also more likely to have impairment in tests of working memory and attention compared to that of younger PLWH who also had detectable viral loads (Cherner et al., 2004).

In addition to neurological complications, as PLWH age, older PLWH experience concomitant conditions. PLWH who have neurological complications experience mental health issues and functional impairment more often than persons without HIV and also persons with cancer who experience chemotherapy-related cognitive difficulties (Bender et al., 2006; Iconomou, Mega, Koutras, Iconomou, & Kalofonos, 2004; Pantanowitz, Schlecht, & Dezube, 2006). Further, aging PLWH experience an increase in the incidence of skin cancers and prostate carcinomas increase with age in addition to the complexities of HIV itself (Martin, Fain, & Klotz, 2008; Pantanowitz et al., 2006).

Diagnosing HIV-associated cognitive impairment. In HIV-associated Neurocognitive Disorders (HAND) research, researchers use the 2007 Frascati criteria to diagnose cognitive impairment (Antinori et al., 2007). The four diagnostic categories include cognitively normal

(HIV-NL), Asymptomatic Neurocognitive Impairment (ANI), Mild Neurocognitive Disorders (MND), and HIV-associated dementia (HAD). There is considerable discussion related to defining symptomatic compared to asymptomatic impairment in cognitive function in the setting of HIV. Nonetheless, mild degrees of impairment in cognitive function still pose a risk for HIV disease progression, particularly among older adults (Heaton et al., 2004). Even in HIV-negative populations, those with mild impairment in cognitive function are at an increased risk of developing dementia than those who do not have impairment in cognitive function (Petersen et al., 2004). The use of HAND diagnosis provides a timely identification of the course of HAD and empowers clinicians to recommend interventions, such as education, exercise, or cognitively stimulating activities, for patients to delay the course of dementia (Mortimer, Snowden, & Markesbery, 2003; Stern, 2003).

Neurological complications are commonly diagnosed in older PLWH. The needs of the older PLWH population are also different from those of the general older population. Thus, clinicians may find the utilization of self-report of cognitive function as an appropriate assessment method to identify older patients' needs (Reilly, Holzemer, Henry, Slaughter, & Portillo, 1997).

Self-report of cognitive function. National surveys demonstrate that more than 50% of younger PLWH have abnormal neuropsychological testing performance; yet, more than 50% of these impaired patients do not self-report cognitive symptoms (Heaton et al., 2004; Valcour, Sithinamsuwan, Letendre, & Ances, 2011). Self-report of impairment in cognitive function is found across populations with HIV and with cancer. Patients with HIV mirror those with cancer, such that those who experience impairment in cognitive function report issues with HRQOL and functional abilities (Campsmith, Nakashima, & Davidson, 2003; Wagner et al., 2009; Wu et al.,

2004). Health care providers found that 33% of their patients with cancer have chemotherapy-related cognitive difficulties and patients found self-perception tools of mental health and functional impairment “very” helpful in getting their physicians to better understand or treat their problems (Spitzer, Kroenke, Williams, & the Patient Health Questionnaire Primary Care Study Group, 1999; Wagner et al., 2009). This translates to PLWH, such that physicians and healthcare providers found self-report of cognitive function and functional impairment to help them better understand and provide better, comprehensive care for PLWH (Arlt et al., 2008; Corless et al., 2000).

Significance

Older PLWH. There is a growing need to understand clinical and cognitive outcomes of those older than 60 years of age and living with HIV. PLWH have a greater life expectancy with the use of cART; therefore, clinical providers need to be aware of the older PLWH’s physical and mental health status (Gebo & Justice, 2009; Valcour & McMurtray, 2009). If patients’ HRQOL is impaired, patients are more likely to practice risky health behaviors and report more physical disabilities and impairment in cognitive function (Mackin & Areán, 2007; Moore et al., 2014), which drive increases in health system costs, HIV-related morbidity and mortality rates, and increase reports of memory problems (Gebo & Justice, 2009; Justice et al., 2004). Patients’ health, cognitive function, and HRQOL decline at a faster rate with the progression of the disease (Doyle et al., 2012).

Prevalence of aging and cognitive impairment in PLWH. Based on data from the CDC, about 50% of the US HIV population will be over the age of 50 by 2016. In the San Francisco Bay area, there are over 3,000 PLWH over the age of 60 years. As the population of older PLWH is aging and living longer, concepts of comorbidities, personalized care,

maximizing function, and integrated management of care are highly relevant to their care (High et al., 2012).

Significance of HIV and impairment in cognitive function. Compared to two decades ago, HIV is now considered a chronic illness with lower mortality levels (Gebo & Justice, 2009), and there is strong evidence of the impact of chronic illness (e.g. cancer and HIV) on cognitive function and HRQOL (Rourke et al., 1999; Wagner et al., 2009). Impairment in cognitive function is due to both HIV and non-HIV factors and the targeted neuro-anatomy of the HIV brain pathology (of the frontal lobes) may also impact a person's insight into his or her own cognitive function. HIV targets the frontal lobes of the brain, which is an area that, when altered, compromises an individual's personal insight (Burgess, Alderman, Evans, Emslie, & Wilson, 1998; Warrington & Weiskrantz, 1982). Chronic illness can affect physical and mental functioning related to activities of daily living (ADLs); altered ADLs exacerbate impairment in cognitive function (Thames et al., 2011).

Although ANI and MND are not severe conditions based on the degree of testing abnormality, the negative effects of ANI and MND on a patient's daily life, including financial management and medication adherence, are well-documented (Heaton et al., 2011). Patients with ANI and MND may benefit from preventative measures, such as cognitively stimulating activities, to delay the onset of severe impairment in cognitive function, including Alzheimer's disease (Wilson et al., 2002) and mental health issues (Krause, May, & Butler, 2012). Consistent mental health services provide earlier and better diagnosis and treatment of cognitive impairment, emotional difficulties, and depression (Krause et al., 2012; Trepanier et al., 2005).

Self-report of cognitive function and depression. Impairment in cognitive function is frequent in older PLWH, and the relationship between self-reported versus clinical measure of

cognitive function has not yet been fully studied in older PLWH. Investigators have found a strong correlation between self-reported cognitive function and depressive symptoms, but a weaker association with a neuropsychological testing summary score (NP test summary) when studied in younger PLWH (Atkins et al., 2010; Thames et al., 2011; Vance, Fazeli, & Gakumo, 2012). In cross-sectional studies, self-report of cognitive function is more correlated to depression than to clinical measure of cognitive function (Corless et al., 2000; Heaton et al., 2004; Sadek, Vigil, Grant, Heaton, & the HNRC Group, 2007). The assessment of both clinician and patient reports on the patient's cognitive function will advance our knowledge in these relationships in older PLWH. The constructs of depression and self-report of cognitive function will advance our knowledge of the extent to which depression directly impacts chronic illness from the patients' perspectives.

Over-estimating cognitive abilities. PLWH overestimate their own cognitive abilities by self-reporting greater impairment in their functional abilities and cognitive performance when compared to their clinically measured cognitive abilities (Blackstone et al., 2012). Altered perceptions of capability will then influence the manner in which patients manage their symptoms and/or enlist the assistance of their family or caregivers. Individuals who are classified as asymptomatic neurocognitive impairment (ANI) by self-reported assessment are not as "asymptomatic" as they report; these patients tend to have more symptomatic impairment in cognitive function when measured clinically by speed of information processing, memory, verbal fluency, attention, working memory, learning, executive function, and motor skills (Blackstone et al., 2012). Though there is a difference between patients' perceptions and clinical measure of cognitive function, multimodal methods of assessing everyday function and cognitive function facilitate the detection of symptomatic HAND diagnosis (Blackstone et al., 2012).

Patients who self-reported more functional impairment—based on memory, language and communication, use of his/her hands, sensory perception, higher level cognitive function and intellectual function, work, and recreation—had higher levels of depressive symptoms. In comparison to clinical assessments (including information processing, memory, verbal fluency, attention, working memory, learning, executive function, and motor skills), patients had over-reported functional impairment (Blackstone et al., 2012). Patients who self-report more impairment in cognitive function also report higher levels of depression (Blackstone et al., 2012; Carter, Rourke, Murji, Shore, & Rourke, 2003; Thames et al., 2011).

Underestimating cognitive abilities. Patients with mild to moderate impairment in cognitive function self-report fewer cognitive difficulties in memory, language and communication, use of his/her hands, sensory perception, higher level cognitive function and intellectual function, work, and recreation when compared to the clinical measures of their cognitive function in speed of information processing, memory, verbal fluency, attention, working memory, learning, executive function, and motor skills (Blackstone et al., 2012). Self-reported measures of cognitive function are sensitive to detect HAD, based on the criteria by Antinori et al. (2007), compared to ANI and MND versus clinical measure of cognitive function (Blackstone et al., 2012). PLWH self-reported more major functional impairment compared to the clinical measure of their functional abilities (Blackstone et al., 2012).

Significance of health-related quality of life. Clinicians' long-term goal is to maximize HRQOL for PLWH. Early detection of impairment in cognitive function helps providers anticipate needs and make appropriate recommendations to ensure safety and to delay the progression of disease in some cases. With a projected increase in the prevalence of older adults living with HIV, the healthcare concerns, particularly HRQOL for older PLWH need to be

addressed. Older adults living with HIV-associated impairment in cognitive function report lower HRQOL scores and more deficits in prospective memory, when compared to younger adults living with HIV-associated impairment in cognitive function (Doyle et al., 2012; Scott et al., 2011; Thames et al., 2011).

HRQOL in PLWH is directly related to the stage and symptoms of the disease, plus their cognitive function (Gebo & Justice, 2009). Symptomatic PLWH report lower scores on physical and independence domains of HRQOL tools, in addition to lower scores on overall HRQOL (Pereira, Martins, Alves, & Canavarro, 2014). The results in the literature have been conflicting regarding specific associations between certain biological markers, including CD4 cell counts, and HRQOL (Pereira et al., 2014). CD4 cell counts do not always relate to how well patients are feeling, nor to the number of complicated symptoms related to HIV, but mainly to mental health aspects of HRQOL, particularly memory (Doyle et al., 2012). PLWH with high CD4 cell counts can have more HIV-related physical complications and impairment in cognitive function, particularly prospective memory, than PLWH with low CD4 cell counts (Doyle et al., 2012; Pereira et al., 2014).

Purpose

This cross-sectional study aims to understand the relationships between depression, HRQOL, patient self-report of cognitive function, and clinical measure of cognitive function in older PLWH. The purpose of this dissertation research is to determine if self-reported cognitive abilities are predictive of objective neuropsychological testing performance and to determine cognitive and behavioral correlates to HRQOL in this aged cohort. Ultimately, the goal of this study is to provide a foundation for future interventional studies aimed to improve the HRQOL of older PLWH.

Innovation

This study has several central innovations. The work investigates both self-report and a clinical measure of cognitive function and HRQOL measures in older PLWH. At this writing, no study has included both self-report and clinician interviews to assess cognitive function or correlates to HRQOL. This allows for immediate comparisons of self-report and clinical measure of cognitive function and their relationship to HRQOL. Very few studies have evaluated the relationship between self-report and a clinical measure of cognitive function, depression, and HRQOL, in older PLWH (Bonnet et al., 2013; Heaton et al., 2011).

Another primary innovation is the interdisciplinary team participating in this research that involves both the UCSF School of Nursing and the UCSF Memory and Aging Center (MAC) within the Department of Neurology and the Division of Geriatric Medicine. This interdisciplinary approach facilitates a unique perspective by using the research and experiential strengths of several disciplines, including nursing, medicine, neurologists, psychologists, and statisticians, to analyze and interpret results related to cognitive function and HRQOL.

The information gained from this study will better inform researchers and clinicians what type of clinical assessments are best suited and more appropriate when assessing PLWH with cognitive disorders. With the increase in prevalence of older PLWH, this research study is timely, addressing the concerns of this unique population.

Impact

Results from this research provide information on the accuracy of a self-reported measure as compared to clinical measure in the identification of cognitive symptoms and relationship to HRQOL in older PLWH. The current method to diagnose cognitive impairment in research with HIV-Associated Neurocognitive Disorders (HAND) is time-intensive and thus renders this

process inappropriate in the primary care setting as administering a full neuropsychological exam at a patient's visit would be time-prohibitive. Furthermore, as patients are living longer with HIV, health care providers will need to understand patients' perceptions and those factors affecting HRQOL to coordinate care for older PLWH. This research informs healthcare providers of the utility of patient self-report tools in the clinical setting, which will enable clinicians to anticipate the needs of their patients and provide appropriate care and resources in a timely manner. The link between HRQOL and living with HIV warrants further study to determine the pathway between the progression of disease and impairment in cognitive function in this unique population (Corless et al., 2000).

This research will have broad implications for clinical care of older PLWH to determine if self-reports are useful tools to screen for cognitive disorders in this population and by determining major contributions to HRQOL for this newly emerging and vulnerable population.

Research Questions and Specific Aims

(1) What is the relationship between self-report and a clinical measure of cognitive function in older PLWH?

Specific Aim 1: Explore the relationship between a clinical measure and self-report cognitive function in older PLWH.

Hypothesis: There will be a significant inverse relationship between self-report and a clinical measure of cognitive function, such that patients who report less cognitive complaints (or perceive higher cognitive function) will have more symptomatic clinical impairments of cognitive function.

Rationale: Patients lack insight into their own cognitive function, despite measurable clinical evidence of impairment in cognitive function on neuropsychological tests (Richardson-Vejlgaard, Dawes, Heaton, & Bell, 2009).

(2) What is the relationship between depression, age, education, and a clinical measure of cognitive function with self-report cognitive function in older PLWH?

Specific Aim 2: Assess the relationship between depression age, education, and a clinical measure of cognitive function with self-report cognitive function in older PLWH.

Hypotheses: Both severity of depressive symptoms and a clinical measure of cognitive function will explain a proportion of variance in self-report cognitive complaints; however, a greater degree of the variance will be explained by depressive symptoms.

Rationale: Depression and self-report of cognitive function are subjective assessments and will have a stronger correlation to each other than those of a clinical measure of cognitive function in younger PLWH (Richardson-Vejlgaard et al., 2009; Thames et al., 2011).

(3) How does cognitive function (self-report and a clinical measure) and depression relate to HRQOL in older PLWH?

Specific Aim 3: Examine the relationship between depression, self-report cognitive function, and a clinical measure of cognitive function to HRQOL in older PLWH.

Hypotheses: Self-report cognitive function has a higher correlation to HRQOL and depression than a clinical measure of cognitive function.

Rationale: Self-report cognitive function will relate more to HRQOL than does a clinical measure of cognitive function to HRQOL. This is hypothesized because self-report and HRQOL tools are both subjective measures and relate more to the patients' own perception (Richardson-Vejlgaard et al., 2009; Schwartz, Kozora, & Zeng, 1996).

Chapter 2: Literature Review and Conceptual Framework

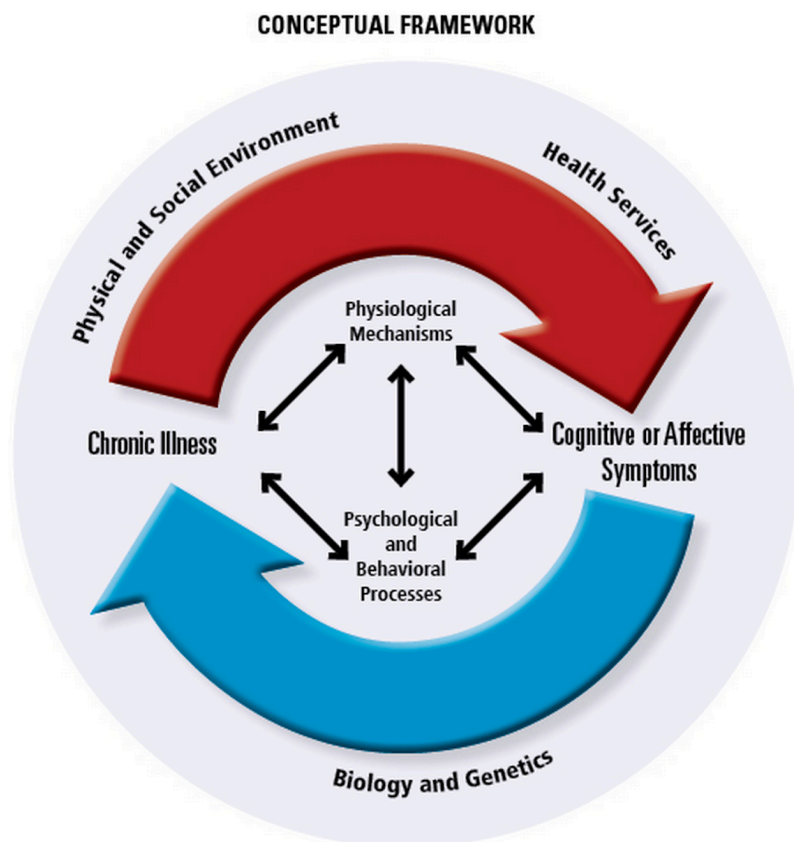


Figure 1: Conceptual Framework for the Center for Neurocognitive Studies (CNS)

Conceptual Framework

Background. Emory University Nell Hodgson Woodruff School of Nursing established the Center for Neurocognitive Studies in 2012. The guiding conceptual framework is a symptom interactional model based on the key concepts of chronic illness and cognitive and affective symptoms. This conceptual framework used for the Center is depicted in Figure 1. The figure shows that cognitive function and emotional distress directly impact chronic illness, and vice-versa. The presence of one symptom may compound the effect of the other, in which the disruption of these pathways may potentially reduce the negative progression of chronic illness.

There is no literature that provides conceptual definitions nor explanations of the variables' relational statements.

For the purpose of this study, an adapted conceptual framework was applied as shown in Figure 2. This adapted version of the model includes the concept of Health-Related Quality of Life (HRQOL) that is superimposed in the middle of the model. Conceptually, without having a true understanding of aging patients' HRQOL, the maintenance of the health of aging patients, in particular those with HIV/AIDS, have the potential of developing cognitive difficulties and it is imperative to support this research to the fullest extent possible.

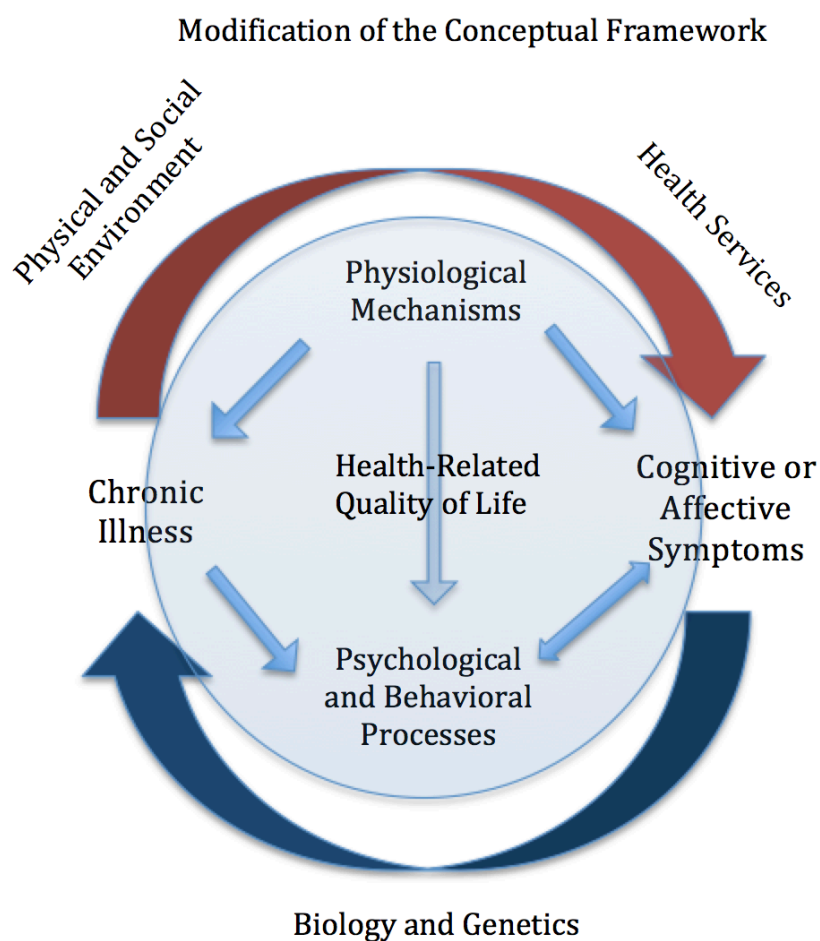


Figure 2: Modified Conceptual Framework for the Center for Neurocognitive Studies (CNS)

The symptom-interactional model in Figure 2 in which this conceptual framework was adapted focuses on the interplay of symptoms or symptom clusters and the underlying mechanisms. This framework is widely used within the Nell Hodgson Woodruff School of Nursing at Emory University, yet nascent, no other universities, institutions, organizations, or countries have not yet explored this conceptual framework and thus this conceptual framework is in development using an iterative process. The modified conceptual framework includes concepts and relationships in older persons living with HIV (PLWH) in order to guide this cross-sectional study.

Constructs, concepts, sub-concepts. Constructs, concepts, relational statements have not been fully defined by the Center. Therefore, I have provided working definitions and explanations for the purpose of this study. According to Meleis, concepts are defined, operationalized, and linked into relationships. A concept denotes some degree of classification and is an abstract representation of reality (Meleis, 2012). Constructs are more abstract than concepts and are not characterized by a direct link between the abstraction and the observations (Meleis, 2012; Watt & Van den Berg, 2002). The linkages between concepts are propositions, which are statements that indicate an informed relationship. Typically, the relational statements describe associations between concepts and are used to describe or predict the nature of the relationship between concepts (Meleis, 2012). The constructs, concepts, sub-concepts, and relational statements have not yet been fully defined. The constructs (physical and social environment, health services, and biology and genetics) concepts (chronic illness and cognitive or affective symptoms), and sub-concepts (physiological mechanisms, psychological and behavioral processes), which can be observed within the phenomenon of older adults with HIV/AIDS and cognitive impairment in this framework, are operationally defined in this section

and the relational statements are discussed in further detail. The following propositions, concepts, and constructs from Emory's framework (Figure 1) are used to explore the relationships among HRQOL, cognitive function, and depression in older PLWH.

Construct of physical and social environment. Physical and social environment is one of the constructs of this conceptual framework, along with health services, and biology and genetics. Health determinants and factors that exacerbate or alleviate symptoms in an individual with chronic illness, such as HIV, cannot be fully understood in isolation from one's physical and social environment. Physical and social environment can be understood within the Dimensions of Episodic Disability (O'Brien, Bayoumi, Strike, Young, & Davis, 2008), which includes extrinsic contextual factors (such as social support and stigma) and intrinsic contextual factors (such as living strategies and personal attributes, including maintaining control, attitudes and beliefs, and aging). Both extrinsic and intrinsic factors exacerbate or alleviate one's disability or ability to function in daily life (O'Brien et al.). The physical environment consists of the external environment, which includes the city and country in which one lives, the community, and housing situations. The social environment consists of social support received or provided by friends, family, partners, pets, and community (O'Brien et al.). Intrinsic factors include strategies to seek interactions with others or through one's own social and physical environment, such as maintaining a sense of control over life, or adopting attitudes, beliefs, or behaviors from one's environment to help cope with living with chronic illness or changes in cognitive or affective symptoms.

The physical and social environment plays a large role in how HIV affects the relationship between chronic illness (HIV) and changes in cognitive or affective symptoms (cognitive function) (Figures 1 and 2). The multiplicity of the human experience and the

subjective realities of PLWH serve as meta-narratives about how family, physical functioning, and the environment drastically impact a person's cognitive abilities and symptom experiences. Older PLWH conceptualize their disability within a social context, such that finances and inability to access needed services, including medications, insurance, or housing, impede an individual's ability to be active in the society (O'Brien et al., 2008). Disability, initially defined as the physical and socio-emotional challenges PLWH experience as a result of the disease in addition to its associated conditions and treatment, expand across physical, mental, emotional, and social domains. Thus, PLWH experience HRQOL within the context of extrinsic and intrinsic contextual factors that include the physical and social environment.

Many PLWH have supportive networks with other PLWH who are also dealing with their illnesses and needs. With fragile networks, PLWH need both formal (i.e. providers) and informal (i.e. friends and family) networks (Brennan-Ing, Seidel, London, Cahill, & Karpiak, 2013) to help them function in their society. The existence of support networks of various kinds indubitably ameliorates the cognitive or affective symptoms of a PLWH, regardless of age. Additional vital roles are those of family, physical functioning, socio-emotional support, and the environment in regard to CF and affective symptoms.

Construct of health services. Health services includes access to care (including barriers), quality of care received, and cost of care (Agency for Healthcare Research and Quality, 2011). The absence of transportation to appointments, adequately trained providers, quality care, patient comprehension, financial resources, and affordable housing are significant barriers to accessing care and services for PLWH (Krause et al., 2012). Generally, HIV education, social support services, and prevention efforts have been geared towards younger populations, because HIV was not considered a chronic illness until recently, and the needs of older adult population

have largely been overlooked (Brennan-Ing et al., 2013). As people are living longer with HIV, health care services should address the unique healthcare and psychosocial needs of PLWH, including older PLWH (Bottonari & Stepleman, 2010; Brennan-Ing et al., 2013).

Access to care. Access to health services for PLWH are limited across the United States due to barriers such as age, insurance status, race, and sexual preference (Brennan-Ing et al., 2013; Uphold & Mkanta, 2005). Older PLWH are often misdiagnosed, because symptoms of HIV or AIDS such as night sweats, fatigue, weight loss, diminished appetite, are dismissed as part of the normal aging process (Lieberman, 2000). Thus, providers do not grant or recommend HIV-related services to older PLWH. In a study conducted in New York City, older PLWH without private insurance or those with Medicare insurance had limited access to health care services (Brennan-Ing et al.). In addition to being older in age, the older gay, lesbian, or bisexual and transgender PLWH must often access services in unwelcoming environments in which providers lack knowledge about their community-specific needs, do not consider sexual orientation or gender identity in patient care, or exhibit negative attitudes toward the patients (Brennan-Ing et al.).

In another study, seventy percent of consult patients who have HIV identified as racial minorities and only 47% of them receive specialized mental health services compared to their White counterparts (Bottonari & Stepleman, 2010). Mental health services were provided to 25% of a southeastern infectious clinic in the United States HIV clinic's patient population, but racial minorities were underrepresented among those seeking specialized mental health services (Bottonari & Stepleman). PLWH, with unique insurance statuses and different sexual preferences, face such barriers to accessing medical care such that quality of care can become compromised.

Quality of care. Patient-provider relationships and continuity of care affect quality of care for PLWH. PLWH face various quality of care issues based on their relationships with their providers and networks. Older PLWH face impairment in cognitive function and do not always report symptoms to providers (Heaton et al., 2010c). The needs of PLWH are traditionally met through multiple formal services at clinics and hospitals such that high-quality treatment, proper follow-up, and continuity of care are more elusive for PLWH (Krause et al., 2012). For example, regular eye exams could provide earlier and better diagnosis and treatment of several comorbidities of HIV, including cytomegalovirus (Krause et al.). However, with lack of follow-up and continuity care, PLWH may receive belated or no diagnosis of comorbid conditions. Also, continual mental health services could provide earlier and better diagnosis and treatment of cognitive impairment, emotional difficulties, and depression (Krause et al.; Trepanier et al., 2005).

High-quality care for older PLWH requires healthcare professionals to screen and provide treatment for the unique needs of the individual and community as well as to encourage patients to have productive, optimal lives. If patients' quality of care is compromised, patients are more likely to practice risky health behaviors, have missed health care appointments, and have decreased medication adherence (Mackin & Areán, 2007).

Cost of care. Furthermore, cost of care affects access to health care services for PLWH. Those with private insurance have access to fee-for service programs and private providers and are more likely to have more economic resources and access to care than those who do not have such coverage (Krause et al., 2012), PLWH suffer the same consequences. For example, for PLWH, the greatest perceived barriers to dental/eye care and exams are cost-related to lack of insurance coverage and lack of financial resources. Health care costs can hinder access to care

for those without high-quality insurance or provide more HIV-related services for those with comprehensive insurance care plans. As people with HIV age, clinical care must involve both the prevention and treatment of age-associated comorbidities (Martin et al., 2008).

