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The Roles of Social Isolation, Loneliness, and Inflammation in Risk of Cognitive Impairment among People Living with HIV

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The Roles of Social Isolation, Loneliness, and Inflammation in Risk of Cognitive Impairment among People Living with HIV

by
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Dedication and Acknowledgements

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Abstract

The Roles of Loneliness, Social Isolation, and Inflammation in Risk of Cognitive Impairment among Older Adults Living with HIV

Sarah Dobbins

Background: Since the onset of the HIV epidemic, antiretroviral therapy (ART) has lengthened the lives of people living with HIV (PLWH). More than half of the population of PLWH are 50 years and older, and as the aging population of PLWH expands it is important to consider the environmental, socio-structural, and biological factors and pathways that impact aging with HIV (Centers for Disease Control and Prevention [CDC], 2018). It is estimated that about a third to one half of HIV-seropositive individuals have some degree of cognitive impairment (Heaton et al., 2010), though prevalence may be lower in populations with sustained viral suppression (V. Valcour, personal communication, December 2018). Studies show that various measures of loneliness and social isolation are associated with risk for cognitive impairment and dementias among the general population (Kuiper et al., 2015, 2019). Literature also indicates that, on average, PLWH experience more loneliness and social isolation than HIV-seronegative individuals (Greene et al., 2018; Grov et al., 2010; Poindexter & Shippy, 2008). In addition to the environmental and social factors that impact risk for cognitive impairment among PLWH, the study of inflammatory processes and biomarkers—and whether these are important for the development of HAND—is an important area of current research (Office of AIDS Research [OAR] Working Group on HIV and Aging, 2012). Current evidence demonstrates an overall increased risk of morbidity and mortality in HIV-positive individuals whose CD4/CD8 ratio fails to normalize above 1.0 (Mussini et al., 2015; Serrano-Villar et al., 2013, 2014). Additionally, a small number of studies show that inverted CD4/CD8 ratio is associated with the development of neurocognitive disorders (Correa et al., 2014; Grauer et al., 2015; Rawson et al., 2015; Vassallo et al., 2017).

Problem Statement: The central hypotheses motivating this dissertation research is that loneliness and social isolation represent two distinct and uniquely important factors in the risk of cognitive impairment

among people aging with HIV, and that CD4/CD8 ratio is an endophenotype that may help elucidate the pathways by which physical health, mental health, and environmental factors impact cognitive impairment among PLWH.

Chapter 2: The 2nd chapter of this dissertation systematically examined the current body of quantitative literature about social support and loneliness and cognitive impairment among PLWH. We used meta-analysis to summarize the association of these variables and used meta-regression to identify moderating variables in N=11 studies. Among the 11 studies reviewed, many were limited by the use of un-validated measures of loneliness and/or social support as well as heterogeneous measures of cognitive symptoms and cognitive performance. The meta-analysis (n=10) showed a positive association between social isolation or loneliness and cognitive impairment. Though there was moderate heterogeneity among the studies analyzed, there was not substantial publication bias. Meta-regression showed moderation of the association by study quality, older age (≥55 years), and study country but not by sample mean CD4 cell count. This paper highlights knowledge gaps in the current body of research and reflects distinctions between performance-based and self-reported measures of cognitive impairment as well as various dimensions of social connectedness.

Chapter 3: Building on the knowledge gaps identified in the second dissertation chapter, the 3rd chapter of this dissertation examined the association of both loneliness and social isolation with performance based cognitive impairment and subjective cognitive complaints in a sample of older adults living with HIV and confirmed HIV-Associated Neurocognitive Disorders (HAND). We performed a cross-sectional, secondary data analysis in a cohort of older adults living with HIV recruited at the Memory and Aging Center (N=171). This paper revealed that loneliness was correlated with mental health variables (depression, anxiety, and perceived stress) while social isolation was correlated with other marginalized conditions and socioeconomic factors (lower years of education, history of Hepatitis C (HCV), history of a substance use disorder, and Black/African American race, and area-level socioeconomic environment). This paper also showed that social isolation, but not loneliness, was associated with higher odds of

impairment in two cognitive domains (Attention and Executive function [ATT] and Speed of Processing [SPD]). We concluded that social isolation may be conceptualized as a pathway of embodiment, reflecting experiences of marginality that could impact risk of HAND.

Chapter 4: The 4th chapter of the dissertation used an exploratory, cross-sectional secondary analysis of the the Hawaii Aging with HIV Cardiovascular Study (HAHCS) cohort-Public Data Set. We aimed to examine the relationships between CD4/CD8 and biomarkers of inflammation among middle-aged and older adults living with HIV (N=103). This study revealed that the lowest tertile of CD4/CD8 ratio (Median: 0.346, range 0.123-0.501) was associated with a higher inflammation profile and higher concentration of mature monocytes in the blood. In elucidating the CD4/CD8 cell ratio among PLWH, this paper contributes to the body of evidence that suggests a link between CD4/CD8 ratio and established risk factors for HAND among middle-aged and older adults with HIV.

Chapter 5: The 5th chapter of the dissertation was a longitudinal study of the Women's Interagency Health Study (WIHS) public data set to examine the intra-individual variability of the CD4/CD8 ratio over 10 years as well as clinical and sociodemographic correlates of CD4/CD8 ratio among women living with HIV (n=1462). This study revealed that, over 10 years, the CD4/CD8 ratio remained relatively stable. Over time, decreased CD4/CD8 ratio was associated with higher age, detectable viral load, and sub-optimal ART adherence. We then examined associations of clinical and sociodemographic with "inverted" CD4/CD8 ratio (≤ 1.0 *versus* >1.0) and "low" CD4/CD8 ratio (≤ 0.70 *versus* >0.70). This paper revealed that inverted and low CD4/CD8 ratio were both associated with detectable viral load and fewer years of educational attainment. Because much of the WIHS sample had a CD4/CD8 ratio that was below 0.50, in addition to the findings from chapter 4 that indicate inflammation is association with the lowest tertile of CD4/CD8 ratio (0.123-0.501), we subsequently performed a follow-up analysis to examine variables associated with "very low" CD4/CD8 ratio (≤0.50 *versus* >0.50). We found that very low CD4/CD8 ratio was associated with older age, detectable viral load, past/current Hepatitis C, white racial group, and lower educational attainment. Overall, the findings from this paper show that CD4/CD8

ratio was relatively stable over time, but was significantly influenced by age, viral load, and adherence to ART medications. We also found that inverted, low, and very CD4/CD8 ratio were all associated with fewer years of education. In linking CD4/CD8 ratio to lower educational attainment, our study implicates immune function as a pathway by which root causes and social determinants of health (SDOH) may impact risk of cognitive impairment among women with HIV.

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List of Abbreviations

AA: African American

ATT: Attention and working memory

ABS: Abstraction and executive function

AIDS: Acquired Immunodeficiency Syndrome

AOR: Adjusted Odds Ratio

ART: Antiretroviral Therapy

cART: Combination ART

CD4: Cluster of differentiation 4

CD8: Cluster of differentiation 8

CES-D: Center for Epidemiologic Studies Depression Scale

CI: Confidence Interval

CMV: Cytomegalovirus

CRP: C-Reactive Protein

FDA: Food and Drug Administration

GDS: Geriatric Depression Scale

HAHCS: Hawaii HIV and Aging Cardiovascular Study

HAND: HIV-Associated Neurocognitive Disorder

HBV: Hepatitis B Virus

HCV: Hepatitis C Virus

HIV: Human Immunodeficiency Virus

IL: Interleukin

IPCW: Inverse Probability of Censoring Weights

INF: Interferon

LPA: Latent Profile Analysis

PAOFI: Patients Assessment of Own Functioning Inventory

PDS: Public Data Set

PLWH: People Living with HIV

QoL: Quality of Life

MAC: Memory and Aging Center

MEM: Memory and Recall

MMSE: Mini-Mental State Examination

MoCA Montreal Cognitive Assessment

MND: Mild Neurocognitive Disorder

NIH: National Institutes of Health

NP: Neuropsychological

NSS: Norbeck Social Support

OR: Odds Ratio

POR: Proportional odds ratio

RNA: Ribonucleic acid

SD: Standard deviation

SE: Standard error

SDOH: Social Determinants of Health

SMD: Standardized mean difference

SMT: Symptom Management Theory

SEP: Socioeconomic position

SPD: Speed of processing domain

TNF: Tumor Necrosis Factor

UCLA: University of California, Los Angeles

VER: Verbal Memory

WIHS: Women's Interagency Health Study

Chapter 1

Introduction to the Dissertation

Statement of Interest

The circuitous path that led me to nursing was marked by various experiences working with marginalized adults. Through my work as a research assistant with the trauma surgery team at San Francisco General Hospital (SFGH), as a nurse at the San Francisco Department of Public Health, and through volunteering with Street Outreach Services (SOS) and Syringe Access Services at the San Francisco AIDS foundation I learned about the syndemics of HIV, substance use disorders, serious mental illness, and cognitive aging.

In 2018 I graduated from the UCSF Masters Entry Program in Nursing program and became a psychiatric nurse practitioner. I joined the Street Medicine & Shelter Health team at San Francisco Department of Public Health. In this work, I provide psychiatric care for unhoused adults with complex trauma, mental health and substance use disorders, and chronic health conditions. I continuously struggle to support my clients with the overwhelming challenges of aging with marginalized conditions, particularly HIV and cognitive impairment. My clinical practice has directly informed and enriched my academic development and research activities as a doctoral student at UCSF.

My mentors have all taught me to value critical scientific inquiry and translational science. My academic background in infectious disease bioscience, public health, and nursing science, as well as my professional experience as a psychiatric nurse practitioner, influenced all aspects of my dissertation work. The framework used for this research was developed to study the symptom of cognitive impairment among older adults with HIV, with a focus in two key areas of nursing research: First, the domain of environment and social conditions that impact health, and second, the domain of biomarkers, including inflammation and immunological characteristics.

Background and Significance

Since the onset of the HIV epidemic, antiretroviral therapy (ART) has lengthened the lives of people living with HIV (PLWH). More than half of the population of PLWH are 50 years and older, and as the aging population of PLWH expands it is important to consider the factors that impact aging with HIV (Centers for Disease Control and Prevention, 2018). It is estimated that about a third to one half of HIV-seropositive individuals have some degree of cognitive impairment (Heaton et al., 2010). The manifestation of HIV-associated neurocognitive disorders (HAND) encompasses a wide range of symptoms including emotional/affective changes, behavioral changes, and cognitive changes in attention and executive function, motor function, and memory (Valcour et al., 2004). Environmental, social, and biological risk factors for developing HIV-associated cognitive impairment have been established, and they include lower education attainment, stigma and depression, certain substance use disorders, access to healthcare, trauma and violence, inflammation, neurotoxic effects of ART medication and of HIV itself, metabolic conditions, and co-occurring infections such as HCV (Winston & Spudich, 2020).

Social isolation and loneliness are tightly linked to outcomes in geriatric medicine (Inouye et al., 2007). Loneliness has been described and defined in different ways, including "a debilitating psychological condition characterized by a deep sense of emptiness, worthless ness, lack of control, and personal threat," (Cacioppo et al., 2015) stress caused by the discordance between actual and desired relationships (Leigh-Hunt et al., 2017), and a negative emotion, distinct from depression, produced by unmet social and intimacy-related needs (Peplau & Perlman, 1982). Likewise, social isolation has been defined as an objective description of a lack of interactions with others or with a wider community (Berkman et al., 2000; Peplau & Perlman, 1982). Although there is still a general lack of consensus for the definitions of social isolation and loneliness, many studies show that various measures of loneliness and social isolation are associated with increased risk of all-cause mortality (Greysen et al., 2013; Holt-Lunstad et al., 2010; Perissinotto et al., 2012) and meta-analyses of longitudinal studies confirm that

social connection and loneliness impact cognitive aging among the general population (Kuiper et al., 2015).

Literature indicates that, on average, PLWH experience more loneliness and social isolation than HIV-seronegative individuals (Greene et al., 2018; Grov et al., 2010; Poindexter & Shippy, 2008). This may be attributed to the higher rates of stigma, depression, and marginalization among PLWH (Grov et al., 2010; Poindexter & Shippy, 2008). There is an abundance of research about the impact of social isolation and loneliness on cognitive impairment in the general population, however fewer studies about these relationships have been carried out among HIV-seropositive adults.

HIV infection is associated with chronic, low-level inflammation throughout the body, which is in turn related to a number of health conditions. Additionally, virally mediated changes in the immune system can lead to acceleration of the aging process, resulting in earlier onset of age-related chronic disease and frailty (OAR Working Group on HIV and Aging, 2012). As such, the National Institute on Aging has called for research examining biomarkers at the cellular, organ, and system levels among older people with HIV. The Food and Drug Administration (FDA)-National Institutes of Health (NIH) Biomarker Working Group provides the following definition of a biomarker: "A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions. Molecular, histologic, radiographic, or physiologic characteristics are types of biomarkers but a biomarker is not an assessment of how an individual feels, functions, or survives." (FDA-NIH Biomarker Working Group, 2016).

The CD4/CD8 cell ratio is a biomarker of inflammation and accelerated aging that has been gaining interest among those who study HIV and aging (Lu et al., 2015; McBride & Striker, 2017; Saracino et al., 2014; Serrano-Villar & Deeks, 2015) **(Figure 1.1).** For some PLWH, despite treatment with ART medications and viral suppression, CD4/CD8 ratio fails to normalize above 1.0 even when CD4 cell count has recovered (Cao et al., 2016). Evidence demonstrates an overall increased risk of morbidity and mortality in HIV-positive individuals whose ratio fails to normalize (Mussini et al., 2015;

Serrano-Villar et al., 2013, 2014). Additionally, lower CD4/CD8 ratio may be associated with the development of neurocognitive disorders (Correa et al., 2014; Grauer et al., 2015; Rawson et al., 2015; Vassallo et al., 2017) **(Table 1.1).** To date, there remains a dearth of evidence about the role of CD4/CD8 ratio in cognitive impairment among older adults with HIV.

Theoretical Framework

HIV is a stigmatized condition and disproportionately affects marginalized communities who have restricted access to socioeconomic resources, systematized barriers to healthcare, and premature morbidity and mortality (Farmer et al., 2006; Stonington et al., 2018). Cognitive impairment in the setting of HIV is known to have a multifactorial etiology and progression (Winston & Spudich, 2020). Therefore, the study of cognitive impairment among older adults with HIV requires particular attunement to environmental risk factors as well as socio-structural processes and determinants of health. The study of health status and symptoms among older adults with HIV is a priority for nursing research; However, the current theoretical model (Symptom Management Theory [SMT], Dodd et al., 2001) that guides symptom science lacks attention to the environment and social determinants of health. This theoretical gap has consequences for nursing research among PLWH. Therefore, for this dissertation work, I rely on a modified theoretical model of symptom science. This model, named the *Ecosocial Model of Symptom Science,* is adapted using propositions from Link & Phelan's theory of fundamental causes of poor health (Link & Phelan, 1995; Phelan et al., 2004), the WHO Social Determinants of Health framework (World Health Organization, 2010), and Nancy Krieger's Ecosocial Theory (Krieger, 1994, 2001). Below the major aspects of this modified theoretical model are described. Additionally, **Table 1.1** provides the definitions for key terms relating to my adapted theoretical model and **Figure 1.2** provides a visual depiction of the model and relationships between the premises.

Environment

One of the core assumptions of SMT is that three key nursing domains influence symptoms: Person, Health/Illness, and Environment. A domain is considered to be the territory and central subject matter of a discipline (Meleis, 2017, p.26), and in the SMT these domains contextualize the core theoretical concepts. The domains of SMT have a heavy focus on the level of the individual with relatively little thought given to the concept of environment. For example, in the environment domain of SMT, "physical, social, and cultural factors"—which largely operate at the individual level—are highlighted. (Meleis, 2017, p.26). In 1989, Stevens proposed a re-conceptualization of 'environment' for nursing theory, which "involves uncovering and critiquing oppressive social structures that constrain persons' health, constrain their life possibilities, and restrict their equal and fully conscious participation in society" (Stevens, 1989, p.59). In the Ecosocial Model of Symptom Science, the environment is a relatively abstract and is one of the most important concepts in the model, encircling and overlaying each aspect of the Ecosocial Model of Symptom Science. It impacts health and patterns of disease, including health disparities, and includes broad socioeconomic & political systems, ecological conditions, and the contingencies of history.

Root causes

The concept of a *root cause*, also known as a fundamental cause, was established by Link and Phelan in 1995 (Link & Phelan, 1995). Root causes are defined as social conditions that are not modifiable at the individual level. According to Link and Phelan (1995), these social conditions include factors that manifest in differences in socioeconomic position (SEP) and social hierarchies falling along the lines of knowledge, power, prestige, and access to resources (Phelan et al., 2004). These authors state that root causes drive health disparities, in part, because people of higher SEP have access to a "wide range of broadly serviceable resources, including money, knowledge, prestige, power, and beneficial social connections, that can be used to one's health advantage" (Phelan et al., 2004). There is substantial overlap between root causes and Social Determinants of Health (SDOH), as defined by the World Health

Organization (WHO) in their framework (2010). Therefore, root causes can be conceptualized as social determinants of health at the structural level. Examples include educational attainment, social class, poverty/income, racism, social capital, and public health and public safety policies.

Pathways of Embodiment

One of the most critical aspects of the Ecosocial Model of Symptom Science is the concept of embodiment, which has been developed by Nancy Kreiger since 1994. In Kreiger's Ecosocial Theory (1994), embodiment is defined as "how we literally embody, biologically, our lived experience, in societal and ecological context, thereby creating population patterns of health and disease" (Krieger, 2001, p.670). Pathways of embodiment are the trajectories of the biological and social development of a body (Krieger, 2005, p.352). In this sense, biological phenomena and aspects of health, such as symptoms, are seen as embodied phenomenon. The Ecosocial Model for Symptom Science relies heavily on Krieger's theory and borrows the language of embodiment to describe the pathways by which root causes may influence the health of people aging with HIV.

Marginalized Conditions

The term marginalize indicates the action of forcing a subject into a position of powerlessness (Baah et al., 2019; Hall, 1999). Marginalization has been defined for nursing science as "the process through which persons are peripheralized based on their identities, associations, experiences, and environment" (Hall et al., 1999, p.25). Those who are marginalized in society are thought to exist on the boundaries of a dominant social structure from a geographical or societal perspective (Hall et al., 1999). Importantly, processes of marginalization are rooted in socio-structural factors, access to resources fundamental to establishing SEP (root causes), and environment (Mathieson et al., n.d.; Popay, 2010).