Construct of biology and genetics. Biology and genetics is discussed within the context of immunology, race, and gender. Immunological changes occur with aging in addition to the progression of HIV. Immunology includes CD4 cell and nadir counts. CD4 nadir is the lowest point to where the CD4 cell count has dropped in a PLWH. CD4 nadir is predictive of long-term morbidity, such that lower values suggest an increased risk of illnesses, in addition to slower immune recovery (Ellis et al., 2013; Moore et al., 2014). Physiological mechanisms, such as decreased CD4 cell counts (Odiase et al., 2007), or psychological and behavioral processes, such as depressed mood states or reports of reduced quality of life (Osowiecki et al., 2000) has effects on the relationship between cognitive or affective symptoms and chronic illness. In one observational study, PLWH aged 35 years and older had lower CD4 cell counts at seroconversion and a steeper decline in CD4 cell count over time (Lodi et al., 2011). Older PLWH also present to care at significantly lower CD4 cell counts on admission due to clinicians' poor HIV screening practices of older adults.

Blood laboratory tests such as CD4 lymphocyte counts, CD4 nadir, and plasma HIV RNA levels are used in clinical settings to estimate the severity of the HIV infection and the effectiveness of combination antiretroviral therapy (cART). Antiretroviral treatment guidelines recommend cART initiation for PLWH with CD4 cell count between 350 cells/ μ l and 500 cells/ μ l and give healthcare providers the option to treat patients with CD4 cell counts above 500 cells/ μ l. Immune recovery occurs after initiation of cART as observed from the CD4 nadir. Some

effects of cART include metabolic derangements that affect brain function or neurodegenerative and cerebrovascular syndromes by crossing the blood-brain barrier.

A participant's race or ethnicity is discussed in relation to their environment or country of residence and gender includes biological sex, gender identity, sexuality, and gender expression. In a national dataset of PLWH in 2001, many eligible PLWH did not receive cART due to racial and ethnic disparities (Gebo et al., 2005). Due to a later initiation of cART (The Collaboration of Observational HIV Epidemiological Research Europe (COHERE) study group, 2008) than their younger counterparts, older PLWH face more medical comorbidities in addition to HIV than their younger counterparts. The literature also reveals gender differences in older PLWH, including within the categories of HIV testing, cognitive function, and mortality (Gebo et al., 2005; Harawa, Leng, Kim, & Cunningham, 2011; Wisniewski, Apel, Selnes, Nath, & McArthur, 2005). HIV testing rates were found to be highest in Black men and White women when compared to the general sample population (Harawa et al.). Furthermore, in another study, women with HIV performed better than men with HIV on a clinical measure of perceptual speed; in addition, women without HIV performed best and men with HIV performed the worst on a clinical measure of verbal memory (Wisniewski et al.).

Concept of chronic illness. Concepts included in this conceptual framework are chronic illness and cognitive or affective symptoms. The United States National Center for Health Statistics defines a chronic illness as a disease that persists for 3 months or more. Chronic illnesses are generally not preventable by vaccines nor are they cured by medication. HIV was once considered a death sentence, but once cART was introduced in 1996, it has enabled people to live longer with HIV (Dieffenbach & Fauci, 2011); therefore, HIV is now considered a chronic illness. More middle-aged and older adults are contracting HIV, and with the medical

advancement of cART, people are living into advanced age with the illness (Balderson et al., 2012). Due to a later initiation of cART (Balderson et al., 2012) than their younger counterparts, older PLWH face more medical comorbidities in addition to HIV than their younger counterparts. Furthermore, the persistent activation of immune cells by HIV increases the susceptibility of PLWH to inflammation-induced diseases in addition to cancer and other cardiovascular, kidney, liver, lung, and bone diseases (Balderson et al., 2012; OAR Working Group on HIV Aging, 2012).

Concept of cognitive or affective symptoms. The concept of cognitive/affective symptoms is defined as cognitive function or symptom relating to or influenced by emotions. A cognitive or affective symptom includes cognitive function, self-report measures of cognitive function, and clinical measures of cognitive function, including measures assessed by neuropsychological test batteries. Cognitive function consists of domains in language, executive functioning, informational processing speed, attention and working memory, attention, mood/affect, learning and memory, psychomotor skills, visuospatial functioning, and motor/manual dexterity functioning. Neuropsychological test batteries are used in research to assess cognitive function. Self-report measures of cognitive function are self-report questionnaires that inquire of a person's own perception of cognitive function.

HIV and Alzheimer's disease affect cognitive function through physiological (brain changes) and psychological/behavioral mechanisms (e.g. coping, self-care compliance). Changes that occur in the subcortical and fronto-striatal brain of PLWH affect emotional processes, similar to Alzheimer's disease (Sacktor et al., 2007; Tozzi, Balestra, & Galgani, 2001). Pathways in the brain affected by HIV include nuclear and mitochondrial genomic DNA damage in the brain (Zhang et al., 2012), while features of Alzheimer's disease are cortical atrophy and high

beta-amyloid plaque deposition (Wirth et al., 2013). Older and younger patients with Alzheimer's disease have aberrant motor behavior in addition to emotional processes such as apathy (Vliet et al., 2012). In HIV, proteins, including gp120 and Tat, and pro-inflammatory cytokines trigger the production of reactive oxygen species (ROS), which lead to DNA and RNA lesions (Zhang et al., 2012). In Alzheimer's disease, there is impaired microvasculature and decreased cerebral flow which causes atrophy of neural structures (Drachman, 2014). Though different parts of the brain are affected in HIV and Alzheimer's disease, both create changes in cognitive and affective symptoms.

Physiological mechanisms. Sub-concepts within the conceptual model are physiological mechanisms and psychological and behavioral process. Physiological mechanisms is defined as comorbidities of HIV, aging, substance use, and effects of cART and its affect on health and chronic illness. Health impacts and comorbidities of HIV include cancer, decreased abilities to perform activities of daily living (ADLs), cardiac issues, and renal issues. The relationships depicted in Figure 2 indicate uni-directionality such that chronic illness is affected by physiological mechanisms and that physiological mechanisms affect psychological and behavioral processes and cognitive or affective symptoms (Figure 2).

Psychological and behavioral process. The sub-concept of psychological and behavioral processes relevant for PLWH includes the stigma of ageism, successful aging, and depression. HIV-related stigma is defined as prejudice, discrimination, discounting, or discrediting directed at PLWH (Emlet, 2006b). Successful aging is multidimensional, encompassing eight different factors: length of life, cognitive efficiency, mental health, biological health, social competence, productivity, life satisfaction, and personal control (Baltes & Baltes, 1990; Rowe & Kahn, 1997; Vance, Wadley, Crowe, Raper, & Ball, 2011b).

Depression can be diagnosed by a physician according to the DSM-V criteria, or self-reported through questionnaires and other measures.

Health-related quality of life. Health-related quality of life (HRQOL) is defined as the functional ability or the ability to perform activities of daily living and the degree to which a person feels satisfaction about his or her life. The result of this ability is positive and encompasses the physical, mental, social, and emotional aspects of every day functioning. HRQOL is not always explored in the context of functionality (O'Brien et al.), but is explored in the context of a meaningful set of relationships, language, and practices through a culture in which a person lives (Ho, Twinn, & Cheng, 2010). HRQOL is a concept that is patient-specific questions about HRQOL is better understood by asking patients themselves rather than solely by objective measurement tools. Quality of life is used interchangeably with HRQOL, and in research, quality of life is referred to as HRQOL (Wu, 2000). When quality of life is considered in the context of health and disease, the term health-related quality of life is used (Healthy People 2020, 2010). HIV and cognitive function have correlations to the aging process and HRQOL for older PLWH (Arlt et al., 2008; Zhang et al., 2012).

Literature Review

Advanced age and HIV. With PLWH living into advanced age and being treated with cART for longer periods of time, the patterns of illness for PLWH more closely resemble those of the general elderly population. cART contributes to increased atherosclerotic disease and cerebrovascular disease (Cruse, Cysique, Markus, & Brew, 2012), also common illnesses in the older adult population living without HIV/AIDS. In addition, HIV infection is associated with ischemic stroke through opportunistic infections, systemic infections including infective endocarditis, and accelerated atherosclerosis (Cruse et al., 2012). These associated conditions

can negatively affect a person's ability to perform activities of daily living and general functioning, as well as psychological and behavioral processes and HRQOL.

Furthermore, older PLWH are at an increased risk of comorbidities associated with aging. Various chronic illnesses in addition to HIV affect older PLWH, including cerebrovascular accidents, strokes, traumatic brain injuries, brain anoxia, central nervous system opportunistic infections, and seizures. Cerebrovascular disease (Valcour et al., 2004b), coronary artery disease (Triant, Lee, Hadigan, & Grinspoon, 2007), chronic pulmonary disease (Crothers et al., 2006), frailty, and dementia are common conditions of aging, found also in PLWH. Researchers found that history of cardiovascular disease and chronic pulmonary disease in addition to the HIV disease affect physical and cognitive function in PLWH (Oursler et al., 2011).

As cART has advanced over the years, AIDS-defining illnesses are less common and the list of HIV-associated non-AIDS (HANA) related conditions are growing (OAR Working Group on HIV Aging, 2012). Some HANA conditions include liver disease such as Hepatitis C (Kirk et al., 2013; Smith & Sterling, 2007; Sulkowski & Thomas, 2003), renal disease (Lucas et al., 2007), cardiovascular disease (Freiberg et al., 2013), infectious and non-infectious cancers (Silverberg et al., 2009; Silverberg et al., 2012; Wang, Silverberg, & Abrams, 2014), and neurocognitive decline (Valcour, Paul, Neuhaus, & Shikuma, 2010). A common theme among these HANA conditions is advancing age and chronic inflammation.

HIV infection and increased age are qualifiers for HIV-associated AIDS-related conditions and HANA and are independently associated with liver fibrosis, chronic hepatitis B infection, and greater hepatitis C RNA levels (Valcour et al., 2010). HIV infection and increased age are independently associated with liver fibrosis, chronic hepatitis B infection, and greater hepatitis C RNA levels (Kirk et al., 2013). PLWH are more likely than those without HIV to

have comorbid conditions including hepatitis C, which interacts with HIV, and with continued or increased alcohol consumption, can lead to more rapid cirrhosis and hepatocellular carcinoma (High, Valcour, & Paul, 2006; Kirk et al., 2013). The prevalence of clinically significant fibrosis with and without cirrhosis was greater in PLWH who had co-infections with hepatitis C than those who only had hepatitis C (Kirk et al., 2013). Liver diseases are common comorbidities found in the older PLWH population (High et al., 2006).

Cancer. PLWH are at great risk for cancers with a known infectious cause, though cancer being a large comorbidity in PLWH has decreased after the cART era (Silverberg et al., 2009). HIV causes a loss of effective immune surveillance, which can be a contributing factor to cancer and other complications (High et al., 2012; OAR Working Group on HIV Aging, 2012). Anal squamous cell carcinoma and Hodgkin's lymphoma are infection-related non-AIDS-defining cancers found more prevalent in PLWH than HIV-negative persons (Silverberg et al., 2009). Though PLWH are found to have a lower rate of prostate cancer, cancers without an infectious cause are moderately increased in PLWH compared to their HIV-negative counterparts (Silverberg et al., 2009). In a retrospective cohort study conducted in California, five-year lung cancer-related survival was significantly lower for PLWH compared to persons without HIV (Marcus et al., 2015). Also, among PLWH, men who have sex with men was the most common HIV-transmission risk factor for all cancers, which reflects the epidemic in California (Marcus et al., 2015). Furthermore, cancer-related mortality was higher in PLWH compared with persons without HIV for lung cancers (Marcus et al., 2015). Regardless of infectious or non-infectious causes of cancer, the incidence of skin cancers and prostate carcinomas increase with age in addition to the complexities of HIV itself (Martin et al., 2008; Pantanowitz et al., 2006).

Dementia. Though HIV-related dementia is much less common now than it used to be due to the effectiveness of cART, older PLWH experience dementia later in life (High et al., 2012). Numerous studies find that older PLWH, in general, perform worse on cognitive measures of memory, attention, reasoning, speed of processing, and executive function compared to older adults without HIV and with younger PLWH (Hardy & Vance, 2009; Vance, McGuinness, Musgrove, Orel, & Fazeli, 2011a; Wilkie et al., 2003).

Substance use effects. Substance use in older populations is well documented. Most individuals that have had a long-standing habit of substance use continue their substance use as they did in younger years (Edelman, Tetrault, & Fiellin, 2014; Emler, 2006b). Substance use that continues throughout a person's life course greatly impacts health outcomes. Alcohol, tobacco, marijuana, heroin, other types of opiates, stimulants, and non-opioid prescribed medications are some substances that older PLWH continue to use into older age (Edelman et al., 2014). Older PLWH who use intravenous drugs are less risky with sharing needles, but are equally likely to engage in sex in exchange for drugs or money and equally unlikely to use condoms as compared with younger counterparts (Martin et al., 2008).

Aging with HIV: Stigma and ageism. When people age and approach later stages in life, older PLWH experience a stigma against their HIV disease. When a person is diagnosed with HIV, the person's social worth is compromised due to the stigmatizing nature of HIV and the person him-/herself is stigmatized by default (Vance et al., 2011a). Overt expressions of stigma to HIV have decreased since the 1990s, but PLWH still face stigma and discomfort related to their HIV status (Emler, 2006b). In one survey conducted in the United States in the 1990s via telephone surveys, a third of responders stated that they expressed some fear of PLWH and approximately one-fourth of responders felt anger or disgust towards PLWH (Herek,

Capitanio, & Widaman, 2002). Also, one-fourth of responders felt uncomfortable at having direct or symbolic contact with a PLWH (Herek et al., 2002). Stigma research in the early 1990s and 2000s did not include older adults, and not until recently have researchers looked into stigma in older PLWH (Emlet, 2006a; Herek et al., 2002). In a recent study, HIV-related stigma was found to be consistent in older versus younger PLWH (Emlet, 2006a). However, older PLWH are less likely to disclose their HIV status than their younger counterparts (Emlet, 2006b; Emlet, 2007). Regardless, the importance of including older PLWH in HIV-stigma research is warranted.

In addition to HIV-related stigma, older PLWH face another type of stigma called ageism. Ageism is defined as the negative attitude toward aging such that aging “makes people unattractive, unintelligent, asexual, unemployable, and mentally incompetent (Atchley & Barush, 2004; Herek et al., 2002).” Ageism exists throughout society, including through the media, personal values, language, and culture (Emlet, 2006a, 2006b). Older PLWH experience ageism through employment discrimination, social discrimination, and internalized ageism (Emlet, 2006b; Herek et al., 2002; High et al., 2006).

Cognitive function in PLWH. Impairment in cognitive function is due to both HIV-related and non-HIV-related factors; the targeted neuro-anatomy of the HIV brain pathology (particularly in the frontal lobes) impacts insight into cognitive function (Scott et al., 2011). Changes in cognitive symptoms due to biological brain processes affect chronic illness. Some researchers found that stroke occurs in persons without HIV as a secondary complication of chronic illness (Berger, Harris, Gregorios, & Norenberg, 1990). Cerebrovascular disease may be a complication of HIV infection and the long-term effects of cART in PLWH (Cruse et al.,

2012). Furthermore, infarctions in regions of the brain with higher cerebral function can cause dementia or dementia syndrome in the general population.

Advanced age and HIV affect cognitive symptoms. Both increased age and HIV are associated with impairment in cognitive function and most studies demonstrate an impact on neuropsychological (NP) testing performance. In addition to complications of the HIV virus, individuals experience changes in cognitive function associated with normal aging, as well as possible changes in cognitive function associated with other chronic illnesses, such as Alzheimer's disease (AD) and cancer (Bender et al., 2006; Gebo & Justice, 2009). Impairment in cognitive function associated with advanced age in PLWH is likely due to both the HIV disease and the aging process (Valcour et al., 2004a; Wendelken & Valcour, 2012). Older PLWH with detectable viral loads are more likely to have impairment in tests of working memory and attention compared to impairment of younger PLWH who also had detectable viral loads (Cherner et al., 2004).

Older adults without HIV perform well on neuropsychiatric tests (including verbal memory and executive functioning) when compared to older adults with HIV/AIDS. People who are HIV-positive are reported to have memory problems measured by the California Verbal Learning Test (CVLT)-II, and with no influence due to age (Scott et al., 2011). The fact that PLWH have poorer memory scores compared to their HIV-negative counterparts may strongly be influenced by the physiological impact of the HIV disease. Furthermore, people who are HIV-positive have been reported to score worse compared to those who are HIV-negative on psychological domains (Valcour et al., 2010).

Older PLWH have lower performance in the following cognitive domains than younger PLWH: verbal memory, visual memory, verbal fluency, and psychomotor speed (Sacktor et al.,

2007). Older PLWH performed significantly lower in these cognitive domains than the younger adults, which indicate that older adults had greater impairment in cognitive function than younger PLWH (Sacktor et al., 2007). In the domain of memory, tested with the Rey Auditory Verbal Learning Test (RAVLT), older PLWH had greater impairment in verbal learning, worse in recognition memory and delayed recall than younger PLWH (Sacktor et al., 2007). In the domain of executive functioning, older PLWH had greater impairment than younger PLWH in verbal fluency as measured by the Verbal Fluency Test (FAS) (Sacktor et al., 2007).

The younger HIV-negative group had faster times on the Trail-making test than the other three groups, which indicates that older PLWH have greater deficits in executive functioning. The only interaction effect found for age and HIV on a NCI measurement was for the CVLT-II Recognition Discriminability Test ($F=9.95$, $p<0.01$). However, with post hoc analysis, this effect was related to the outstanding performance of the younger HIV group. The investigators found that advanced age and HIV infection independently increase the risk of neurocognitive impairment, but the combination of age and HIV did not reflect an additive effect of cognitive deficits (Scott et al., 2011).

As compared to patients aging without HIV, PLWH have seen changes in their cognitive function with respect to viral loads as they age with HIV (Cruse et al., 2012; Tozzi et al., 2001). Older PLWH have more impairment in cognitive function than their younger counterparts above a certain threshold of CSF viral load (Cherner et al., 2004). Older PLWH with detectable viral loads are more likely to have impairment in tests of working memory and attention compared to that of younger PLWH who also had detectable viral loads (Cherner et al., 2004). In one study, older PLWH had mean HIV-RNA levels of 1.98 log₁₀ copies of HIV RNA versus 2.65 for those not on HAART and authors found that older adults not on cART were 19% more likely to have

impairment in cognitive function than those on cART (Cherner et al., 2004). Neuropsychological domains of abstraction, attention/working memory, learning, and motor skills are found to have an interaction between CSF viral load and age, such that older PLWH have more impairment than younger PLWH. PLWH on cART with medically asymptomatic or minimally symptomatic HIV disease have higher rates of impairment in cognitive function than those who were not on cART (Heaton et al., 2011).

Aging (Miller, O'Callaghan, & Ali, 2000) and HIV (Valcour & Shiramizu, 2004) are also associated with mitochondrial function in the brain, which affects mental health and cognitive efficiency. Among PLWH receiving anti-retroviral therapy (ART), difficulties with cognitive performance remain highly prevalent, and these difficulties are also be attributable to the aging process (Heaton et al., 2010a). Older PLWH experience changes in cognitive function associated with normal aging and changes associated with chronic illnesses. The aging process or comorbid events that occur with aging leads to impairment in cognitive function in older adults (Gebo & Justice, 2009; Pratt, Gascoyne, Cunningham, & Tunbridge, 2010).

Risk factors for cognitive impairment in PLWH. Immunological changes that occur with aging, insulin resistance and neurological changes that occur with Alzheimer's disease, such as the presence of APOE4 proteins, are risk factors for impairment in cognitive function (Hardy & Vance, 2009; Valcour et al., 2004a). Risk factors for cerebrovascular diseases (including hypertension, cardiac disease, and diabetes mellitus) increase significantly with age (Cruse et al., 2012; Valcour et al., 2004a). HIV and age function independent of each other on patients' neuropsychological performance.

Findings indicate that advanced age does not significantly influence neuropsychological testing performance in PLWH when compared with their matched sero-negative control group

(Valcour et al., 2010). Overall, older adults without HIV perform well on neuropsychiatric tests (including verbal memory and executive functioning) when compared to older PLWH (Valcour et al., 2010). Furthermore, race and gender affect cognitive function in PLWH. In one study, HIV testing rates were highest in African American men and White women (Harawa et al., 2011). In addition, investigators have revealed strong relationships between impairment in cognitive function and HRQOL or HIV status in White and Nigerian women living with HIV (Odiase et al., 2007; Osowiecki et al., 2000; Valcour et al., 2010). One study found that the severity of immune suppression (defined with CD4+ T lymphocyte cell counts) is a strong determining factor of cognitive decline in Nigerians living with HIV. Furthermore, in a study where participants were identified mainly White and were highly educated, the group with HIV tended to score worse on all neuropsychological domain scores than that of the HIV-negative group, specifically those with low CD4 cell counts (Valcour et al., 2010). Regardless of race, however, those with symptomatic HIV experienced more impairment in cognitive function than those without HIV (Odiase et al., 2007; Valcour et al., 2010). Physiological mechanisms, such as decreased CD4 cell counts (Odiase et al., 2007), or psychological and behavioral processes, such as depressed mood states or lower reports of quality of life (Osowiecki et al., 2000) has effects on the relationship between cognitive or affective symptoms and chronic illness.

Aging. Some societal attitudes about aging and HIV/AIDS include: (1) old people are no longer having sex, (2) old people are not drug users or abuses, and (3) if old people have sex, it is in the context of a heterosexual, monogamous relationship (Lieberman, 2000). Health care professionals should be aware of this sociological assumption and take aging as a physiological mechanism into consideration when caring for older PLWH. Aging (Miller et al., 2000) and HIV (Valcour & Shiramizu, 2004) are also associated with mitochondrial function in the brain, which

affects mental health and cognitive efficiency. Among PLWH receiving anti-retroviral therapy (ART), difficulties with cognitive performance remain highly prevalent, and these difficulties may also be attributable to the aging process (Heaton et al., 2010c). Older PLWH experience changes in cognitive efficiency and cognitive function associated with normal aging and possibly changes associated with chronic illnesses common in old age, including Alzheimer's disease and cancer (Bender et al., 2006; Corless et al., 2000; Gebo & Justice, 2009; Sacktor et al., 2007).

cART. As people are aging with HIV, cART affects morbidity and mortality through effects of inflammation, treatment-related toxicity, co-morbid diseases associated with advanced age, and interactions with other chronic viral infections. cART is recommended for all patients regardless of CD4 cell counts, but cART is important for older PLWH because they have a greater risk for serious non-AIDS related complications and a more inhibited immunological response to cART than their younger counterparts. PLWH who are treated on virologically suppressive cART have a very low-level residual viremia detectable in the cerebrospinal fluid (CSF) (Brew et al., 2015). HIV affects the brain during primary HIV infection and during untreated HIV infection (Brew et al.). Researchers have found that HIV infection invades the central nervous system of the brain as evidenced by HIV RNA found in the cerebral spinal fluid as early as 8 days after HIV estimated exposure (Brew et al.). There is evidence for low-level HIV replication in some patients. Patients on Raltegravir have had low-level HIV replication in the central nervous system of the brain (Hatano et al., 2013). Raltegravir is suggested to prevent low-level HIV viral replication from completely integrating into the host DNA (Hatano et al.). Some studies use a drug concentration penetration effectiveness (CPE) score to estimate the central nervous system penetration of a drug regimen (Cysique et al., 2009; Letendre, Marquie-Beck, Capparelli, & et al., 2008; Marra et al., 2009). This categorizes central nervous system

drug penetration based on pharmacological and virological data that has been validated (Letendre et al., 2008). If PLWH are prescribed a cART regimen early in their disease process, HIV is prevented from crossing the blood-brain barrier. Once HIV crosses the blood-brain barrier, the HIV virus can infect glial cells, which support neuronal functioning (Vance, 2004). Studies have not yet determined if it is important to determine if early intervention with cART may address long-term consequences in the central nervous system.

Some studies have found that cART medications penetrate through the central nervous system and thusly produce a positive effect (Cysique & Brew, 2009; Vassallo et al., 2014). Some randomized control trials found that patients on cART have less cognitive deterioration and lower risk of cognitive worsening (Brew et al., 2015; Cysique & Brew, 2011; Cysique et al., 2009; Vassallo et al., 2014). Effective cART affects the immune system, such that t-cell responses are activated within the brain causing an inflammation against viral or mycobacterial antigens (McArthur, Steiner, Sacktor, & Nath, 2010). Patients with cognitive deterioration had lower CSF cART drug concentration penetration effectiveness (CPE) scores than those with improved cognitive function or stable cognitive performance on neuropsychological exams (including tests for learning, recall episodic memory, working memory, attention/concentration, executive function, language, motor/psychomotor speed, and visual agnosia) (Vassallo et al., 2014). CPE scores of cART are indicative of brain penetration and are crucial to achieve the goal of maximal HIV suppression. However, one study found that strong concentrations of cART in the brain were toxic and detrimental to cognitive function and may lead to worse cognitive outcomes (Marra et al., 2009).

One randomized control study to date found cART regimens with good central nervous system penetration, as measured by CPE scores, were associated with poorer neurocognitive

function, as measured by composite neuropsychological test scores (Marra et al., 2009). Most studies find cART to have a protective or neutral effect on cognitive function for PLWH (Cysique et al., 2009). Nonetheless, cART regimens with good central nervous system penetration are more effective than regimens with poorer central nervous system penetration in controlling HIV replication in the CSF, regardless of the number of medications in the cART regimen (Cysique et al., 2009; Marra et al., 2009).

Self-report and a clinical measure of cognitive function. One's self-perception is important when conducting a psychological assessment. It provides comprehensive information for patients' clinical assessments. Older adults who are HIV-positive are reported to be diagnosed 50% more likely to suffer from impairment in CF (Heaton et al., 2010c). Studies suggest that PLWH's self-report of impairment in cognitive function is incongruent with nurses' and physicians' ratings of patients' HIV-related cognitive function (Fontaine, Larue, & Lassaunière, 1999; Reilly et al., 1997), such that health care providers predicted different symptom and cognitive complaints than those the patients reported themselves. Self-report measures may reflect the integration of multiple sensations and feelings, in addition to patients' own interpretation of the systems over a period of time, whereas clinical or objective measures are more one-dimensional and transient.

Self-report of cognitive function. Self-report of cognitive function are more correlated with depression than with clinical measures of cognitive function (Chachamovich, Fleck, Laidlaw, & Power, 2008; Mavandadi, Zanjani, Ten Have, & Oslin, 2009; Richardson-Vejlgaard et al., 2009). Global functional impairment and symptoms of depression each significantly and uniquely contributed to patients' self perception of cognitive function score, while biological markers (CD4 and AIDS status) did not (Heaton et al., 2004). Moreover, providers' perceptions

of their patients' symptoms do not provide an accurate assessment of symptoms experienced by patients or objective NP performance. Thus, there is a critical gap in our ability to identify cognitive impairment in clinics. Self-reported measures may be a valuable predictive tool of cognitive performance for patients; but, to date, there is no data to inform impairment in cognitive function in older PLWH.

Clinical perception of cognitive function. Health care providers fail to recognize symptoms reported by their patients; additionally, the overall report of physical symptoms is incongruent between patients and their providers (Arlt et al., 2008; Robinson-Papp, Elliott, & Simpson, 2009). In a study conducted by Fontaine, Larue, & Lassaunière (1999), physicians reported the presence of fatigue and anxiety in PLWH more than the patients themselves reported. The physicians associated HIV with a poor prognosis, including more anxiety and fatigue. Health care providers also incongruently assumed symptoms of fatigue, weight loss, skin problems, cough, and dry mouth in PLWH, whereas the individual PLWH reported less of those symptoms. PLWH complained more of fever than that objectively measured at the clinician's office.