The effects of marginalization are socially and psychologically damaging, and can impact domains of health through multiple mechanisms (Braveman & Gruskin, 2003). As a result, marginalized populations are subjected to substantial health disparities/inequalities and a higher burden of symptom

morbidity and mortality (Hall, 1999; Marmot, 2005). Marginalized populations are comprised of diverse people with dynamic, intersecting experiences and identities. Therefore, it is a pragmatic approach to focus on marginalization both in terms of process attributes pertaining to health and healthcare systems as well as health outcomes. Using this approach, I identified a population characterized as *people experiencing marginalized conditions* (PEMC). Marginalized conditions can generally be characterized by stigma, criminalization, barriers to healthcare, trauma associated with healthcare systems, and premature aging, morbidity, and mortality. These conditions include HIV, substance use disorders (particularly illicit substances and injection drug use), serious mental illness (particularly psychotic disorders, personality disorders, PTSD, and mood disorders), homelessness, hepatitis C, and others. While this approach to defining a population provides a useful heuristic device that can be clearly defined and identified, it is important to note that marginalized conditions should not themselves be used to define the process of marginality as this logic would be teleological. Rather, we may define marginalized conditions by virtue of the socio-political, historical, and oppressive processes that restrict access to resources and shape root causes of health for the people who come to experience them.

Symptoms, Signs, and Biomarkers

Symptoms, defined as "an objective experience reflecting changes in the bio-psychosocial function, sensations, or cognition of an individual" (Bender et al., 2018; Dodd et al., 2001), are one primary focus of symptom science in nursing. In contrast to a symptom, a sign is considered observable rather than perceived and is defined as "as any abnormality indicative of disease that is detectable by the individual or by others" (Harver & Mahler, 1990 in Dodd et al., 2001). Similarly, it is explicit in the definition of a biomarker that it is not an "assessment of how an individual feels, functions, or survives" but rather a measure of a biological process (FDA-NIH Biomarker Working Group, 2016). In contrast to a symptom, which is experiential and subjective, signs and biomarkers are observable and relatively objective. Using Kreiger's ecosocial theory, the core aspects of embodiment can be used to modify the

boundaries of SMT—in particular, the theoretical boundaries pertaining to the subject matter of symptoms.

According to Kreiger, the construct and process of embodiment is based on three important tenants: "(1) bodies tell stories about—and cannot be studied divorced from—the conditions of our existence; (2) bodies tell stories that often—but not always—match people's stated accounts; and (3) bodies tell stories that people cannot or will not tell, either because they are unable, forbidden, or choose not to tell." (Krieger, 2001, p.350). These stories are not just told through the language of the subject (symptoms), but also through the language of biological and physical processes (biomarkers and signs). Nursing scientists fundamentally seek to understand that story of the body, which is inextricably linked to the environment and root causes. As such, the Ecosocial Model of Symptom Science incorporates additional concepts, which serve to extend the reach on nursing inquiry beyond the constraints of symptoms.

This modification of SMT is also necessary because the prioritization of symptoms above signs and biomarkers constrains the utility of symptom science among PEMC. This is especially true among those who suffer from marginalized conditions that are often characterized by disordered subjectivity, including loss of insight, disorganized thought processes and behaviors, dissociation, emotional dysregulation, cognitive dysfunction, and poor awareness of one's own symptoms. For many PEMC, as Krieger describes above, cognitive impairment is a story told by the body that may not match the one's stated account. Therefore, in order to study of cognitive impairment among PLWH, the additional domains of *sign* and *biomarker* were added to the theoretical model (**Figure 1.2**).

Problem Statement

An abundance of studies in HIV-seronegative populations show that measures of social connectedness are associated with poor physical, mental health, and cognitive outcomes in aging (Gerst-Emerson & Jayawardhana, 2015; Luo et al., 2012). Meta-analyses of longitudinal studies among the general population confirm that social isolation and loneliness impact risk of neurocognitive disorders (Kuiper et al., 2015); however, these relationships are understudied in the population of PLHW. The CD4/CD8 cell ratio is an emerging biomarker of chronic inflammation and immune dysfunction among people aging with HIV (Lu et al., 2015), and a small number of studies suggest an association between CD4/CD8 and HAND (Correa et al., 2014; Grauer et al., 2015; Rawson et al., 2015; Vassallo et al., 2017). The central hypothesis motivating this dissertation research is that loneliness and social isolation represent two distinct and uniquely important factors in the risk of cognitive impairment among people aging with HIV, and that CD4/CD8 ratio is an embodied endophenotype that may help elucidate the pathways by which physical health, mental health, and environmental factors impact cognitive impairment among PLWH.

Purpose and Specific Aims

Aim 1: Systematically review and synthesize evidence on the association of cognitive impairment with social isolation and loneliness among adults living with HIV. Among the general population, meta-analyses of longitudinal studies confirm that social connection and loneliness impact risk of neurocognitive disorders (Kuiper et al., 2015); However, these relationships among PLWH have never been systematically synthesized nor examined using meta-analysis techniques.

Objective 1: Systematically review and narratively synthesize the extant quantitative scientific literature about association between cognitive impairment and social isolation and/or loneliness among adult PLWH.

Objective 2: Estimate the pooled association between cognitive impairment and social isolation & loneliness and among PLWH using meta-analysis.

Objective 3: Perform sub-group comparisons to estimate the pooled association of social isolation and loneliness with cognitive performance and self-reported cognitive impairment.

Objective 4: Perform a meta-regression to examine moderation of the association of social isolation and loneliness and cognitive impairment by age, study country, study quality, and mean CD4 cell count.

Aim 2: Examine the association of cognitive impairment and social isolation/loneliness among older adults with symptomatic HIV-associated neurocognitive disorders (HAND). The impact of social isolation and loneliness on cognitive impairment in HIV-seronegative adult populations has been firmly established, but a knowledge gap concerning these relationships among older adults living with HIV still exists.

Objective 1: Explore the social network structure and degree of loneliness among older adults living with symptomatic HAND.

Objective 2: Examine the correlates of social isolation and loneliness among older adults living with symptomatic HAND.

Objective 3: Examine the association of cognitive performance with social isolation and loneliness among older adults living with symptomatic HAND.

Objective 4: Examine the association of self-reported cognitive impairment with social isolation and loneliness among older adults living with symptomatic HAND.

Aim 3: Perform an exploratory analysis of the associations between CD4/CD8 cell ratio, immunologic biomarkers, and clinical characteristics among middle-aged and older adults with HIV. CD4/CD8 ratio is an emerging biomarker of inflammation and immune dysregulation in HIV. Evidence demonstrates an overall increased risk of morbidity and mortality in HIV-positive individuals whose ratio fails to normalize (Mussini et al., 2015; Serrano-Villar et al., 2014). In some, low ratio is associated with the development of neurocognitive disorders (Correa et al., 2014; Grauer et al., 2015; Rawson et al., 2015; Vassallo et al., 2017). A better understanding of the role this ratio plays in risk of HAND is still needed.

Objective 1: Explore the relationships between CD4/CD8 cell ratio with sociodemographic and clinical characteristics among adults 40 years and older in the HAHCS cohort.

Objective 2: Explore the relationships between CD4/CD8 cell ratio and peripheral inflammation among adults 40 years and older in the HAHCS cohort.

Objective 3: Explore the relationships between CD4/CD8 cell ratio and peripheral blood monocyte subsets among adults 40 years and older in the HAHCS cohort.

Aim 4: Examine the intra-individual variability in CD4/CD8 ratio over time and the correlation of low CD4/CD8 ratio with clinical and sociodemographic characteristics among HIV+ women.

CD4/CD8 ratio, an emerging biomarker in HIV, is thought to be a marker of chronic inflammation. The precise threshold for what to consider a low CD4/CD8 cell ratio among PLWH is still debated, and there is a paucity of studies that confirm the clinical and population health relevance of this biomarker at various cut-points. Similarly, there is little information about clinical and environmental factors associated with low CD4/CD8 cell ratio and the subject-specific variability of this ratio over time has not yet been established in the HIV literature.

Objective 1: Examine the intra-individual variability of the CD4/CD8 cell ratio over 10 years among HIV+ women in the Women's Interagency Health Study (WIHS).

Objective 2: Examine the clinical and sociodemographic characteristics associated with change in the CD4/CD8 cell ratio over 10 years among HIV+ women in the WIHS.

Objective 3: Examine the clinical and sociodemographic characteristics associated with very low (<0.50), low (<0.50), and inverted (<1.0) CD4/CD8 ratio among HIV+ women in the WIHS.

Overview of Papers

This dissertation is organized into four parts. The first study systematically examines the current body of quantitative literature on the association between loneliness, social isolation, and cognitive impairment among PLWH, and used meta-analysis to summarize the reported associations. The second study of this dissertation examines the association of loneliness and social isolation with performance based cognitive impairment and subjective cognitive complaints in a sample of older adults living with HIV and confirmed HAND. The third study of the dissertation explors the relationships between CD4/CD8 ratio and biomarkers of inflammation in a sample of middle-aged and older adults (40+ years) living with HIV. The fourth study in this dissertation focused on further understanding the CD4/CD8 ratio. I examine the inter-individual variability of CD4/CD8 ratio as well as the associations of very low CD4/CD8 ratio (≤0.50 *versus* >0.50), low CD4/CD8 ratio (≤0.70 *versus* >0.70), and inverted CD4/CD8 ratio (≤1.00 *versus* >1.00) with clinical and sociodemographic factors over 10 years among women living with HIV.

References

Baah, F. O., Teitelman, A. M., & Riegel, B. (2019). Marginalization: Conceptualizing patient vulnerabilities in the framework of social determinants of health—An integrative review. *Nursing Inquiry*, *26*(1), e12268. https://doi.org/10.1111/nin.12268

Berkman, L. F., Glass, T., Brissette, I., & Seeman, T. E. (2000). From social integration to health: Durkheim in the new millennium. *Social Science & Medicine (1982)*, *51*(6), 843–857.

Cacioppo, S., Grippo, A. J., London, S., Goossens, L., & Cacioppo, J. T. (2015). Loneliness: Clinical Import and Interventions. *Perspectives on Psychological Science : A Journal of the Association for Psychological Science*, *10*(2), 238–249. https://doi.org/10.1177/1745691615570616

Cao, W., Mehraj, V., Kaufmann, D. E., Li, T., & Routy, J.-P. (2016). Elevation and persistence of CD8 T-cells in HIV infection: The Achilles heel in the ART era. *Journal of the International AIDS Society*, *19*(1), 20697. https://doi.org/10.7448/IAS.19.1.20697

Centers for Disease Control and Prevention. (2018, September 18). *HIV Among People Aged 50 and Over*. https://www.cdc.gov/hiv/group/age/olderamericans/index.html

Dodd, M., Janson, S., Facione, N., Faucett, J., Froelicher, E. S., Humphreys, J., Lee, K., Miaskowski, C., Puntillo, K., Rankin, S., & Taylor, D. (2001). Advancing the science of symptom management. *Journal of Advanced Nursing*, *33*(5), 668–676. https://doi.org/10.1046/j.1365-2648.2001.01697.x

Farmer, P. E., Nizeye, B., Stulac, S., & Keshavjee, S. (2006). Structural Violence and Clinical Medicine. *PLoS Medicine*, *3*(10). https://doi.org/10.1371/journal.pmed.0030449

FDA-NIH Biomarker Working Group. (2016). *BEST (Biomarkers, EndpointS, and other Tools) Resource*. Food and Drug Administration (US). http://www.ncbi.nlm.nih.gov/books/NBK326791/

Gerst-Emerson, K., & Jayawardhana, J. (2015). Loneliness as a public health issue: The impact of loneliness on health care utilization among older adults. *American Journal of Public Health*, *105*(5), 1013–1019.

Greene, M., Hessol, N. A., Perissinotto, C., Zepf, R., Hutton Parrott, A., Foreman, C., Whirry, R., Gandhi, M., & John, M. (2018). Loneliness in Older Adults Living with HIV. *AIDS and Behavior*, *22*(5), 1475–1484. https://doi.org/10.1007/s10461-017-1985-1

Greysen, S. R., Horwitz, L. I., Covinsky, K. E., Gordon, K., Ohl, M. E., & Justice, A. C. (2013). Does social isolation predict hospitalization and mortality among HIV+ and uninfected older veterans? *Journal of the American Geriatrics Society*, *61*(9), 1456–1463. https://doi.org/10.1111/jgs.12410

Grov, C., Golub, S. A., Parsons, J. T., Brennan, M., & Karpiak, S. E. (2010). Loneliness and HIV-related stigma explain depression among older HIV-positive adults. *AIDS Care*, *22*(5), 630–639. https://doi.org/10.1080/09540120903280901

Hall, J. M. (1999). Marginalization Revisited: Critical, Postmodern, and Liberation Perspectives. *Advances in Nursing Science*, *22*(2), 88–102. https://journals.lww.com/advancesinnursingscience/Abstract/1999/12000/Marginalization_Revisited__Critical,_Postmodern,.9.aspx

Heaton, R. K., Clifford, D. B., Franklin, D. R., Woods, S. P., Ake, C., Vaida, F., Ellis, R. J., Letendre, S. L., Marcotte, T. D., Atkinson, J. H., Rivera-Mindt, M., Vigil, O. R., Taylor, M. J., Collier, A. C., Marra, C. M., Gelman, B. B., McArthur, J. C., Morgello, S., Simpson, D. M., … Grant, I. (2010). HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy. *Neurology*, *75*(23), 2087. https://doi.org/10.1212/WNL.0b013e318200d727

Holt-Lunstad, J., Smith, T. B., & Layton, J. B. (2010). Social relationships and mortality risk: A meta-analytic review. *PLoS Medicine*, *7*(7), e1000316. https://doi.org/10.1371/journal.pmed.1000316

Inouye, S. K., Studenski, S., Tinetti, M. E., & Kuchel, G. A. (2007). Geriatric syndromes: Clinical, research, and policy implications of a core geriatric concept. *Journal of the American Geriatrics Society*, *55*(5), 780–791. https://doi.org/10.1111/j.1532-5415.2007.01156.x

Krieger, N. (1994). Epidemiology and the web of causation: Has anyone seen the spider? *Social Science & Medicine (1982)*, *39*(7), 887–903. https://doi.org/10.1016/0277-9536(94)90202-x

Krieger, N. (2001). A glossary for social epidemiology. *Journal of Epidemiology & Community Health*, *55*(10), 693–700. https://doi.org/10.1136/jech.55.10.693

Krieger, N. (2005). Embodiment: A conceptual glossary for epidemiology. *Journal of Epidemiology & Community Health*, *59*(5), 350–355. https://doi.org/10.1136/jech.2004.024562

Kuiper, J. S., Zuidersma, M., Oude Voshaar, R. C., Zuidema, S. U., van den Heuvel, E. R., Stolk, R. P., & Smidt, N. (2015). Social relationships and risk of dementia: A systematic review and meta-analysis of longitudinal cohort studies. *Ageing Research Reviews*, *22*, 39–57. https://doi.org/10.1016/j.arr.2015.04.006

Leigh-Hunt, N., Bagguley, D., Bash, K., Turner, V., Turnbull, S., Valtorta, N., & Caan, W. (2017). An overview of systematic reviews on the public health consequences of social isolation and loneliness. *Public Health*, *152*, 157–171. https://doi.org/10.1016/j.puhe.2017.07.035

Link, B. G., & Phelan, J. (1995). Social conditions as fundamental causes of disease. *Journal of Health and Social Behavior*, 80–94.

Luo, Y., Hawkley, L. C., Waite, L. J., & Cacioppo, J. T. (2012). Loneliness, health, and mortality in old age: A national longitudinal study. *Social Science & Medicine*, *74*(6), 907–914.

Marmot, M. (2005). Social determinants of health inequalities. *The Lancet*, *365*(9464), 1099–1104.

Mathieson, J., Popay, J., Enoch, E., Escorel, S., Hernandez, M., Johnston, H., & Rispel, L. (n.d.). *Social Exclusion Meaning, measurement and experience and links to health inequalities*. 91.

Meleis, A. I. (2017). *Theoretical Nursing: Development and Progress*. Lippincott Williams & Wilkins.

Mussini, C., Lorenzini, P., Cozzi-Lepri, A., Lapadula, G., Marchetti, G., Nicastri, E., Cingolani, A., Lichtner, M., Antinori, A., Gori, A., & Monforte, A. d'Arminio. (2015). CD4/CD8 ratio normalisation and non-AIDS-related events in individuals with HIV who achieve viral load suppression with antiretroviral therapy: An observational cohort study. *The Lancet HIV*, *2*(3), e98–e106. https://doi.org/10.1016/S2352-3018(15)00006-5

OAR Working Group on HIV and Aging. (2012). HIV and Aging: State of Knowledge and Areas of Critical Need for Research. *Journal of Acquired Immune Deficiency Syndromes (1999)*, *60*(Suppl 1), S1-18. https://doi.org/10.1097/QAI.0b013e31825a3668

Peplau, L. A., & Perlman, D. (1982). *Loneliness: A sourcebook of current theory, research, and therapy*. Wiley. http://ucsf.summon.serialssolutions.com/2.0.0/link/0/eLvHCXMwdV07C8IwED6kXbr5xDf-gUqbpsaMIoqDi6BIXUraJKMO4uC_9662oqJjCDmScHz3yH0XgIhNA_8LE3Ibouc8N4qrmHxmFWg2YzrjMdOhNEROXqyi3UEcEyrVqT6qu-VX-0Hrx_GruqbIYFAHceL6utTHjjvgYuCYnCqNolc0LkVQUNEFldMhGldtd8px0YEP5b6ZlXUdHKIaNKBmzk3wXlh0b4G3vZyJKY441IbRerVfbnxanpbplrTaU8Q64GAIb7owydEIzmJpYpFZLrWVSnGrhM7RO1AYgfSg81tG_9_EALxQztkzGTAE16KymtHzJOPyFh7RdmU3

Perissinotto, C. M., Stijacic Cenzer, I., & Covinsky, K. E. (2012). Loneliness in older persons: A predictor of functional decline and death. *Archives of Internal Medicine*, *172*(14), 1078–1083. https://doi.org/10.1001/archinternmed.2012.1993

Phelan, J. C., Link, B. G., Diez-Roux, A., Kawachi, I., & Levin, B. (2004a). "Fundamental causes" of social inequalities in mortality: A test of the theory. *Journal of Health and Social Behavior*, *45*(3), 265–285.