HIV-associated Neurocognitive Disorders (HAND) criteria. In the HIV-related literature on cognitive function, researchers use certain criteria to diagnose CI in PLWH. Some researchers use the 2007 HIV-associated Neurocognitive Disorders (HAND) Frascati criteria to diagnose CI (Antinori et al., 2007). The four diagnostic categories include cognitively normal (HIV-NL), Asymptomatic Neurocognitive Impairment (ANI), Mild Neurocognitive Disorders (MND), and HIV-associated dementia (HAD) (Table 1). There is considerable discussion related to defining symptomatic compared to asymptomatic cognitive impairment in the setting of HIV. Nonetheless, a mild degree of cognitive impairment still pose a risk for HIV disease progression,

particularly in older adults (Heaton et al., 2004). In HIV-negative populations, those with mild cognitive impairment are at an increased risk of developing dementia (Petersen et al., 2004). The use of HAND diagnosis will provide a timely identification of the course of HAD and empower clinicians to recommend interventions, such as education, exercise, or cognitively stimulating activities, for patients to delay the course of dementia (Mortimer et al., 2003; Stern, 2003).

Table 1: HIV-Associated Neurocognitive Disorders (HAND) diagnostic criteria and definitions

HAND	HIV-associated neurocognitive disorders
Asymptomatic neurocognitive impairment (ANI)	<p>Involves impairment in at least two cognitive domains</p> <ul style="list-style-type: none"> Defined by a score of one standard deviation or more below the mean for norms on standardized neuropsychological testing <p>No symptomatic or observable functional impairment with activities of daily living</p>
Mild neurocognitive disorder (MND)	<p>Involves impairment in at least two cognitive domains</p> <ul style="list-style-type: none"> Defined by a score of one standard deviation or more below the mean for norms on standardized neuropsychological testing <p>Mild symptomatic or observable functional impairment with activities of daily living</p>
HIV-associated dementia (HAD)	<p>Involves impairment in at least two cognitive domains</p> <ul style="list-style-type: none"> Defined by a score of two standard deviations or more below the mean for norms on standardized neuropsychological testing <p>Severe symptomatic or observable functional impairment with activities of daily living</p>

Health-related quality of life in PLWH. Physical, social, and environmental domains within Health-Related Quality of Life (HRQOL) are reported to have effects in PLWH (Scott et al., 2011). Physical aspects of HRQOL are worse in older PLWH than in younger PLWH (Pereira & Canavarro, 2011; Scott et al., 2011). In the “Social Relationships” domain, longer duration of education, younger in age, and being less depressed significantly correlated to a

better QOL score for all genders and ages. In the “Environmental” domain, having less psychopathological symptoms, longer duration of education, and having a social relationship or partner was significantly correlated to higher QOL scores (Pereira & Canavarro, 2011). Physical domains of HRQOL are worse in older PLWH compared to younger, while those over 45 years of age report lower HRQOL. Those over the age of 45 years report the lowest scores across all quality of life factors. This means that younger PLWH report better quality of life than their older counterparts. Furthermore, PLWH with a more severe HIV stage as outlined by the CDC, Stage C, result in lower ratings on Physical Health aspects of HRQOL than those with less severe HIV status (Trepanier et al., 2005).

Health-related quality of life and mental health. Depressive symptoms and cognitive functioning independently contribute to physical health factors of HRQOL. This indicates that HRQOL depends on an individual’s ability to engage in physical and mental activities of daily living and that neuropsychological and emotional capacity are important determinants of perceived HRQOL (Tozzi et al., 2004; Trepanier et al., 2005). Impairment in cognitive function and emotional distress negatively impact HRQOL, especially when neurobehavioral complications co-exist (Cherner et al., 2004; Tozzi et al., 2004; Trepanier et al., 2005). HRQOL is a complex construct that consists of multiple domains and descriptors. In addition to objective measures of HRQOL and the health care provider reports of a patients’ quality of health, as well as self-report from patients should be included in the plan of care that they receive. Having less psychopathological symptoms, longer duration of education, and having a social relationship or partner was significantly correlated to higher HRQOL scores (Pereira & Canavarro, 2011).

High-quality care for older PLWH requires healthcare professionals to screen and provide treatment for the unique needs of the individual and community and to encourage

patients to have productive, optimal lives. This may entail using screening questionnaires used to detect depressive symptoms, establish a baseline, and also provide as objective measures (Valente, 2003). As reported, screening tools to measure depression has been shown to be correlated with impairment in cognitive function and HRQOL, as well as anxiety and somatization (Pereira & Canavarro, 2011). Depression and subjective mood status have a significant influence on mental health dimensions for HRQOL in PLWH (Chachamovich et al., 2008; Corless et al., 2000; Trepanier et al., 2005). In an international sample of older adults, minor or even slight levels of depression were significantly associated with decreased HRQOL and with negative attitudes toward aging (Chachamovich et al., 2008). The mental health factor for the HRQOL measure of the MOS-HIV has a great effect on depression, but no significant effects for neuropsychological status (Trepanier et al., 2005). Patient reports of mental health problems (Trepanier et al., 2005) and reports of cognitive function (Corless et al., 2000) significantly relate to reports of depression.

Relationship of health-related quality of life and cognitive function with depression.

Results suggest that cART influences HRQOL in patients with impairment in cognitive function (Tozzi et al., 2004), furthermore, depression or impairment in cognitive function affect HRQOL. For example, researchers have found three factors that affect HRQOL: fatigue, cognitive functioning, and overall health (Tozzi et al., 2004). PLWH who report problems with medication management report higher levels of depression than those who do not report problems (Thames et al., 2011). Furthermore, patients may have fragile social and/or support networks that may be unable to support them as they age, and PLWH need high-quality care to meet their demanding physiological needs, including care of overall health and cognitive function.

HRQOL and attitudes toward aging are rated lower in PLWH who have depression than in those without depression regardless of age (Thames et al., 2011). A slight increase in depression is a large predictor of compromises in HRQOL and attitudes toward aging (Chachamovich et al., 2008). Chachamovich et al. found that all scores for HRQOL and attitudes toward aging were significantly lower in the depressed group than in the non-depressed group ($p < 0.001$). The magnitude of the effect was much higher in patients with depression than other variables, which suggests that a slight increase in depression is a large predictor of compromises in QOL and attitudes toward aging (Chachamovich et al.).

Physical health in PLWH. Physical well-being affects PLWH and is a reliable predictor for various clinical outcomes, such as psychological functioning and comorbid health conditions (Heckman, 2003). Poor physical health can increase pain, fear of death, anxiety, and decreased function in activities of daily living.

Depressive symptoms and cognitive functioning independently contribute to Physical Health factors of HRQOL. This indicates that HRQOL depends on an individual's ability to engage in physical and mental activities of daily living and that neuropsychological and emotional capacity were found to be important determinants of perceived HRQOL (Tozzi et al., 2004; Trepanier et al., 2005).

Mental health in PLWH. Mental health consists of mental distress, cognition, and energy levels (Heckman, 2003). Patients with diagnosed psychiatric disorders also have lower mental health, health perceptions, and social function compared to those without psychiatric disorders (Wisniewski et al., 2005; Wu, 1999).

Social relationships and networks also affect mental health for PLWH. Longer extent of education, reduced age, and bearing less depression all significantly correlated to a better

HRQOL score and positive reports of social relationships. Many PLWH have supportive networks with other PLWH who are also dealing with their illnesses and needs. PLWH with stronger social support groups are more likely to receive encouragement, empathy, and validation, which in turn enhances the individual's self-esteem, self-efficacy, and worth (Heckman, 2003). With fragile networks, PLWH need both formal (i.e. providers) and informal (i.e. friends and family) networks (Brennan-Ing et al., 2013) to help them function in their society.

Self-report versus clinical measures of cognitive function. Self-reports of impairment in cognitive function are related more to depression than to objective measures of cognitive performance (Richardson-Vejlgaard et al., 2009). Global functional impairment, symptoms of depression as measured by the Geriatric Depression Scale or Profile of Mood States (Scott et al., 2011) and low scores of HRQOL significantly and uniquely contribute to patients' assessment of their cognitive function (as measured by the Patients' Assessment of Own Functioning Inventory) score (Osowiecki et al., 2000), while biological markers (CD4 and AIDS status) did not contribute to a patients' assessment of their cognitive function (Heaton et al., 2004). Depression, low scores in HRQOL measures, and objective measures of impairment in cognitive function relate to the patients' own assessment of cognitive function, though depression is found to be more highly correlated to objective measures of cognitive function than to the patients' own assessment of cognitive function (Heaton et al., 2010c). Regardless, both self-report measures and objective measures together provide a more comprehensive assessment of a patient's cognitive function (Blackstone et al., 2012).

Summary and Conclusion

In summary, constructs, concepts, and relational statements were provided for the Emory University Nell Hodgson Woodruff School of Nursing Conceptual Framework for the Center for Neurocognitive Studies. The Conceptual Framework of the Center for Neurocognitive Studies emphasizes the fact that cognitive impairment and emotional distress directly impact chronic illness. The existence of one symptom may compound the effect of the other, in which the disruption of these pathways may potentially reduce the negative progression of chronic illnesses. As it relates to the proposed study, PLWH may over-estimate their capacity or self-report impairment in cognitive function when compared to clinical measures of cognitive function.

The literature review discussed the impact of age and other comorbidities in PLWH. Chronic illness affects the ability to perform activities of daily living and has a direct negative influence on cognitive function. Cancer, dementia, and substance use effects are some conditions older PLWH face more frequently than their younger counterparts. In addition, older PLWH experience ageism in addition to the HIV stigma itself, which magnifies a negative HRQOL.

Patients who report more cognitive impairment also report higher levels of depression and lower scores on HRQOL measurement tools. Altered perceptions of capacity will then influence the manner in which patients manage their symptoms and/or enlist the assistance of others. Depression, self-report of cognitive function, clinical measure of cognitive function have high correlations to HRQOL, and these relationships warrant further research in the oldest population of PLWH. As the population is aging, the assessment of both clinician reports and patient reports of own function may advance health care providers' knowledge in these

relationships among PLWH; the variables of depression and HRQOL will advance health care providers' knowledge of the extent to which emotional distress directly impacts chronic illness.

Chapter 3: Approach/ Research Design and Methods

Study Design

This is a secondary data analysis of cross-sectional data from a longitudinal cohort study about cognitive function and aging in older persons living with HIV (PLWH).

Description of Parent Study

The parent study “University of California, San Francisco (UCSF) HIV Over 60 Cohort” is funded by the National Institute of Aging (grant: 1K23AG032872-01) under Dr. Victor Valcour and is a longitudinal cohort study of persons, age 60 and older, who were living with the human immunodeficiency virus (PLWH) and were enrolled in a study within the UCSF Memory and Aging Center (MAC) from 2009-2014. Participants were assessed annually with a goal of completing 5 visits. This research utilized data obtained from the parent study to conduct a secondary data analysis.

Assessments. Participants were assessed annually with a goal of 5 visits: a baseline visit plus four additional visits. At the baseline visit, participants filled out questionnaires and completed the following: neuropsychological testing, neurological exam, functional assessment, assessment of geriatric syndromes, blood draw (including CD4 nadir, CD4 cell count), an MRI exam, medical history (including the duration of HIV, CD4 nadir, medication history, medication adherence, other opportunistic infections, and HIV-specific diagnoses). For the other four visits, participants also underwent neuropsychological testing, neurological exam, functional assessment, assessment of geriatric syndromes, blood draw (including CD4 nadir, CD4 cell count), and an MRI exam. For some subsequent visits, participants completed a Health-Related Quality of Life (HRQOL) tool. The data set for each participant was specific to the clinic visit date.

Description of Research Setting

Procedures

Recruitment procedures and sampling technique. Participants were recruited from the San Francisco Bay area community using advertising, flyers, peers, and referrals through AIDS service organizations and referring physicians, to provide a representative sample. Participants were also recruited from HIV/AIDS foundations, hospitals in the San Francisco Bay area, infectious disease medical offices, and educational talks at universities. The UCSF Veteran's Affairs (VA) Medical Center was also a source for referrals.

UCSF research staff identified all potential participants who met the study criteria (see inclusion criteria below) and were contacted via telephone or email. Participants were asked if they were interested in enrolling in the study and then were screened over the phone. With verbal consent, potential participants were asked a series of questions related to the exclusion/inclusion criteria. If eligible, the participant was asked to complete a baseline visit at the UCSF Memory and Aging Center. Consent for the study, with a detailed description of the cohort study and procedures, was obtained at the baseline visit (see section on Consent). Participants were enrolled independent of their cognitive status.

Procedure for informed consent. Participants were asked to consent to enroll into the cohort study with a Committee on Human Research (CHR)-approved consent form that contained pertinent information about the study, including the study protocol, measures, purpose, routine and additional optional procedures. Participants were given a human subject's Bill of Rights (Appendix 1) before beginning the study. The research coordinator explained the purpose of the study, the procedures, and the risks and benefits associated with the study. The participant was given ample time to ask questions about the study. The research coordinators ensured that

participants understood protocols and procedures by answering participant's questions and providing additional resources for further questions. Participants signed IRB-approved consents after they verbalized understanding of procedures.

Data collection

Routine clinical intake and tests. All participants underwent comprehensive evaluations for each visit. The parent study clinical evaluations included the following: (1) full cognitive/behavioral review of symptoms, (2) medical history, (3) medications, (4) family history, (5) mood and psychiatric illnesses, (6) neurological examination with a neuropsychological test battery (NTB), (7) proxy interview using the Clinical Dementia Rating scale (CDR), (8) patients' assessment of their own cognitive function using the Patient's Assessment of Own Functioning Inventory (PAOFI), and (9) depressive symptoms using the Geriatric Depression Scale (GDS). A HRQOL tool using the Medical Outcomes Survey-HIV (MOS-HIV) was added later in the study, and some participants completed the MOS-HIV in subsequent visits. The parent study extended the cognitive evaluations to capture more in-depth characterization specific to individual diseases and a more comprehensive neuropsychological testing battery. The following measurement instruments were also collected for each participant at every visit: a functional assessment, assessment of depressive and psychiatric comorbidities, geriatric measures, clinical laboratory measures, and brain imaging.

Steps to minimize risk and maintain privacy in research setting. Both electronic and hard copies of data were stored in locked facilities at UCSF MAC. The database was password-protected on a secure server that is also maintained in a locked room in a badge-protected suite at the MAC. Appropriate firewalls are in place. The electronic database is maintained by the information technology center at MAC. Potential adverse events related to participation in the

study were assessed at each study visit with open-ended questions. Potential adverse events included the following: injury due to phlebotomy or accidental disclosure of HIV testing results or HIV serostatus.

Sample

Human subjects assurance. Prior to implementation of all research procedures, the study protocol received human subjects review approval from the University of California, San Francisco's Committee on Human research (see Appendix 2). Participants provided written informed consent following procedures approved by the UCSF Committee for Human Research.

Nature and size of sample. For Specific Aim 1, the sample size of 73 participants provided power of 80% at an alpha level of 0.05 to detect a small to moderate effect size or unique contribution (R-square change) of one independent variable of approximately 8.7% (Cohen, 1988). Assuming the other 2 variables in the model already explain at least 13% of the total variance in the dependent variable (DV), the Patient's Assessment of Own Functioning Inventory (PAOFI). For Specific Aim 2, the sample size of 73 participants also provided power of 80% at an alpha level of 0.05 to detect a small to moderate effect size or unique contribution (R-square change) of one independent variable of approximately 8.7% (Cohen, 1988). Assuming the other 2 variables in the model already explain at least 13% of the total variance in the DV (PAOFI). For Specific Aim 3, the sample size of 32 participants provided power of 80% at an alpha level of 0.05 to detect a medium to large effect size or unique contribution (R-square change) of one independent variable of approximately 15% (Cohen, 1988). Assuming the other 2 variables in the model already explain at least 26% of the total variance in the dependent variable's Mental Health Summary score (MHS) and Physical Health Summary score (PHS).

The sample size allows for detection of a statistically significant difference with the different models.

Criteria for sample selection. The following criteria were used for selecting participants in the current study:

Inclusion criteria: Inclusion criteria were self-report of HIV infection and minimum age of 60 years. All participants identified English as their primary language of communication and were able to provide consent.

Exclusion criteria: Exclusion criteria included individuals who were younger than 60 years of age, were negative for HIV, had a history of stroke, schizophrenia, loss of consciousness for more than 30 minutes due to head injury, current or past brain opportunistic infection, and active illicit drug use within the past 6 months. Language other than English as the main language for oral and written communication, alcohol or substance abuse as a major cause of dementia, and significant systemic medical illnesses (including cancer requiring chemotherapy) or end-stage cardiac insufficiency were additional exclusion criteria.

Withdrawal criteria. Participants also had a right to refuse to answer questionnaires and to withdraw their consents to participate in the study at any time. No participants withdrew their consents for this study.

Data Collection Methods

The variables of interest and instruments used for this dissertation included the participants' perception of cognitive function as gauged by the Patient's Assessment of Own Functioning Inventory (PAOFI), depression as measured by the Geriatric Depression Scale (GDS), clinical measure of cognitive function as measured by a selection of tests from the neuropsychological battery (refer to Table 2 for more information), and health-related quality of

life (HRQOL) as measured by the Medical Outcomes Survey-HIV (MOS-HIV). In the following section, each measure's conceptual definition, operational definition, and the validity and reliability of the instruments will be discussed in further detail.

Definitions, Validity, and Reliability of the Instruments

The psychometric properties of the various measurement instruments are provided in the following section. According to Nunnally and Bernstein (1994), internal consistencies should be 0.80 or higher to for scales to be considered accurate or reliable within an instrument. The validity of an instrument is contingent on a population (Streiner & Norman, 1995), and when the instrument is used with a different population, validity must be reestablished. For the purpose of this paper, an item analysis including the Cronbach's alpha for each subscale was completed for the PAOFI because the validity and reliability of the PAOFI had not been assessed in PLWH, particularly older PLWH.

Patient's Assessment of Own Functioning Inventory (PAOFI). The Patient's Assessment of Own Functioning Inventory (PAOFI) is a 33-item instrument that assesses patient's self-report of his or her cognitive function and is completed by the patient. The instrument focuses on cognitive symptoms and is frequently used by the HIV Neurobehavioral Research Center in San Diego, California to determine the American Academy of Neurology diagnosis of symptomatic versus asymptomatic impairment in cognitive function (Heaton et al., 2004). PLWH who have asymptomatic impairment in cognitive function do not report severe interference with activities of daily living (Heaton et al., 2004). PLWH who display symptomatic impairment in cognitive function, conversely, experience severe hindrances to their activities of daily living.

PAOFI conceptual definition. The Patient's Assessment of Own Functioning Inventory is designed to evaluate a patient's own sense of functional capacity in everyday activities. This instrument was originally derived from actual complaints of participants referred for psychiatric and neurological testing (Chelune, Heaton, & Lehman, 1986; Richardson-Vejlgaard et al., 2009; Schwartz et al., 1996).

PAOFI operational definition. The instrument includes four subscales: (1) memory (to assess the participants' ability to recall information related to daily living), which includes 10 items, (2) language and communication (to assess the participants' verbal communication skills), which includes 9 items, (3) sensory, perceptual and motor skills (to assess psychomotor skills), which includes 5 items, and (4) higher cognitive function (assess executive function, including planning and organizing), which includes 9 items. Scores range on a continuous scale with values from 0-165; a higher number indicates more complaints/poorer condition. Each question offered response options as follows: Almost never, Very infrequently, Once in a while, Fairly often, Very often, and Almost always. Each answer was rated on a 6-point scale (1-6) as follows: 1 = Almost never; 2 = Very infrequently; 3 = Once in a while; 4 = Fairly often; 5 = Very often; and 6 = Almost always. These numbers were recoded (0-5) as follows to calculate the composite score: 0 = Almost never; 1 = Very infrequently; 2 = Once in a while; 3 = Fairly often; 4 = Very often; and 5 = Almost always, as commonly used in the literature (Rourke et al., 1999).

The total score was calculated for each of the subscales. Ten items were offered for the memory subscale, and the subscale score ranged from 10-60 (recoded to 0-50). The language and communication subscale included 9 items, with Question #15 having two parts. Part A asks, "When you speak, are your words indistinct or improperly pronounced?" and Part B asks, "If this happens, how often do people have difficulty understanding what words you are trying to say?"

and the answer options were as follows: Almost never, Very infrequently, Once in a while, Fairly often, Very often, and Almost always. The subscale score ranged from 9-54 (recoded to 0-45). Part B was not included in the score but was used only as additional information. The sensory, perceptual and motor skills segment included 5 items with one question having two parts. Question #24, Part A asks, “Lately, do you have more difficulty than you used to in seeing all of what you are looking at, or all of what is in front of you (in other words, are some areas of your vision less clear or less distinct than others)?” Part B asks, “If you are having this kind of trouble with your vision, is it more difficult to see things located to your right or to your left?” Answer options were as follows: To the left, To the right, Cannot tell whether one side is worse than the other. Part B was not calculated in the score but was used only as additional information. The subscale score ranged from 5-36 (recoded to 0-25). Lastly, the higher cognitive function subscale included 9 items, and the subscale score ranged from 9-54 (recoded to 0-45). There was no justification in recoding the PAOFI and research studies have utilized the total score or the main score for analysis (Richardson-Vejlgaard et al., 2009; Rourke et al., 1999).

The participants’ ratings in each of the four subscales were summed. The total subscale score was then divided by the number of items in each major area to reflect a mean rating of each complaint area (Rourke et al., 1999). The total PAOFI score was the sum of the 33 items divided by 33 to reflect a mean level of total subjective neurocognitive complaints; this score was called the mean PAOFI score and was used for calculations.

PAOFI validity and reliability. The validity and reliability of this instrument has not been assessed in PLWH. The psychometric properties of this instrument were assessed in non-HIV populations: (1) women with breast cancer (n=259) with a mean age of 60 years (Bell, Terhorst, & Bender, 2013) and (2) substance-using participants (n=74) with a mean age of 48.2

years and non-clinical controls (n=150) with a mean age of 42.7 years (Richardson-Vejlgaard et al., 2009). The subscales of the PAOFI were assessed for reliability using Cronbach's alpha and correlations with the fatigue scale of the Profile of Mood States test and with the physical and mental subscales of the SF-36 instrument (Bell et al., 2013).

The PAOFI subscale reliabilities were adequate for three of the four domains in women with breast cancer ($\alpha = .82$ for Memory 1, $\alpha = .74$ for Memory 2, $\alpha = .79$ for Language & Communication, and $\alpha = .88$ for Cognitive/Intellectual Functions). The sensorimotor function was not reliable in women with breast cancer with a mean age of 60 years ($\alpha = .57$) (Bell et al., 2013). Regardless, the sensorimotor function scale was significantly correlated to the SF-36 Physical component scale ($r = -0.32$). For substance-using participants, construct validity of memory, language and communication, and higher-level cognitive function subscales was established (Richardson-Vejlgaard et al., 2009). PAOFI scores between the substance-using participants and non-clinical controls established discriminant validity (Richardson-Vejlgaard et al.). Substance-using participants reported twice as many cognitive complaints (higher PAOFI scores) overall, compared to participants in the non-clinical group ($p < .001$).

Convergent validity was not supported with this instrument in substance-using participants; Pearson correlations between factor scores of the individual neuropsychiatric test scores and the PAOFI scores were not significant. Substance-using participants reported a significantly higher amount of cognitive complaints on the PAOFI than those in the clinical sample, which supports discriminant validity of the PAOFI (Richardson-Vejlgaard et al., 2009).

Geriatric Depression Scale (GDS). The Geriatric Depression Scale (GDS) is a 30-item instrument designed to assess depressive symptoms in older adults through self-report measures (Mackin & Areán, 2007) and excludes somatic symptoms of depression, such as fatigue, chronic

illness, or weight loss (Heckman, Berlin, Heckman, & Feaster, 2011). Somatic symptoms of depression are dominant symptoms in primary care (Tylee & Gandhi, 2005) and can exist as confounding factors in PLWH.

This study utilized the Geriatric Depression Scale (GDS), because this sample was older in age (60 years and older). Other authors have utilized different measurement tools to assess depression, such as the Beck Depression Inventory (Rourke et al., 1999; Thames et al., 2011). For this study, because the population includes older adults, a depression scale that was reliable, valid, and specific for older adults were used.

GDS conceptual definition. The GDS assesses the presence of affective, cognitive, as well as behavioral symptoms of depression in the past seven days for the patient (Heckman et al., 2011). The higher the score is indicates greater reports of depression.

GDS operational definition. Each item is a dichotomous variable (Yes or No) and yields scores from 0-30. The responses were coded: 1= Yes, symptom present and 0= No, no symptom present. The summed GDS scores are categorized as the following: No depression (scores 1-10), Mild depression (scores 11-20), and Moderate-to-severe depression (21-30). Nineteen of the items indicate the presence of depression when answered positively; the rest (questions number 1, 5, 7, 9, 15, 19, 21, 27, 29, 30) indicate depression when answered negatively).

GDS validity and reliability. The GDS consists of 30-items, and was originally intended for screening depression in older adults without dementia (Kørner et al., 2006). Convergent reliability was found in the GDS; the Cornell Scale for Depression in Dementia, the Hamilton Depression Rating Scale, and the Clinical Global Impression were significantly correlated to the GDS. Based on the ROC analysis, sensitivity and specificity were obtained of the GDS with ICD-10. The analysis was completed in three groups of adults age 65 years and older with and

without dementia: n=145 of all participants, n=98 of all participants with dementia, and n=37 of participants with only dementia. The GDS was found to be highly valid and reliable in participants without severe dementia (Kørner et al., 2006). Furthermore, another study found the GDS highly reliable and valid in a population of PLWH age 50 and older (Heckman et al., 2011). There were 83 whites and 204 African Americans. Results from the multi-group confirmatory factor analysis found the GDS to have a goodness of fit model such that the three models were significant. The GDS demonstrated good coefficient alpha and test-retest reliability for both ethnic population groups (Cronbach's alpha= 0.87 and Cronbach's alpha= 0.85) and good measurement invariance for both groups (Heckman et al.). This suggests that there are appropriate between-group comparisons for white PLWH and African American PLWH for the GDS instrument (Heckman et al.). This instrument is found to be reliable in participants across race/ethnicity (Heckman et al.) but is less optimal when applied to a population of participants with severe cognitive function, including dementia (Kørner et al.).

Neuropsychological Battery. The neuropsychological battery is designed to evaluate cognitive function. This battery requires several hours to administer and requires trained personnel or neuropsychologists to interpret the results (Barber et al., 2013).

Table 2: Neuropsychological Battery grouped by domain tested

Cognitive Domain	Neuropsychological Tests
Memory	CVLT-II, Story Recall (immediate and delayed recall), and Benson Figure recall
Executive Function	Modified Trails task, Trails B, Stroop Interference, Lexical Fluency (D words), digits span (backwards)
Psychomotor Speed	Trails A, WAIS-I Digit Symbol, Stroop Color Naming
Visuospatial	VOSP, Benson Figure Copy
Motor	Grooved Pegboard, Finger Tapping
Attention	CVLT-II Trial 5, Digits forward
Notes:	
CVLT: California Verbal Learning Test	
WAIS: Wechsler Adult Intelligence Scale	
VOSP: Visual Object and Space Perception Battery	

Researchers in the field of neurology and HIV-associated neurocognitive disorders utilize a series of various neuropsychological tests to assess different domains of cognitive function (See Table 2). For the purpose of this dissertation, the scores of each participant's neuropsychological tests were computed into a summed Z-score for a Neuropsychological Global Composite. The Neuropsychological Global Composite was used for analysis (see Neuropsychological Global Composite conceptual definition for details of the individual tests).

Neuropsychological battery conceptual definition, validity, and reliability. A neuropsychological battery consists of multiple tests that assess different domains of cognitive function (see Table 2). Various neuropsychological instruments test a patient's memory, executive function, psychomotor speed, visuospatial skills, motor or manual dexterity, language, and attention skills.