Phelan, J. C., Link, B. G., Diez-Roux, A., Kawachi, I., & Levin, B. (2004b). "Fundamental causes" of social inequalities in mortality: A test of the theory. *Journal of Health and Social Behavior*, *45*(3), 265–285.

Poindexter, C., & Shippy, R. A. (2008). Networks of older New Yorkers with HIV: Fragility, resilience, and transformation. *AIDS Patient Care and STDs*, *22*(9), 723–733. https://doi.org/10.1089/apc.2007.0260

Popay, J. (2010). Understanding and tackling social exclusion. *Journal of Research in Nursing*, *15*(4), 295–297. https://doi.org/10.1177/1744987110370529

Serrano-Villar, S., Gutiérrez, C., Vallejo, A., Hernández-Novoa, B., Díaz, L., Abad Fernández, M., Madrid, N., Dronda, F., Zamora, J., Muñoz-Fernández, M. Á., & Moreno, S. (2013). The CD4/CD8 ratio in HIV-infected subjects is independently associated with T-cell activation despite long-term viral suppression. *Journal of Infection*, *66*(1), 57–66. https://doi.org/10.1016/j.jinf.2012.09.013

Serrano-Villar, S., Pérez-Elías, M. J., Dronda, F., Casado, J. L., Moreno, A., Royuela, A., Pérez-Molina, J. A., Sainz, T., Navas, E., Hermida, J. M., Quereda, C., & Moreno, S. (2014). Increased Risk of Serious Non-AIDS-Related Events in HIV-Infected Subjects on Antiretroviral Therapy Associated with a Low CD4/CD8 Ratio. *PLOS ONE*, *9*(1), e85798. https://doi.org/10.1371/journal.pone.0085798

Stevens, P. (1989). A critical social reconceptualization of environment in nursing: Implications for methodology. *Advances in Nursing Science*, *11*(4), 56–68. insights.ovid.com

Stonington, S. D., Holmes, S. M., Hansen, H., Greene, J. A., Wailoo, K. A., Malina, D., Morrissey, S., Farmer, P. E., & Marmot, M. G. (2018). Case Studies in Social Medicine—Attending to Structural Forces in Clinical Practice. *N Engl J Med*, *379*(20), 1958–1961. https://doi.org/10.1056/NEJMms1814262

Valcour, V. G., Shikuma, C. M., Watters, M. R., & Sacktor, N. C. (2004). Cognitive impairment in older HIV-1-seropositive individuals: Prevalence and potential mechanisms. *AIDS (London, England)*, *18 Suppl 1*, S79-86.

Winston, A., & Spudich, S. (2020). Cognitive disorders in people living with HIV. *The Lancet HIV*, *7*(7), e504–e513. https://doi.org/10.1016/S2352-3018(20)30107-7

World Health Organization. (2010). *A conceptual framework for action on the social determinants of health: Debates, policy & practice, case studies.* http://apps.who.int/iris/bitstream/10665/44489/1/9789241500852_eng.pdf

Table 1.1: Summary of Studies Examining Cognitive Impairment and CD4/CD8 Cell Ratio among PLWH

Study	CD4/CD8 variable	Cognitive assessment	Findings
Vassallo et al., 2017	Continuous	Standard neuropsychological test battery over 3 years	CD4/CD8 decreased in those with worsening HAND (60% vs 31%, p = 0.008); Decreasing CD4/CD8 ratio & lower CSF-penetrating ART regimens independently associated with cognitive decline
Correa et al., 2014	< 1.0	Brief Neuropsychological Assessment; Mini-Mental State Examination inventory	The older adults with inverted CD4:CD8 ratio had impairments in some cognitive dimensions and had more functional disability and dependency (p = 0.01)
Rawson et al., 2015	< 1.0	Brief NeuroCognitive Screen	Neurocognitive impairment subjects were 8% more likely to have inversion of CD4:CD8 ratio and higher median peak CD8 cell counts reported compared to non-impaired subjects
Grauer et al., 2015	Continuous	Standard neuropsychological test battery; MRI	Degree of cognitive impairment severity and MRI signal abnormalities correlated with decreasing CD4/CD8-ratios

Table 1.2: Summary of Key Terms in the Ecosocial Model of Symptom Science			
Source	Key Term	Attribute	Principle(s) and Definition(s)
Link & Phelan, 1995; Phelan, et al., 2004	Root Cause (Also called a fundamental cause)	Concept; Structural determinants of health	Root causes "involve a person's relationships to other people. These include everything from relationships with intimates to positions occupied within the social and economic structures of society." (Link & Phelan, 1995, p.81). Root causes encompass factors that are fundamental to health and generate difference in SEP along the lines of knowledge, power, prestige, and access to resources (Phelan et al., 2004).
WHO, 2010	Socioeconomic position (SEP)	Construct	"People attain different positions in the social hierarchy according, mainly, to their social class, occupational status, educational achievement and income level. Their position in the social stratification system can be summarized as their socioeconomic position." (WHO, 2010, p.27). Root causes are fundamental to establishing SEP.
WHO, 2010	Social Determinants of Health (SDOH)	Concepts; Conceptual Framework	"The conditions in which people are born, grow, work, live, and age, and the wider set of forces and systems shaping the conditions of daily life." (WHO, 2010, p.27). Refers to both the social factors that impact the health of individuals/ populations *and* to the "social processes underlying the unequal distribution of these factors between groups occupying unequal positions in society." (WHO, 2010, p.27)
Braveman, 2006 Braveman & gruskin 2003	Health disparities/health inequalities	Construct; Process	A type of difference in health or influences on health. "Health disparities/inequalities are potentially avoidable differences in health (or in health risks that policy can influence) between groups of people who are more and less advantaged socially; these differences systematically place socially disadvantaged groups at further disadvantage on health"

Table 1.2: Summary of Key Terms in the Ecosocial Model of Symptom Science *Continued*			
WHO, 2003	Social Exclusion	Process	The "dynamic, multi-dimensional processes driven by unequal power relationships" that interact across various structural mechanisms and at different levels such as individual, group, community, country, and ecosystem
Hall et al., 1994; Hall, 1999; Baah et al., 2019; Hall, Stevens, & Meleis, 1994, p. 25).	Marginalization	Process; Construct	A "process through which persons are peripheralized based on their identities, associations, experiences, and environment"
Author-defined	Marginalized conditions	Heuristic device	Generally characterized by social exclusion, stigmatization, criminalization, barriers to healthcare, trauma associated with healthcare systems and healthcare professionals, accelerated aging, increased burden of morbidity, and premature death
Krieger, 1994, 2001, 2001, 2005, 2012	Embodiment	Construct	A construct referring to how we "literally incorporate, biologically, the material and social world in which we live, from in utero to death; a corollary is that no aspect of our biology can be understood in the absence of knowledge of history and individual and societal ways of living." (Krieger, 2005, p.352).
	Pathways of embodiment	Processes	Pathways of embodiment are "structured simultaneously by (a) societal arrangements of power, property, and contingent patterns of production, consumption, and reproduction, and (b) constraints and possibilities of our biology, as shaped by our species' evolutionary history, our ecological context, and individual histories—that is, trajectories of biological and social development." (Krieger, 2005, p.352).

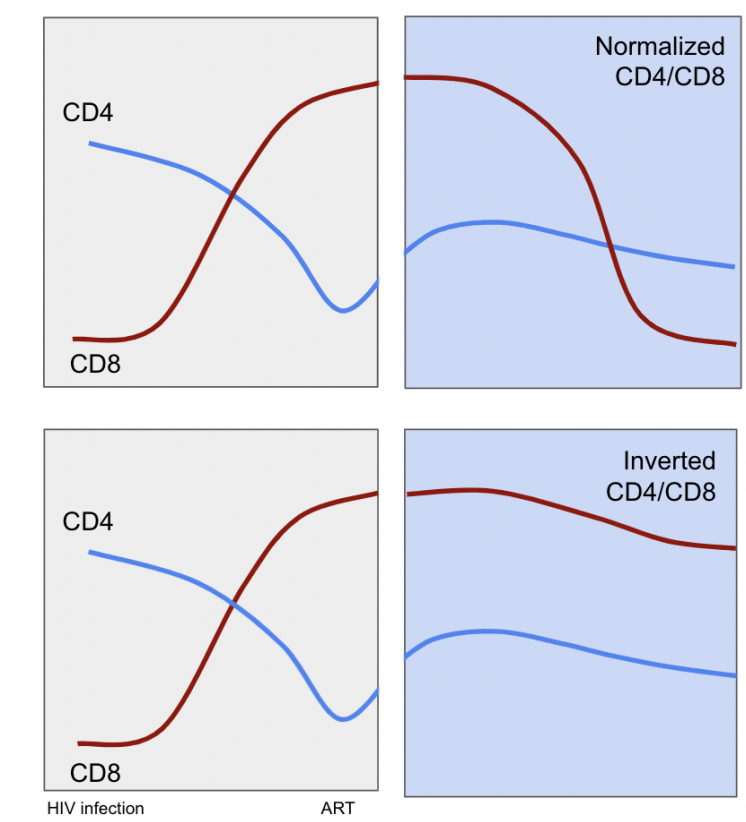

Figure 1.1: Visual Depiction of a Normalized and Inverted CD4/CD8 Cell Ratio in HIV Infection

Upon HIV seroconversion, HIV virus infects human CD4 T-cells (line in blue). As HIV kills CD4 T-cells, CD8 T-cells (line in red), which are a key part of the cellular immune response, simultaneously expand in response to the virus. If a person with HIV is treated with ART medications, they may restore/normalize their CD4 counts and CD8 count will decline, leading to normalization of the CD4/CD8 cell ratio (upper panel). For some, despite ART medications and viral suppression, CD4/CD8 ratios fail to improve even when CD4 cell count has recovered (lower panel) (Cao et al., 2016).

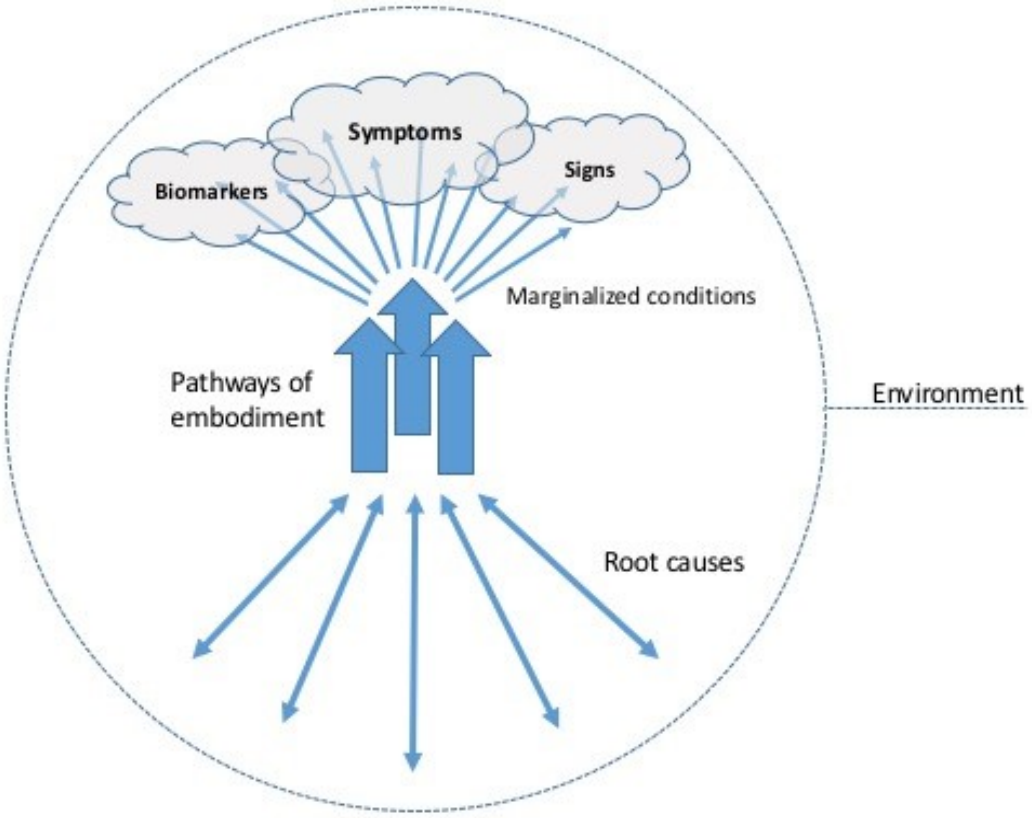

Figure 1.2: Visual Depiction of the Ecosocial Model of Symptom Science

The environment overlays each dimension of the EMSS model. *Environment* denotes the broad context in which root causes, pathways of embodiment, and the symptoms, signs and biomarkers of marginalized conditions interact. It includes broad socioeconomic & political systems, ecological conditions, and historical contingencies. *Root causes* are social conditions, not modifiable at the individual level, that "involve a person's relationships to other people." (Link & Phelan, 1995, p.81). They encompass many SDOH and factors that are fundamental to health, which manifest in differences in SEP and social hierarchies along the lines of knowledge, power, prestige, and access to resources. Root causes include educational attainment, social class, poverty/income, racism, social capital, and public health, public safety, and healthcare systems, policies, and infrastructures. *Embodiment* describes "how we literally embody, biologically, our lived experience, in societal and ecological context, thereby creating population patterns of health and disease" (Krieger, 2001, p.670). *Marginalized conditions* can generally be characterized by stigma, criminalization, barriers to healthcare, trauma associated with healthcare systems, and premature aging, morbidity, and mortality. These conditions include HIV, substance use disorders (particularly illicit substances and injection drug use), serious mental illness (particularly psychotic disorders, personality disorders, PTSD, and mood disorders), homelessness, and hepatitis C. *Symptoms*, *signs*, and *biomarkers* reflect critical domains of nursing scientific inquiry; Though often measured at the individual level, and they are inextricably linked to the environment and to root causes of health.

Chapter 2

Systematic Review and Meta-Analysis of the Association between Social Isolation & Loneliness and Cognitive Impairment among Adults Living with HIV

Sarah Dobbins

Abstract

It is estimated that about a one third to one half of people living with HIV (PLWH) have some degree of cognitive impairment (Heaton et al., 2010). Literature indicates that, on average, PLWH experience more loneliness and social isolation than HIV-seronegative individuals (Greene et al., 2018a; Grov et al., 2010; Poindexter & Shippy, 2008; Shippy & Karpiak, 2005). There is an abundance of research about the impact of social isolation/social support and loneliness on cognitive impairment in the general population, however fewer studies about these relationships have been carried out among HIV-seropositive adults. The purpose of this review and meta-analysis is to evaluate and synthesize existing scientific evidence concerning the extent to which social isolation and loneliness are associated with cognitive impairment in adults living with HIV. Using PRISMA guidelines, a systematic review of manuscripts indexed by Medline and Embase was conducted (Welch et al., 2012). We then performed a meta-analysis and meta-regression on the selected studies to estimate the pooled association of social isolation and loneliness on cognitive impairment among PLWH. Our review and analyses suggest an association between increased social connectedness and more cognitive impairment among PLWH across the globe. The eleven studies reviewed used diverse measures of cognitive symptoms and cognitive status, which varied in their established construct validity and overall reliability. Additionally, the studies were limited by the use of un-validated scales and measures of loneliness and social support. Nevertheless, the meta-analysis showed a positive association between social connectedness (social isolation or loneliness) and cognitive impairment. Though there was moderate heterogeneity, there was not substantial publication bias. In sub-group analyses, there was a significant positive association between a) self-reported cognitive impairment and loneliness or social isolation, b) performance based cognitive impairment and either loneliness or social isolation, and c) social isolation and either self-report or performance based cognitive impairment. There was not a significant association between loneliness and either self-report or performance based cognitive impairment. Meta-regression showed that the

estimated effect was moderated by study quality, older age (≥55 years), and study country but not by mean CD4 cell count of the study sample.

Introduction

Since the onset of the HIV epidemic, antiretroviral therapy (ART) has lengthened the lives of people living with HIV (PLWH). More than half of the population of PLWH are 50 years and older, and as the aging population of PLWH expands it is important to consider the factors that impact aging with HIV (Centers for Disease Control and Prevention, 2018). It is estimated that about a one third to one half of HIV-seropositive individuals have some degree of cognitive impairment (Heaton et al., 2010). These prevalence estimates vary based on population and assessment methods, and are likely lower in populations with sustained viral suppression.

Neurocognitive disorders in the setting of HIV have a multifactorial etiology and progression (Winston & Spudich, 2020). Furthermore, HIV is a marginalized condition and PLWH experience stigma and substantial health disparities and inequities (Farmer et al., 2006; Rhodes et al., 2005). Therefore, it is important to understand the environmental and psychosocial impacts on cognitive symptoms and cognitive status among older PLWH.

Social Connectedness and Cognitive Impairment

Social isolation and loneliness are tightly linked to outcomes in geriatric medicine (Inouye et al., 2007). However, these constructs are not always closely correlated with one another (Golden et al., 2009; McHugh et al., 2017; Perissinotto & Covinsky, 2014), suggesting that social isolation and loneliness may reflect distinct experiences that affect health through different pathways. Social isolation and lack of social support has been defined as an objective description of a lack of interactions with others or with a wider community (Berkman et al., 2000). It has also been described as a key component of social capital, a social determinant of health (World Health Organization, 2010). In contrast, loneliness has been described and defined as a "debilitating psychological condition characterized by a deep sense of emptiness, worthlessness, lack of control, and personal threat," (Cacioppo et al., 2014), stress caused by the discordance between actual and desired relationships (Leigh-Hunt et al., 2017), and

a negative emotion, distinct from depression, produced by unmet social and intimacy-related needs (Peplau & Perlman, 1982). Although there is still a general lack of consensus for the definitions of social isolation and loneliness, many studies show that various measures of loneliness and social isolation are associated with increased risk of all-cause mortality (Greysen et al., 2013; Holt-Lunstad et al., 2010; Perissinotto et al., 2012) and meta-analyses of longitudinal studies confirm that social connection and loneliness are associated with incident dementia among the general population (Kuiper et al., 2015).