The cognitive domains of interest include memory, executive function, psychomotor speed, visuospatial skills, motor skills, and attention. These cognitive domains were the variables

of interest to evaluate participants' self-awareness of their capacity to perform activities of daily living as described in the literature (Chiao et al., 2013; Williamson et al., 2010). Attention, memory, language, psychomotor speed, executive function, memory, and motor skills have been used to evaluate participants' self-perception of cognitive function in the literature (Rourke et al., 1999).

The memory domain included the three tests: California Verbal Learning Test-II (CVLT-II), Story recall, and the Benson Figure Recall. The CVLT measures verbal learning, immediate and delayed recall, and recognition memory (Delis, Kramer, Kaplan, & Ober, 2000). It requires participants to learn a list of 16 words over 5 trials (verbal learning) (Trial 1) and the participant is required to recall (Trial 2) as many words as possible after an interference trial (immediate free recall). After a 10- to 15-minute delay (Trial 3), participants are again asked to recall the words (short delay free recall). Participants are then asked (Trial 4) to recall the words based on a particular category (i.e. furniture, vegetables, ways of traveling, and animals) (short delay cued recall). This completes the first part of the CVLT-II and begins the long-delay interval. Another test, such as the Stroop test (see below for more information), is administered. After 10-15 minutes (Trial 5, free recall), participants are given a list of 36 words, two at a time, and are asked which word of the pair was on the original list (recognition memory). Test-retest stability was found in PLWH (Duff, Westervelt, McCaffrey, & Haase, 2001). The test-retest stability is important, because test-retest stability coefficients determine whether change across time is attributed to an independent variable or by chance (Duff et al., 2001). The CVLT-II was found to be valid and reliable in older adults and patients with mild neurocognitive impairment (Delis, Kaplan, & Kramer, 2001; Delis et al., 2000) and was found to have strong content validity in patients with traumatic brain injury (McKay, Casey, Wertheimer, & Fichtenberg, 2007).

However, this has not been assessed in PLWH. For the purpose of this study, the immediate free recall and delayed recall scores were the variables of interest.

The validity and reliability of the Story Recall test and the Benson Figure Recall has not been explored in PLWH. The Story Recall test was found to be a sensitive measure in persons who are experiencing the normal aging process, who have mild cognitive impairment, and who have Alzheimer's Disease (Baek et al., 2011; Weintraub et al., 2009). The Story Recall test was found to be highly correlated to the Wechsler Memory Scale-III in the same population group (Baek et al., 2011; Weintraub et al., 2009); the Wechsler Memory Scale-III also assesses memory as well. This test's validity and reliability have not been explored in PLWH. The immediate and delayed recall scores were the variables of interest. While the Benson Figure Recall's validity and reliability have not been assessed in any population group, it has been used with PLWH (Chiao et al., 2013).

Executive function was measured using: the Modified Trail Making test B, Modified Stroop interference, lexical fluency (D words), and digit span (backwards). The Modified Trail Making test B and lexical fluency (D words) were used in patients with fronto-temporal dementia, semantic dementia and Alzheimer's disease (Kramer et al., 2003) and is used in more than 80% of Alzheimer's Disease research centers (n=21) (Weintraub et al., 2009). Trail Making Test-Form B assesses for divided attention (Lonie et al., 2009), as a measure of executive function. This test was found to be valid and reliable in persons with fronto-temporal dementia, semantic dementia and Alzheimer's disease; this test was also found to have high degree of specificity to assess for impairment in executive function (Kramer et al., 2003). The Trail Making Test-Form B requires, after a brief practice, the participant to make connection by pencil lines to alternate between 20 encircled numbers (numbers 1-20) and 20 encircled letters (A

through T) positioned randomly on a A4-sized sheet of paper (Burgess et al., 1998). The time taken to complete the task directly correlates with psychomotor speed (Reitan & Wolfson, 1993). The Stroop interference test takes approximately 10-15 minutes to administer. The performance measures for the Stroop test are often multifactorial and not as sensitive and specific to frontal lobe pathology as cited by Kramer et al. (2003) (Stuss et al., 2002). This test's validity and reliability have not been assessed in PLWH. Lexical fluency (D words) has been used in persons with fronto-temporal dementia, semantic dementia and Alzheimer's disease (Delis et al., 2001; Kramer et al., 2003) but the validity and reliability have not been assessed in PLWH. The digit span (backwards) test was found to have content validity in participants with HIV infection and AIDS dementia complex (Cysique, Maruff, Darby, & Brew, 2006) and has been used in PLWH and asymptomatic to symptomatic cognitive impairment (Chiao et al., 2013).

Psychomotor speed was measured using: Trail Making Test Form A, Wechsler Adult Intelligence Scale (WAIS-I) Digit Symbol, and the Stroop Color Naming. The Trail Making Test-A assesses psychomotor speed, in addition to visual scanning and alternating attention, (Lonie et al., 2009) and requires, after a brief practice, the connection by pencil lines of 20 encircled numbers (numbers 1-20) positioned randomly on a A4-sized sheet of paper (Burgess et al., 1998). The participant would draw a line from 1-2-3-4, etc. The time taken to complete the task directly correlates with psychomotor speed (Reitan & Wolfson, 1993). The Trail Making Test Form A has been used in PLWH (Heaton et al., 2004) and with patients with neurodegenerative disease and mild cognitive impairment (Pa et al., 2010) but the validity and reliability has not been assessed in PLWH. For the WAIS-I Digit Symbol test, the participant is shown 10 symbols with a corresponding letter or number and is asked to translate a document with these symbols as quickly and accurately as possible (Reitan & Wolfson, 1993). The WAIS-I

Digit Symbol test has not been validated or found reliable in PLWH. However, the WAIS-III Digit Symbol test was found to be reliable, high degrees of diagnostic accuracy in PLWH with neuropsychological impairment (Carey et al., 2004). The WAIS-III Digit Symbol test was found to have good specificity with another neuropsychological test that assesses verbal learning and memory called the Hopkins Verbal Learning Test Revised (Benedict, Schretlen, Groninger, & Brandt, 1998). The WAIS-III is also commonly used in patients with Alzheimer's disease (Weintraub et al., 2009) and is also widely used in PLWH (Chiao et al., 2013; Heaton et al., 2010b).

Visuospatial skills were measured with the Visual Object and Space Perception (VOSP) Battery and the Benson Figure Copy. The Visual Object and Space Perception Battery consists of eight tests each designed to assess a specific aspect of an object or space perception and has also been used in PLWH (Chiao et al., 2013) yet the validity and reliability of the test has not been assessed in PLWH. This test is un-timed and is administered at a pace suitable for each participant. The VOSP has been developed, standardized, and validated in the Psychology Department at the National Hospital for Neurology and Neurosurgery in Queen Square, London and has been used and referenced in more than 250 publications (Lezak, Howieson, & Loring, 2004). This test has only been validated in persons with stroke (Radford & Lincoln, 2004). The Benson Figure Recall is a test of visual memory function and is adapted from the Rey-Osterrieth Complex Figure (Possin, Laluz, Alcantar, Miller, & Kramer, 2011). It requires the participant to copy a figure and advised to study the figure for 5 seconds afterwards. After a delay, the participant is then asked to draw the figure again from memory (delayed recall). The validity and reliability of this tool has not been explored in PLWH, but has been used in research for PLWH (Chiao et al., 2013). Memory and delayed recall were the variables of interest for this study.

Motor or manual dexterity was measured using the Grooved Pegboard test and finger tapping. The Grooved Pegboard test assesses for manual dexterity, psychomotor speed and processing speed. Participants are asked to place asymmetrical metal pins into a grooved pegboard while being timed. The test is completed two times: with the dominant hand and with the non-dominant hand (Spreeen & Strauss, 1998). The Grooved Pegboard test was found to be sensitive to measure motor dexterity and psychomotor speed in PLWH and persons with AIDS dementia complex (Cysique et al., 2006). In a meta-analysis of seven databases, all studies that assessed motor skills utilized the Grooved Pegboard test (Kamminga, Cysique, Lu, Batchelor, & Brew, 2013). The Grooved Pegboard test is the most commonly used tool to assess motor dexterity and function. This test paired with the Hopkin's Verbal Learning Test was found to have high specificity in PLWH (Kamminga et al., 2013). The finger tapping is another tool to measure motor dexterity. The validity of this tool has been explored in PLWH in Africa with the internalized HIV Dementia scale (Kamminga et al., 2013) and has been used in PLWH (Chiao et al., 2013).

Attention was measured using the CVLT-II Trial 5 and the Digit Span test (forward). The CVLT-II Trial 5 has been used in PLWH (Chiao et al., 2013) and has also been used to assess recognition memory (see above in memory). For the CVLT-II Trial 5, participants are given a list of 36 words (10-15 minutes after the first part of the exam; see Memory section above), two at a time, and are asked which word of the pair was on the original list (recognition memory and attention). Test-retest stability was found in PLWH (Duff et al., 2001). The Digit Span test measures auditory-focused attention and working memory. Participants are asked to repeat a series of numbers that was first read to them (The Psychological Corporation, 1997). The examiner tries a string, which is one digit more than the previous list, and continues to ask the

participant to repeat the series of numbers in that order (forward trial). The backward trial of the Digit Span is a test that measures working memory and the ability to manipulate information presented. In the backwards trial, participants are asked to repeat the series in reverse order. For example, if a list of numbers is 1-2-3-4-5, the participant is asked to repeat this list backwards (5-4-3-2-1). Higher scores indicate that the participant can remember a longer series of numbers. The variable of interest was the forward trial. The majority of Alzheimer's Disease Research centers utilize this test to assess attention (Weintraub et al., 2009). The Digit Span test is derived from the Wechsler Memory scale-revised and two scores are derived: one is the total trials and the other is the longest digit sequence (span) (Weintraub et al.). The validity and reliability of this test has not been assessed in PLWH.

A neuropsychological battery assesses multiple domains of cognitive function, and the most common domains used in Alzheimer's disease research centers and in PLWH include: memory, executive function, psychomotor speed, visuospatial skills, motor skills, and attention (Heaton et al., 2011; Weintraub et al., 2009). Memory tests differentiate between normal aging, Alzheimer's Disease, and HIV/AIDS-associated dementia (Weintraub et al.). However, the discriminant power is lost for detecting Alzheimer's Disease because of the decline to floor levels of participants with Alzheimer's disease. Tests of attention, executive function, and word fluency are used to address this effect. Furthermore, executive function deficits have been cited to predict the progression of mild cognitive impairment to Alzheimer's Disease (Albert, Moss, Albert, Tanzi, & Jones, 2001). For this research study, clinical assessment of cognitive function is assessed within the domains of memory, executive function, psychomotor speed, visuospatial speed, motor function, attention, and other domains, including mathematical comprehension and syntax comprehension (see Table 2).

Neuropsychological Global Composite operational definition. Raw test scores were converted to percentiles and t-scores, based on multiple normative datasets including the Neuropsychological Assessment Battery manual (Stern & White, 2003) and the Memory and Aging Center at UCSF (with age gender and education-matched controls at the Alzheimer's Disease Research Center). The scores for the CVLT-II (delayed and immediate recall trials) was based on a normative, dataset published by Delis et al. (2001). The scores for the Story Recall, Trails A and B, Digit Span (forwards and backwards), and the WAIS Digit Symbols test was based on a normative dataset published by Weintraub (2009). The Benson Figure (delayed recall), Modified Trails, Stroop interference, Lexical fluency (d words), Stroop color naming, VOSP, Benson figure copy, and the Grooved pegboard was based on a normative, unpublished dataset at the UCSF Memory and Aging Center. The scores for the Modified Trails also utilized a normative dataset published by Kramer et al. (2003). Lastly, the scores for the finger tapping test was based on a normative dataset published by Heaton et al. (Heaton, 2004). Z scores were calculated based on the normative data.

For the purpose of this dissertation, the Neuropsychological Global Composite was used for final calculations. The Neuropsychological Global Composite is the average of all the single neuropsychiatric tests' Z-score values (see Table 2).

Neuropsychological Global Composite validity and reliability. Limitations to the overall validity of neuropsychological test summaries include the low capability to distinguish among different causes of performance impairment and some tests although never developed as neuropsychological assessments, have become useful to assess cognitive function (Reitan & Wolfson, 2001). Furthermore, each research center uses a unique subset of customized batteries that the customized batteries lack psychometric data (Faust, Ziskin, & Hiers, 1991), though some

of the individual tests have specific psychometric data. This leads to limitations in the overall validity and reliability of neuropsychological test summaries from customized batteries.

Medical Outcomes Survey-HIV (MOS-HIV). The Medical Outcomes Survey-HIV (MOS-HIV) was designed to measure the health-related quality of life in PLWH; the MOS-HIV is a 35-item instrument that assesses well-being and functioning with 10 subscales. The 10 subscales to the MOS-HIV are as follows: Health transition, Social functioning, Role functioning, Bodily pain, Physical functioning Energy/ vitality/ fatigue, Cognitive function, Health perception, Health distress, and Mental health.

The MOS-HIV 20-item short form was developed to be of practical use in most clinical settings. However, it does not include all the dimensions of health relevant to HIV such as energy, distress (specifically to health problems), and cognitive function (Wu et al., 1991). Hence for this study, the MOS-HIV in its full form was used.

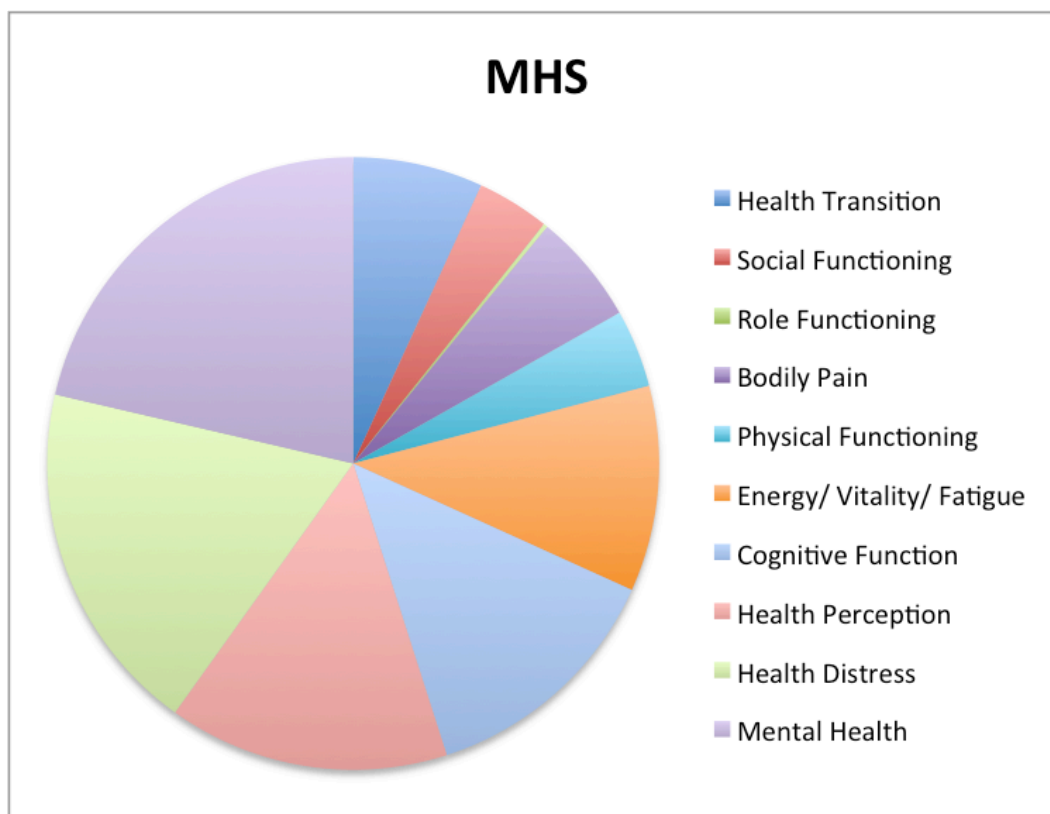


Figure 3: Medical Outcomes Survey-HIV Instrument. Subscales to Mental Health Summary score (MHS)

For the MOS-HIV, the final score ranges from 0-165 (higher number indicative of more complaints/poorer condition). Questions are based on Likert scales, while 2 questions are dichotomous (yes/no). Questions were drawn from a large pool of existing questions drawn from the Medical Outcomes Study, a large multi-site study to assess the effects of ways to deliver medical care (Wu et al., 2004). The ten domains of the MOS-HIV comprise a component of the Mental Health Summary (MHS) score (Figure 3) and the Physical Health Summary (PHS) score (Figure 4). Each domain contributes to both scores, with different subscales loading more or less on either of the summary scores (PHS or MHS) (see Figure 5).

MOS-HIV conceptual definition. Quality of life considers 10 dimensions of health status including health transition, social function, role function, bodily pain, physical function, energy/ vitality/ fatigue, cognitive function, health perception, health distress, and mental health.

MOS-HIV operational definition. Scores for each domain were calculated and transformed linearly to a 0-100 scale with 0 indicating the lowest possible score (self-report of poorer health) and 100 indicating the highest possible score (self-report of better health). When half or more than half of the items were missing, the scale score was set to missing. When less than half of the items were missing, values were imputed using mean substitution. This was done in accordance to the MOS-HIV manual (Wu, 1999).

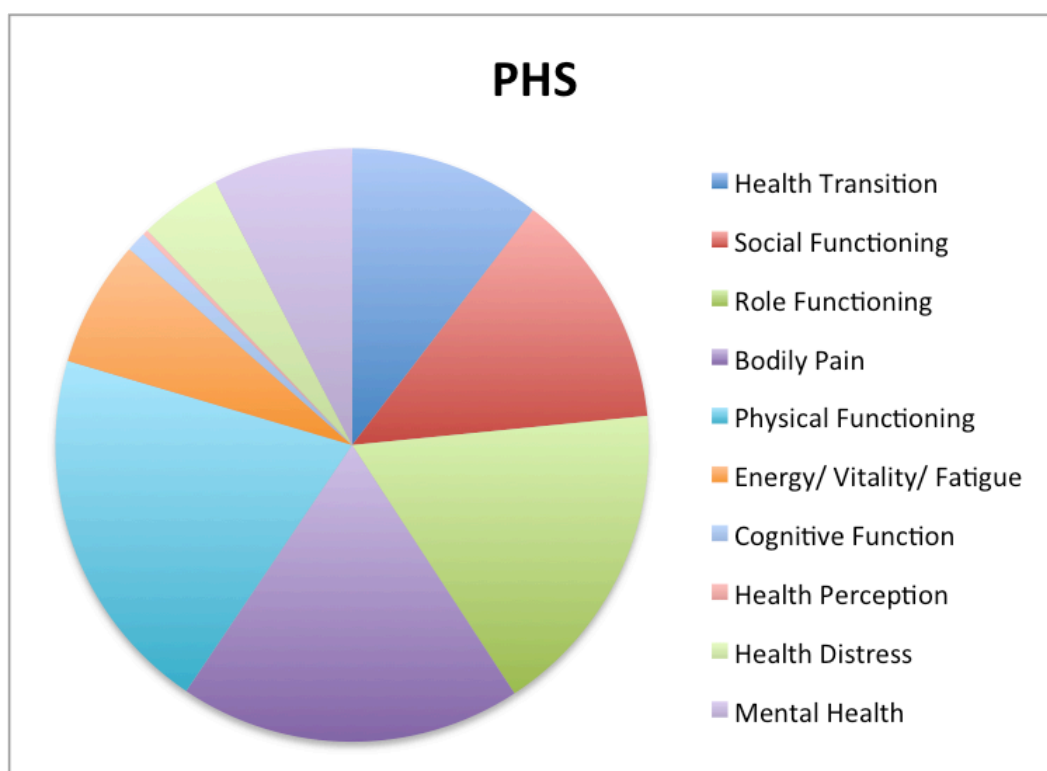


Figure 4: Medical Outcomes Survey-HIV Instrument. Subscales to the Physical Health Summary Score (PHS)

For the MOS-HIV instrument, physical health (PHS) and mental health (MHS) factors were derived based on exploratory and confirmatory factor analyses of MOS-HIV data from over 2,500 participants with HIV disease (Wu, Revicki, Jacobson, & Malitz, 1997). All ten subscales contributed to both the MHS and the PHS summary scores although each to different degrees (Figure 5). For the physical health summary (PHS) score, the physical function, pain and role

function scale scores loaded most strongly. For the mental health summary score (MHS) score, the mental health, health distress, health transition or changes in health status and cognitive function scales loaded most strongly. The vitality, general health and social function scales contributed to both factors.

To analyze the instrument, the 10 subscales were scored as summated rating scales with a range from 0-100 (higher scores indicate better health). For multi-item scales (two or more items), mean substitution was used for missing items if no more than 50% of the items are missing. If more than 50% of the items are missing, the participant's data were considered incomplete.

The MOS-HIV includes 35-items to evaluate ten dimensions of health: pain (PN), physical functioning (PF), social functioning (SF), role functioning (RF), mental health (MH), general health (GH) perceptions, energy/vitality/fatigue (VT), health distress (HD), cognitive function (CF), and health transition (QL) (Trepanier et al., 2005; Wisniewski et al., 2005; Wu et al., 1997). The range of each subscale is unique to the subscale and reverse scores were used where necessary. MH_Z is the Z-score for mental health and ranges from 5-30. HD_Z is health distress and ranges from 4-24. QL_Z is health transition and ranges from 1-5. CF_Z is cognitive function and ranges from 4-24. VT_Z is energy/ vitality/ fatigue and ranges from 4-24. PF_Z is physical functioning and ranges from 6-18. PN_Z is bodily pain and ranges from 2-11. RF_Z is role functioning and ranges from 2-4. SF_Z is social functioning and ranges from 1-6. GH_Z is health perception and ranges from 5-25. Scores for each scale were then transformed to dimensions of 0-100. For each scale, the z-score transformation was calculated to standardize the scores based on a normative dataset of the Roche patient population, corrected for age,

education, and gender (Wu, 1999; Wu et al., 1997; Wu et al., 1991). The following equations were used for each subscale:

$$\begin{aligned} PF_Z &= (PF - 80.4395425) / 24.2176719 \\ GH_Z &= (GH - 56.792402) / 24.550145 \\ PN_Z &= (PN - 64.7941176) / 28.8807702 \\ RP_Z &= (RP - 73.1371549) / 40.7722411 \\ SF_Z &= (SF - 84.6862745) / 21.2559432 \\ MH_Z &= (MH - 69.2284314) / 18.8444325 \\ VT_Z &= (VT - 62.130719) / 20.3233407 \\ HD_Z &= (HD - 71.1437908) / 24.0487778 \\ CF_Z &= (CF - 83.5147059) / 20.4626273 \\ QL_Z &= (QL - 69.1421569) / 19.7661596 \end{aligned}$$

Next, the PHS and MHS summary scores were computed using the scoring coefficients based on a normative dataset of the Roche patient population (Wu, 1999; Wu et al., 1997; Wu et al., 1991). The transformed scale scores were multiplied by the scoring coefficients and aggregated. The formulas for calculating PHS and MHS were:

$$\begin{aligned} PHS &= (MH_Z * -.13017) + (HD_Z * -.07680) + (QL_Z * -.00504) + (CF_Z * .01866) + \\ & (VT_Z * .11785) + (PF_Z * .34370) + (PN_Z * .31854) + (RF_Z * .29617) + \\ & (SF_Z * .22165) + (GH_Z * .17829) \end{aligned}$$

$$\begin{aligned} MHS &= (MH_Z * .31592) + (HD_Z * .27676) + (QL_Z * .21939) + (CF_Z * .19615) + \\ & (VT_Z * .16052) + (PF_Z * -.06072) + (PN_Z * -.08665) + (RF_Z * -.00325) + \\ & (SF_Z * .05690) + (GH_Z * .10158) \end{aligned}$$

The summary scores were then transformed to have a mean of 50 with a standard deviation of 10. The final summary score was calculated as follows (Wu, 1999):

$$\begin{aligned} \text{Physical Health Summary Score} &= 50 + (PHS * 10) \\ \text{Mental Health Summary Score} &= 50 + (MHS * 10) \end{aligned}$$

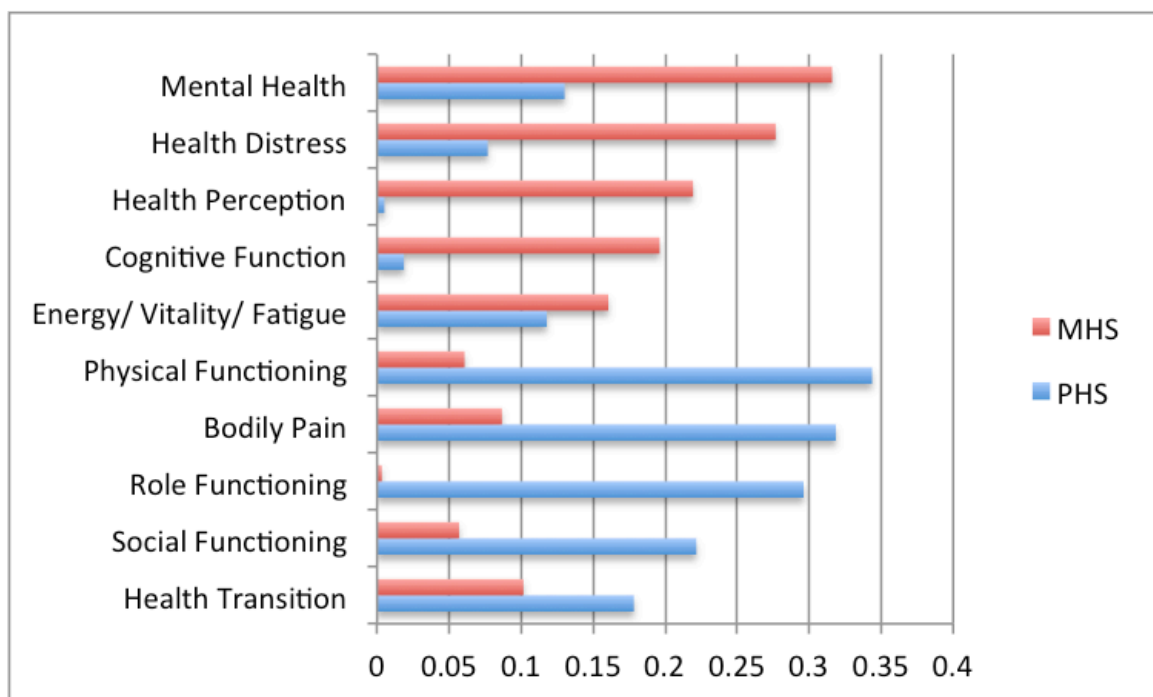


Figure 5: Medical Outcomes Survey-HIV Instrument. Relative Weights of Subscales for Physical Health Summary (PHS) score and Mental Health Summary (MHS) score

MOS-HIV validity and reliability. The MOS-HIV scales have good reliability and valid scores (Cronbach's $\alpha > 0.78$) for people across different stages of HIV, with lower reliability scores for Role Function (Cronbach's $\alpha = 0.50$) (Wu et al., 1997). The SF-20 and SF-36 also have been used in conjunction with the MOS-HIV, though authors have found that the instruments provide no difference in the HRQOL scores for PLWH (Shahriar, Delate, Hays, & Coons, 2003). Concurrent validity was validated for each scale using validation variables of CD4 count, lower scores with more severe disease, and moderate correlations with the overall quality of life score (Schifano et al., 2003). The concurrent validity analysis shows that all the scales had a significant ($p < 0.05$) positive correlation with the global quality of life question. The three scales of physical functioning, social functioning, and role-functioning showed significant negative correlations with the severity stage of the disease at baseline (Schifano et al., 2003).

Construct validity was established with exploratory and confirmatory factor analysis. Construct validity was conducted using two randomly selected subsample groups A and B in the population in the United States (Revicki et al., 1998). A factor analysis with oblique rotation was used to find that two scales (physical health and mental/emotional health) were correlated (Schifano et al., 2003). For the PHS, physical function, role function, and pain loaded the strongest and for the MHS, health distress, cognitive function, and quality of life loaded strongest. The magnitude of each domain loads differently for the PHS and MHS (see Figure 5). Negative values denote negative standard deviations of scores as calculated by the authors of the instrument (Wu et al., 1991).