Literature indicates that, on average, PLWH experience more loneliness and social isolation than HIV-seronegative individuals (Greene et al., 2018a; Grov et al., 2010; Poindexter & Shippy, 2008, 2008; Shippy & Karpiak, 2005). This may be attributed due to the higher rates of stigma, depression or marginalization among PLWH (Grov et al., 2010; Poindexter & Shippy, 2008). Social support and loneliness influence health-related outcomes among PLWH. For example, increased social support is associated with viral load suppression (Burgoyne, 2005) and decreased HIV-related physical health symptoms (Ashton et al., 2005). Among PLWH, loneliness is associated with depression and HIV symptoms (Fekete et al., 2018), CD4-cell count (Miller et al., 1997), sexual behaviors (Hubach et al., 2015), and substance use (Greene et al., 2018b; Mannes et al., 2016, 2017). Furthermore, it is thought that loneliness as well as depression, stress, and anxiety may contribute to dysregulated inflammatory processes in both HIV- and HIV+ populations (Cole et al., 2011; Hackett et al., 2012; Miller et al., 1997; Schutter et al., 2017).

There is an abundance of research about the impact of social isolation/social support and loneliness on cognitive impairment in the general population, however fewer studies about these relationships have been carried out among HIV-seropositive adults. The purpose of this review and meta-analysis is to evaluate and synthesize existing scientific evidence concerning the extent to which social isolation and loneliness are associated with cognitive impairment in adults living with HIV.

Methods

Using PRISMA guidelines, a systematic review of manuscripts indexed by Medline and Embase will be conducted (Welch et al., 2012). These bibliographic databases will be queried for relevant literature published between January 1st, 1996 until December 31st, 2021. First an initial search was made in Pubmed using the Medical Subject Heading (MESH) terms "HIV," "neurocognitive disorders," "Cognitive Dysfunction," "social isolation," "social support," and "loneliness." Several additional MESH terms, synonyms, and keywords were identified and included in the final search syntax (**Appendix 2.1**). Complementary search strategies included: 1) Conferring with an expert in the field of HAND (V. Valcour); 2) A citation chaining search method from the bibliographies of key publications. Subsequently, we performed a meta-analysis and meta-regression on studies meeting inclusion and exclusion criteria to estimate the pooled association of social isolation and loneliness on cognitive impairment among PLWH.

Studies in the systematic review were included in the meta-analysis and meta-regression if they reported effect sizes for the association between cognitive impairment and social isolation or loneliness. Studies with both HIV-seropositive and seronegative samples were included in the review, but only effect sizes from analyses in HIV-seropositive samples were included in the meta-analysis and meta-regression.

Measures/Variables

The following data elements were gathered from each study included in the systematic review: Country in which the sample was recruited, year of publication, study approach, sample size, sample demographics, ART medication status of the baseline sample, study hypotheses or aims, type of social connectedness variable and measurement instrument, type of cognitive variable and measurement instrument, depression variable and measurement instrument, other variables examined, analysis method, and relevant study findings.

The crucial role of inflammation in the etiology of HAND has been firmly established (Kallianpur et al., 2013; Sharma et al., 2020; Valcour et al., 2011). Social support has also been linked to faster progression to AIDS (Leserman et al., 2000) and increased inflammation (Ellis et al., 2021). Therefore, biomarkers that have been associated with loneliness and/or social isolation as well as cognitive impairment/HAND is an important component of this systematic review. Based on literature in the general population and OAR working group, biomarkers were also identified as an important variable for extraction as a data item (OAR Working Group on HIV and Aging, 2012). We defined a biomarker using the FDA/NIH Biomarker Working Group definition: "A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions. Molecular, histologic, radiographic, or physiologic characteristics are types of biomarkers but a biomarker is not an assessment of how an individual feels, functions, or survives." (FDA-NIH Biomarker Working Group, 2016). The biomarkers included in our review include CD4 T-cell count, nadir CD4 T-cell count, viral load, HCV antibodies, C-reactive protein, gait speed and the Veterans Aging Cohort Study (VACS) index, which is comprised of age, sex, race, CD4 count, HIV viral load, liver fibrosis-4 score, hemoglobin, renal function, and hepatitis C co-infection.

For our meta-analysis, the following additional variables were collected: Effect size and study quality/risk of bias. To determine risk of bias, we reviewed each article for methodological quality using the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (NIH, 2021). A quality rating was assigned based on the NIH framework and included in the meta-analysis and meta-regression. In the framework of this tool, bias is assigned based on the internal validity of the study. For example, was the exposure assessed prior to outcome measurement? Were different levels of the exposure and outcome of interest measured? Were the exposure and outcome measurement tools or methods used to measure exposure accurate and reliable, and have they been validated? Were key potential confounding

variables measured and adjusted for, such as by statistical adjustment for baseline differences? (NIH, 2021). The details of the framework are provided in the Appendix (**2.3**).

Statistical Methods

The optimal estimator of association for our meta-analysis is Cohen's *d*, a measure of the standardized mean difference (SMD). Since studies in our review reported different effect size measures (e.g., odds ratio, correlation coefficients, or regression coefficients), we derived Cohen's *d* as a common outcome measure for our meta-analysis. Cohen's *d* was derived for each study using the formulae published in the literature (Thalheimer & Cook, 2002). The precision of effect size was estimated deriving a standard error (SE) of Cohen's *d* using the formulas recommended by Borenstein et al (2009), Thalheimer & Cook (2002), and Friendman, 1968 (**Appendix 2.2**).

Using Cohen's *d* and the variance of *d*, procedures for meta-analysis in Stata 15 were implemented (StataCorp, 2017). We chose to use random effects models for statistical analysis of pooled associations along with forest plots and measures of heterogeneity. The random-effects meta-analysis model results represent the average intervention effect. The random effects model, in contrast to a fixed effects model, relies on the assumption that observed differences among study results are due to a combination of both random chance and heterogeneity. To examine statistical heterogeneity among the studies, Cochran's Q (a Chi^2 statistic) and the I^2 statistic were computed and assessed for the pooled model and for sub-analyses. Cochran's Q statistic indicates whether or not heterogeneity exists, and the I^2 statistic measures of the proportion of variability between studies that is due to heterogeneity rather than random chance (Higgins & Thomas, 2021). Following standard the approach: Mild heterogeneity if I^2 is less than 30%, moderate heterogeneity if I^2 is between 30% to 50%, and high heterogeneity if I^2 is greater than 50% (Higgins & Thomas, 2021). Publication bias was assessed with a funnel plot and the Egger's weighted regression test.

We implemented random-effects meta-regression to examine whether the overall effect estimate could be explained by one or more explanatory variables. We carried out models to test the effect of the following explanatory variables: Country, study quality/risk of bias, mean CD4 cell count, and age of study samples (mean sample age ≥55 years *versus* <55 mean age) on cognitive impairment. The statistical significance of the regression coefficient indicates whether there is a relationship between the outcome variable and the explanatory variables. For the purposes of interpretation, the regression coefficient describes how the outcome variable of cognitive impairment (Pooled *d*) varies with the explanatory variables.

Results

Figure 2.1 shows a PRISMA flowchart describing the algorithm used to select studies for this review. Initially 329 records were identified for review using search criteria and citation chaining. Of these, 230 were unique records. After initial screening, 204 were excluded because they did not meet one or more inclusion criteria (**Table 2.1**). Twenty-six full text articles were left to review based on inclusion and exclusion criteria. Of these, 11 were excluded after the full text screening and 4 studies were excluded in the data abstract phase because the variables not meet inclusion criteria. This left 11 studies to be included in this systematic review (**Figure 2.1**).

Summary of Data Elements

In the following section, we review eleven (11) research studies among adults with HIV that examined associations between loneliness or social isolation and cognitive impairment in older adults living with HIV (Atkins et al., 2010; Bourgeois et al., 2020; Chan et al., 2007; Eaton et al., 2020; S. Han et al., 2021; S. D. Han et al., 2017; Harris et al., 2020; Moore et al., 2018; Subramanian et al., 2020; Wubetu et al., 2021; Zhu et al., 2019). Of these, over half (6/11) were published in 2020 and 2021, which highlights the increased interest in the influence of social connectedness on cognitive impairment among older adults with HIV. Every study included in the final review was a cross-sectional study.

Table 2.2 summarizes the study characteristics, hypotheses/study aims, and sample demographics in the eleven studies reviewed. One study was carried out in Hong Kong, two in China, three in the United States, two in Canada, two in Africa, and one in India. In the eleven studies reviewed, the sample sizes ranged from 90 to 856 participants. The majority (7/11) studies included primarily male participants (ranging from 27.7% to 100% male), and no studies reported gender groups other than male or female. The pooled mean age of the participants in the nine studies was 59.47 years, with age means ranging from 35 to 58.8 years among the studies. One study did not report a mean age, and is not included in the pooled mean. Six of the eleven studies had a mean age above 55 years or above. Wubetu et al., 2021 did not report a mean age, but 92.4% of their participants were 60 years or younger and were therefore categorized as having a mean age ≤ 55 years. Racial or ethnic groups were reported in most (9/11) studies, but groups were categorized in various ways. Participants in the studies had a range of educational attainment, with the lowest among the Tanzanian sample, in which 77% had less than 8 years of formal education (Eaton et al., 2020), and the highest in the study sample from San Francisco, CA, USA in which 71.7% had some college or more (Bourgeois et al., 2020). Most (9/11) studies reported some measure of ART medication use in their sample. The reported measures included ART prescription or treatment, ART adherence in the past 30 days, and taking ART by self-report. Viral load was reported in less than half (4/11) studies (Bourgeois et al., 2020; Chan et al., 2007; Han et al., 2017; Moore et al., 2018) while a recent or baseline CD4+ T-cell count was reported by most (9/11) studies (Bourgeois et al., 2020; Chan et al., 2007; Eaton et al., 2020; Han et al., 2017; Moore et al., 2018; Subramanian et al., 2020; Zhu et al., 2019).

The study hypotheses or study aims and statistical approaches are also summarized in **Table 2.2**. Most studies examined adjusted regression models or analysis of covariance to test hypotheses, except one study that carried out descriptive analysis and unadjusted tests for associations. **Table 2.3** summarizes the key variables, measurement tools and instruments, and findings of the nine studies reviewed. These results are presented in detail below. This table also includes which biomarkers were

examined, if any. Findings listed in this table are limited to those relevant and pertaining to social connectedness and cognitive variables. **Table 2.4** includes data summarizing the overall risk of bias according to the NIH study quality assessment tool. Overall, the studies ranged from moderate to high risk of bias.

Narrative Review of Studies

Chan et al (2007) performed a cross sectional study of PLWH 18 to 50 years old in Hong Kong (n=90). They used path analysis to examine the relationships between social support, depression, and cognitive impairment among a sample of middle-aged PLWH. They had four hypotheses, including that depressive mood is a mediator between subjective memory complaints and the variables of social support and medical symptoms. The sample had a mean age of 39 years, and 82% were male. Social support was measured by the Social Provisions Scale (Cutrona & Russell, 1987), memory impairment measured with the Hong Kong List Learning Test for verbal memory (a performance based measure), memory complaints were measured with the Patient's Assessment of Own Functioning (PAOFI) (a self-report measure) (Chelune et al., 1986), depression measured by the Beck Depression Inventory (BDI) (Beck et al., 1988), and physical symptoms measured by the Adherence Baseline Questionnaire developed by the Adult AIDS Clinical Trials Group (Chesney et al., 2000). The authors concluded depression mediated the relationship between social support and subjective memory complaints, but not performance based memory impairment. The correlation between social support and performance based memory impairment was evaluated and the result was not significant (r= 0.16). Overall, this study reflects the important interrelationships of depression and memory impairment symptoms and highlights the difficulty in phenotyping cognitive symptoms among PLWH (Chan et al., 2007). Because the measurements in this sample were taken at the same time point, the interpretation of mediation is not valid (VanderWeele, 2016). This study had a high risk of bias due to statistical conclusion validity, construct validity and reliability of their measures, and lack of adjustment for age in their final models.

Atkins et al (2010) performed a cross sectional study of men 18 years and older living HIV in Toronto, Canada (n=357). They used linear regression analyses to examine the relationship between cognitive symptom burden an social support among middle-aged males with HIV. They had a number of hypotheses, including increased social support for people with neuropsychological impairment is associated with lower cognitive symptom burden, and that higher levels of social support reduces the association between depression and cognitive symptom burden. The sample had a mean age of 1.54 years, and 100% were male. Depression was measured with the BDI (Beck et al., 1988) and social support was measured by an investigator-constructed single item question: "Identify whether participant had people in their lives they could turn to for social support" (Atkins et al., 2010). Cognitive symptom burden measured by the PAOFI (Chelune et al., 1986), and neuropsychological/cognitive status measured by a battery of neuropsychological tests based on the guidelines from the National Institute of Mental Health Workshop on Neuropsychological Assessment Approaches of AIDS-related Cognitive Changes (Butters et al., 2011). Despite over a third of sample meeting criteria for AIDS, only approximately half (51.5%) were classified as cognitively normal, which may reflect their relatively younger sample. The authors had a number of findings that showed significant relationships between their variables. First, higher mean cognitive symptom burden score was associated with depression and less social support (β=-9.213 (SE 3.500, p=0.009). Second, there was an interaction by both neuropsychological status and social support: Those with higher depression and higher neuropsychological impairment were more more likely to report more cognitive symptoms, and those with low levels of depression and greater social support were less likely to have cognitive symptoms. The authors concluded that that higher levels of social support may have a buffering effect on cognitive symptoms among those with depression. This study used an un-validated measure of social support comprised of one question, therefore the extent to which they were able to truly measure the construct of social support is unknown. We determined that the study by Atkins et al. (2010) had moderate risk of bias due to validity issues with their social support measure, lack of age adjustment in their model, and data granularity that may have been lost when continuous variables were dichotomized.

Han et al. (2017) performed a cross-sectional study of HIV+ and HIV- controls in Chicago, Illinois. They used linear regression models with interaction effects to examine the association of loneliness and cognitive impairment in older black adults with HIV (Han et al, 2017). They hypothesized that older Black adults with HIV have greater loneliness than older white adults with HIV, and that more loneliness among older Black adults with HIV is associated with poorer cognitive function. The sample had a mean age of 58 years, and 73.5% were male. They measured cognitive status with a battery of 19 cognitive measures and they measured loneliness with a modified version of the De Jong-Gierveld Loneliness Scale (Gierveld & Van Tilburg, 2010). Overall, they found that older Black participants had lower loneliness score than older white participants (2.44 [SD 0.77] *versus* 2.68 [SD 0.77]), which was contrary to their hypothesis and expectations. In linear regression models adjusting for the effects of age, education, sex, income, and race there were no associations between loneliness and a global measure of cognition in the HIV-seropositive sample (β= 0.0369, SE 0.1761, p=0.8344). However, there was an interaction between race and loneliness such that greater loneliness was associated with lower global cognition in older Black PLWH (r=−0.2413, p=0.0069) but not White PLWH (r=0.1971, p=0.1573). The significant three-way interaction between race, loneliness, and HIV status indicated that higher loneliness in older Black adults with HIV was associated with lower cognitive function ($\beta_{\text{loneliness*race}}$= -0.274, SE 0.114, p=0.017). In order to test the generalizability of their findings, the authors separately analyzed n=1,180 HIV-seronegative, older participants without dementia from separate cohort studies. We did not report these results in this review, as our research question pertains to HIV-seropositive adults only (Han et al., 2017). Important threats to the validity of the study by Han et al (2017) include the lack of measurement of depression or other mental health disorders. Additionally, the reliability and validity of the modified loneliness measure for Han et al.'s study may be in question because of the modifications made, and no psychometrics for the scale were reported for the modified version (Han et al, 2017). The notable interaction of Black race reflects the possibility that racism influences effects of loneliness on cognition among PLWH. We determined that this study had low-to-moderate risk of bias due to the validity of the loneliness measure and lack of depression variable in the models.

Moore et al. (2018) conducted a Cross sectional analysis older adults living with HIV+ and HIV- in Southern California (n=145). They used ANCOVA to examine the outcome termed successful cognitive aging (SCA). SCA was defined as: a) no cognitive impairment, b) no functional impairment, and c) no major depressive disorder. They sought to examine differences in SCA between HIV+ and HIV− subjects, but we restricted our review to results in the HIV-seropositive sample only. The sample had a mean age of 59 years, and 79% were male. Moore et al. measured cognitive status with a comprehensive neurocognitive test battery. They measured instrumental activities of daily living (IADLs) with the commonly used Lawton and Brody tool (Edwards, 1990) and they measured depression was diagnosed with the Composite International Diagnostic Interview (CIDI) according to Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV diagnostic criteria (American Psychiatric Association, 2013). One of the ten positive psychological factors measured social support using a 4-item sub-scale from the Duke Social Support Index (DSSI) (Koenig et al., 2016). While the DSSI has been validated, the reliability and validity of the use of the sub-scales has not. The authors found that those who had HIV and SCA had higher scores on 8 out of 10 measures of positive psychological factors as well as better health related quality of life. Twenty-nine percent (29/99) of the HIV seropositive sample met criteria for SCA. The authors determined that social support was not significantly associated with SCA groups at the omnibus level (p=0.06). Social support on the DSSI did not differ between HIV+/SCA−, HIV+/SCA+ groups (Mean 8.83 [SD 1.85] *versus* mean 8.33 [SD 1.82]). We determined that this study had moderate risk of bias due to the validity of the DSSI and unclear explanation of covariates in the model.

Zhu et al. (2019) performed a Cross sectional analysis of survey data among PLWH ages 45 or older in China (n=324). They used linear and ordinal regression to examine the association of self-reported cognitive abilities with discrimination, social support, depressive symptoms, psychological function, and health behaviors. The sample had a mean age of 56 years, and 65% were male. They measured cognitive impairment with 5 items from the AIDS Health Assessment Questionnaire (AIDS-HAQ) (Lubeck & Fries, 1997), which they analyzed as a summed total score ranging from m 0 to 15. This

subscale asks about slow reactions, being confused, forgetting things that occurred recently, having difficulty concentrating, and having difficulty reasoning during the past 4 weeks. They measured social support with 3 social support domain items in the same AIDS-HAQ (Lubeck & Fries, 1997). These 3 questions ask about the intensity and frequency with which health problems interfered with social activities and how much time respondents spent talking with others during the past 4 months. They measured depression with the Chinese version of the PHQ-2 (Kroenke et al., 2003) and included this variable as a covariate in their adjusted regression models. Zhu et al. (2019) found that perceived discrimination was associated with more severe difficulty in cognitive ability (β=−0.121, p=0.036). They report no association of social support with self-reported cognitive ability (β= 0.064, p=0.234). However, this association does not match the findings reported in their tables: They report a significant association between social support and 'difficulty reasoning' in their multivariate regression model (β=0.114, p=0.048), and this finding was not discussed by the authors. Domains of the AIDS-HAQ were used as both outcome and exposure variables. In the original publication about the AIDS-HAQ, this tool was noted to have high internal consistency, which is a determination of the extent to which the items are correlated and how well they predict each other. Indeed, Lubeck & Fries (1997) showed that the social functioning sub-scale and the cognitive functioning sub-scale had a strong, positive correlation (r=0.53). Without examining the crude models, which are not presented in the paper, the use of AIDS-HAQ as both outcome and exposure variables poses a threat to the statistical conclusions of this study. We determined this study to have high risk of bias due to statistical conclusions and construct validity of scales used.

Harris et al. (2020) performed a cross-sectional study among adults living with HIV in four Canadian cities (n=856). They used proportional odds regression models to examine the association of cognition, mental health, quality of life, and loneliness. They hypothesized that cognition, mental health, and quality of life are consequences of loneliness. In the sample from the Positive Brain Health Now cohort, the mean age was 53 and 85% were male. The authors measured objective cognitive status with five cognitive tests comprising the Brief Cognitive Ability (B-CAM) computerized NP test battery

(Brouillette et al., 2019). Subjective cognitive status was measured by the Perceived Deficit Questionnaire (PDQ). Loneliness and social support were both measured using items from the Older Americans Resources and Services Social Resource (OARS) Scale (Burholt et al., 2007). Loneliness was assessed with one item from the OARS and social support was measured with another item from the OARS. Depression was measured with the RAND SF-36 Mental Health Inventory (Hays et al., 1998) depression subscale and was included in the proportional odds regression examining contributors to loneliness. They found that so-called "lifestyle factors" (physical activity, smoking, and other substance use) were consequences of loneliness. In their final statistical model, cognitive ability, cognitive symptoms, stress, depression, anxiety, health-related quality of life, and overall quality of life were associated with loneliness (Harris et al., 2020). We included only results pertaining to cognitive symptoms in our meta-analysis and meta-regression. Harris et al. (2020) found that more loneliness increased the odds of cognitive symptoms (Quite often lonely *versus* almost never lonely proportional odds ratio (POR)=5.62, 95% CI:[3.82, 8.27]; Sometimes lonely *versus* almost never lonely POR= 2.35, 95% CI:[1.77, 3.11]). Likewise, more loneliness increased the odds of worse performance on cognitive tests (Quite often lonely *versus* almost never lonely POR=2.38, 95% CI:[1.62, 3.51]; Sometimes lonely *versus* almost never lonely POR= 1.80, 95% CI:[1.34-3.51]). The authors aimed to assess "consequences" of loneliness, but their data was collected at one time-point, therefore claims about temporality cannot be supported by their data structure. This issue was not addressed in the paper, nor was possible collinearity of related variables (e.g. depression, anxiety, loneliness), which may have affected their models. Additionally, they did not state why data on social support and stigma, which were both collected, were omitted from the analysis. We determined this study to have moderate risk of bias due to unknown reliability and validity of the OARS items measuring social support and loneliness, lack of adjustment for age, and issues with interpretation of antecedents and consequences.

Eaton, et al. (2020) performed a cross sectional study of PLWH aged 50 years and over in Moshi, Tanzania, Africa (n=253). They used regression analysis to identify factors independently associated with

symptomatic HAND. In the sample, the mean age was 58 years and 85% were male. They measured HAND according to the Frascati criteria (Antinori et al., 2007) and comprehensive neurocognitive assessment battery adapted for low-literacy settings and with normative controls from a similar population. A binary response variable for living alone represented the construct of social support. Depression was measured with the 15-item Geriatric Depression Scale (GDS) (Sheikh & Yesavage, 1986). They found that 28.3% of participants living alone had symptomatic HAND and 13.8% of those living alone had no symptomatic HAND. The authors then constructed a multivariable regression model for symptomatic HAND vs no symptomatic HAND by including any independent variable that had a significance value $\alpha < 0.10$ in their initial unadjusted tests of association (aged over 65 years, illiteracy, living alone, and greater age at diagnosis). Accordingly, depression was not included in their final model. They found that symptomatic HAND was independently associated with living alone (OR=2.566, 95% CI: [1.202, 5.479]). An important aspect of this study was the use of locally validated cognitive test battery and local normative data to avoid exaggerating the magnitude of impairment through bias. However, the authors interpreted living alone as a reflection of social support and loneliness. Literature in both seronegative and seropositive populations of older adults show that living alone is not necessarily indicative of social isolation or of loneliness (Perissinotto et al., 2012; Perissinotto & Covinsky, 2014; Steptoe et al., 2013), therefore there may be threats to the construct validity of the study. We determined this study to have low-to-moderate risk of bias, primarily because of the construct validity and interpretation.

Bourgeois et al. (2020) performed a cross sectional study of HIV+ patients ages 50 or older in San Francisco, California (n=359). They used Poisson regression to calculate prevalence ratios (PRs) for each covariate and its association with abnormal MoCA scores (< 26). In this sample from the Silver Project cohort, the mean age was 57 years and 85% were male. The authors hypothesized that participants with lower scores on geriatric social, physical, functional, and psychiatric assessments would be more likely to experience cognitive impairment. They measured cognitive status with the Montreal Cognitive

Assessment (MoCA) (Nasreddine et al., 2005), using the standard cutoff of ≤26. They measured loneliness with the UCLA 8-item Loneliness Scale (Hays and DiMatteo, 1987), physical social support with the Lubben Social Network Scale (Lubben et al., 2006) and perceived support with the Social Provisions Scale (Cutrona et al., 1986). Depressive symptoms were measured with the Patient Health Questionnaire (PHQ-9) (Kocalevent et al., 2013) and were not included in the final model because there was no association between depression and MoCA in the unadjusted analysis. They calculated unadjusted prevalence ratios for each covariate and its association with abnormal MoCA scores, and adjusted prevalence ratios are reported for variables in the final model. In their final model, less social support was associated with an increased risk of abnormal MoCA score (Social support abnormal *versus* normal prevalence ratio [PR]=1.72, 95% CI: [1.16–2.57]). Although the MoCA was originally developed as a screening tool for dementia the general population, this measure has not been validated for diagnosis of HAND and is not considered a reliable measure of cognitive status (Milanini et al., 2014; Rosca et al., 2019). We determined this study to have low to moderate risk of bias, primarily due to the validity and reliability of the MoCA as a measure of cognitive impairment among older adults with HIV.

Wubetu et al., 2021 performed a cross sectional study of adult PLWH on ART in public hospitals in Ethiopia (n=422). They used bivariate and multivariable binary logistic regression to identify factors associated with HIV-associated neurocognitive deficits. In the sample, 45.7% were ages 30-39.9 years, 46.7% were ages 40-59.9 years, 7.6% were age 60 years and older and 39.8% were male. They aimed to determine the prevalence of HIV-associated neurocognitive impairment among the sample and identify factors associated with HAND. The authors measured social support with the Oslo-3 item Social Support (OSS-3) scale, which they report is widely used in Ethiopia. The OSS-3 was scored according to total points ranging from 3–14; "poor support" 3–8, "moderate support" 9–11, and "strong support." No validation studies of the OPSS-3 in Ethiopian populations could be found, but in a study of the OSS-3 in Nigeria, the scale had a low Cronbach's alpha coefficient (α=0.50) and females were found to have higher mean scores than males (Abiola et al., 2013). However, the scale performed somewhat better in a German

sample (α=0.64, no difference in gender groups), indicating unexplained population-specific variability in its psychometric properties (Kocalevent et al., 2018). Additionally, Wubetu did not report the Cronbach's alpha value of the OSS-3 to support its use in their sample. They measured cognitive impairment with the Mini-Mental State Examination (MMSE) (Nakazato et al., 2014). The MMSE is an interviewer-administered questionnaire that tests five cognitive domains (orientation, memory registration, attention and calculation, memory recall, and language). The cutoff score used by the authors was 25/30, and scores <13, 14–19, 21–24 were labeled with severe, moderate, and mild neurocognitive impairment respectively. They found that 50%, 20.1%, and 29.9% had poor, moderate, and strong social support, respectively. Those with poor social support had 3.65 higher odds of impairment when compared with those who had strong social support (95% CI: 1.86, 7.17). The biomarker in their study was CD4 cell count, which was not associated with neurocognitive impairment. We determined this study to have moderate risk of bias, primarily due to the reliability of the MMSE as a measure of cognitive impairment among older adults with HIV and the unknown validity of the OSS-3.

Han et al., 2021 performed a cross sectional study of PLWH 45 years and older in China (n=321). They used structural equation models (SEM) to examine paths among perceived discrimination, symptoms of cognitive dysfunction (SOCD), mental health symptoms, and social isolation. Social support was a secondary variable of interest. In the sample, the mean age was 55.7 and 64.8% were male. The authors hypothesized that perceived discrimination may influence SOCD through social isolation. Their other hypotheses did not concern social isolation and so are not reviewed here. They used SEM path analysis to test their hypotheses. They examined SCOD in four domains: difficulty in concentrating, forgetting things that occurred recently, difficulty in thinking and solving problems, and difficulty in learning new knowledge and skills. SCOD was measured by the subscale of the World Health Organization Quality of Life HIV Instrument (WHO-QOL HIV Group, 2004; Fang et al., 2002). They conceptualized "participation in social activities" as a behavioral implication of social isolation and measured this variable with the 3-item social functioning subscale of the AIDS Health Assessment

Questionnaire (Lubeck & Fries, 1997). They found that increased SOCD score was associated with increased social isolation score (ß=0.219, *p*=0.001, no SE or CI reported). Similar to other studies reviewed, the only biomarker used was CD4 cell count, which was non-significant in their models. We determined this study by Han et al. (2021) to have moderate risk of bias, primarily due to the reliability of using a QoL sub-scale to represent cognitive impairment and another sub-scale measure to determine social support.

Subramanian et al. (2020) performed a cross-sectional study of HIV+ adults in New Delhi, India (n=109). They used descriptive analysis and unadjusted measures of association to examine self-reported cognitive functioning as a dimension of quality of life (QOL). In the sample, the mean age was 35 and 57% were male. They aimed to assess how social support influences QoL. Subjective cognitive functioning, a dimension of QoL, was measured by the Medical Outcomes Study HIV Health Survey (MOS- HIV) (Wu et al., 1997). The MOS-HIV contains 35 items representing various dimensions of QoL including general health, physical functional status, pain, role function, social function, mental health, energy/vitality, cognitive function, health-related distress, and overall quality of life. Social support was measured by the Multidimensional Scale of Perceived Social Support (MSPSS) tool, which consists of 12 items about the perception of support from family, friends, and a significant other (Zimet et al., 1988). Depression was measured with the BDI and was found to be associated with less overall social support. This study did not examine an adjusted model to test their study aims, and therefore we cannot make inference about the independent association between variables. In their results, better cognitive function was associated with overall social support, support from friends, and support from significant others, but not from family. However, only the p-values were reported so the effect size of the association is unknown. The authors measured perceived cognitive function as a dimension of quality of life. In order to avoid threats to construct validity, the interpretation of the data should center on perceived quality of life rather than symptoms of underlying cognitive dysfunction. We determined this study to have high risk of bias based on the lack of clear study hypotheses, lack of details about recruitment and sampling, threats to

construct validity, and lack of adjustment for confounding by age or depression. Furthermore, because no effect sizes were reported, we did not include this study results in the meta-analysis or meta-regression.

Meta-Analysis

Pooled meta-analysis. Ten (10) studies were included in the full meta-analysis, as we excluded the study by Subramanian et al. (2020) because they did not report effect sizes in their manuscript. We included only the effect size estimates and corresponding sample sizes among the HIV-seropositive participants reported in two studies that enrolled both HIV-seronegative and HIV-seropositive participants (Han, et al., 2017; Moore et al., 2018). For our pooled, all study analysis we included prioritized adjusted regression results (n=10 studies). In the pooled analysis of all eligible studies, the pooled d =0.365 (95% CI: 0.247, 0.482). This indicates that across studies, increased cognitive impairment was associated with increased social isolation or loneliness. We found moderate heterogeneity (I^2=41.6%) for the pooled model (**Table 2.5, Figure 2.2**). We found little evidence for publication bias, both through use of a funnel plot (**Figure 2.7**) and statistical testing for funnel asymmetry. We observed a generally symmetrical plot, with two studies falling on the funnel line (Han et al., 2017 & Zhu et al., 2019). The Egger test for small-study effects was non-significant (z=-0.39, p=0.7000).

Sub-Group Analyses. In several studies, there were multiple relationships tested and therefore several different effect size estimates. Accordingly, we performed four sub-analyses that included relevant relationships and effect size estimates. We examined the following relationships through these sub-analyses: a) Self-report cognitive impairment and either loneliness or social isolation (n=5 studies); b) Performance based cognitive impairment and either loneliness or social isolation (n=7 studies); c) Loneliness and either self-report or performance based cognitive impairment (n=3 studies); d) Social isolation and either self-report or performance based cognitive impairment (n=8 studies) (**Table 2.5, Figures 2.3-2.6**). There was a significant positive association between self-report cognitive impairment and either loneliness or social isolation (d_{pooled}=0.463, 95% CI: 0.175, 0.752, I^2=85.3%). This indicates

that increases in self-reported cognitive impairment are associated with increased loneliness or social isolation. There was also a significant positive association between performance based cognitive impairment and either loneliness or social isolation (d_{pooled}=0.374, 95% CI: 0.216, 0.532, I^2=*36.6*%). There was not a significant association between loneliness and either self-report or performance based cognitive impairment (d_{pooled}=0.263, 95% CI: -0.046, 0.571, I^2=59.7%). Lastly, there was a significant positive association between social isolation and either self-report or performance based cognitive impairment, such that increased social isolation associated with increased cognitive impairment (d_{pooled}=0.380, 95% CI: 0.253, 0.507, I^2=34.1%).

Meta-Regression. In our meta-regression, we found evidence for moderation by study quality/risk of bias (β=0.265, 95% CI: 0.014, 0.515, p=0.038). This indicates that studies with high compared to moderate/low risk of bias showed an increased association between cognitive impairment and social isolation or loneliness. We found that studies from Africa and Canada were significant moderators, both showing increased association with cognitive impairment (β=0.384, 95% CI: [0.037, 0.730] and β=0.277 95% CI: [0.015, 0.539], I^2=19.43%). In a post-hoc sub-group analysis, we pooled studies into North America (USA and Canada, n=5) versus all other countries (n=5). We found similar estimates for pooled *d* and degree of heterogeneity, and there was no significant difference between groups (p=0.848) (North America d_{pooled}=0.355, 95% CI: [0.196, 0.514], I^2=45.24%; All other countries d_{pooled}=0.380, 95% CI: [0.177, 0.584], I^2=51.65%). This suggests that moderation seen in the meta-regression may be impacted by low precision due to the small number of studies in each country. Lastly, we found statistically significant moderation by older age (≥55 years) on the association between cognitive impairment and social isolation and loneliness, such that those in the older age group have an attenuated association of social connectedness and cognitive impairment in pooled models (β=-0.208, 95% CI:[-0.399, -0.018], p=0.032, I^2=12.4%). In a follow-up analysis, we used mean age of study sample as a continuous variable and excluded the results from the study by Wubetu et al. (2020), in which mean age was not reported. The

results from this analysis showed a non-significant moderation effect of age (β =-0.009, 95% CI:[-0.025, 0.008]) (**Table 2.6)**.

Discussion

We performed a systematic review and meta-analysis of studies examining the relationship between cognitive impairment and social isolation and loneliness among adults living with HIV. Our review and analyses suggest a general association between social connectedness on cognitive impairment. Overall, the eleven studies were reviewed were limited by the use of un-validated scales and measures of loneliness and social support as well as heterogeneous measures of cognitive symptoms and cognitive status. Of the eleven studies reviewed, eight supported a relationship between social support or loneliness and performance based measures of neuropsychiatric status (Chan et al., 2007; Harris et al., 2020; Subramanian et al., 2020; Zhu et al., 2019; Moore et al., 2018; Bourgeois, et al., 2020; Wubetu et al., 2021). This includes the study by Han et al., (2017), which did not find this relationship in pooled models but rather only in interaction of loneliness by race (Han et al., 2017). In our meta-analysis of ten studies in the review, there was evidence for a significant association of social connectedness, measured by social isolation and loneliness, with cognitive impairment, measured by both self-report and performance based measures.

The eleven studies included in the systematic review used diverse measures of cognitive symptoms and cognitive status, which varied in their established construct validity and overall reliability. Our meta-analyses indicated that there is a significant association of increased loneliness and social isolation with worse self-reported and performance based cognitive impairment. The estimated effect was stronger for self-reported cognitive impairment, although the corresponding measure of heterogeneity in this sub-group was also substantially higher.

Previous studies among PLWH show that “spotty” impairments in different cognitive domains are common and that fluctuation in level of impairments is common, therefore a full battery of cognitive

tests is the gold standard for evaluating cognitive impairments (Antinori et al., 2007). Of the seven studies that included performance-based testing to assess cognitive status, all but Chan et al. (2007), Bourgeois et al. (2020), and Wubetu et al. (2021) used a neurocognitive test battery. Chan et al. (2007) used the Hong Kong List Learning Test (HKLLT), a test of verbal memory, which is validated in the general Hong Kong population but has not been examined in PLWH in Hong Kong or elsewhere. Of note, Chan did not find a significant relationship of the HKLLT with their measure of social support. Bourgeois et al. (2020) used the MoCA, a single instrument testing nine cognitive domains, which has been determined to have limited reliability in screening for cognitive impairment in populations of older adults with HIV (Rosca et al., 2019; V. Valcour, Paul, et al., 2011). Likewise, Wubetu used the MMSE, which has been shown to be a less robust instrument to detect HAND (Oshinaike et al., 2012; Skinner et al., 2009). One study reported a sensitivity of 23.81% at the cutoff score of 24 to detect normal cognition *versus* HAND (Joska et al., 2016), which is lower than reported sensitivity of the MoCA to detect HAND (Nasreddine et al., 2005). Although the MoCA and MMSE are not robust instruments for detecting HAND, their implementation is more straightforward and these tests are feasible to administer in clinical settings compared to neuropsychological test batteries, therefore they may retain some value as a tool in translational research studies.