Methods and Analysis Plan

Descriptive statistics were provided for all study variables in this secondary data analysis; Cronbach's alpha reliability coefficients to assess for internal consistency were calculated for the functional measures. Descriptive statistics, measures of central tendency, and all variables were reported. Data were analyzed using SPSS (Version 22). Definitions of the research question, independent variables and dependent variables were disclosed.

Multiple linear regressions were used to model relationships between two or more explanatory or independent variables and a response or dependent variable by fitting a linear equation to observed data. Covariates were used for specific aims 1 and 2, but were not used for specific aim 3 due to the given small sample size.

Linear regression equations were used to specify the relationship between the variables in the specific aims. Multiple linear regressions were used to control for covariates and to explore the relationship between the independent and dependent variables. The equation used is such that the mean value of the outcome variable (Y) for each specific combination of predictor variables

is a linear function of each predictor variable. The slope β is the rate of increase (+) or decrease (-) of Y for each unit increase in X_n . The error component E reflects the difference between an individual's observed response Y and the true average response.

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 \dots + \beta_n X_n + E$$

where n is the number of independent variables.

Research Question 1. What is the relationship between self-report and a clinical measure of cognitive function in older PLWH?

IV: Clinical measure of cognitive function (NTB Composite) (See Table 2), age, education

DV: Self-report cognitive function (PAOFI)

The equation used for this aim is as follows:

$$(\text{PAOFI}) = \beta_0 + \beta_1(\text{NTB Composite}) + \beta_2(\text{age}) + \beta_3(\text{education}) + E$$

The mean value of the PAOFI for each specific combination of predictor variables, including age, education, and NTB Composite, is a linear function of each predictor variable. The slope β is the rate of increase (+) or decrease (-) of the PAOFI score for each unit increase in each predictor variable (age, education, and NTB Composite). The error component E reflects the difference between an individual's observed response in PAOFI and the true average response.

Pearson correlations (first step) and multiple regression analyses (second step) was used to examine the relationship between clinical measure of cognitive function (NTB Composite) and self-report cognitive function (PAOFI). Initially, age and education was treated as potential confounding variables. Age and education was added to the model to adjust for potential confounding effects. Zero order correlations between the independent variable as measured by

Neuropsychological testing performance and the dependent variable as measured by PAOFI, as well as the inter-correlations between the variables (including age and education, if applicable), was examined. Then the overall R-squared and its significance, in addition to the unique contribution of the independent variable (IV) was assessed with its R-squared change value.

Research Question 2. How does depression, age, education, and a clinical measure of cognitive function relate to self-report cognitive function?

IV: Depressive symptoms (GDS), age, education, a clinical measure of cognitive function (NTB Composite) (See Table 1)

DV: Self-report cognitive function (PAOFI)

The equation used for this aim is as follows:

$$(\text{PAOFI}) = \beta_0 + \beta_1(\text{GDS}) + \beta_2(\text{NTB Composite}) + \beta_3(\text{age}) + \beta_4(\text{education}) + E$$

The mean value of the PAOFI for each specific combination of predictor variables, including age, education, depression, and NTB Composite, is a linear function of each predictor variable. The slope β is the rate of increase (+) or decrease (-) of PAOFI score for each unit increase in each predictor variable (age, education, depression, and NTB Composite). The error component E reflects the difference between an individual's observed response in PAOFI and the true average response.

Pearson correlations (first step) and multiple regression analyses (second step) was used to examine the relationship among depression (GDS), clinical measure of cognitive function (NTB Composite), and self-report cognitive function (PAOFI). Initially, age and education were treated as potential confounding variables. If there were no high correlations found with age and education, one or both variables were excluded for the final model. Age and education were added to the model to adjust for potential confounding effects. Zero order correlations among the

independent variables (GDS and NTB Composite) and the dependent variable (PAOFI), as well as the inter-correlations among the variables (including age and education, if applicable) were examined. The overall r-squared and its significance, in addition to the unique contribution of the independent variables (IV), was tested by assessing its r-squared change value.

Research Question 3. How does cognitive function (self-report and a clinical measure) and depression relate to HRQOL in older PLWH?

IV: Self-report cognitive function (PAOFI), a clinical measure of cognitive function (NTB Composite) (See Table 2), depression (GDS)

DV: HRQOL (MOS-HIV)

The equations used for this aim, as MOS-HIV has 2 subscales are as follows:

$$(PHS) = \beta_0 + \beta_1(PAOFI) + \beta_2(GDS) + \beta_3(NTB \text{ Composite}) + E$$

$$(MHS) = \beta_0 + \beta_1(PAOFI) + \beta_2(GDS) + \beta_3(NTB \text{ Composite}) + E$$

The mean value of the PHS or MHS (MOS-HIV instrument) for each specific combination of predictor variables, including self-report cognitive function, depression, and NTB Composite, is a linear function of each predictor variable. The slope β is the rate of increase (+) or decrease (-) of the PHS or MHS score for each unit increase in each predictor variable (self-report cognitive function, depression, and NTB Composite). The error component E reflects the difference between an individual's observed response in PHS or MHS and the true average response.

Pearson correlations and multiple regression analyses were used to examine the relationship between HRQOL (MOS-HIV), neuropsychological performance (NTB Composite), depression (GDS), and self-report of cognitive function (PAOFI). In the regression, Neuropsychological test performance, depression, and PAOFI were the independent variables

and the HRQOL subscale PHS and MHS were the dependent variables. Since the dependent variable HRQOL was measured in two subscales, two multiple regression analyses were conducted (MHS and PHS) (Wu et al., 2004; Wu et al., 1997).

Zero order correlations among the 3 independent variables and the dependent variables, as well as the inter-correlations among the variables, were tested. The overall r-squared and its significance, followed by the unique contribution of each IV by assessing its r-squared change value, was also assessed.

Rigor

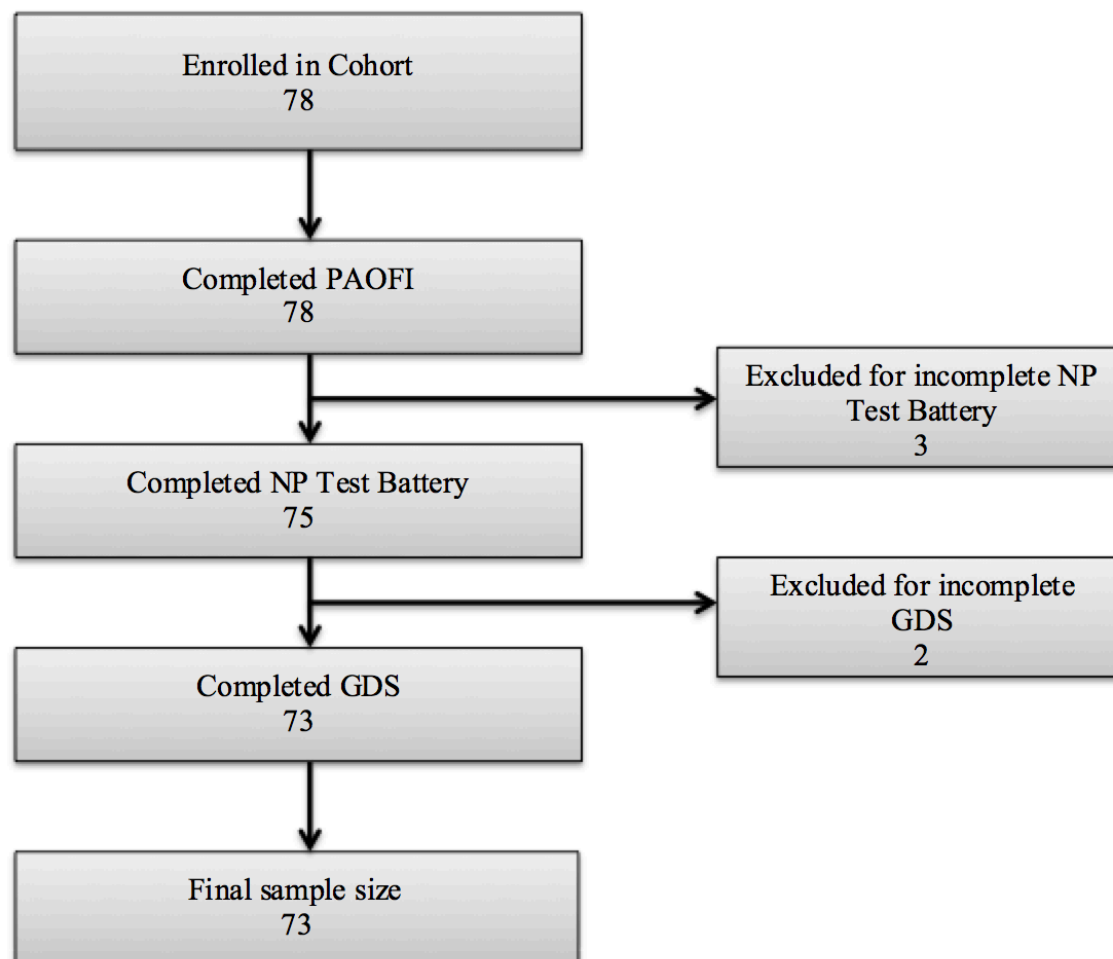
Internal validity was assessed when the statistical inferences about causal effects are valid for the population being studied. In this study, hypothesis tests and zero order correlations were conducted to assess the relationship among the different independent variables with the dependent variable. Thus, omitted variable bias and imprecise measurement of independent variables were prevented.

External validity was assessed when statistical inferences about causal effects can be generalized from the population and setting being studied to other populations and settings. In this study, the relationship among the independent variables can be generalizable to the older HIV population mainly of White race, but not to the general older population. The majority of this sample was from a White race and was highly educated, and thus this limits the external validity to the general older HIV population, particularly of racially/ethnically diverse backgrounds.

Chapter 4: Results

This chapter provides the results of the research findings. In addition to the description of the sample characteristics, the organization of this chapter corresponds to the three study aims. Specific aims 1 and 2 used one sample (Sample A) and specific aim 3 used another sample (Sample B). The final sample size for specific aims 1 and 2 was 73 (See Figure 1), while the final sample size for specific aim 3 was 32 (See Figure 2).

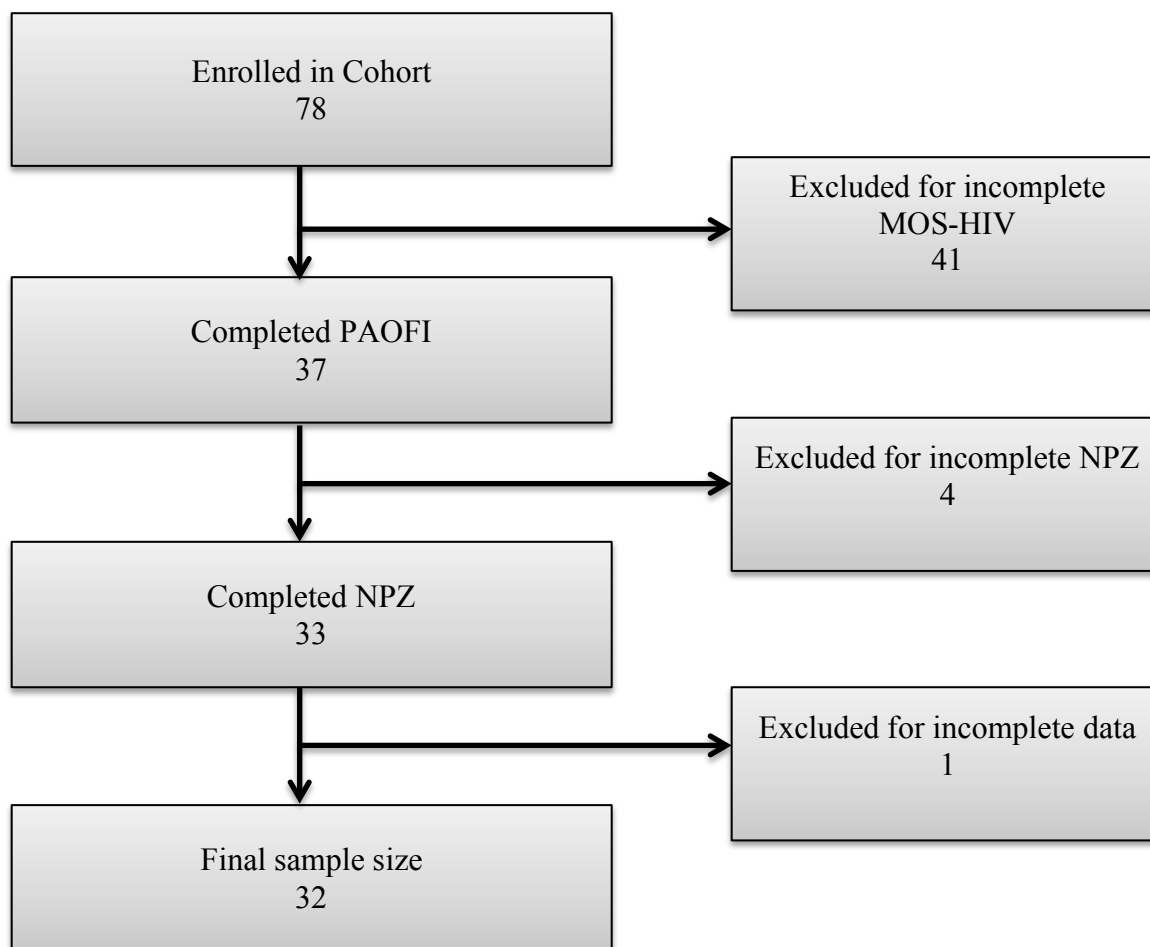
For sample A, seventy-eight participants met the inclusion criteria and four participants were excluded; three participants did not complete the Neuropsychological Test battery (NTB), and three additional participants did not complete the Geriatric Depression Scale (GDS). One refused to answer the GDS and the other two had > 50% missing answers. Therefore, seventy-five older PLWH completed the NTB, and the final number of participants included in the analysis was $n=73$ (Figure 1).



Note: NP= Neuropsychological
 GDS= Geriatric Depression Scale
 PAOFI= Patient's Assessment of Own Functioning Inventory

Figure 6: Sample A for Specific Aims 1 and 2

For sample B, thirty-seven participants met the inclusion criteria and three were excluded; two participants did not complete the GDS and one participant did not complete the Geriatric Depression Scale (GDS) and Neuropsychological Test Battery (NTB). These participants were a different sample population than those in sample A. The final number of participants included in the study was n=32.



Note: MOS-HIV= Medical Outcomes Survey-HIV
 NP= Neuropsychological
 GDS= Geriatric Depression Scale
 PAOFI= Patient's Assessment of Own Functioning Inventory

Figure 7: Sample B for Specific Aim 3

Sample characteristics for sample A

Demographics of sample A. An overview of the sample characteristics is presented in Table 3. The sample of 73 older persons living with HIV (PLWH) had a mean age of 66.7 years (SD= 4.5). The mean years of schooling was 16.3 years (SD= 2.4), with more than 60% of the sample reported some graduate school education. Thirty-percent of the sample completed some graduate school and 38.4% of them completed a graduate degree. The majority of the sample were males (87.7%) and White (93.2%). One hundred percent of the sample were HIV-positive.

Table 3: Demographic Characteristics for Sample A (n=73)

Characteristics	Participants
	<i>Mean (SD, range)</i>
Age	66.7 yrs (4.5, 60-84)
Education	16.3 yrs (2.4, 12-21)
	<i>n (percentage)</i>
Sex	
Male (%)	64 (87.7)
Female (%)	9 (12.3)
Race/ Ethnicity	
Black/ African American (%)	3 (4.1)
White/Caucasian (%)	68 (93.2)
Hispanic or Latino (%)	2 (2.7)
Education	
Some high school	0 (0)
High school Graduate	6 (8.2)
Some college/ trade school	9 (12.3)
College graduate	8 (11)
Some graduate school	22 (30.1)
Graduate school completed	28 (38.4)

Note: SD = Standard Deviation

HIV variable characteristics of sample A. Variable characteristics of the 73 participants are listed in Table 4. The mean CD4 cell count was 541.8 cells/mm³. The average years of living with HIV was 7 years. Participants scored below the standardized mean on the Neuropsychological test battery (NTB) (mean = -.39, SD=.64), including measures for executive function (mean = -.37, SD=.80). The mean score for the 30-item Geriatric Depression Scale (GDS) was 8.71 (SD= 7.31), and the mean score for the Patient's Assessment of Own Functioning Inventory (PAOFI) was 1.01 (SD= .68).

Table 4: HIV Variable Characteristics (n=73)

Characteristic	Participants		
	<i>Mean</i>	<i>SD</i>	<i>Range</i>
CD4 counts	541.8	243.8	-9 – 1069
Years HIV-positive	7.0	20.0	1 – 35
NP test-executive function	-.37	.80	-2.55 – 1.52
NP test- summary score	-.39	.64	-2.15 – 1.29
GDS	8.71	7.21	0 – 28
PAOFI	1.01	.68	0 – 3.12

Notes: SD= Standard Deviation

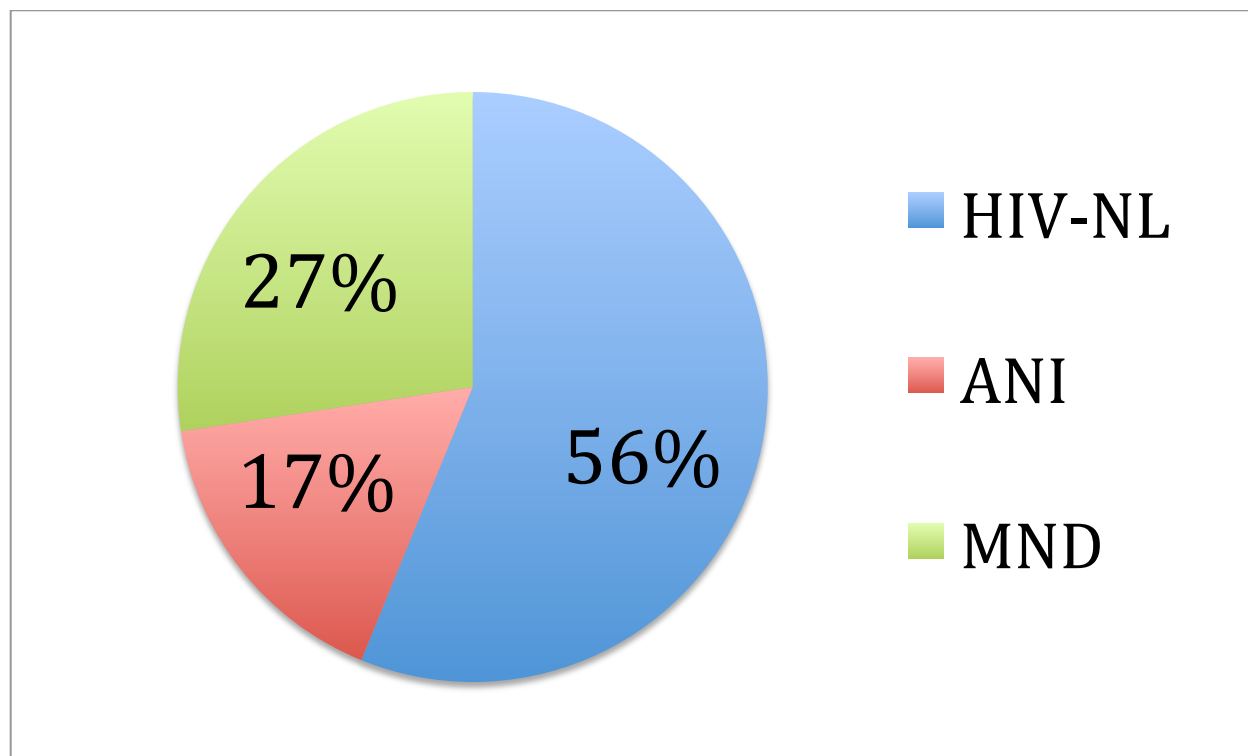
NP= Neuropsychological

GDS= Geriatric Depression Scale

PAOFI= Patient's Assessment of Own Functioning Inventory

All variables analyzed using independent t-tests.

HAND diagnostic criteria for sample A. The HAND diagnostic criteria groups are presented in Figure 1. In the sample of 73 older PLWH, 56% of the sample were HIV-normal (HIV-NL), 17% of the sample were classified as having Asymptomatic Neurocognitive Impairment (ANI), and 27% as having Mild Neurocognitive Disorder (MND). No one in the sample was classified as having HIV-Associated Dementia (HAD).



Note: HIV-NL= HIV-Normal (n=41, 56%)

ANI= Asymptomatic Neurocognitive Impairment (n=12, 17%)

MND=Mild Neurocognitive Disorder (n=20, 27%)

Figure 8: Cognitive characterization of older PLWH age 60 and older. Frequency of HAND in the HIV-population age 60 and older (%), n=73

Demographic characteristics by HIV-Associated Neurocognitive Disorders.

Demographic characteristics by HIV-Associated Neurocognitive Disorders (HAND) diagnostic groups are listed in Table 3. The differences among the three groups were not significant on age, education, years with HIV, and CD4 count. The sample average age was 66 years for those HIV-normal and ANI, while PLWH with MND was 67 years. Those who were HIV-NL had a higher sample mean level of education (mean= 16.7 years, SD= 2.17), compared to the ANI group (mean= 15.7 years, SD= 2.39) and the MND group (mean= 15.9 years, SD= 2.65). The sample mean years living with HIV for those who were HIV-normal (mean= 20.8 years, SD=7) and

those with MND (mean= 20.5 years, SD=6.7) were longer compared to those with ANI (mean= 16.8 years, SD=6.8). CD4 cell count sample means were lowest in the MND group (mean= 474 cells/mm³, SD= 214 cells/mm³), followed by the ANI group (mean= 513 cells/mm³, SD= 219 cells/mm³). CD4 in the HIV-Normal group (mean= 583 cells/mm³, SD= 214 cells/mm³) was highest compared to the other groups.

Table 3. Demographics by HAND (n=73)

Characteristics (SD, range)	HAND diagnostic criteria (n, %)		
	HIV-Normal (41, 56.2)	ANI (12, 16.4)	MND (20, 27.4)
Age ^a (years)	66.5 (4.3, 60-84)	66.4 (5.6, 62-82)	67.4 (4.3, 62-80)
Education ^a (years)	16.73 (2.17, 12-21)	15.67 (2.39, 12-19)	15.9 (2.65, 12-21)
Years with HIV ^a (years)	20.8 (7.0, 1-35)	16.8 (6.8, 7-27)	20.5 (6.7, 3-28)
CD4 count ^a (cells/mm ³)	583.1 (214.9, 130-1000)	513.1 (219.4, 278-1000)	474.2 (302.0, 0-1069)

Notes: SD= Standard Deviation

HAND= HIV-Associated Neurocognitive Disorders

ANI= Asymptomatic Neurocognitive Impairment

MND=Mild Neurocognitive Disorder

Continuous variables analyzed using independent t-tests.

^a Not statistically significant at 0.05

Measurement tools by HIV-Associated Neurocognitive Disorders groups.

Participants' scores on measurement tools based on HAND diagnostic groups are presented in Tables 4 and 5. One-way ANOVA was used to compare the three groups (HIV-normal, ANI, and MND) on PAOFI scores, depression symptoms on the GDS, Neuropsychological test battery (NTB) composite, and NP executive function scores. There were statistically significant differences among the three groups on the four variables.

A Bonferroni correction for the 3 pairwise comparisons, among the three HAND diagnostic groups, was performed, resulting in a significance criterion of $p=.0167$ ($.05/3$). The

significant pairwise contrasts are shown in Table 4. For the NTB Composite, the HIV-Normal group scored significantly better than both the ANI and MND groups. The ANI and MND groups were not significantly different from each other. This pattern of differences was also seen for the NP test for executive function. For the PAOFI, the HIV-Normal and ANI groups had significantly fewer cognitive complaints than the MND group. The HIV-normal and ANI groups were not significantly different from each other. For the GDS, the HIV-normal and ANI groups reported less depression than the MND group. The HIV-normal and ANI groups were not significantly different from each other. NP Test Battery Composite scores grouped by HAND diagnostic groups are also shown in Figure 3.

Table 4. Scores on Measurement Tools Stratified by HAND Diagnostic Groups (N=73)

Tool Mean (SD)	HAND Diagnostic Criteria			Overall p-value	Significant Pairwise contrasts
	1. HIV- Normal	2. ANI	3. MND		
NTB Composite	-0.04 (0.51)	-0.97 (.35)	-0.78 (.54)	< .001*	1 > 2 & 3
NP test Executive	-0.02 (.68)	-0.90 (.46)	-0.77 (.83)	< .001*	1 > 2 & 3
PAOFI mean	.83 (.54)	.88 (.68)	1.47 (.74)	.002*	1 & 2 > 3
GDS	6.95 (6.55)	7.00 (5.54)	13.35 (7.58)	.002*	1 & 2 < 3

Notes: *Statistically significant at 0.01

SD= Standard Deviation

NP= Neuropsychological

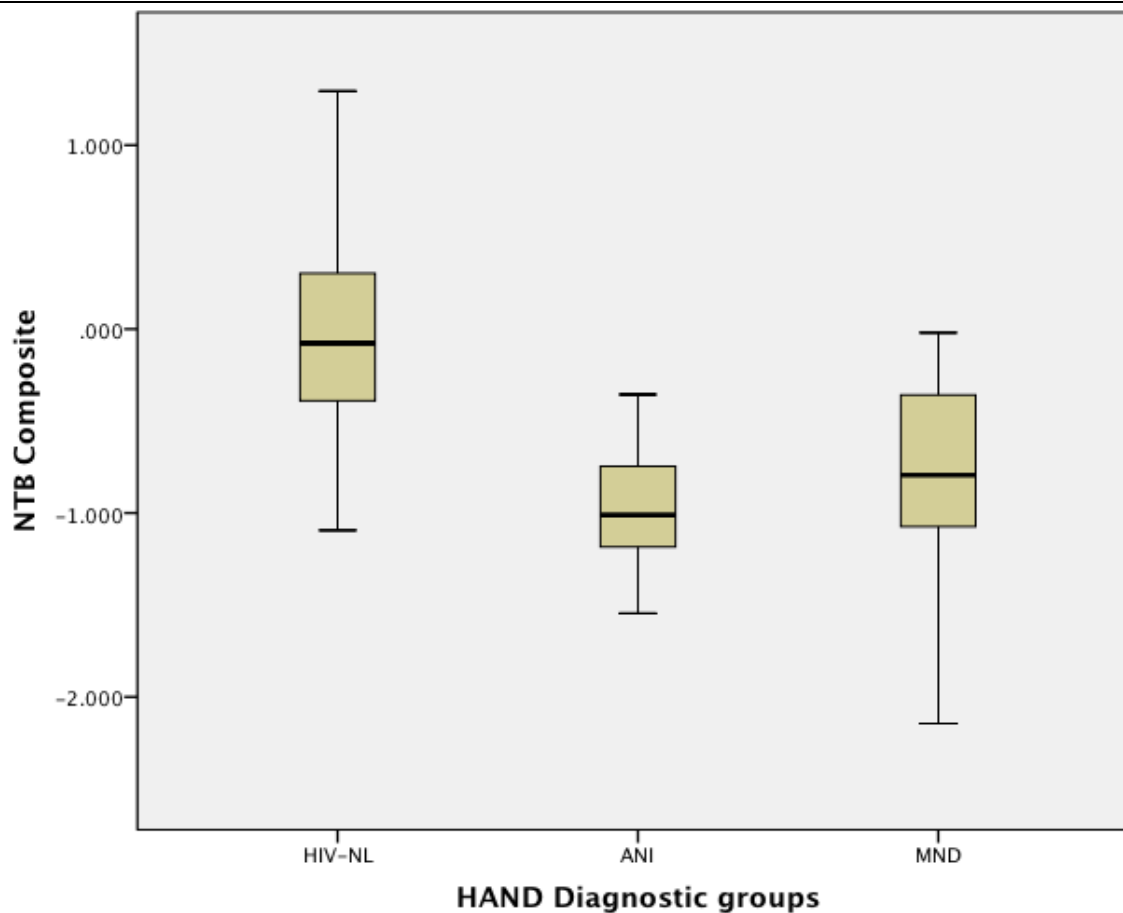
GDS= Geriatric Depression Scale

PAOFI= Patient's Assessment of Own Functioning Inventory

HAND= HIV-Associated Neurocognitive Disorders

ANI= Asymptomatic Neurocognitive Impairment

MND=Mild Neurocognitive Disorder



HAD= HIV/AIDS Associated Dementia

All variables analyzed using independent t-tests.

* Statistically significant at 0.05

Note: HAND= HIV/AIDS Associated Neurocognitive Disorders

HIV-NL= HIV-Normal

ANI= Asymptomatic Neurocognitive Impairment

MND=Mild Neurocognitive Disorder

Figure 9: Neuropsychological Test Battery Composite by HAND diagnostic groups

Covariates of gender, education, CD4 counts, and years living with HIV were included in the regression analysis to control for confounding variability. All these covariates were not significant contributors. A one-way ANOVA was completed for quantitative variables (Table 4) and a chi-square test was completed for categorical variables (Table 5), and a p-value <.05 was considered statistically significant.

Chi-square analysis

Chi-square analysis was completed for the categorical variables of gender, ethnicity, and educational groups. The overall Chi-square indicated a significant difference among the groups for gender (see Table 8). However, none of the post-hoc pairwise comparisons (Bonferroni alpha) were statistically significant, because sample sizes were too small (See Table 9). Due to sample results, the MND group had a higher percentage of females compared to the other two groups (HIV-NL and ANI).

A Bonferroni correction for 3 comparisons (among 3 HAND diagnostic groups) was done at a $p=.0167$ ($.05/3$) significance, as calculated by other researchers (Kallianpur et al., 2013). Chi-square values are found in Table 5. Overall Chi-square indicated a difference somewhere with gender. However, none of the post-hoc pairwise comparisons (Bonferroni) were statistically significant, because sample sizes are too small. However, looking at sample results, Group 3 (PLWH with MND) had a higher percentage of females compared to the other two groups. But we cannot claim a statistical difference (0% vs 30%). Post hoc pairwise contrasts did not uncover any statistically significant differences in gender between the sets of two groups (1 vs 2, 1 vs 3, or 2 vs 3). However, when the HIV-Normal (group 1) and ANI (group 2) groups were combined and compared to the MND (group 3) group, there was a statistically significant difference in gender (see Table 5). Three of the 53 Group 1 and 2 patients (5.7%) were female. Six of the 20 Group 3 patients were female (30.0%). The difference between the 5.7% and the 30.0% was significant at $p=.011$.

Table 5: Chi-square values among HAND diagnostic groups

% (n)	HAND diagnostic groups			Overall p-value	Significant pairwise contrasts (by groups)
	Group 1 HIV-NL	Group 2 ANI	Group 3 MND		
Gender*				.013	
Male	92.7 (38)	100.0 (12)	70.0 (14)		
Female	7.3 (3)	0 (0)	30.0 (6)		(1+2) < 3
Race/Ethnicity				.777	
White/ Caucasian	95.1 (39)	91.7 (11)	90.0 (18)		
Black/ African American	2.4 (1)	8.3 (1)	5.0 (1)		
Hispanic/ Latino	2.4 (1)	0 (0)	5.0 (1)		
Educational Group				.053	
High school Graduate	7.3 (3)	16.7 (2)	5.0 (1)		
Some college/ trade school	2.4 (1)	8.3 (1)	35.0 (7)		
College graduate	9.8 (4)	16.7 (2)	10.0 (2)		
Some graduate school	39.0 (16)	25.0 (3)	15.0 (3)		
Graduate school completed	41.5 (17)	33.3 (4)	35.0 (7)		

Note: *Significant at $p < .05$

HAND= HIV/AIDS Associated Neurocognitive Disorder

HIV-NL= HIV-Normal

ANI= Asymptomatic Neurocognitive Impairment

MND=Mild Neurocognitive Disorder

Gender. Chi-square analysis was completed for the association between gender and HAND diagnostic groups. The assumption for the goodness-of-fit is violated because 2 cells had an expected count less than 5 (33%) and thus the likelihood ratio was used. A chi-square test for independence (with the likelihood ratio) indicated a significant association between gender and the HAND diagnostic groups overall, $\chi^2 (1, n=73) = 8.62, p = .013$, Kendall's tau-b = .24.

There were no significant differences found between the groups when a chi-square analysis was completed for gender; values are found in Table 6. The proportion of males who

were HIV-NL or had ANI are not significantly different from the proportion of females who were HIV-NL or had ANI, $\chi^2 (1, n=53) = .65, p = .799$. The proportion of males who were HIV-NL or had MND are not significantly different from the proportion of females who were HIV-NL or had MND, $\chi^2 (1, n=53) = 3.84, p = .05$. The proportion of males who had ANI or MND are not significantly different from the proportion of females who had ANI or MND, $\chi^2 (1, n=53) = 2.68, p = .102$. Though there were more females in the group of PLWH with MND, we cannot claim a statistical difference between the two groups.

Table 6: Gender comparisons between HAND diagnostic groups

Groups	n	χ^2 ^a	p
1 to 2	n=53	.065	.799
1 to 4	n=61	3.84	.05
2 to 4	n=32	2.68	.10

^aPearson's χ^2

Group 1: HIV-Normal

Group 2: Asymptomatic Neurocognitive Impairment

Group 4: HIV/AIDS Associated Dementia

Race/Ethnicity. Chi-square analysis was completed for the association between ethnicity and HAND diagnostic groups. The assumption for the goodness of fit is violated because 6 cells had an expected count less than 5 (66.7%) and thus the likelihood ratio was used. A chi-square test for independence (with the likelihood ratio) revealed no significant association between ethnicity and HAND diagnostic groups, $\chi^2 (1, n=73) = 1.78, p = .78$.

Educational groups. Chi-square analysis was completed for the association between educational groups and HAND diagnostic groups. The assumption for the goodness-of-fit is violated because 10 cells had an expected count less than 5 (66.7%) and thus the likelihood ratio was used. A chi-square test for independence (with the likelihood ratio) revealed no significant association between educational groups and HAND diagnostic groups, $\chi^2 (1, n=73) = 15.31, p = .053$.

Results for Specific Aim 1

What is the relationship between self-report and a clinical measure of cognitive function in older PLWH? Does this relationship change if age and education are included in the model?

Correlations between the variables are found in Table 7. Age and education were treated as potential confounding variables. As seen in Table 7, the composite score for the Neuropsychological test battery (NTB) was negatively correlated to Patient's Assessment of Own Functioning Inventory (PAOFI) ($r=-.21$, $p=.07$). As NTB scores increased, PAOFI scores tended to decrease. Considered by itself, NTB explains approximately 4.6% of the variance in PAOFI. As seen in Table 7, age and education were not highly correlated to PAOFI. Age and education were highly correlated with each other, such that higher levels of education were associated with younger age ($p=.01$).

Table 7: Correlations among PAOFI and NTB, age, and education (n=73)

Scale	PAOFI	NTB	Age
PAOFI			
NTB	-.21	-	
Age	-.03	.01	-
Education	-.08	.13	-.30*

Notes: *Significant at $p < .05$

Dependent Variable: PAOFI

PAOFI= Patient's Assessment of Own Functioning Inventory

NTB= Neuropsychological Test Battery

Multiple linear regression analysis was conducted in which NTB, age, and education were entered simultaneously into the model. Preliminary analyses were conducted to ensure no violation of the assumptions of normality, linearity, multicollinearity, and homoscedasticity were present. Although the correlations of age and education with PAOFI were small and insignificant, they were added to the multiple linear regression model to see if their inclusion

affected the relationship between NTB and PAOFI (see Table 8). With age and education in the model, NTB still has a small but not significant relationship with PAOFI. In the regression, NTB uniquely accounts for 4.2% of the variance in PAOFI, after controlling for the effects of age and education.

Table 8: Multiple Regression Summary, Overall $R^2=.05$, $p=.31$

N=73	B	S.E.	t	p	95% CI for B		R ² change
					Lower	Upper	
NTB	-.22	.13	-1.74	.09	-.47	.03	.042
Age	-.01	.02	-.42	.67	-.05	.03	.003
Education	-.02	.04	-.52	.61	-.09	.05	.004

Note: Dependent variable: Patient's Assessment of Own Functioning Inventory total score
 NTB= Neuropsychological Test Battery
 GDS= Geriatric Depression Scale

Reliability for the PAOFI. An item analysis was completed for each item of the subscale in this patient population. Cronbach's alpha was conducted on the original 78 participants in the study (see Figure 1). Cronbach's alpha for the PAOFI was .91, which indicated a high level of internal consistency for the scale with this specific sample. An item-total statistics was conducted for the entire tool and the four subscales: (1) memory, (2) language and communications, (3) sensory and motor function, and (4) higher level and intellectual functions. The validity and reliability of the PAOFI tool has not been studied in PLWH, and this researcher conducted a corrected item-total analysis for the PAOFI in this sample population of older PLWH.

The corrected item-total correlation for the 33 items ranged from .318 for question #20 (part of the sensory and motor subscale) to .730 for question #2 (part of the memory subscale). Because the corrected item-total correlation was .318 for question #20, if this item was removed,

Cronbach's alpha would be .940. But because the Cronbach's alpha for the entire tool was high (Cronbach's alpha =.94), the researcher did not remove any items for this study.

Three of the four subscales of the PAOFI had Cronbach's alpha $>.80$. Sensory and motor skills had the lowest Cronbach's alpha score and this subscale was found to not be reliable in this population. This subscale also had the least number of items (3 items) and assessed functionality of the right and left hand. These questions did not adjust for a participant being right-hand dominant or left-hand dominant, which may have altered the participants' answers to the questions.

Memory. For the memory subscale, there were a total of 10 items. All 78 participants answered all the questions for memory. The total Cronbach's alpha for this subscale was .91. The removal of any one of the 10 questions would lower the Cronbach's alpha to the lowest value of .90. The corrected item-total correlation for the 10 items ranged from .46 for question #8 to .77 for question #2.

Language and communications. For the language and communications subscale, there were a total of 9 questions. Two participants were excluded because they did not answer all the questions. The total Cronbach's alpha for this subscale was .83. The removal of any one of the 9 questions would lower the Cronbach's alpha to the lowest value of .80. The corrected item-total correlation for the 9 items ranged from .39 for question #14 to .65 for question #18.

Sensory and motor function. For the motor function subscale, there were a total of 5 questions. One participant was excluded because he/she did not answer all the questions. The total Cronbach's alpha for this subscale was .68. The removal of any one of the 5 questions would lower the Cronbach's alpha to the lowest value of .55. The corrected item-total correlation for the 5 items ranged from .18 for question #20 to .66 for question #23. Since the corrected

item-total correlation was low for question #20, removing this question may increase the Cronbach's alpha for this subscale to a .74.

Higher level and intellectual functions. For the higher level and intellectual function subscale, there were a total of 9 questions. Three participants were excluded because they did not answer all the questions. The total Cronbach's alpha for this subscale was .90. The removal of any one of the 9 questions would lower the Cronbach's alpha to the lowest value of .88. The corrected item-total correlation for the 9 items ranged from .61 for question #28 to .80 for question #33.

Total PAOFI score. For the total PAOFI score, there were a total of 33 questions. Six participants were excluded because they did not answer all the questions and answered less than 50% of the questions. The total Cronbach's alpha was .94. The removal of any one of the 33 questions would lower the Cronbach's alpha to the lowest value of .94. The corrected item-total correlation for the 33 items ranged from .32 for question #20 (part of the sensory and motor subscale) to .73 for question #2 (part of the memory subscale).

Results for Specific Aim 2

What is the relationship between depression, age, education, and a clinical measure of cognitive function with self-report cognitive function in older PLWH?

Pearson correlations (first step) and multiple regression analyses (second step) were used to examine the relationship between age, education, depression, clinical measure of cognitive function (Neuropsychological Test battery) with self-report cognitive function (PAOFI). Age and education were treated as potential confounding variables. As seen in Table 9, age and education were significantly correlated ($r = -.30, p = .01$). As participants were older in age, they had fewer

years of education. Furthermore, depression and PAOFI were significantly associated ($r=.61$, $p<.001$). As depression increased, participants' complaints of cognitive function also increased.

Table 9: Correlations among PAOFI and NTB, depression, age, and education (n=73)

Scale	PAOFI	NTB	Age	Education
PAOFI				
NTB	-.21	-		
Age	-.03	.01	-	
Education	-.08	.13	-.30*	-
Depression	.61**	-.16	-.11	.06

Notes: * Significant at $p<.05$

** Significant at $p<.01$

Dependent Variable: PAOFI

PAOFI= Patient's Assessment of Own Functioning Inventory

NTB= Neuropsychological Test Battery

Multiple linear regression analysis was run in which age, education, NTB, and depression were entered simultaneously into the model (see Table 10). Preliminary analyses were conducted to ensure no violation of the assumptions of normality, linearity, multicollinearity, and homoscedasticity were present. In the regression, NTB was not significant in the model, and NTB explained only 1.1% of the variance in PAOFI, after controlling for the effects of depression, age, and education. Depression as assessed by the GDS uniquely and significantly accounts for 33.9% of the variance in PAOFI, after controlling for the effects of age, education, and NTB ($p<.001$). Higher depression scores were strongly related to more complaints in cognitive impairment.

Table 10: Multiple Regression Analysis for Specific Aim 2, $R^2=.39$, $p<.001$

N=73	B	S.E.	t	p-value	95% CI for B		R ² change
					Lower	Upper	
Age	.01	.02	.06	.95	-.03	.03	.000
Education	-.03	.03	-.91	.37	-.08	.03	.007
GDS*	.06	.01	6.14	<.001	.04	.07	.339
NTB Composite	-.12	.10	-1.12	.27	-.32	.09	.011
Constant	.87	1.24	.70	.49	-1.61	3.34	

Note: *Significant at $p < .05$

Dependent variable: Patient's Assessment of Own Functioning Inventory total score

NTB= Neuropsychological Test Battery

GDS= Geriatric Depression Scale

Results for Specific Aim 3

Demographics of sample B. An overview of the sample characteristics is presented in Table 11. The sample of 32 older persons living with HIV (PLWH) had a mean age of 69.7 years (SD= 4.9). The mean years of schooling was 16.3 years (SD= 2.1), with more than 70% of the sample who reported a graduate school level education. Thirty-three percent of the sample had gone through some graduate school and 37.5% of them completed a graduate degree. The majority of the sample were males (90.6%) and White (96.9%). One hundred percent of the sample reported being HIV-positive.

Table 11: Demographic Characteristics for Sample B (n=32)

Characteristics	Participants <i>Mean (SD, range)</i>
Age ^a	69.7 yrs (4.9, 65-87)
Education ^a	16.3 yrs (2.1, 12-20)
	<i>n (percentage)</i>
Sex ^b	
Male (%)	29 (90.6)
Female (%)	3 (9.4)
Race/Ethnicity ^b	
Black/ African American (%)	1 (3.1)
White/ Caucasian (%)	32 (96.9)
Education ^b	
Some high school	0 (0)
High school Graduate	2 (6.3)
Some college/ trade school	4 (12.5)
College graduate	3 (9.4)
Some graduate school	11 (33.4)
Graduate school completed	12 (37.5)

Notes: SD = Standard Deviation

^a Continuous variables analyzed using independent t-tests.

^b Categorical variables analyzed using chi-square or Fisher's Exact test.

HIV Variable characteristics of sample B. For specific aim 3, the final sample was 32 participants, because 41 participants did not complete the MOS-HIV (Figure 7). Variable characteristics of the 32 participants are listed in Table 12. The mean CD4 cell count was 604 cells/mm³ for n=29, because 3 participants lab results were missing. The average years of living with HIV was 24 years. Participants scored below the standard deviation on the Neuropsychological test battery overall (NP test Composite, mean = -.24, SD=.62), including measures for executive function (mean = -.24, SD=.74). The mean score for the Geriatric Depression Scale was 8.3 (SD= 7.5), and the mean score for the Patient's Assessment of Own Functioning Inventory was 1.06 (SD= .62). Participants reported a mean score of 49.1 on the

Physical Health Summary (PHS) Score (SD=10.2) and a mean score of 54.8 on the Mental Health Summary Score (SD=9.0) of the Medical Outcomes Survey-HIV (MOS-HIV).

Table 12: HIV Variable Characteristics (n=32)

Characteristic	Participants		
	Mean	SD	Range
CD4 counts (n=29)	604.0	235.8	205-1092
Years HIV-positive	23.9	7.4	4-35
NP test-executive function	-.24	.74	-2.16 – 1.44
NP test Composite	-.24	.62	-1.55 – 1.33
GDS	8.3	7.5	0-27
PAOFI	1.06	.62	.03 – 2.48
PHS	49.1	10.2	26.7-61.8
MHS	54.8	9.0	26.7-66.9

Notes: SD= Standard Deviation

NP= Neuropsychological

GDS= Geriatric Depression Scale

PAOFI= Patient's Assessment of Own Functioning Inventory

PHS= Physical Health Summary Score of Medical Outcomes Survey-HIV

MHS= Mental Health Summary Score of Medical Outcomes Survey-HIV

Demographics and Measurement Tool Scores by HIV-Associated Neurocognitive

Disorders groups. Participants' demographic characteristics by HAND diagnostic groups are represented in Table 13. About seventy-three percent of the participants (n=24) did not report any cognitive symptoms and were labeled as HIV-Normal. There was only one participant for each of the Asymptomatic Neurocognitive Impairment (ANI) and HIV/AIDS Associated Dementia (HAD) groups and thus standard deviations were unavailable. About eighteen percent of the participants had Mild Neurocognitive Disorder (MND) (n=6). The average age of the HIV-Normal group was 68.5 years (SD=2.5), while those with MND was 71.8 years (SD=7.9) ($p>.05$). The average years with HIV for the HIV-NL group was 23.6 years (SD=7.6), while for the MND group it was 25.7 years (SD=7.6). The average CD4 cell count for the HIV-NL group was 595.4 mm^3 (SD=298.1), while for the MND group it was 369.2 mm^3 (SD=233.5). The two groups HIV-NL and MND did not differ on age, years of HIV, and CD4 count.

Table 13: Demographics by HAND (n=32)

HAND Diagnostic Groups (n, %)	Age Mean (SD)	Years with HIV Mean (SD)	CD4 count Mean (SD)
HIV-Normal (24, 72.7)	68.5 (2.5)	23.6 (7.6)	595.4 (298.1)
ANI (1, 3)	85.0	28	439
MND (6, 18.2)	71.8 (7.9)	25.7 (7.6)	369.2 (233.5)
HAD (1, 3)	68.0	16	551

Notes: SD= Standard Deviation

HAND= HIV-Associated Neurocognitive Disorders

ANI= Asymptomatic Neurocognitive Impairment

MND= Mild Neurocognitive Disorder

HAD= HIV/AIDS Associated Dementia

Participants' scores on measurement tools based on HAND diagnostic groups are in Table 14. There was only one participant for each of the Asymptomatic Neurocognitive Impairment (ANI) and HIV/AIDS Associated Dementia (HAD) groups and thus standard deviations were unavailable. The mean NTB Composite score for all groups and participants were below the standard average. The HIV-Normal group (mean =-0.04, SD=0.5) had a significantly higher NTB Composite score than the MND group (mean =-0.82, SD=0.5) ($p=.003$). The differences between the HIV-NL and MND groups were not significant for GDS and PAOFI.

Table 14: Mean (SD) scores on Measurement Tools Stratified by HAND diagnostic groups (n=32)

HAND Diagnostic Groups (n, %)	NTB Composite Mean (SD)	GDS Depression Mean (SD)	PAOFI Total Mean (SD)
HIV-Normal (24, 72.7)	-0.04 (.5)	7.0 (7.2)	.94 (.58)
ANI (1, 3)	-1.2	4	.85
MND (6, 18.2)	-0.82 (.5)	11.5 (6.5)	1.46 (.71)
HAD (1, 3)	-0.7	23	1.73

Notes: SD= Standard Deviation

NTB= Neuropsychological Test Battery

PAOFI= Patient's Assessment of Own Functioning Inventory

HAND= HIV-Associated Neurocognitive Disorders

ANI= Asymptomatic Neurocognitive Impairment

MND=Mild Neurocognitive Disorder

HAD= HIV/AIDS Associated Dementia

How does cognitive function (self-report and a clinical measure) and depression relate to HRQOL in older PLWH?

Zero-order correlations are found in Tables 15 and 16. Preliminary analyses were performed to ensure no violation of the assumptions of normality, linearity, and homoscedasticity were present.

Table 15: Correlations among PHS, PAOFI, and depression (n=32)

Scale	PHS score	PAOFI	NTB Composite	GDS
1. PHS				
2. PAOFI	-.53*	-		
3. NTB Composite	.34	-.29	-	
4. GDS	-.70*	.59*	-.34	-

Notes: *Significant at $p < .01$

Dependent Variable: PHS

PHS= Physical Health Summary of the Medical Outcomes Survey- HIV

PAOFI= Patient's Assessment of Own Functioning Inventory

NTB= Neuropsychological Test Battery

GDS= Geriatric Depression Scale

Table 16: Correlations among MHS, PAOFI, and depression (n=32)

Scale	MHS score	PAOFI	NTB Composite	GDS
1. MHS				
2. PAOFI	-.39*	-		
3. NTB Composite	.51**	-.29	-	
4. GDS	-.74**	.59**	-.34	-

Notes: *Significant at $p < .05$

**Significant at $p < .01$

Dependent Variable: MHS

MHS= Mental Health Summary

PAOFI= Patient's Assessment of Own Functioning Inventory

NTB= Neuropsychological Test Battery

GDS= Geriatric Depression Scale

Physical Health Summary scale. Correlations are reported in Table 15. Inter-correlations among the independent variables were not high (range of magnitude was -.34 to .59) and thus there were no concerns for multicollinearity. Correlations are reported in Table 15. The PHS score of the Medical Outcomes Survey- HIV (MOS-HIV) had a moderate, negative, zero-order correlation with PAOFI scores ($r = -.53$, $n=32$, $p=.002$). Participants who reported more cognitive complaints as assessed by the PAOFI also reported lower PHS scores. There was a strong, negative correlation between PHS and the Geriatric Depression Scale (GDS) scores, with higher PHS quality of life scores associated with less reports of depression ($r = -.70$, $n=32$, $p < .001$). PAOFI and NTB composite scores were not highly correlated ($r=.34$).

Multiple regression model for Physical Health Summary. The results of the multiple linear regression analysis for Physical Health Summary (PHS) scores are found in Table 17. Preliminary analyses were conducted to ensure no violation of the assumptions of normality, linearity, multicollinearity, and homoscedasticity. The overall model that seeks to explain the variance in PHS from the 3 independent variables (PAOFI, NTB Composite, and GDS) considered simultaneously significantly explains 51.9% of the total variance in PHS, $F(3,28) = 10.06$, $p < .001$. Only one of the independent variables made a significant unique contribution to explaining the total variance in PHS. Depression significantly and uniquely accounts for 20.1% of the variance ($p=.002$) in the model. As depression increases, PAOFI scores decrease (less reports of cognitive complaints). The PAOFI ($R\text{-square change}=.018$, $p=.32$) and NTB Composite ($R\text{-square change}=.008$, $p=.51$) explained negligible variance. PAOFI was not significant in the model.

Table 17: Multiple Regression Analysis for Physical Health, $R^2=.519$, $p<.001$

N=32	B	S.E.	t	p-value	95% CI for B		R ² change
					Lower	Upper	
PAOFI	-2.75	2.70	-1.02	.316	-8.28	2.77	.018
NTB Composite	1.58	2.34	.68	.505	-3.21	6.36	.008
GDS*	-.77	.23	-3.42	.002	-1.24	-.31	.201
Constant	58.82	2.66	22.12	< .001	53.37	64.27	

Note: *Significant at $p < .01$

Dependent variable: Physical Health Summary score of Medical Outcomes Survey-HIV

CI= Confidence Interval

SE= Standard Error

PAOFI= Patient's Assessment of Own Functioning Inventory

NTB= Neuropsychological Test Battery

GDS= Geriatric Depression Scale

Mental Health Summary scale. Correlations are found in Table 16. Inter-correlations among the independent variables were not high (range of magnitude was -.34 to .59) and thus there were no concerns for multicollinearity. There was a moderate, negative correlation between PAOFI and Mental Health Summary (MHS) score of the Medical Outcomes Survey- HIV (MOS-HIV); participants who reported better MHS quality of life reported fewer complaints of cognitive impairment ($r=-.39$, $p<.05$). There was a moderate, positive correlation between NTB composite and MHS; participants who scored better on the NTB also significantly reported better MHS quality of life ($r=.51$, $p <.01$). There was a strong, negative correlation between MHS and the Geriatric Depression Scale (GDS) scores, with higher MHS quality of life scores associated with less reports of depression ($r= -.74$, $p <.001$). There was a moderate, positive correlation between GDS and PAOFI; higher depression scores were significantly associated with more complaints of cognitive impairment ($r=.59$, $p<.01$).

Multiple regression model for Mental Health Summary. The results of the multiple linear regression analysis for Mental Health Summary (PHS) scores are found in Table 18. Preliminary analyses were conducted to ensure no violation of the assumptions of normality, linearity, multicollinearity, and homoscedasticity were present. The overall model that seeks to explain the variance in MHS from the 3 independent variables (PAOFI, NTB Composite, and GDS) considered simultaneously significantly explains 63.1% of the total variance in MHS, $F(df) = 15.942(3,28)$, $p < .001$.

Table 18: Multiple Regression Analysis for Mental Health, $R^2 = .631$, $p < .001$

N=32	B	S.E.	t	p-value	95% CI for B		R ² change
					Lower	Upper	
PAOFI	1.57	2.07	.76	.453	-2.66	5.80	.008
NTB Composite*	4.37	1.79	2.44	.021	.71	8.04	.078
GDS**	-.83	.17	-4.81	< .001	-1.19	-.48	.306
Constant	61.01	2.04	29.99	< .001	56.90	65.24	

Note: *Significant at $p < .05$

**Significant at $p < .01$

Dependent variable: Mental Health Summary score of Medical Outcomes Survey-HIV

CI= Confidence Interval

SE= Standard Error

PAOFI= Patient's Assessment of Own Functioning Inventory

NTB= Neuropsychological Test Battery

GDS= Geriatric Depression Scale

NTB and GDS made significant unique contributions to explaining the total variance in MHS. Depression uniquely accounted for 30.6% of the variance ($p < .001$), while NTB uniquely accounted for 7.8% of the variance ($p < .05$). The PAOFI (R-square change=0.008, $p = .453$) explained negligible variance in the model.

Chapter 5: Discussion

This secondary analysis study was the first multivariate study to find that self-report of cognitive had no relationship with a clinical measure of cognitive function in older persons living with HIV (PLWH). In addition, older PLWH who performed better on clinical measures of cognitive function reported better mental health-related quality of life (HRQOL). Older PLWH who reported better mental and physical health-related quality of life reported fewer depressive symptoms and self-reported fewer complaints in cognitive impairment. This study provided a foundation in which to study HRQOL, depression, and cognitive function correlates in the oldest of old PLWH (60 years and older).

Main Findings

Specific Aim 1: Self-report versus clinical measures of cognitive function. A primary finding was self-report of cognitive function did not correlate with clinical measures of cognitive function in older PLWH. In this study, participants were enrolled regardless of cognitive symptoms, and about one-half of the sample of older PLWH had cognitive impairment as defined by the HIV/AIDS Associated Neurocognitive Disorders (HAND) Frascati criteria, which is characteristic of the general HIV-positive population (Antinori et al., 2007; Heaton et al., 2010c).