Six (6) studies examined self-reported cognitive impairment symptoms and all analyzed the relationship of self-reported symptoms and a social connection variable (Atkins et al., 2010; Chan et al., 2007; Harris et al., 2020; Subramanian et al., 2020; Zhu et al., 2019; Han et al., 2021). The PAOFI, a widely used scale to assess subjective cognitive complaints, was used by Atkins et al (2010) and Chan et al (2007). However, the PAOFI has not been validated to detect cognitive impairment in PLWH (Rourke et al., 1999). Atkins et al (2010) and Chan et al (2007) studies showed that more subjective cognitive symptoms on the PAOFI were associated with increased depressive symptoms, and this aligns with other literature in this area (Thames, Kim, et al., 2011). The Perceived Deficit Questionnaire (PDQ) is another commonly used instrument to assess subjective cognitive symptom burden (Brouillette et al., 2015).

Harris et al (2020) used this instrument in their study and found that PDQ score increased with loneliness in adjusted models, although the contribution of age, education, substance use, and clinical factors were not included in their model for this relationship. Subramanian et al. (2020), Zhu et al. (2019), and Han et al. (2021) assessed subjective cognitive function variables with a sub-domains of existing tools measuring other constructs. None of these studies strongly supported the reliability of the sub-domain measures in their populations, which threatens construct validity and poses more risk of bias in these studies.

Cognitive impairment among PLWH, which is measured by neuropsychological test batteries as a gold standard, often does not closely associate with self-reported cognitive complaints in the same individual. This is observed in in both the general population as well as HIV seropositive populations (Caracciolo et al., 2012; Thames, Becker, et al., 2011). Additionally, depression, anxiety, and other mental health symptoms are often closely related to self-reported cognitive functioning rather than objective cognitive status (Laverick et al., 2017). This is an important consideration when assessing confounding between social connection variables and cognitive impairment.

In our sub-analyses, there was a significant pooled effect of social isolation, but not of loneliness, on degree of cognitive impairment. While this may be impacted by the sample size and weight of the studies that examined loneliness, it suggests that social isolation and loneliness may represent distinct constructs that may influence cognitive health in different ways (Berkman, 2000; McHugh et al., 2017; Perissinotto & Covinsky, 2014). As knowledge in this area develops, particular attention should be paid to these separate constructs and the social experiences they reflect.

Eight of the eleven (8/11) studies examined a measure of social isolation/support, three (3/11) examined a measure of loneliness, and two (2/11) studies measured both variables. The methods for assessing loneliness and social isolation varied among the studies, ranging from validated scales or sub-scales to a single investigator-constructed question. Additionally, one study examined status of living alone, which was framed by the authors as a reflection of social support (Eaton et al., 2020). The variability in measures of social connection reflects a crucial lack of consistency and reliability in the

approach to measurement of this variable. One recent review of the reliability of social support scales among PLWH excluded studies that relied on sub-scales due to issues with validation and construct validity (Wallace et al., 2019). Social connection is complex with a variety of theoretical underpinnings, therefore understanding the distinctions between these constructs, and how they impact cognitive function, is an important area of future research.

In addition to the issues with construct validity and measurement of social connection variables, there are also factors that may influence the generalizability of these results. For example, social support may differ across countries and cultures with different levels of social capital, cultural norms of social caretaking, and access to government or state support. The varying degrees of marginalization, stigmatization, and criminalization of PLWH and associated identities among countries represented—and the degree to which these factors impact social capital, social connectedness, and determinants of brain health—may limit the generalizability of these findings to a global population of PLWH (Baghaei Lakeh & Ghaffarzadegan, 2017; Marmot, 2005).

As PLWH age, social connectedness decreases as the burden of loss and chronic health conditions impacts social network size (Wallach & Brotman, 2013). On average, older people living with HIV experience more loneliness and social isolation than their HIV-seronegative counterparts (Greene et al., 2018; Grov et al., 2010a; Poindexter & Shippy, 2008). The Research on Older Adults with HIV (ROAH) study described loneliness among older HIV-positive adults as "fragile," and found loneliness to be correlated with depression and stigma (Shippy & Karpiak, 2005). Older adults with HIV who are socially isolated report getting less assistance, less support availability and adequacy, more stigma and psychological distress, and decreased well-being compared to people who were more socially integrated (DeMarco & Cao, 2015). In the general population and among PLWH, those in older age groups are therefore considered to be at higher risk of isolation and loneliness, as well as cognitive impairment. Our hypothesis that these variables would moderated by age was not supported by our meta-analysis findings; However, the meta-regression was underpowered and also relied on a dichotomous variable for age,

which may not provide information on the nuanced relationship between age, cognitive impairment, and social isolation or loneliness. Indeed, our follow-up meta-regression analysis of age showed non-significant moderation by age. As this body of literature continues to expand, age effects should be further examined.

We chose to examine a biomarker in our meta-regression based on the crucial role of inflammation and immune system status in the etiology of HAND (Kallianpur et al., 2013; Sharma et al., 2020; Valcour et al., 2011). CD4 cell count is a marker of immune function among PLWH and generally correlates with other markers of overall and general health. There was not moderation of the association between cognitive impairment and loneliness or social isolation by mean CD4-cell count of the study samples. The lack of association may have been due to the dichotomization of CD4 cell count, which was necessary because of the varied ways CD4 cell count was reported in the included studies, or due to the lack of heterogeneity in mean CD4 cell count among the 10 study samples. There remains a role for the study of biomarkers in future research about HAND and social connectedness, as well the inter-related symptoms of depression, stress and stigma, among PLWH.

Limitations

This study has several limitations, including the review of only English-language papers and that human error may be introduced during the study screening and inclusion phase and the data extraction phase. The nascence of this area of study poses a limitation in the number of articles eligible for inclusion, though this area is growing at a rapid pace. Additionally, there was low power for the meta-regression and certain assumptions for conversions to Cohen's *d* may not be verifiable by the information given in the studies. Because all studies included in the meta-analysis were cross sectional, the temporal sequence between loneliness and social support and cognitive impairment is unknown and no causal inferences can be made. Although certain studies reviewed referred to mediation or "consequences" in their results, implying possible causality, the assumptions for this interpretation are not met by the available data. Future studies should examine longitudinal data to consider both temporality and cognitive changes over

time. When examining these studies in this review in terms of the threats to validity, reliability, and bias we found that most studies had at least moderate, if not more, risk of bias on the NIH study quality assessment tool. Furthermore, our meta-regression showed significant moderation study quality. The most common threats to internal validity of the studies include use of un-validated or unreliable measures of exposure and/or outcome variables and lack of adjustment for confounding by depression and age. While some studies made a choice to exclude depression or age from final effect estimates, others did not explain the exclusion of these variables. However, when we used only the studies with low-moderate risk of bias in the meta-analysis, we found a stronger overall effect (n=8, Pooled d=0.414, 95% CI: [0.302, 0.525]) and heterogeneity was reduced (I^2=23.53%). While this bias analysis lends credence to our results, it also indicates that further, rigorous research in this area of inquiry is needed. Future research in this area would benefit from the use of consistent, reliable, validated scales for social support or loneliness and "gold standard" measures of cognitive status and symptoms.

Conclusions

Our review and analyses suggest an association between increased social connectedness and more cognitive impairment among PLWH across the globe. The eleven studies reviewed used diverse measures of cognitive symptoms and cognitive status, which varied in their established construct validity and overall reliability. Additionally, the studies were limited by the use of un-validated scales and measures of loneliness and social support. The meta-analysis showed a positive association between social connectedness (social isolation or loneliness) on cognitive impairment. Though there was moderate heterogeneity, there was not substantial publication bias. In sub-group analyses, there was a significant positive association between a) self-reported cognitive impairment and loneliness or social isolation, b) performance based cognitive impairment and either loneliness or social isolation, and c) social isolation and either self-report or performance based cognitive impairment. Overall, our results point to the potential impacts of marginalized conditions, such as HIV, on neurocognitive health and risk for cognitive impairment. Although more research is needed, our review suggests that interventions targeting social

connectedness and social integration at various levels—including structural, environmental, and individual—may result in improved health outcomes among aging PLWH.

References

Abiola, T., Udofia, O., & Zakari, M. (2013). Psychometric properties of the 3-item oslo social support scale among clinical students of Bayero University Kano, Nigeria. *Malaysian Journal of Psychiatry*, *22*(2), 32–41.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders: DSM-5* (Fifth). American Psychiatric Association.

Antinori, A., Arendt, G., Becker, J. T., Brew, B. J., Byrd, D. A., Cherner, M., Clifford, D. B., Cinque, P., Epstein, L. G., Goodkin, K., Gisslen, M., Grant, I., Heaton, R. K., Joseph, J., Marder, K., Marra, C. M., McArthur, J. C., Nunn, M., Price, R. W., … Wojna, V. E. (2007). Updated research nosology for HIV-associated neurocognitive disorders. *Neurology*, *69*(18), 1789–1799. https://doi.org/10.1212/01.WNL.0000287431.88658.8b

Ashton, E., Vosvick, M., Chesney, M., Gore-Felton, C., Koopman, C., O'Shea, K., Maldonado, J., Bachmann, M. H., Israelski, D., Flamm, J., & Spiegel, D. (2005). Social support and maladaptive coping as predictors of the change in physical health symptoms among persons living with HIV/AIDS. *AIDS Patient Care and STDs*, *19*(9), 587–598. https://doi.org/10.1089/apc.2005.19.587

Atkins, J. H., Rubenstein, S. L., Sota, T. L., Rueda, S., Fenta, H., Bacon, J., & Rourke, S. B. (2010). Impact of social support on cognitive symptom burden in HIV/AIDS. *AIDS Care*, *22*(7), 793–802. https://doi.org/10.1080/09540120903482994

Baghaei Lakeh, A., & Ghaffarzadegan, N. (2017). Global Trends and Regional Variations in Studies of HIV/AIDS. *Scientific Reports*, *7*(1), 4170. https://doi.org/10.1038/s41598-017-04527-6

Beck, A. T., Steer, R. A., & Carbin, M. G. (1988). Psychometric properties of the Beck Depression Inventory: Twenty-five years of evaluation. *Clinical Psychology Review*, *8*(1), 77–100.

Berkman, L. F. (2000). Which influences cognitive function: Living alone or being alone? *Lancet (London, England)*, *355*(9212), 1291–1292. https://doi.org/10.1016/S0140-6736(00)02107-3

Berkman, L. F., Glass, T., Brissette, I., & Seeman, T. E. (2000). From social integration to health: Durkheim in the new millennium. *Social Science & Medicine (1982)*, *51*(6), 843–857.

Bourgeois, J. A., John, M., Zepf, R., Greene, M., Frankel, S., & Hessol, N. A. (2020). Functional deficits and other psychiatric associations with abnormal scores on the Montreal Cognitive Assessment (MoCA) in older HIV-infected patients. *International Psychogeriatrics*, *32*(1), 105–118. Embase. https://doi.org/10.1017/S1041610219000413

Brouillette, M.-J., Fellows, L. K., Finch, L., Thomas, R., & Mayo, N. E. (2019). Properties of a brief assessment tool for longitudinal measurement of cognition in people living with HIV. *PloS One*, *14*(3), e0213908. https://doi.org/10.1371/journal.pone.0213908

Burgoyne, R. W. (2005). Exploring direction of causation between social support and clinical outcome for HIV-positive adults in the context of highly active antiretroviral therapy. *AIDS Care*, *17*(1), 111–124. https://doi.org/10.1080/09540120412331305179

Burholt, V., Windle, G., Ferring, D., Balducci, C., Fagerström, C., Thissen, F., Weber, G., & Wenger, G. C. (2007). Reliability and Validity of the Older Americans Resources and Services (OARS) Social Resources Scale in Six European Countries. *The Journals of Gerontology: Series B*, *62*(6), S371–S379. https://doi.org/10.1093/geronb/62.6.S371

Butters, M. A., Bhalla, R. K., Andreescu, C., Wetherell, J. L., Mantella, R., Begley, A. E., & Lenze, E. J. (2011). Changes in neuropsychological functioning following treatment for late-life generalised anxiety disorder. *The British Journal of Psychiatry*, *199*(3), 211–218. PsycINFO. https://doi.org/10.1192/bjp.bp.110.090217

Cacioppo, S., Capitanio, J. P., & Cacioppo, J. T. %J P. B. (2014). *Toward a neurology of loneliness*. *140*(6), 1464.

Caracciolo, B., Gatz, M., Xu, W., Pedersen, N. L., & Fratiglioni, L. (2012). Differential distribution of subjective and objective cognitive impairment in the population: A nation-wide twin-study. *Journal of Alzheimer's Disease: JAD*, *29*(2), 393–403. https://doi.org/10.3233/JAD-2011-111904

Centers for Disease Control and Prevention. (2018, September 18). *HIV Among People Aged 50 and Over*. https://www.cdc.gov/hiv/group/age/olderamericans/index.html

Chan, I., Chan, E., Au, A., Leung, P., Li, P., Lee, M. P., Chung, R., & Yu, P. (2007). Subjective memory complaints of Chinese HIV-infected patients in Hong Kong: Relationships with social support, depressive mood and medical symptoms. *AIDS Care*, *19*(9), 1149–1156. https://doi.org/10.1080/09540120701402780

Chelune, G. J., Heaton, R. K., Lehman, R. A., & Goldstein, G. (1986). Advances in clinical neuropsychology. *US: Springer*, 95–126.

Chesney, M. A., Ickovics, J. R., Chambers, D. B., Gifford, A. L., Neidig, J., Zwickl, B., Wu, A. W., & Group (AACTG), P. C. C. & A. W. G. of the O. C. of the A. A. C. T. (2000). Self-reported adherence to antiretroviral medications among participants in HIV clinical trials: The AACTG adherence instruments. *AIDS Care*, *12*(3), 255–266.

Cole, S. W., Hawkley, L. C., Arevalo, J. M. G., & Cacioppo, J. T. (2011). Transcript origin analysis identifies antigen-presenting cells as primary targets of socially regulated gene expression in leukocytes. *Proceedings of the National Academy of Sciences of the United States of America*, *108*(7), 3080–3085. https://doi.org/10.1073/pnas.1014218108

Cutrona, C. E., & Russell, D. W. (1987). The provisions of social relationships and adaptation to stress. *Advances in Personal Relationships*, *1*(1), 37–67.

DeMarco, R. F., & Cao, C. (2015). HIV Prevention, Stigma, and Care in Ho Chi Minh City and Da Lat Vietnam. *Journal of Cultural Diversity*, *22*(4), 127–133.

Eaton, P., Lewis, T., Kellett-Wright, J., Flatt, A., Urasa, S., Howlett, W., Dekker, M., Kisoli, A., Rogathe, J., Thornton, J., McCartney, J., Yarwood, V., Irwin, C., Mukaetova-Ladinska, E. B., Akinyemi, R., Gray, W. K., Walker, R. W., Dotchin, C. L., Makupa, P. C., … Paddick, S.-M. (2020). Risk factors for symptomatic HIV-associated neurocognitive disorder in adults aged 50 and over attending a HIV clinic in Tanzania. *International Journal of Geriatric Psychiatry*, *35*(10), 1198–1208. Embase. https://doi.org/10.1002/gps.5357

Edwards, M. M. (1990). The reliability and validity of self-report activities of daily living scales. *Canadian Journal of Occupational Therapy*, *57*(5), 273–278.

Ellis, R. J., Iudicello, J., Sun-Suslow, N., Grelotti, D., Cherner, M., Morgan, E., Letendre, S. L., & Heaton, R. K. (2021). Social Isolation Is Linked to Inflammation in Aging People With HIV and Uninfected Individuals. *JAIDS Journal of Acquired Immune Deficiency Syndromes*, *86*(5), 600–606. https://doi.org/10.1097/QAI.0000000000002596

Fang, C.-T., Hsiung, P.-C., Yu, C.-F., Chen, M.-Y., & Wang, J.-D. (2002). Validation of the World Health Organization quality of life instrument in patients with HIV infection. *Quality of Life Research*, *11*(8), 753–762. https://doi.org/10.1023/A:1020870402019

Farmer, P. E., Nizeye, B., Stulac, S., & Keshavjee, S. (2006). Structural Violence and Clinical Medicine. *PLoS Medicine*, *3*(10). https://doi.org/10.1371/journal.pmed.0030449

FDA-NIH Biomarker Working Group. (2016). *BEST (Biomarkers, EndpointS, and other Tools) Resource*. Food and Drug Administration (US). http://www.ncbi.nlm.nih.gov/books/NBK326791/

Fekete, E. M., Williams, S. L., & Skinta, M. D. (2018). Internalised HIV-stigma, loneliness, depressive symptoms and sleep quality in people living with HIV. *Psychology & Health*, *33*(3), 398–415. https://doi.org/10.1080/08870446.2017.1357816

Gierveld, J. D. J., & Van Tilburg, T. (2010). The De Jong Gierveld short scales for emotional and social loneliness: Tested on data from 7 countries in the UN generations and gender surveys. *European Journal of Ageing*, *7*(2), 121–130.