While neurological complications are increasingly common in PLWH, national surveys report that more than 50% of younger PLWH have abnormal neuropsychological testing performance; yet, more than 50% of these participants do not report symptoms to their healthcare providers (Heaton et al., 2004; Valcour et al., 2011). In the literature, older PLWH experience HAND at disproportionately higher rates of impairment in cognitive function (Valcour et al., 2004a) and show highest impairment in domains of psychomotor speed, executive function, and

memory (Cherner et al., 2004; Sacktor et al., 2007). Neuropsychological testing also confirms that longitudinal psychomotor speed performance is compromised in PLWH (Janssen et al., 2015; Sacktor et al., 2007). Likewise, in this dissertation study, there were no correlations of both the NTB composite and executive function to self-report of cognitive function. Future studies should assess the cognitive domains of psychomotor speed and memory in this older PLWH population and explore if this relationship is also similar in this unique cohort of the oldest of old.

In the literature, there are mixed reports of the relationship between self-report and a clinical measure of cognitive function; researchers have utilized functional assessment tools in addition to a clinical measure of cognitive function as assessed by a NTB. One study by Heaton et al. (2004) found that a global functional impairment score as assessed by laboratory-based tools (Direct Assessment of Functional Status tool, Advanced Finances tool, Medication Management Test) and depressive symptoms significantly and uniquely contributed to the model in explaining the variance in PAOFI scores, whereas an NTB Composite score and biological markers (CD4 and AIDS status) did not in PLWH. Higher levels of functional impairment and depression were highly associated with self-report cognitive complaints. Various tools that assessed the participant's activity of daily living, different from a NTB, assessed functional impairment. Another study found that persons with Systemic Lupus Erythematosus (SLE) reported more cognitive complaints as assessed by the PAOFI, had more cognitive impairment as assessed by a clinical measure of cognitive impairment, and also had high rates of depression compared to those without SLE (Kozora, Ellison, & West, 2006). Similar to the results of this study, those who had more complaints on the PAOFI also had high scores of depression. Depressed mood may contribute to cognitive or functional disability or may only negatively

affect participants' perception of every day functioning. In contrast to these findings, one study found that in patients with breast cancer, higher memory complaints with combined chemotherapy and radiation treatments had poorer verbal memory performance on the NTB and higher depressive symptoms (Ganz et al., 2013).

Furthermore, in the literature, those who did not adhere to cART had more deficits in cognitive function than those who did adhere to cART in PLWH (Janssen et al., 2015). PLWH compared to controls (persons who did not have the HIV illness) showed worse performance on information processing speed and motor function in addition to more cognitive complaints. One study found that HIV has minor impacts on the brain and cognition in PLWH who are healthy and have maintenance of their HIV illness with combination Anti-Retroviral Therapy (cART) (Janssen et al., 2015). Participants in this dissertation study were generally healthier; older PLWH had a shorter sample mean duration of years living with HIV and had lower CD4 cell counts (indicative of healthy maintenance of their HIV illness) compared to participants in other studies (Janssen et al., 2015). The sample for this dissertation study had a higher sample mean CD4 cell counts, higher levels of education (measured in sample mean years), and a shorter sample mean duration of the HIV illness (measured in sample mean years).

This current study found no relationship between clinical measures of cognitive function and self-report of cognitive function. The literature indicates that self-report of cognitive function predicts the outcome of clinical measures of cognitive function (Janssen et al., 2015). Researchers found that a PLWH's self-report and clinical measures of cognitive function were highly correlated (Blackstone et al., 2012; Carter et al., 2003; Grant et al., 2014; Janssen et al., 2015). An inference from this current study's results is that the oldest of old PLWH may not self-report cognitive impairment or may under-report or over-report symptoms of cognitive

impairment. This indicates that the population for this current study may not recognize symptoms related to loss of cognitive function or simply not ready to acknowledge their deficits. Another explanation is that PLWH, like participants who have fronto-temporal lobe dementia, may lack insight into one's clinical condition (Snowden, Neary, & Mann, 2002) or cognitive abilities. This is a problem for older PLWH, because if older PLWH are found to have cognitive impairment as assessed by a clinical measure of cognitive function (NTB) but do not report symptoms, older PLWH with cognitive impairment will not be diagnosed appropriately and referrals for cognitive impairment will be missed in older PLWH.

According to the results of this study, older PLWH who have cognitive impairment do not self-report symptoms. This is an issue to the provider, because providers may miss asymptomatic or mild cognitive impairment in older PLWH. This is also an issue for older PLWH, because those assessed with only self-report will miss appropriate cognitive health care services in the clinical setting. Those who are assessed with clinical measures of cognitive function, such as the Neuropsychological Test Battery (NTB), are more likely assessed later in their cognitive disease process and also have more access to healthcare and follow-up than those who are not diagnosed or suspected to have any impairment in cognitive function (Bottonari & Stepleman, 2010). Further research is needed to assess the health status and self-report of cognitive function and its correlates to clinical measures of cognitive function in older PLWH.

Age and education were also examined between self-report and clinical measures of cognitive function. In one model, age and education were excluded, which revealed a moderate but non-significant correlation between self-perception of cognitive function and clinical measures of cognitive function. This meant that age and education have no influence on the relationship between self-report and clinical measures of cognitive function in older PLWH. In

another model, a sensitivity analysis was conducted in which age and education were included. When age and education were listed as covariates, the association between the variables of self-report of cognitive function and clinical measures of cognitive function were weakened, and results continued to be insignificant. Nevertheless, results for the model with age and education were reported in order to lean on the conservative side of measurement. Regardless, results for the model including age and education were reported for conservative measures. In the literature, when age and education are included in a model, younger PLWH are compared with older PLWH (Grabar, Weiss, & Costagliola, 2006). PLWH in this dissertation study were the oldest of old and a comparison group was unavailable. Thus, a novel finding of this dissertation study that adds to the literature of older PLWH is that age and education in the oldest of old PLWH have no influences on the relationship between self-perception of cognitive function and clinical measures of cognitive function.

One unique fact about this dissertation study is that though self-report of cognitive function did not relate to clinical measures of cognitive function in older PLWH, the sample for this current study had well-maintained HIV illnesses in old age. Self-report of cognitive function have been found to be correlated to clinical measures of cognitive function in the general population of PLWH, including those with symptomatic cognitive impairment (Grant et al., 2014; Heaton et al., 2010c). This relationship should be further assessed in a more diverse population of older PLWH, because this was a small sample with no comparison groups. Nonetheless for this current study, three explanations could be that (1) this relationship was insignificant due to a small sample size and/or (2) PLWH are unaware of their cognitive function regardless of age and/or (3) other variables (i.e. depression) could further explain the relationship

between self-report and clinical measures of cognitive function. Explanation three was explored in specific aim 2.

Specific Aim 2: Depression and correlates to self-report cognitive function versus a clinical measure of cognitive function. For specific aim 2, depression was significantly correlated to self-report cognitive function, while a clinical measure of cognitive function, as assessed by the NTB, was not significantly correlated to self-report cognitive function. One study in the literature found that cognitive complaints of prospective memory were related more to depression than clinical measures of cognitive performance (NTB) for older PLWH (Avci, Loft, Sheppard, & Woods, 2016). In the literature, researchers found depression to explain 12% of the variance in self-report measures of cognitive function, as assessed by the Patient's Assessment of Own Functioning Inventory (PAOFI) score for participants with substance abuse and 44% for a sample of veterans; cognitive complaints were related more to depression than cognitive performance for all participants (Richardson-Vejlgaard et al., 2009). Similar to the findings of this dissertation study, self-report of cognitive function (PAOFI score) were highly correlated with depression (Chachamovich et al., 2008; Mavandadi et al., 2009).

In this dissertation study, the oldest of old PLWH have cognitive characteristics similar to the younger PLWH: the correlation between self-report of cognitive function and depressive symptoms was stronger than the correlation between reports of cognitive function and clinical measures of cognitive function. Investigators have found a strong correlation between self-report of cognitive function and depressive symptoms, but a weak association with clinical measures of cognitive function as assessed by the NTB, when studied in younger PLWH (Atkins et al., 2010; Thames et al., 2011; Vance et al., 2012). Rourke et al. (1999), one of the first studies utilizing the PAOFI as a self-report measure of cognitive function, conducted a study with PLWH and also

found that older PLWH who self-report more impairment in cognitive function also report more depressive symptoms. The finding by Rourke et al. in 1999 is not different from the dissertation study's sample of the oldest of old population of PLWH.

Depression was also found to be associated with clinical measures of cognitive function and age was associated with levels of depression. Older PLWH who have cognitive impairment as measured by the NTB may be more aware of their cognitive limitations and also report more depression. However, causality cannot be inferred in this study and further research should be conducted to assess this relationship. Similar to the findings of the dissertation study, one study conducted in a cohort of aging PLWH in Hawaii found that depressive symptoms were associated with clinical measures of cognitive impairment in younger (49 years and younger) PLWH but not in older (50 years and older) PLWH (Shimizu et al., 2011). In the Hawaii cohort of older PLWH, the mean age of participants was 54.5 years and years infected was 11.8 years, while in this study, the mean age of participants was 66.7 years and the years infected was 7 years. The dissertation study sample was older in age but had fewer years of HIV infection compared to the Hawaii cohort. Nonetheless, both study results are similar. In this dissertation study, though the trend was seen that older PLWH who report more depression also have poorer scores on the NTB, this relationship was not significant. Alternatively, older PLWH who report depression do not necessarily score poorly on the NTB.

This suggests that as PLWH are living longer with HIV, regardless of age, neuropsychological decline is not associated with depression. NTB had no significant correlations with self-perception of cognitive function when controlling for depression. The findings of this current study are consistent with the literature that the duration of HIV illness and age are not related to depression, and depression is not related to clinical measures of

cognitive function (Gold et al., 2014; Shimizu et al., 2011). Older age is not indicative of depression or cognitive impairment. Instead, older adults who were diagnosed with HIV at a later stage in life are not prone to depression or cognitive impairment. One might expect that PLWH who are diagnosed with HIV at older age does not cause regret, remorse, or higher depressive symptoms more than those PLWH diagnosed with HIV at younger age. Older PLWH who have cognitive impairment may or may not report severe depressive symptoms as cognitive impairment may not be a factor in PLWH who are depressed. This is consistent with the literature of PLWH regardless of age (Cysique, Dermody, Carr, Brew, & Teesson, 2016).

However, the dissertation study did find a relationship between depression and self-report of cognitive function. Older PLWH who reported more depression reported more impairment in cognitive function. One explanation is that self-report measurement tools address the participant's perspective and if the participant reports more depression, the participant will report more complaints of cognitive impairment (Cysique et al., 2016). On the other hand, self-report of cognitive function and clinical measures of cognitive function had no significant relationship. Hence participants who reported more depression also reported more cognitive complaints though they did not score poorly on clinical measures of cognitive function. This is also seen in the literature with PLWH who have deficits in prospective memory (Avci et al., 2016; Woods et al., 2014). PLWH generally self-report more cognitive impairment (Woods et al., 2007) and more depression (Sadek et al., 2007) than their HIV-negative counterparts and thus the results of this current study are not consistent with the literature. The results of this dissertation support the findings in the literature that depression explained more of the variance in predicting self-reported cognitive complaints (Blackstone et al., 2012; Gold et al., 2014; Sadek et al., 2007).

Importantly, the results of this dissertation study suggest that healthcare providers should assess for depression in older PLWH if their patients report impairment in cognitive function.

Furthermore, the sample of participants for the dissertation study was unique and different from other studies; this dissertation study sample consisted of highly educated PLWH who were diagnosed at later stages in life (diagnosed when they were in their 40s or 50s) (Doyle et al., 2012; Gold et al., 2014). Unlike this dissertation study, other studies found a strong correlation between self-report and a clinical measure of cognitive function in their sample population who were more cognitively impaired at baseline. PLWH who are more educated and diagnosed with HIV at later stages in life do not report self-report cognitive impairment because they are functioning well in society (Thames et al., 2011). Also, older PLWH may have more cognitive impairment than they personally believe or realize, because they lack insight into their cognitive function.

Specific Aim 3: Health-related quality of life and its correlates. For this specific aim, a new concept, HRQOL, was introduced. HRQOL is a complex construct that consists of various domains (see Chapter 3). In specific aim 3, there were no significant correlations between patients' self-report of cognitive impairment with clinical measure of cognitive function and HRQOL. There was a small, positive correlation between NTB composite and Physical Health Summary (PHS) scores, but this relationship was not significant. However, there was a significant moderate, positive correlation between NTB composite and mental health summary (MHS) scores of the Medical Outcomes Survey-HIV (MOS-HIV). Participants with better NTB composite scores significantly reported better mental health scores for HRQOL. One explanation is that participants who report better mental health HRQOL actually do better on NTB exams, although not congruent with the literature. A study found that participants with higher self-

complaints of cognitive impairment, also significantly reported lower HRQOL scores for the PHS and MHS (Doyle et al., 2012).

While the study results for specific aims 1 and 2 did not support the relationship between clinical measures of cognitive function with self-reported cognitive complaints, results did show that the relationships of these clinical measures of cognitive function and self-reported cognitive complaints with mental HRQOL and physical HRQOL differ. Clinical measures of cognitive function as assessed by the Neuropsychological Test Battery (NTB) Composite test scores were correlated to mental scores of HRQOL but not to physical scores of HRQOL, when controlling for depression. The results indicated that depressive symptoms accounted for most of the variance in the relationship with patient's perception of cognitive function and HRQOL.

Depression accounted for a significant and majority of the variance in the model explaining the total variance in the physical health domain. Physical score on the MOS-HIV was not correlated to self-report of cognitive function nor clinical measures of cognitive function. However, there was a significant positive correlation between depression and PAOFI. Depression was correlated to MHS and PHS, but not to self-report of cognitive function. Higher depression scores were significantly associated with more patients' complaints of cognitive function as similar to the results of specific aims 1 and 2. Other studies have found similar findings; self-report measures of cognitive function may be influenced by depressive symptoms (Blackstone et al., 2012; Cysique et al., 2016). Depression is common in PLWH, in which PLWH complain of sleep and appetite disturbance and alteration in mood more than their HIV-negative counterparts (Gold et al., 2014). In addition, side effects of cART can cause agitation, depressed mood, decreased cognitive function and insomnia (Burgess, Zeuli, & Kasten, 2015; Gold et al., 2014).

Furthermore, the mental health summary score of the MOS-HIV was the only measure that correlated with self-report and clinical measure of cognitive function. In this current study, older PLWH who are at risk for cognitive impairment reported low HRQOL scores, specifically in the domain of mental health, and reported depressive symptoms, whereas these same individuals had no correlations between the domain of physical health and a clinical measure of cognitive function. A unique finding of this dissertation study is that utilizing the MOS-HIV, particularly the MHS, one can find correlations to not only depression and self-report of cognitive function, but also to a clinical measure of cognitive function, not yet found in the literature.

Clinical measures of cognitive function and depression scores both made significant unique contributions to explaining the total variance in MHS. Patients who report better mental health-related quality of life, reported less depression and also scored higher on clinical measures of cognitive function. On the contrary, researchers have reported that older PLWH experience more depression, cognitive impairment, financial concerns, and noncompliance to cART than their younger PLWH counterparts (Burgess et al., 2015; Moore et al., 2014). Domains of health perception and health distress weigh heavily on MHS scores for HRQOL. One explanation as to why older PLWH in this current study reported higher depressive symptoms and lower MHS scores could be that older PLWH are cognitively aware of their health distress and report worse mental health when they are more depressed. Nonetheless, health care providers who find impairment in cognitive function in their older PLWH population should also assess for mental HRQOL and depression.

The concept of MHS scores for HRQOL may be a concept closely related to but not the same as depression. Another positive design of this study was in utilizing the MOS-HIV long

form and not the MOS-HIV short form. The MOS-HIV long form includes domains of energy and distress related to health problems, which the short form does not. This resulted in the observation of the difference between HRQOL and depression.

PAOFI was significantly and moderately correlated with HRQOL scores (PHS and the MHS). This finding suggests that participants who self-reported greater impairment in cognitive function also reported poorer physical and mental health scores for HRQOL. HRQOL scores (both the PHS and MHS) were also significantly and largely related to depression scores. This dissertation study revealed that depressive symptoms accounted for the majority of the variance that explained complaints in cognitive function and physical and mental health reports of HRQOL. Studies have found that PLWH self-report cognitive complaints correlated to their clinical measures of cognitive function (Brouillette et al., 2015b) or PLWH were accurately aware of their cognitive abilities (Rourke et al., 1999). This was true for this current study as well. HRQOL and depression are strongly correlated in PLWH. PLWH who report more depressive symptoms may report lower HRQOL or PLWH who report low HRQOL scores may also be depressed. Due to the cross-sectional nature of this study, causality cannot be inferred.

General Findings

Participants in this sample were mainly highly educated, white, and male. Because of these demographics, results of this study are not generalizable to the HIV-positive population. A sample including more women, ethnic minorities, and less educational attainment may reflect different relationships between self-report of cognitive function, depression, and HRQOL. Furthermore, data on socioeconomic status may have different implications for HRQOL and depression. Socioeconomic status and ethnicity affect PLWH and their access to care, as well as their quality to care (Brennan-Ing et al., 2013; Uphold & Mkanta, 2005). Mental health services

were provided to 25% of a HIV clinic's patient population, but racial minorities were underrepresented among those seeking specialized mental health services (Bottonari & Stepleman, 2010). Different sample populations, including community-based samples or PLWH who were of African American, Latino, Asian, or Native American race could provide different findings and more generalizable results.

HIV/AIDS-Associated Neurocognitive Disorders diagnostic groups for sample A.

Based on HAND Diagnostic criteria, older PLWH who were in the HIV-Normal group scored higher on the NTB composite and tests on executive function than those in the Asymptomatic Neurocognitive Impairment (ANI) group and those in the Mild Neurocognitive Disorder (MND) group in this sample population of older PLWH. There were no participants in the HIV-Associated Dementia (HAD) group. Also, older PLWH in the HIV-Normal group and the ANI group both self-reported less cognitive complaints and also reported less depressive symptoms compared to the group with MND. In the literature, ANI is the most prevalent form of HAND (Grant et al., 2014). The majority of older PLWH in this sample were diagnosed as HIV-Normal, which indicates that the majority of the sample had no cognitive impairment based on the HAND criteria.

Nonetheless, there were significant differences found among the three groups on the NTB Composite, neuropsychological tests on executive function, depression, and the self-report of cognitive function. However, when t-tests were completed to assess the differences between groups (HIV-normal versus ANI, HIV-normal versus MND, and ANI versus MND), the results were not significant due to a small sample size. To address this limitation, two groups (the HIV-normal group and ANI group) were combined and compared to the MND group to assess for differences on all the measures (self-report of cognitive function, clinical measure of cognitive

function, and depression). However, post-hoc analysis found that there was no difference when the groups were compared. In the literature, ANI groups differ significantly on self-report measures of cognitive function and clinical measures of cognitive function compared to the HIV-Normal groups (Grant et al., 2014). This is similar to the findings of this current study; ANI groups are not cognitively normal and need assessment of cognitive impairment equally as those with MND groups do.

Furthermore, older PLWH in the HIV-Normal group and the ANI group both self-reported less cognitive complaints and less depressive symptoms compared to the group with MND. This current study found that the ANI group self-reported less cognitive complaints and less depressive symptoms compared to the group with MND. One can infer that older PLWH are more aware of their cognitive abilities based on HAND diagnostic groups. Other studies have found a significant difference between the ANI groups and MND/HAD groups. However, a limitation is that there was no separate HAD group due to this study's small sample size to assess for between group differences. For this study, three groups of HIV-Normal, ANI, and MND were compared. According to the literature, there are considerable discussions related to defining symptomatic (ANI) compared to asymptomatic (MND/HAD) cognitive impairment in the setting of HIV (Grant et al., 2014; Heaton et al., 2011). Hence, a study with a bigger sample size to compare symptomatic to asymptomatic cognitive impairment in older PLWH is warranted.

In this current study, MND groups reported more depressive symptoms and self-reported more cognitive complaints compared to the HIV-Normal and ANI groups. The difference was found to be significant among the groups, but t-tests revealed no statistically significant differences between group pairs. In the literature, ANI groups significantly differ with HIV-Normal groups when compared on symptoms of depression, self-report of cognitive function,

and clinical measure of cognitive impairment (Blackstone et al., 2012; Grant et al., 2014). Further research with a larger sample size should be conducted so that all groups could be compared across all variables. This would add to the literature base of older PLWH, because this has not yet been studied in the literature. Nonetheless, this finding alerts health care providers to continually assess cognitive impairment and depression for older PLWH who self-report no complaints to mild complaints of cognitive impairment. In addition, the differentiation of asymptomatic, mild symptomatic and severe cognitive impairment in older PLWH is warranted.

The literature has recently shifted the focus from comparing symptomatic to asymptomatic participants with cognitive impairment to comparing asymptomatic to mild symptomatic participants with cognitive impairment. Mild degrees of cognitive impairment pose a risk for HIV disease progression, particularly in older adults (Grant et al., 2014; Heaton et al., 2004). In populations without HIV, those with mild cognitive impairment are at an increased risk of developing dementia (Petersen et al., 2004). One researcher found that neurocognitive tests combined with assessing depressive symptoms allowed for good discrimination of dementia, particularly Alzheimer's disease, but poorer discrimination of mild cognitive impairment (Dierckx, Engelborgh, De Raedt, De Deyn, & Ponkaert-Kristoffersen, 2007). Contrary to the findings of this study, in the literature, PLWH who are asymptomatic as assessed by the HAND diagnostic criteria (or diagnosed with ANI) self-report fewer cognitive complaints but also score poorly on clinical measures of cognitive function (Blackstone et al., 2012; Petersen et al., 2004). A study that assesses asymptomatic versus mild symptomatic impairment in cognitive function warrants further research, because health care providers may not necessarily screen for cognitive impairment if patients do not self-report impairment in cognitive function. Older PLWH who have mild cognitive impairment progress to severe forms of cognitive impairment at a faster rate

(Petersen et al., 2004) than those who are not cognitively impaired and thus this ANI group warrants further study and attention.

Patients with severe dementia or cognitive impairment may not be fully aware of the questions being asked in a HRQOL measurement tool and thus the HRQOL of the PLWH may not be fully understood. Adding another measure, such as the Clinical Dementia Rating scale, or another tool, which incorporates caregivers or family members' intake could also be useful to understanding a patient's comprehensive cognitive function and abilities (Arlt et al., 2008; Weintraub et al., 2009). Furthermore, patients with severe cognitive impairment may not be physically able to answer questions on a self-administered measurement tool. Older PLWH in this current study were able to answer this tool. Only one participant who had HAD was taken out of the study because he could not answer the measurement tool himself; his caregiver had answered the tool for him (see Chapter 4).

Discussion on Measurement Tools

PAOFI and measures of reliability and validity. Authors have utilized the PAOFI tool to assess patient's self-perceptions of cognitive impairment and found that patients' complaints of cognitive impairment were correlated significantly with depression and neuropsychological tests on attention, memory, psychomotor skills, and learning efficiency in PLWH (Rourke et al., 1999). In this current study, self-report of cognitive function correlated with depression and physical HRQOL scores, but self-report had no relationship with the clinical measure of cognitive function. The nature of the relationship between PAOFI with NTB scores did not provide a basis for utilizing the PAOFI to screen and observe cognitive impairment in older PLWH. Thus, the instrumentation and development of the tool warrants further research in older PLWH. For example, future studies could assess intra-rater reliability of the PAOFI tool by

administering the tool in older PLWH and then administer it again the following week or two weeks.

Assessment of Quality of Life for PLWH. HRQOL has been found in this current study and in the literature to have higher correlations to depression above other variables, including cognitive impairment (Cherner et al., 2004). Regardless, HRQOL tools have not been fully tested in patients with severe impairment in cognitive function, including those with HAD (as based on the HAND diagnostic criteria) and thus warrants further research (Arlt et al., 2008), especially in older PLWH.

Though the MOS-HIV is used widely in PLWH and well validated within the HIV-population, it provides a generic assessment of health-related quality of life. One study found that health distress and vitality subscales of the MOS-HIV were closely connected in persons with AIDS than those earlier in the HIV disease process, which posed a greater association of these concepts with the advanced form of HIV (Schifano et al., 2003). This current study's population consisted of older PLWH who were in their earlier processes of their HIV illness or were well managed with their HIV illness on cART. Thus, generally speaking, PLWH generally report worse HRQOL than their HIV-negative counterparts (Janssen et al., 2015) regardless of the severity of their HIV illness.

The HRQOL measure was changed for future cohorts of the parent study to reflect a composite HRQOL score that encompasses variables including social support and financial measures in older PLWH. A measurement tool, the World Health Organization Health-Related Quality of Life- HIV (WHOQOL-HIV) that assesses one general score (rather than physical and mental health) for HRQOL with more diverse domains for older PLWH was used in future iterations of the parent study, because the MOS-HIV did not include a social support domain.

This too, WHOQOL-HIV and the WHOQOL-HIV abbreviated version (WHOQOL-HIV Bref) have been found valid and reliable in older PLWH (Pereira et al., 2014; Steinbüchel, Lischetzke, Gurny, & Eid, 2006). The briefness and multidimensionality of this tool allows for a practical and comprehensive assessment of HRQOL in both clinical and research settings. Though the MOS-HIV utilized in this current study is brief and provides a comprehensive assessment of HRQOL, the WHOQOL-HIV Bref is another HRQOL measure to assess the concept HRQOL with domains specific to older PLWH.

The WHOQOL-HIV or the WHOQOL-HIV Bref (used for more time constraints) could be used to assess other domains of HRQOL vital for older PLWH. The WHOQOL-HIV assesses levels of independence, social relations, and spiritual relations (Skevington, 2012; WHOQOL HIV Group, 2004). Both tools assess for some similar domains as the MOS-HIV but also include more domains vital for older PLWH. Such domains include personal relations, level of independence, psychological health, spirituality, social relations, and environmental health. One study found that older PLWH actually reported better HRQOL compared to younger PLWH on all domains of the WHOQOL-HIV, except sleep, energy, and sex-life and that the social domain of HRQOL, which includes personal relationships, social support, spirituality, religiousness, personal beliefs, and sex-life, had a paramount importance in older PLWH (Skevington, 2012).

Domains including the social domain, spirituality, religiousness, and personal beliefs, and central independence are important for older PLWH. Social relationships and social support are important and beneficial domains for improving HRQOL for older PLWH (Coates et al., 2014; Mayo, Brouillette, & Fellows, 2016; Skevington, 2012). In the literature, social support accounts for health care, health perceptions, and positive feelings of support, which increases an older PLWH's HRQOL (Atkins et al., 2010; Burgoyne & Renwick, 2004; Mayo et al., 2016). In the

sample population for this study, measures of social relationships or social support were not collected. Interestingly, different measures including the Clinical Dementia Rating (CDR) scale were collected, but some older PLWH in this study had difficulties naming one friend or family member consistent and involved in their lives. Including the concept of social support could add to the depth of the concept of HRQOL for future studies. Or utilizing a HRQOL that incorporates social support like the WHOQOL-HIV or WHOQOL-HIV Bref could also help assess for a more comprehensive measure of HRQOL.

Neuropsychological test battery. Neuropsychological test batteries are useful in detecting subtle cognitive impairment and in documenting change over time. Brief assessments should be recommended for patients who are more severely cognitively impaired or have acute phases of brain injury, because the longevity of the NTB may cause testing fatigue, exaggerate the estimates of impairment, or would confirm the clinically obvious diagnosis. Because NTB requires a long period of time (approximately two hours), neuropsychological evaluations are not recommended as referral questions, but should be used as a follow-up, guided by the preliminary mental status assessment conducted by a physician, particularly a neurologist (Reitan & Wolfson, 2001).

Other tools, such as the Montreal Cognitive Assessment (MoCA) or the Mini Mental State Exam (MMSE) could be used to assess clinical measures of cognitive function in the clinical setting (Brouillette et al., 2015a; Brouillette et al., 2015b; Freitas, Prieto, Simoes, & Santana, 2014). These tools have been found to be valid and reliable in PLWH and have been used to assess cognitive function in older adults and in PLWH (Freitas et al., 2014; Hoops et al., 2009; Sweet et al., 2011) and are not as time intensive as the NTB. Nurses can assist physical therapists or physicians in the clinical setting by administering these exams.