Golden, J., Conroy, R. M., Bruce, I., Denihan, A., Greene, E., Kirby, M., & Lawlor, B. A. (2009). Loneliness, social support networks, mood and wellbeing in community-dwelling elderly. *International Journal of Geriatric Psychiatry*, *24*(7), 694–700. https://doi.org/10.1002/gps.2181

Greene, M., Hessol, N. A., Perissinotto, C., Zepf, R., Hutton Parrott, A., Foreman, C., Whirry, R., Gandhi, M., & John, M. (2018a). Loneliness in Older Adults Living with HIV. *AIDS and Behavior*, *22*(5), 1475–1484. https://doi.org/10.1007/s10461-017-1985-1

Greene, M., Hessol, N. A., Perissinotto, C., Zepf, R., Hutton Parrott, A., Foreman, C., Whirry, R., Gandhi, M., & John, M. (2018b). Loneliness in Older Adults Living with HIV. *AIDS and Behavior*, *22*(5), 1475–1484. https://doi.org/10.1007/s10461-017-1985-1

Greysen, S. R., Horwitz, L. I., Covinsky, K. E., Gordon, K., Ohl, M. E., & Justice, A. C. (2013). Does social isolation predict hospitalization and mortality among HIV+ and uninfected older veterans? *Journal of the American Geriatrics Society*, *61*(9), 1456–1463. https://doi.org/10.1111/jgs.12410

Grov, C., Golub, S. A., Parsons, J. T., Brennan, M., & Karpiak, S. E. (2010). Loneliness and HIV-related stigma explain depression among older HIV-positive adults. *AIDS Care*, *22*(5), 630–639. https://doi.org/10.1080/09540120903280901

Hackett, R. A., Hamer, M., Endrighi, R., Brydon, L., & Steptoe, A. (2012). Loneliness and stress-related inflammatory and neuroendocrine responses in older men and women. *Psychoneuroendocrinology*, *37*(11), 1801–1809. https://doi.org/10.1016/j.psyneuen.2012.03.016

Han, S. D., Adeyemi, O., Wilson, R. S., Leurgans, S., Jimenez, A., Oullet, L., Shah, R., Landay, A., Bennett, D. A., & Barnes, L. L. (2017). Loneliness in Older Black Adults with Human Immunodeficiency Virus Is Associated with Poorer Cognition. *Gerontology*, *63*(3), 253–262. https://doi.org/10.1159/000455253

Han, S., Hu, Y., Wang, L., Pei, Y., Zhu, Z., Qi, X., & Wu, B. (2021). Perceived Discrimination and Symptoms of Cognitive Dysfuntion Among Middle-Age and Older Persons Living With HIV in China: A Multicenter Cross-Sectional Study of the Mediating Role of Mental Health Symptoms and Social Isolation. *The Journal of the Association of Nurses in AIDS Care: JANAC*, *32*(4), 442–452. https://doi.org/10.1097/JNC.0000000000000264

Harris, M., Brouillette, M.-J., Scott, S. C., Smaill, F., Smith, G., Thomas, R., Fellows, L. K., & Mayo, N. E. (2020). Impact of Loneliness on Brain Health and Quality of Life Among Adults Living With HIV in Canada. *Journal of Acquired Immune Deficiency Syndromes (1999)*, *84*(4), 336–344. Medline. https://doi.org/10.1097/QAI.0000000000002355

Hays, R. D., Prince-Embury, S., & Chen, H. (1998). *RAND-36 health status inventory*. Psychological Corporation San Antonio, TX.

Heaton, R. K., Clifford, D. B., Franklin, D. R., Woods, S. P., Ake, C., Vaida, F., Ellis, R. J., Letendre, S. L., Marcotte, T. D., Atkinson, J. H., Rivera-Mindt, M., Vigil, O. R., Taylor, M. J., Collier, A. C., Marra, C. M., Gelman, B. B., McArthur, J. C., Morgello, S., Simpson, D. M., … Grant, I. (2010). HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy. *Neurology*, *75*(23), 2087. https://doi.org/10.1212/WNL.0b013e318200d727

Higgins & Thomas. (2021). *Cochrane Handbook for Systematic Reviews of Interventions, Version 6.2*. https://training.cochrane.org/handbook

Holt-Lunstad, J., Smith, T. B., & Layton, J. B. (2010). Social relationships and mortality risk: A meta-analytic review. *PLoS Medicine*, *7*(7), e1000316. https://doi.org/10.1371/journal.pmed.1000316

Hubach, R. D., Dodge, B., Li, M. J., Schick, V., Herbenick, D., Ramos, W. D., Cola, T., & Reece, M. (2015). Loneliness, HIV-related stigma, and condom use among a predominantly rural sample of HIV-positive men who have sex with men (MSM). *AIDS Education and Prevention : Official Publication of the International Society for AIDS Education*, *27*(1), 72–83. https://doi.org/10.1521/aeap.2015.27.1.72

Inouye, S. K., Studenski, S., Tinetti, M. E., & Kuchel, G. A. (2007). Geriatric syndromes: Clinical, research, and policy implications of a core geriatric concept. *Journal of the American Geriatrics Society*, *55*(5), 780–791. https://doi.org/10.1111/j.1532-5415.2007.01156.x

Joska, J. A., Witten, J., Thomas, K. G., Robertson, C., Casson-Crook, M., Roosa, H., Creighton, J., Lyons, J., McArthur, J., & Sacktor, N. C. (2016). A Comparison of Five Brief Screening Tools for HIV-Associated Neurocognitive Disorders in the USA and South Africa. *AIDS and Behavior*, *20*(8), 1621–1631. https://doi.org/10.1007/s10461-016-1316-y

Kallianpur, K. J., Shikuma, C., Kirk, G. R., Shiramizu, B., Valcour, V., Chow, D., Souza, S., Nakamoto, B., & Sailasuta, N. (2013). Peripheral blood HIV DNA is associated with atrophy of cerebellar

and subcortical gray matter. *Neurology*, *80*(19), 1792–1799. https://doi.org/10.1212/WNL.0b013e318291903f

Kocalevent, R.-D., Berg, L., Beutel, M. E., Hinz, A., Zenger, M., Härter, M., Nater, U., & Brähler, E. (2018). Social support in the general population: Standardization of the Oslo social support scale (OSSS-3). *BMC Psychology*, *6*(1), 31. https://doi.org/10.1186/s40359-018-0249-9

Kocalevent, R.-D., Hinz, A., & Brähler, E. (2013). Standardization of the depression screener patient health questionnaire (PHQ-9) in the general population. *General Hospital Psychiatry*, *35*(5), 551–555.

Koenig, N., Fujiwara, E., Gill, M. J., & Power, C. (2016). Montreal Cognitive Assessment Performance in HIV/AIDS: Impact of Systemic Factors. *Can J Neurol Sci*, *43*(1), 157–162. https://doi.org/10.1017/cjn.2015.306

Kroenke, K., Spitzer, R. L., & Williams, J. B. W. (2003). The Patient Health Questionnaire-2: Validity of a two-item depression screener. *Medical Care*, *41*(11), 1284–1292. https://doi.org/10.1097/01.MLR.0000093487.78664.3C

Kuiper, J. S., Zuidersma, M., Oude Voshaar, R. C., Zuidema, S. U., van den Heuvel, E. R., Stolk, R. P., & Smidt, N. (2015). Social relationships and risk of dementia: A systematic review and meta-analysis of longitudinal cohort studies. *Ageing Research Reviews*, *22*, 39–57. https://doi.org/10.1016/j.arr.2015.04.006

Laverick, R., Haddow, L., Daskalopoulou, M., Lampe, F., Gilson, R., Speakman, A., Antinori, A., Bruun, T., Vassilenko, A., Collins, S., & Rodger, A. (2017). Self-Reported Decline in Everyday Function, Cognitive Symptoms, and Cognitive Function in People With HIV. *J Acquir Immune Defic Syndr*, *76*(3), e74–e83. https://doi.org/10.1097/qai.0000000000001468

Leigh-Hunt, N., Bagguley, D., Bash, K., Turner, V., Turnbull, S., Valtorta, N., & Caan, W. (2017). An overview of systematic reviews on the public health consequences of social isolation and loneliness. *Public Health*, *152*, 157–171. https://doi.org/10.1016/j.puhe.2017.07.035

Leserman, J., Petitto, J. M., Golden, R. N., Gaynes, B. N., Gu, H., Perkins, D. O., Silva, S. G., Folds, J. D., & Evans, D. L. (2000). Impact of stressful life events, depression, social support, coping, and cortisol on progression to AIDS. *The American Journal of Psychiatry*, *157*(8), 1221–1228. https://doi.org/10.1176/appi.ajp.157.8.1221

Lubben, J., Blozik, E., Gillmann, G., Iliffe, S., von Renteln Kruse, W., Beck, J. C., & Stuck, A. E. (2006). Performance of an abbreviated version of the Lubben Social Network Scale among three European community-dwelling older adult populations. *The Gerontologist*, *46*(4), 503–513.

Lubeck, D. P., & Fries, J. F. (1997). Assessment of quality of life in early stage HIV-infected persons: Data from the AIDS Time-oriented Health Outcome Study (ATHOS). *Quality of Life Research: An International Journal of Quality of Life Aspects of Treatment, Care and Rehabilitation*, *6*(6), 494–506. https://doi.org/10.1023/a:1018404014821

Mannes, Z. L., Burrell, L. E. 2nd, Dunne, E. M., Hearn, L. E., & Whitehead, N. E. (2017). Contextualizing Psychosocial Determinants of Alcohol Use by Age Cohorts of Adults Living With HIV, Ages 50 and Older. *The Journal of the Association of Nurses in AIDS Care : JANAC*, *28*(2), 279–288. https://doi.org/10.1016/j.jana.2016.11.005

Mannes, Z. L., Burrell, L. E., Bryant, V. E., Dunne, E. M., Hearn, L. E., & Whitehead, N. E. (2016). Loneliness and substance use: The influence of gender among HIV+ Black/African American adults 50+. *AIDS Care*, *28*(5), 598–602. https://doi.org/10.1080/09540121.2015.1120269

Marmot, M. (2005). Social determinants of health inequalities. *The Lancet*, *365*(9464), 1099–1104.

McHugh, J. E., Kenny, R. A., Lawlor, B. A., Steptoe, A., & Kee, F. (2017). The discrepancy between social isolation and loneliness as a clinically meaningful metric: Findings from the Irish and English longitudinal studies of ageing (TILDA and ELSA). *International Journal of Geriatric Psychiatry*, *32*(6), 664–674. https://doi.org/10.1002/gps.4509

Milanini, B., Wendelken, L. A., Esmaeili-Firidouni, P., Chartier, M., Crouch, P.-C., & Valcour, V. (2014). The Montreal Cognitive Assessment (MoCA) to screen for cognitive impairment in HIV

over age 60. *Journal of Acquired Immune Deficiency Syndromes (1999)*, *67*(1), 67–70. https://doi.org/10.1097/QAI.0000000000000220

Miller, G. E., Kemeny, M. E., Taylor, S. E., Cole, S. W., & Visscher, B. R. (1997). Social relationships and immune processes in HIV seropositive gay and bisexual men. *Annals of Behavioral Medicine : A Publication of the Society of Behavioral Medicine*, *19*(2), 139–151. https://doi.org/10.1007/BF02883331

Moore, D. J., Fazeli, P. L., Moore, R. C., Woods, S. P., Letendre, S. L., Jeste, D. V., Grant, I., & HIV Neurobehavioral Research Program. (2018). Positive Psychological Factors are Linked to Successful Cognitive Aging Among Older Persons Living with HIV/AIDS. *AIDS and Behavior*, *22*(5), 1551–1561. https://doi.org/10.1007/s10461-017-2001-5

Nakazato, A., Tominaga, D., Tasato, D., Miyagi, K., Nakamura, H., Haranaga, S., Higa, F., Tateyama, M., & Fujita, J. (2014). Are MMSE and HDS-R neuropsychological tests adequate for screening HIV-associated neurocognitive disorders? *J Infect Chemother*, *20*(3), 217–219. https://doi.org/10.1016/j.jiac.2013.10.005

Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., Cummings, J. L., & Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society*, *53*(4), 695–699.

NIH, N. (n.d.). *Study Quality Assessment Tools*. Retrieved December 22, 2020, from https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools

OAR Working Group on HIV and Aging. (2012). HIV and Aging: State of Knowledge and Areas of Critical Need for Research. *Journal of Acquired Immune Deficiency Syndromes (1999)*, *60*(Suppl 1), S1-18. https://doi.org/10.1097/QAI.0b013e31825a3668

Oshinaike, O. O., Akinbami, A. A., Ojo, O. O., Ojini, I. F., Okubadejo, U. N., & Danesi, A. M. (2012). Comparison of the Minimental State Examination Scale and the International HIV Dementia Scale in Assessing Cognitive Function in Nigerian HIV Patients on Antiretroviral Therapy. *AIDS Research and Treatment*, *2012*, 581531. https://doi.org/10.1155/2012/581531

Peplau, L. A., & Perlman, D. (1982). *Loneliness: A sourcebook of current theory, research, and therapy*. Wiley. http://ucsf.summon.serialssolutions.com/2.0.0/link/0/eLvHCXMwdV07C8IwED6kXbr5xDf-gUqbpsaMIoqDi6BIXUraJKMO4uC_9662oqJjCDmScHz3yH0XgIhNA_8LE3Ibouc8N4qrmHxmFWg2YzrjMdOhNEROXqyi3UEcEyrVqT6qu-VX-0Hrx_GruqbIYFAHceL6utTHjjvgYuCYnCqNolc0LkVQUNEFldMhGldtd8px0YEP5b6ZlXUdHKIaNKBmzk3wXlh0b4G3vZyJKY441IbRerVfbnxanpbplrTaU8Q64GAIb7owydEIzmJpYpFZLrWVSnGrhM7RO1AYgfSg81tG_9_EALxQztkzGTAE16KymtHzJOPyFh7RdmU3

Perissinotto, C. M., & Covinsky, K. E. (2014). Living alone, socially isolated or lonely—What are we measuring? *Journal of General Internal Medicine*, *29*(11), 1429–1431. https://doi.org/10.1007/s11606-014-2977-8

Perissinotto, C. M., Stijacic Cenzer, I., & Covinsky, K. E. (2012). Loneliness in older persons: A predictor of functional decline and death. *Archives of Internal Medicine*, *172*(14), 1078–1083. https://doi.org/10.1001/archinternmed.2012.1993

Poindexter, C., & Shippy, R. A. (2008). Networks of older New Yorkers with HIV: Fragility, resilience, and transformation. *AIDS Patient Care and STDs*, *22*(9), 723–733. https://doi.org/10.1089/apc.2007.0260

Rhodes, T., Singer, M., Bourgois, P., Friedman, S. R., & Strathdee, S. A. (2005). The social structural production of HIV risk among injecting drug users. *Social Science & Medicine (1982)*, *61*(5), 1026–1044. https://doi.org/10.1016/j.socscimed.2004.12.024

Rosca, E. C., Albarqouni, L., & Simu, M. (2019). Montreal Cognitive Assessment (MoCA) for HIV-Associated Neurocognitive Disorders. *Neuropsychology Review*, *29*(3), 313–327. https://doi.org/10.1007/s11065-019-09412-9

Rourke, S. B., Halman, M. H., & Bassel, C. (1999). Neuropsychiatric Correlates of Memory-Metamemory Dissociations in HIV-Infection. *Journal of Clinical and Experimental Neuropsychology*, *21*(6), 757–768. https://doi.org/10.1076/jcen.21.6.757.852

Schutter, N., Holwerda, T. J., Stek, M. L., Dekker, J. J. M., Rhebergen, D., & Comijs, H. C. (2017). Loneliness in older adults is associated with diminished cortisol output. *Journal of Psychosomatic Research*, *95*, 19–25. https://doi.org/10.1016/j.jpsychores.2017.02.002

Sharma, V., Bryant, C., Montero, M., Creegan, M., Slike, B., Krebs, S. J., Ratto-Kim, S., Valcour, V., Sithinamsuwan, P., Chalermchai, T., Eller, M. A., Bolton, D. L., & SEARCH007/SEARCH011 Study Groups. (2020). Monocyte and CD4+ T-cell antiviral and innate responses associated with HIV-1 inflammation and cognitive impairment. *AIDS (London, England)*, *34*(9), 1289–1301. https://doi.org/10.1097/QAD.0000000000002537

Sheikh, J. I., & Yesavage, J. A. (1986). Geriatric Depression Scale (GDS): Recent evidence and development of a shorter version. *Clinical Gerontologist: The Journal of Aging and Mental Health*.

Shippy, R. A., & Karpiak, S. E. (2005). The aging HIV/AIDS population: Fragile social networks. *Aging & Mental Health*, *9*(3), 246–254. https://doi.org/10.1080/13607860412331336850

Skinner, S., Adewale, A. J., DeBlock, L., Gill, M. J., & Power, C. (2009). Neurocognitive screening tools in HIV/AIDS: comparative performance among patients exposed to antiretroviral therapy. *HIV Med*, *10*(4), 246–252. https://doi.org/10.1111/j.1468-1293.2008.00679.x

StataCorp. (2017). *Stata Statistical Software: Release 15*. StataCorp LLC.

Steptoe, A., Shankar, A., Demakakos, P., & Wardle, J. (2013). Social isolation, loneliness, and all-cause mortality in older men and women. *Proceedings of the National Academy of Sciences of the United States of America*, *110*(15), 5797–5801. https://doi.org/10.1073/pnas.1219686110

Subramanian, A., Mohan, A., Nandi, P. K., & Rajeshwari, K. (2020). Perceived social support, depression and their impact on quality of life of people living with HIV in India. *AIDS Care - Psychological and Socio-Medical Aspects of AIDS/HIV*, *(Subramanian A., drsanuradha@gmail.com; Mohan A.; Nandi P.K.; Rajeshwari K.) ART Center, Maulana Azad Medical College and Associated Lok Nayak Hospital, New Delhi, India*. Embase. https://doi.org/10.1080/09540121.2020.1810620

Thalheimer, W., & Cook, S. (2002). *How to calculate effect sizes from published research articles: A simplified methodology*. 9. https://www.bwgriffin.com/gsu/courses/edur9131/content/Effect_Sizes_pdf5.pdf

Thames, A. D., Becker, B. W., Marcotte, T. D., Hines, L. J., Foley, J. M., Ramezani, A., Singer, E. J., Castellon, S. A., Heaton, R. K., & Hinkin, C. H. (2011). Depression, Cognition, and Self-Appraisal of Functional Abilities in HIV: An Examination of Subjective Appraisal Versus Objective Performance. *The Clinical Neuropsychologist*, *25*(2), 224–243. https://doi.org/10.1080/13854046.2010.539577

Thames, A. D., Kim, M. S., Becker, B. W., Foley, J. M., Hines, L. J., Singer, E. J., Heaton, R. K., Castellon, S. A., & Hinkin, C. H. (2011). Medication and finance management among HIV-infected adults: The impact of age and cognition. *J Clin Exp Neuropsychol*, *33*(2), 200–209. https://doi.org/10.1080/13803395.2010.499357

Valcour, V., Sithinamsuwan, P., Letendre, S., & Ances, B. (2011). Pathogenesis of HIV in the central nervous system. *Current HIV/AIDS Reports*, *8*(1), 54–61. https://doi.org/10.1007/s11904-010-0070-4

VanderWeele, T. J. (2016). Mediation Analysis: A Practitioner's Guide. *Annual Review of Public Health*, *37*(1), 17–32. https://doi.org/10.1146/annurev-publhealth-032315-021402

Wallace, D. D., Pack, A., Castonguay, B. U., Stewart, J. L., Schalkoff, C., Cherkur, S., Schein, M., Go, M., Devadas, J., Fisher, E. B., & Golin, C. E. (2019). Validity of Social Support Scales Utilized among HIV-infected and HIV-affected Populations: A Systematic Review. *AIDS and Behavior*, *23*(8), 2155–2175. https://doi.org/10.1007/s10461-018-2294-z

Wallach, I., & Brotman, S. (2013). Ageing with HIV/AIDS: A scoping study among people aged 50 and over living in Quebec. *Ageing & Society*, *33*(7), 1212–1242. https://doi.org/10.1017/S0144686X12000529

Welch, V., Petticrew, M., Tugwell, P., Moher, D., O'Neill, J., Waters, E., White, H., & group, P.-E. B. (2012). PRISMA-Equity 2012 extension: Reporting guidelines for systematic reviews with a focus on health equity. *PLoS Medicine*, *9*(10), e1001333.