Limitations

There were several limitations to this study. Though the PAOFI did not correlate to a clinical measure of cognitive function in older PLWH, the use of self-report tools in measuring cognitive function is warranted. Self-report measures have several benefits in providing a comprehensive care plan for older PLWH. Self-report provides a source of evidence that delivers ecological validity to clinical measures of cognitive function as found in previous studies (Brouillette et al., 2015b). In addition, self-reports are easy and quick to obtain and can inform the provider the domains of cognitive function that require further investigation. Following up with specific tests of the NTB can be utilized to further assess those cognitive domains in the individual patient.

Power analysis and sample size. A possible explanation for the relationship between NTB and PAOFI not being statistically significant in this study is a small sample size. One of the drawbacks of a secondary data analysis is that the sample size cannot be changed and in this study, it was a sample size of 73. According to Cohen (1988), a small R-square change provides a unique contribution with a small (2-13%), moderate (14-25%), or large (26% or greater) effect in a multiple regression model. Because N was fixed due to the nature of a secondary data analysis and adequate power was at least 80% (Cohen, 1988) and any one variable adding variance to the model with a respective R-square change is reported as significant. Cohen's criteria was used to determine the minimum effect size change for significance given a sample size (Cohen, 1988).

For sample A (specific aims 1 and 2), a power analysis revealed that a sample size of 73 participants using an alpha level of .05 would have power of at least 80% to detect a unique contribution (R-square change) of one independent variable (e.g., NTB) of approximately 8.7%,

if the other variables in the model explained a medium effect (Cohen, 1988). Since the unique contribution of NTB to explaining the variance in PAOFI was only approximately 4% (4.2% for model 1 and 4.6% for model 2 which included age and education as covariates), it is not surprising that its contribution was not statistically significant. In order to have adequate power (80%) to detect the unique contribution of NTB of approximately 4.2% to be significant at an alpha level of .05, the sample size would need to have been approximately 180 participants. This was not possible given the time constraints and limitations on funding.

For sample B (specific aim 3), the sample size of 32 patients provided a power of 80% at an alpha level of 0.05 to detect a medium to large effect size or unique contribution (R-square change) of one independent variable of approximately 15% (Cohen, 1988), assuming the other 2 variables in the model already explain at least 26% of the total variance in the dependent variables, the mental health summary score (MHS) and the physical health summary score (PHS) of the Medical Outcomes Survey- HIV (MOS-HIV) tool. For this study, depression significantly accounted for 20.1% of the total variance in PHS, controlling for NTB and PAOFI. NTB only accounted for 0.8% of the total variance in PHS and the results were not significant. Participants' clinical measures of cognitive function were not related to the PHS of the HRQOL scale. Though depression accounted for more of the total variance in MHS, controlling for the NTB composite and self-report of cognitive impairment, a larger sample size could provide different results.

There were adequate sample sizes for specific aims 1 and 2, but the sample size for specific aim 3 was small. With a sample size of $n=30$, subtle effects are not detectable. However, in this sample size, the independent variables explained a large portion of the variance. If the sample size for specific aims 1 and 2 were larger, a significant effect might have been detected. Though sample size was a limiting factor for specific aim 3, a clinically relevant conclusion

should be made. If there is a moderate to large effect found in the model with significance, further studies should replicate this study to assess the relationship among the variables of depression, self-report cognitive function, clinical measure of cognitive function, and HRQOL. Furthermore, secondary data analysis cannot provide the flexibility to explore a more diverse research question and the research questions are limited to the variables obtained.

Relevance to Nursing and Healthcare Providers

This research provides information on the use of a self-report measure compared to a clinical measure in the identification of cognitive symptoms in older PLWH. Self-report measurement tools may not always be significantly related to a clinical measure of self-report or depression, but assessing for HRQOL, specifically domains of mental health, may have implications into a patient's cognitive function. Thus, nurses should include the patient's reports of HRQOL in the patient's assessment. Nurses are expected to anticipate the needs of their patients based on their patients' physical and mental status, and provide appropriate care and resources in a timely manner. Thus, patients' HRQOL may provide a basis into their cognitive or mental health status. While it is noted in the literature that clinical and self-report measures of cognitive function are not always highly correlated, the inclusion of clinical or objective data (NTB) provided additional information on the significance of clinical utility. Also, depression and HRQOL, self-report measures, provided additional information into a person's perception of their health. This research alerts healthcare professionals that both clinical and self-report measurement tools should be used with older PLWH.

When assessing HRQOL in older PLWH, nurses should not ignore depressive symptoms nor minimal to no self-report of cognitive impairment. As noted in the literature and in this current study, older PLWH who are asymptomatic and do not report any cognitive impairment

are still at risk for mental health disorders and worsening cognitive function. Interventions can be started earlier in the course of cognitive impairment, delaying the progression of dementia. Furthermore, as health care professionals interacting with patients the most frequently, nurses observe physical, mental, and psychological symptoms in older PLWH and can provide interventions and recommendations to the older PLWH's healthcare providers in a timely manner.

With health care advancing and exploring options to have standardized measures of care for PLWH, the discussion of measuring depression, cognitive function, and HRQOL warrants attention particularly for older PLWH. Throughout clinical practice over the past decade, researchers and clinical practices have utilized the 9-item Patient Health Questionnaire (PHQ-9) to measure depression (Grant et al., 2014; Spitzer et al., 1999) and the MoCA or MMSE to measure cognitive function in the clinical setting (Hoops et al., 2009).

Nonetheless, nurses and health care providers should also keep in mind that though neuropsychological tests have been designed to identify impairment in cognitive function stemming from a brain insult or injury, the vast majority of these tests were not designed to predict how these patients were likely to return to their activities of daily living or real-world settings, to live independently, or to maintain competitive careers/employment (Grant et al., 2014). Not one neuropsychological test can predict how an individual who has a brain injury can function in everyday or vocational settings (Grant et al.). Thus, more comprehensive measures to assess for cognitive function that can assess particular tasks that closely simulate older PLWH's everyday or vocational activities are warranted. As nurses are constantly at the bedside assessing patients and as those who are patient advocates, nurses should advocate for comprehensive measures of cognitive function. Individualized plans of care require unique attention for older

PLWH. Other objective data needs to include reports from caregiver/family members, in addition to assessments such as the MoCA or MMSE to assess cognitive function in older PLWH.

Older age and HIV infection independently increase the risk of impairment in cognitive function (Pereira & Canavarro, 2011; Robinson-Papp et al., 2009; Tozzi et al., 2004) and care for this increasingly growing cohort of older PLWH warrants much attention. Impairment in cognitive function and HIV/AIDS impact HRQOL in persons of all ages, gender, and race. This study highlights the need for interventions with symptomatic and asymptomatic cognitively impaired PLWH. Future interventional studies can be done to explore the effects of cART on cognitive function and can also include assessments of social support/social relationships. Furthermore, mental health and access to health care services are additional factors of importance when considering care for older PLWH.

The characterization of capabilities, cognitive function, and depression in older PLWH can be used to construct a management or rehabilitation plan for the patient. In addition, if recovery or decline in cognitive function and abilities are anticipated, serial assessments may be used to quantify the degree of longitudinal change over time. Future studies to build on this project can assess the psychometric properties of the measurement tools as well as assess the validity and reliability of the various tools in this population group.

Future Research for Older Adults Living with HIV

Future research could examine differences in cognitive impairment and HRQOL in older PLWH in different stages of the HIV illness. Studies focusing on specific cognitive domains, including psychomotor/ processing speed and working memory, that may show additive affects of aging and HIV are needed. This is important to examine in further detail, because there is an added risk factor burden that can decrease HRQOL in older PLWH. In addition, low scores of

HRQOL can increase or potentiate risks for functional or cognitive impairment such as ability to adhere to cART and other medications (Scott et al., 2011) or travel to healthcare appointments.

Future research could also compare different sample populations of older PLWH, including community-based populations, more ethnically diverse populations, and PLWH with/without cognitive insight. These types of studies could compare the relationships of variables in patients newly diagnosed with HIV compared to those living with HIV for a longer period of time. Older PLWH with asymptomatic versus symptomatic cognitive impairment could also be assessed on measures of cognitive function, HRQOL, and depression. Furthermore, including the concept of social support/relationships can also add to the comprehensive plan of care for the HRQOL of older PLWH. The relationship of depression, HRQOL, and somatic complaints in PLWH with cognitive impairment and insight versus PLWH with cognitive impairment and without insight should also be compared. Lack of insight may be characteristic of older PLWH with HAND, and the relationships of these variables should be further explored in older PLWH.

Finally, studies could assess the relationships proposed in this research study in PLWH with severe cognitive impairment and other severe neurological diseases such as Alzheimer's disease (AD) and fronto-temporal dementia. In Alzheimer's disease, memory, language, reasoning, and problem solving skills are often impaired, while attention and visuospatial skills are relatively less impaired (Jacobs 1998). In HIV, prospective memory such as retrieval cue type and delay interval are affected in older PLWH (Avci et al., 2016). This current study did not separate measures of attention, working memory, psychomotor skills, and learning efficiency, but utilized a composite score. There were no significant relationships between self-report of cognitive function and the NTB composite in this study and thus future studies should assess the

relationship of specific neuropsychological domains (i.e. attention, working memory, psychomotor skills, and learning efficiency) with HRQOL. In addition, future research in older PLWH with severe dementia should also assess caregiver and staff report of HRQOL and cognitive function; other studies have found that observations from staff and caregivers provided measures for HRQOL for persons with severe dementia (OAR Working Group on HIV Aging, 2012; Weintraub et al., 2009).

Conclusion

In conclusion, this research study was the first study to explore HRQOL and its correlates to depression, self-report of cognitive function, and clinical measures of cognitive function in the oldest of old population of PLWH. Self-report and clinical report of cognitive function had no relationship in older PLWH. However, self-report of cognitive function was correlated with depression, which indicated that when older PLWH report more depression, they also self-report more cognitive impairment. Furthermore, depression strongly correlated with both mental and physical scores of HRQOL; when older PLWH reported more depression, they reported lower HRQOL scores. Though the PAOFI tool and the physical health summary score of the MOS-HIV did not correlate with clinical measures of cognitive function, the mental HRQOL correlated with self-report of cognitive function, clinical measures of cognitive function, and depression. The mental health summary score of the MOS-HIV was the only tool that correlated with self-report and clinical measures of cognitive function and thus, patient reports on HRQOL measures, particularly mental health summary scores, should be assessed in older PLWH who are at risk for cognitive impairment.

Interventions aimed at education or health care services may provide better health care and HRQOL in older PLWH. Health care providers should be assess for cognitive function in all

older PLWH Academic health centers and clinics could partner with local community providers to provide educational and service opportunities for students in dentistry, medicine, and allied health professions, who in turn provide care for PLWH (Krause et al., 2012). The link between physical, social, and emotional aspects and cognitive function requires further study to determine the pathway between progression of the HIV disease and HRQOL.

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Appendices

Appendix 1

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO EXPERIMENTAL SUBJECT'S BILL OF RIGHTS

The rights below are the rights of every person who is asked to be in a research study. As an experimental subject I have the following rights:

- 1) To be told what the study is trying to find out,
- 2) To be told what will happen to me and whether any of the procedures, drugs, or devices is different from what would be used in standard practice,
- 3) To be told about the frequent and/or important risks, side effects, or discomforts of the things that will happen to me for research purposes,
- 4) To be told if I can expect any benefit from participating, and, if so, what the benefit might be,
- 5) To be told of the other choices I have and how they may be better or worse than being in the study,
- 6) To be allowed to ask any questions concerning the study both before agreeing to be involved and during the course of the study,
- 7) To be told what sort of medical treatment is available if any complications arise,
- 8) To refuse to participate at all or to change my mind about participation after the study is started. This decision will not affect my right to receive the care I would receive if I were not in the study,
- 9) To receive a copy of the signed and dated consent form,
- 10) To be free of pressure when considering whether I wish to agree to be in the study.

If I have other questions I should ask the researcher or the research assistant. In addition, I may contact the Committee on Human Research, which is concerned with protection of volunteers in research projects. I may reach the committee office by calling: (415) 476-1814 from 8:00 AM to 5:00 PM, Monday to Friday, or by writing to the Committee on Human Research, Box 0962, University of California, San Francisco, CA 94143.

Call 476-1814 for information on translations.

Appendix 2

**UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
CONSENT TO PARTICIPATE IN A RESEARCH STUDY**

Study Title: UCSF HIV Over 60 Cohort Study

This is a medical research study. Your study doctors, Drs. Victor Valcour, Bruce Miller, Howard Rosen, and Katherine Rankin, or their staff from the Memory and Aging Center of the UCSF Department of Neurology, will explain this study to you.

Medical research studies include only people who choose to take part. Take your time to make your decision about participating. You may discuss your decision with your family and friends and with your health care team. If you have any questions, you may ask your study doctor.

You are being asked to participate in this study because you are a healthy volunteer or are HIV positive. This study is part of the Memory and Aging Center's Alzheimer's Disease Research Center (ADRC) which conducts numerous research studies. The purpose of the Center is to collect large amounts of information from various tests of brain function in different populations over time with the goal of improving early detection and clinical care for patients with dementia. The scientific data collected without personal identification information may be shared under strict guidelines with collaborating researchers at 30 National Institutes of Health funded Research Centers and pharmaceutical research teams working toward developing treatments.

Why is this study being done?

The purpose of this study is to look at factors that impact the cognitive health of HIV+ individuals over the age of 60 in comparison to other groups enrolled at the UCSF ADRC. We will focus on the relationship between cognition and function as well as risk for age-related neurodegenerative diseases such as Alzheimer's disease.

This study is sponsored by UCSF and the National Institutes of Health

How many people will take part in this study?

About 250 people will take part in this study.

What will happen if I take part in this research study?

Questionnaires: I will be asked to answer questions regarding my medical history, including current medications and HIV status and history, mood, and functional and cognitive abilities. I may fill these out on my own, or in the presence of the study coordinator or doctor. All information is kept confidential.

Function and Memory Tests: I will be asked to do a set of memory and thinking tests (neuropsychological and functional testing). The tests will include paper and pencil tests, computer tests, tests of manual dexterity, and tests of everyday function. This could include being asked to perform tasks such as managing simple finances (writing checks,

making change, etc.), remembering or interpreting instructions, navigating using a map, or other such everyday tasks.

Neurological Exams: I will undergo an exam of the nerves and muscles (neurological examination) by a neurologist.

Initial

Blood drawing (venipuncture): I will be asked to give a blood sample for laboratory tests and serum and plasma storage. Approximately 8 teaspoons of blood will be drawn by inserting a needle into a vein in my arm for these tests. Samples of my blood, serum, and plasma will be stored for future analysis at the AIDS Specimen Bank of the AIDS Research Institute at 513 Parnassus Avenue.

Initial

Genetic testing: A sample of my blood (approximately 1 teaspoon) DNA analysis will be drawn from my arm through a small needle placed in a vein by a licensed phlebotomist for genetic tests that may be useful in identifying people at risk for cognitive problems. The results of the analysis will not be released to me. DNA samples will be stored at UCSF's Genomics Core Facilities at the Mission Bay Campus.

Initial

My blood may also be used to generate cell lines. Cell lines are made from white blood cells that are mixed with a solution that allows for permanent cell growth, immortalizing my cells for future genetic research. The cell lines will be stored at The National Cell Repository for Alzheimer's disease (NCRAD) and/or the AIDS Research Institute (ARI) – Specimen Bank (for viable cells), which are National Institutes of Health funded facilities that provides genetic materials to researchers throughout the country. The cell lines stored at NCRAD/ARI will be de-identified. Other researchers will not receive my name or other identifying information. De-identified data linked to cell lines will be kept on a secure computer at NCRAD/ARI. This information can only be accessed by authorized investigators. A summary of de-identified data will be made available to researchers via a website that will be maintained by NCRAD/ARI. I agree that some blood samples and certain medical information about me (for example, diagnosis, age) may be shared with other researchers studying Alzheimer's disease and other neurodegenerative disorders of the brain. This may include researchers at other academic centers or companies in the biotechnology or pharmaceutical industry.

These genetic samples or their by-products may have therapeutic or commercial value. By signing this consent I am agreeing to such uses. I am being asked allow the blood and cell line samples to be stored indefinitely for these future studies. If these samples are sent to other researchers, only de-identified data, which does not include anything that might directly identify me, will be shared. If I decide later that I do not want my samples to be used for future research, I will notify the Principal Investigator and any remaining identifiable samples will be destroyed. Genetic counseling will be available to answer any questions about genetic issues.

HIV Testing: If I am HIV negative, some of the blood taken for laboratory tests will be used to test for HIV. I will receive the test results in person and will be counseled about the meaning of these results before and after the test.

Initial

MRI: At each visit I will undergo a Magnetic Resonance Imaging (MRI) scan. This will be done at the NCRU at UCSF's Mission Bay Campus. The scan will take approximately 1 hour. I will be screened for any metal before entering the magnet. I may be asked to change out of my clothing and remove any undergarments that contain metal (such as a brassiere). I will be provided with a hospital garment to wear for the procedure. I will lie down on a narrow surface which will then be placed in a tunnel that is 6 feet long by 22 inches wide and open at each end. I will need to lie there quietly for about one hour, during which time there will be a loud banging noise. I may feel warm during this procedure. A speaker and microphone allow communication with the technicians running the scanner. Earplugs will be provided to reduce the sound level. Headphones will also be supplied. It is my responsibility to tell the study staff if I have any metal in my body.

Initial

Lorazepam 1-2mg may be administered 30 minutes before undergoing the procedure if I express concern about claustrophobia or if I think I will have difficulty remaining still for the time required. Lorazepam is a medicine that reduces anxiety and helps one to relax. If I receive lorazepam, I will be monitored by a machine that measures the oxygen level in my blood by a sensor taped to my finger, and I will be removed from the magnet if oxygenation state significantly decreases during the procedure. It is my responsibility to tell the study staff if I have any medication allergies and I will need to arrange a ride home if I use lorazepam.

Study Partner: If I am HIV positive, I will be asked to provide contact information for a study partner - someone that can provide information about me. My study partner will be interviewed about my health, cognitive and functional abilities, and day-to-day activities either in person or on the phone.

Initial

Other Studies: I may be asked to participate in additional studies including smaller pilot studies or novel assessment techniques or treatments. Each of these studies have their own informed consent which describes in detail the procedures required and will be reviewed with me requires my signature. I am free to decline participation. I agree to be contacted by phone by MAC staff members if there is a study that is available for which I might be eligible now or in the future.

Initial

Annual Follow-Up: I will be contacted annually for follow-up visits where all of the above procedures will be repeated. I may choose to participate in other studies at the Memory and Aging Center.

Initial

Optional procedures requiring separate consent:

Initial

Autopsy: I will be asked to enroll in the Autopsy Program and give permission for my entire brain to be removed from my body and examined after my death. I may be asked to donate other nervous system tissue and fluids as well, such as my spinal cord. This tissue will be stored indefinitely for future research. Tissue and fluids will be stored either at UCSF or at one of the National Institute of Health's funded brain banks in the NeuroAIDS Tissue Network, such as the California NeuroAIDS Tissue Network at UCSD.

Investigators responsible for writing the neuropathological autopsy report may be provided with my name, clinical diagnosis, and dates of birth, death and the evaluations completed at the Memory and Aging Center. In addition, these direct identifiers will be included in the neuropathological report which may be released to my next-of-kin. If samples are sent to other researchers, only de-identified data, which does not include anything that might directly identify me, will be shared. If I choose to enroll in the Autopsy Program, my next-of-kin will be asked to provide legal consent for the autopsy. Participation in the Autopsy Program is voluntary. I may withdraw my participation from the Autopsy Program at any time.

Study location: All study procedures will take place at the University of California, San Francisco (UCSF) Mission Bay campus in the NCRU, located at 675 Nelson Rising Lane, San Francisco, CA 94158.

How long are study visits and how long will I be in this study?

The main study visits will range from 4-6 hours total and may be split between two days. A separate portion of the study to measure geriatric syndrome and function takes about 2 hours and the MRI takes about 1 hour. We will try to arrange these visits to meet your schedule. Visits will occur once a year for up to 10 years (10 visits), as funding allows.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop your participation safely.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest, if you do not follow the study rules, or if the study is closed.

What side effects or risks can I expect from being in the study?

You may have side effects while in the study. Everyone taking part in the study will be watched carefully for any side effects. You should talk to your study doctor about any side effects you experience while taking part in the study.

Risks and side effects related to the study include those which are:

Likely

- **Tests of Mental Abilities:** There is the possibility that some of the testing and questions may be fatiguing, stressful or produce unpleasant feelings, but you will be able to stop or take a break at any time if you feel uncomfortable.
- **Neurological Exam:** There are minimal risks associated with a neurological exam, although certain tests may cause mild discomfort. You are encouraged to let the neurologist know if you are unable to continue at any point.

- **HIV Testing:** Being tested for HIV may cause anxiety regardless of the test results. A positive test indicates that you have been infected with the HIV virus, but no one knows for certain when, if ever, you will become sick with AIDS or a related condition. Receiving positive results may make you very upset. If your test is negative, there is still the possibility that you could be infected with the HIV virus and test positive at some time in the future. Also, it is always possible that the test results could be wrong.

Less Likely

- **Blood drawing (venipuncture) risks:** Drawing blood may cause temporary discomfort from the needle stick, bruising, and infection.
- **MRI scans:** brain imaging is considered to be safe, however, the following risks must be considered. The MRI machine acts like a large magnet, and there is a small possibility that magnetic objects will accidentally fly into the magnet, possibly causing physical injury. Precautions are taken to prevent such an event from happening; for example you must remove any metal object, like watches, coins, key chains, or any clothing or shoes that have magnetic parts before entering the MRI room. If you have a piece of metal in your body, such as a fragment in your eye, aneurysm clips, ear implants, spinal nerve stimulators, or a pacemaker, you will not be allowed to take part in the study. It is your responsibility to tell the study staff. Because the information in the magnetic strip on credit cards may be erased by the magnet, you will be asked to leave these items outside the MRI room as well. You cannot wear any jewelry.

Having an MRI may mean some discomfort, such as feeling claustrophobic or bored. There is also a loud banging noise during the study, which may be bothersome. To help reduce the volume of noise, you will be offered disposable earplugs. If you are too uncomfortable and prefer not to continue for any reason, you will be removed from the magnet. After lying still within the magnet for a relatively lengthy period of time, you may experience mild dizziness. You will be asked to sit briefly before leaving the MRI room.

Sometimes, the MRI scans will identify the possibility that there is an abnormality that could impact your health. Since our images are not designed for clinical use, there may be follow-up required, including, in some cases, a clinical MRI to confirm the possible finding. Should there be such an abnormality, you and your doctor will be notified; however, the study will not be able to cover costs for this clinical evaluation.

- **Lorazepam:** Drowsiness, fatigue, and unsteady gait are common side effects of lorazepam. Because the effects will last for several hours you will be asked not to drive for the rest of the day if you take the medication. These medications may slow down your breathing, however, you will wear a monitor during the study so the investigators can monitor this. If you are allergic to lorazepam you must tell the study staff and doctor and you should not request the medication. The major risks of lorazepam are those produced by over-sedation. An extremely rare complication of these drugs would include respiratory depression and possibly death. Elderly subjects are more susceptible

to these effects, and the dosage will be reduced accordingly. Because the risks to a fetus from MRI are unknown, pregnant women cannot participate in this study.

Rare but serious

- **Unknown Risks:** This study does not include any experimental treatments, and therefore, involves little to no unknown risks. The researchers will let you know if they learn anything that might make you change your mind about participating in the study.
- For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the study?

There will be no direct benefit to you from participating in this study. However, this study will help doctors learn more about how HIV impacts memory and cognition, and if HIV infection increases risk of neurodegenerative disorders, and it is hoped that this information will help in the treatment of future patients. Information about your cognitive testing performance and MRI will be shared with you and your doctor and may be helpful for your clinical care.

What other choices do I have if I do not take part in this study?

- There is no treatment offered in this study. Your choice is not to participate.

Will my medical information be kept private?

We will do our best to make sure that the personal information in your medical record is kept private. However, we cannot guarantee total privacy.

Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your personal information will not be used.

A medical record will be created because of your participation in this study. Your consent form and some of your research test results will be included in this record. Therefore, your other doctors may become aware of your participation. Hospital regulations require that all health care providers treat information in medical records confidentially.

Dr. Valcour and his research team, as well as other sites associated with this study, will have access to information about you. The UCSF Committee on Human Research and other University of California personnel also may review or receive information about you to check on the study. All records will be stored in a secure database and information transmitted by electronic mail will be protected by password or encryption. As with any use of electronic means to store data, there is a risk of breach of data security. If information collected for this research is required by federal or state laws to be reported to appropriate officials, such as elder abuse, study personnel will follow such legal guidelines. This may include reporting you to the Department of Motor Vehicles for additional testing if Memory and Aging Center physicians believe driving may be a danger to yourself or others.

What are the costs of taking part in this study?

You will not be charged for any of the study activities. We will validate your parking for the amount of time you are in the center (up to 8 hours of each visit).

Will I be paid for taking part in this study?

You will be paid \$50 in debit card once you have completed the main study visits for each year (except the MRI). Once you complete the functional and geriatric measures, you will receive an additional \$25. This can be done on the same day. This will not be done every year. You may also be eligible for a brain MRI and we will provide \$50 for this exam.

We will not be able to provide partial payment for partial completion of the study visits. You must complete all parts of the study visit to receive the compensation.

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor, Dr. Victor Valcour, if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call his assistant at (415) 476-1688.

Treatment and Compensation for Injury: If you are injured as a result of being in this study, treatment will be available. The costs of the treatment may be covered by the University of California or the study sponsor, depending on a number of factors. The University and the study sponsor do not normally provide any other form of compensation for injury. For further information about this, you may call the office of the Committee on Human Research at (415) 476-1814.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

Who can answer my questions about the study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor, Dr. Victor Valcour through his assistant at (415) 476-1688.

For questions about your rights while taking part in this study, call the office of the Committee on Human Research, UCSF's Institutional Review Board (a group of people who review the research to protect your rights) at (415) 476-1814.

CONSENT

You have been given copies of this consent form and the Experimental Subject's Bill of Rights to keep.

You will be asked to sign a separate form authorizing access, use, creation, or disclosure of health information about you.

PARTICIPATION IN RESEARCH IS VOLUNTARY. You have the right to decline to participate or to withdraw at any point in this study without penalty or loss of benefits to which you are otherwise entitled.

If you wish to participate in this study, you should sign below.

As part of your participation in research, you will receive research-related mailings such as educational mailings and scheduling confirmations.

Yes, I **do** want to receive research-related mailings such as educational mailings, invitations to events and scheduling confirmations. This may be done by using a postcard (not in an envelope) that includes information about our group (Memory and Aging Center) and our research.

No, I **do not** want to receive research-related mailings such as educational mailings and scheduling confirmations.

Date

Participant's Signature for Consent

Date

Participant's Printed Name for Consent

Date

Person Obtaining Consent – Signature

Date

Person Obtaining Consent – Print name

AND/OR:

The person being considered for this study is unable to consent for him or herself because he or she is cognitively impaired or is not capable of reading or signing the consent form. I have been asked to give my permission to include this person in this study. I know of no reason why he or she would refuse were it possible to do so. I agree to sign a self-certification of surrogate decision maker form (by signing the surrogate form I am stating I am the best person to make decisions regarding research

participation for the person and will state my relationship to the person and provide my contact information).

Date

Legally Authorized Representative - Signature

Date

Legally Authorized Representative - Print

Date

Person Obtaining Consent - Signature

Date

Person Obtaining Consent - Print

Publishing Agreement

It is the policy of the University to encourage the distribution of all theses, dissertations, and manuscripts. Copies of all UCSF theses, dissertations, and manuscripts will be routed to the library via the Graduate Division. The library will make all theses, dissertations, and manuscripts accessible to the public and will preserve these to the best of their abilities, in perpetuity.

Please sign the following statement:

I hereby grant permission to the Graduate Division of the University of California, San Francisco to release copies of my thesis, dissertation, or manuscript to the Campus Library to provide access and preservation, in whole or in part, in perpetuity.

Hank J. Yang

Author Signature

June 7, 2016

Date