Winston, A., & Spudich, S. (2020). Cognitive disorders in people living with HIV. *The Lancet HIV*, *7*(7), e504–e513. https://doi.org/10.1016/S2352-3018(20)30107-7

World Health Organization. (2010). *A conceptual framework for action on the social determinants of health: Debates, policy & practice, case studies.* http://apps.who.int/iris/bitstream/10665/44489/1/9789241500852_eng.pdf

Wu, A. W., Revicki, D. A., Jacobson, D., & Malitz, F. E. (1997). Evidence for reliability, validity and usefulness of the Medical Outcomes Study HIV Health Survey (MOS-HIV). *Quality of Life Research*, *6*(6), 481–493.

Wubetu, A. D., Asefa, K. K., & Gebregiorgis, B. G. (2021). Prevalence of Neurocognitive Impairment and Associated Factors Among People Living with HIV on Highly Active Antiretroviral Treatment, Ethiopia. *HIV/AIDS (Auckland, N.Z.)*, *13*, 425–433. https://doi.org/10.2147/HIV.S298141

Zhu, Z., Hu, Y., Xing, W., Guo, M., & Wu, B. (2019). Perceived discrimination and cognitive function in middle-aged and older adults living with HIV in China. *AIDS Care - Psychological and Socio-Medical Aspects of AIDS/HIV*, *31*(9), 1061–1068. Embase. https://doi.org/10.1080/09540121.2019.1601674

Zimet, G. D., Dahlem, N. W., Zimet, S. G., & Farley, G. K. (1988). The multidimensional scale of perceived social support. *Journal of Personality Assessment*, *52*(1), 30–41.

Table 2.1. Inclusion and Exclusion Criteria

Inclusion Criteria	
Population	HIV-seropositive adults
Variables	HIV-Associated Neurocognitive Disorders (HAND) diagnosis, neurocognitive or neuropsychological test performance, or cognitive impairment symptoms Social Isolation, Social Support, Loneliness
Study Design	Experimental, Longitudinal, and Cross Sectional
Language	English
Setting	Global
Date Range	01/01/1996- 12/31/2020
Publication Status	Published in peer-reviewed journal
Exclusion Criteria	
Study Design	Studies not making statistical inference hypotheses (e.g. Case series/case study, prevalence study, literature review) Meta-analysis
Population	Samples in which none had access to/exposure to ART medications

Table 2.2: Study Characteristics, Hypotheses, and Methods

Study	Locality	Study type, Population/Cohort	Sample size	Demographics	Hypothesis or Study Aims	Analysis method
Chan, 2007	Hong Kong	Cross sectional study of HIV+ 18 to 50 years old	90	Male 82.2% Mean age 39.24 (SD: 6.51) Race not reported 72% secondary school graduates Taking ART 96.70% Undetectable viral load (<50 copies/mmoL) 44.4% Latest CD4+ count: 386.86 cells/mm3 (SD: 222.61)	1: Social support and medical symptoms have a direct association with depressive mood; 2: Depressive mood is a mediator between subjective memory complaints and the two variables of social support and medical symptoms; 3: There is a direct relationship between objective memory performance and subjective memory complaints; 4: There is no relationship between depressive mood and objective memory performance	Path analysis with post hoc model modification
Atkins, 2010	Toronto, ON (Canada)	Cross sectional study of HIV+ men 18 years and older	357	Mean age 41.5 (SD 8.3) White 86.7% Mean education level of 13.9 years (SD: 2.7) 76% treated with ART; 70% were treated with HAART Viral load: Not reported CD4 cell count: not reported	1: Neuropsychological impairment is associated with higher levels of cognitive symptom burden; 2: Higher levels of reported depressive symptoms are associated with increased cognitive symptom burden; 3: The presence of both neuropsychological impairment and depression exacerbates cognitive symptom burden; 4: Increased social support for people with neuropsychological impairment will be associated with lower cognitive symptom burden; 5: Higher levels of social support will reduce the association between depression and cognitive symptom burden	Hierarchical multivariate linear regression analysis

Table 2.2: Study Characteristics, Hypotheses, and Methods *Continued*

Han, 2017	Chicago, IL (USA)	Cross-sectional analysis of HIV+ and HIV- controls (Rush Center of Excellence on Disparities in HIV and Aging (CEDHA))	370 (n=177 HIV+, n=193 HIV-)	Male 73.5% Mean age 58.79 (SD: 6.19) Black racial group 31.08% Mean Education 13.38 years (SD: 2.88) ART not reported Viral loads ranging from undetectable to 50,000 copies Mean CD4+ cell count 617.9 cells/mm3 (SD: 282.7)	1: Older Black adults with HIV have greater loneliness than older White adults with HIV 2: Greater loneliness among older Black adults with HIV is associated with poorer cognitive function.	Linear regression models with interaction effects on global cognition score
Moore, 2018	Southern California/ mostly San Diego County, (USA)	Cross sectional analysis older HIV+ and HIV-	(n=99 HIV+) (n=46 HIV−)	Male (79%) Mean age 58.7 (6.81) range 50–79 years White (76%) Mean years of education 14.28 (SD:2.64) All HIV+ currently taking antiretroviral therapy Mean CD4+ cell count 592.28 (variance no reported) Viral load undetected in 93% HIV+/SCA+ and 91% in HIV+/SCA-	1: Estimate proportion of older HIV+ and HIV− adults with successful cognitive aging (SCA) 2: Compare subjective self-rated successful aging (SRSA), positive psychological factors, and health-related quality of life across SCA groups.	ANCOVA to determine differences in SCA between HIV+ and HIV− subjects with covariate adjustment and with follow-up confirmatory analyses
Zhu, 2019	Shanghai, Hengyang, Kunming, Nanning, Changning, (China)	Cross sectional analysis of survey data among HIV+ ages 45 or older	324	Male 65.12% Mean age 55.8 (SD: 8.51) Han 76.9%, Minority 23.1% Primary school or below 37.9%, Secondary school 53.1%, Post-secondary 6.2%, University or above 2.8% 97.53% prescribed ART Viral load: Not reported Mean CD4+ 342.91 cells/mm3 (SD: 251.7)	1: Describe the severity of cognitive impairments and perceived discrimination in middle-aged and older PLWH; 2: Examine associations between self-reported cognitive ability and perceived discrimination, depressive symptoms, psychological function, social support, and health behaviors	Multiple linear regression; Ordinal regression models of domains of cognitive status

Table 2.2: Study Characteristics, Hypotheses, and Methods *Continued*

Subramanian, 2020	New Delhi, (India)	Cross-sectional study of HIV+ adults	109	Male 56.9% Racial groups: NR Mean age 35 (SD: 7.5 years) 73.4% prescribed ART Viral load: Not reported Median CD4+ 373 cells/mm3 (No variance reported)	1: Assess how social support influences QOL	Descriptive profile analysis and unadjusted measures of association
Harris, 2020	Montreal, Toronto, Hamilton, Vancouver (Canada)	Cross sectional study of HIV+ over 35 (Positive Brain Health Now cohort)	856	Male 85% Mean age 53 (SD: 8.3) White 73% University education 32.3% ART not reported Viral load >50 copies/mL 0.08% Mean CD4+ 432.86 cells/mm3	1: Demographic, environmental, and biological variables contribute to loneliness; 2: Cognition, mental health, and quality of life are consequences of loneliness.	Proportional odds regression for 3 ordinal responses to loneliness item
Eaton, 2020	Moshi, Tanzania (Africa)	Cross sectional study of HIV+ aged 50 years and over	253	Female 72.3% Racial groups: NR Mean age 57.9 (SD: 6.198) 77% < 8 years formal education On ART 94.8% Viral load: Not reported Median CD4+ 500 cells/mm3 (IQR 316 to 672	1: Exploration of risk factors for symptomatic HAND	Regression analysis to identify factors independently associated with cognitive status
Bourgeois, 2020	San Francisco, CA (USA)	Cross sectional study of HIV+ patients ages 50 or older (Silver Project Cohort)	359	Male 85.0% Mean age 57.4 (SD: 5.9) Non-white 42.61%, Latino 10.6% < high school 12.3% High school or GED 16.1% Some college or more 71.6% 98% reported taking ART in the past 30 days Undetectable viral load: 83% UCSF, 81% at SFGH) CD4+ mean 526.2 cells/mm3 (SD: 285.4)	1: Those who who scored poorly on geriatric social, physical, functional, and other psychiatric assessments are more likely to experience cognitive impairment.	Poisson regression to calculate prevalence ratios (PRs) for each covariate and its association with abnormal MoCA scores (< 26)

Table 2.2: Study Characteristics, Hypotheses, and Methods *Continued*						
Wubetu, 2021	Amhara, Ethiopia (Africa)	Cross sectional study of adult PLWH on HAART	422	Male 39.8% Ages: Young adult (20–39.9) 45.7%, middle adult (40–59.9) 46.7% older adult (60–64), 7.6% Unemployed 86% Ethnic groups: Amhara 94.1%, Tigre 4.3%, Others 1.7% Education: Able to read/write 30.6%, secondary school 32.7%, diploma and above 36.7% CD4 cell count ≤200: 8.8%	1. Determine the prevalence of HIV-associated neurocognitive impairment among adult people living with HIV and on HAART, and; 2. To identify factors associated with HAND	Bivariate and multivariable binary logistic regression to identify factors associated with HIV-associated neurocognitive deficit.
Han, 2021	Shanghai, Kunming, Nanning, Hengyang, & Changning (China)	Cross sectional study of HIV+ middle aged and older adults (45+ years)	321	Male 64.8% Mean age 55.65 (SD: 8.06) Ethnic groups: Han 76.9%, Minority 23.1% Unemployed 70.1% Education: Primary school or less 38.3%, Junior school 34.9%, Senior high school 18.4%, College 5.6%, University 2.5%, Master's or above 0.3% CD4 cell count mean 342.95 (SD 252.16)	1. Perceived discrimination can influence SOCD through anxiety and depressive symptoms; 2. Perceived discrimination can influence SOCD through social isolation; and 3. Perceived discrimination can influence SOCD through anxiety and depressive symptoms and then through social isolation.	Multiple linear regression models to investigate associations between variables, and to filter the variables that enter the SEM. SEM was used to examine paths among perceived dis-crimination, cognitive symptoms, mental health symptoms, and social isolation.

Table 2.3: Study Variables and Key Findings

Study	Cognitive Impairment Variable		Social Connectedness Variable			Depression	Other Variables	Relevant Associations/Findings
	Performance Based	Self-Report	Loneliness	Social Support	Other			
Chan, 2007	Hong Kong List Learning Test (HKLLT)	Patient's Assessment of own Functioning Inventory (PAOFI)	--	Social Provisions Scale (SPS)	--	21-item Beck Depression Inventory (BDI) (Somatic items excluded); Included as mediator	Sociodemographic and clinical characteristics Experience of physical symptoms Biomarkers: Latest CD4+ cell count	*Social support* SPS mean score 71.00 (SD: 10.09) *Cognitive symptoms (subjective)* Depressive mood was directly related to subjective memory complaints. Social support contributed indirectly to subjective memory complaints, mediated by depressive mood. The direct effect of social support on cognitive symptoms was not reported. Medical symptoms had no role in subjective memory complaints. Mean score PAOFI 4.61 (SD: 0.72) *Cognitive/NP Status (objective)* Mean total learning z-score HKLLT -0.33 (Range -3.38 - -1.62, SD: 0.93). Objective memory performance had no relationship with subjective memory complaints. The relationship between social support and objective memory performance was not evaluated.

Study	Cognitive Impairment Variable		Social Connectedness Variable			Depression Variable	Other Variables	Relevant Associations/Findings
	Performance Based	Self-Report	Loneliness	Social Support	Other			
Atkins, 2010	NP test battery (classified as "normal" or "impaired")	Patient's Assessment of Own Functioning Inventory (PAOFI)	--	Investigator-constructed question: Identify whether participant had people in their lives they could turn to for social support.	--	21-item Beck Depression Inventory (BDI) (Somatic items excluded); Included as interaction term	Sociodemographic and clinical characteristics Biomarkers: None	*Social support* Social support classified as high (vs low) 49.3% *Cognitive symptoms (subjective)* Mean cognitive symptom burden 52.89 (SD: 27.4) Higher levels of cognitive symptom burden were significantly associated with depression; Lower levels of cognitive symptom burden were significantly associated with greater social support and higher level of education. There was a significant interaction such that social support was associated with a lower cognitive symptom burden for non-depressed individuals. *Cognitive/NP Status (objective)* NP status was examined as an independent variable. 48.5% had impaired NP status. Significant interaction between NP status and depression such that the presence of NP impairment with depression was associated with higher levels of cognitive symptom burden.

Study	Cognitive Impairment Variable		Social Connectedness Variable			Depression Variable	Other Variables	Relevant Associations/Findings
	Performance Based	Self-Report	Loneliness	Social Support	Other			
Han, 2017	A battery of 19 cognitive measures (average of Z-scores)	--	Modified version of the de Jong-Gierveld Loneliness Scale	--	--	Not assessed	Sociodemographic and clinical characteristics Biomarkers: CD4+ cell count	*Loneliness* JGLS mean score2.51 (SD: 0.77) *Cognitive/NP status (objective)* Mean global cognition z-score 0.10 (SD: 0.53). Older Black adults had less overall loneliness than White adults. An interaction between race and loneliness was observed such that older Black adults who indicated greater loneliness showed poorer cognitive function relative to White adults.
Moore, 2018	Successful cognitive aging (NP test battery, Instrumental activities of daily living (IADLs) with the Lawton and Brody tool, Composite International Diagnostic Interview (CIDI)			Duke Social Support Index (DSSI) (4-item Social Interaction subscale sum)		Composite International Diagnostic Interview (CIDI)	Sociodemographic and clinical characteristics Self-rated successful aging (SRSA) Ten positive psychological factors Health Related Quality of Life (Mental and Physical Health Composite Scores of the Medical Outcomes Study SF-36) DSM-IV substance abuse or dependence Biomarkers:	*Successful cognitive aging* Twenty-nine percent (29/99) of the HIV+ sample met study-defined SCA criteria as compared to 61% (28/46) in the HIV− sample. *Social Support* Social support ($p = 0.06$) was not significantly associated with SCA groups at the omnibus level. Social support differed between HIV+/SCA− and HIV−/SCA+ and differed between HIV+/SCA− and HIV−/SCA− at $p < 0.10$. There was not a significant difference between the

							CD4+ cell count, undetectable VL, CD4 nadir, HCV antibodies	HIV+/SCA− and HIV+/SCA+ groups.
Zhu, 2019	--	5 items in the AIDS Health Assessment Questionnaire (sum of scores, range 0-15)	--	3 items in the AIDS Health Assessment Questionnaire	--	Chinese version of the Patient Health Questionnaire -2	Sociodemographic and clinical characteristics, Discrimination, Psychological function, Daily behaviors (Smoking, drinking alcohol, engaging in sex, exercise) Biomarkers: CD4+ cell count	*Social support* Mean social support score: 9.64 (SD: 2.24) *Cognitive symptoms (subjective)* Mean cognitive symptom score 1.54 (SD: 2.48). Social support was not independently associated with self-reported cognitive ability.
Subramanian, 2020	--	Cognitive functioning as a dimension of quality of life (Medical Outcomes Study HIV Health Survey)	--	Multidimensional Scale of Perceived Social Support	--	"Becks Depression Inventory-2"[*sic*]	Sociodemographic and clinical characteristics Other domains of Quality of Life Biomarkers: CD4+ cell count	*Social support* 43.1% reported high social support overall, 44.0% reported high support from their immediate family, 40.4% reported high support from their immediate friends, and 67.9% reported high support from a significant other. *Cognitive symptoms (subjective)* Mean cognitive function score not reported. Based on pilot study no n=10, correlation r=0.342 of overall quality of life (including cognition) with social support. In ANOVA with n=109, social support (from family/friends/others) was associated with cognitive functioning as a construct of QoL.

Study	Cognitive Impairment Variable		Social Connectedness Variable			Depression Variable	Other Variables	Relevant Associations/Findings
	Performance Based	Self-Report	Loneliness	Social Support	Other			
Harris, 2020	Brief cognitive ability measure (B-CAM), a computerized battery of cognitive tests	Perceived Deficit Questionnaire (PDQ)	1 item from Older Americans Resources and Services Social Resource (OARS) Scale ("Do you find yourself feeling lonely: quite often, sometimes, or almost never?")	1 Item from OARS Social Resource Scale, (How many people do you know well enough to visit in their homes? "5 or more," "3 to 4," "1 to 2," "none.")	--	RAND SF-36 Mental Health Inventory depression subscale	Sociodemographic and clinical characteristics, Functional Status, Physiological Symptoms Biomarkers: C-reactive protein CD4 count, viral load	*Loneliness* 18% reported being lonely "quite often" and 46% reported loneliness "sometimes." Loneliness had the largest effect on mental health outcomes. *Social support* OARS item score not reported/assessed *Cognitive symptoms (subjective)* Mean PDQ score 34.1 (SD: 16.8) Loneliness increased the odds of cognitive symptoms, low mood, stress, and poor physical health. *Cognitive/NP status (objective)* Mean B-CAM score 20.8 (SD 4.7). Loneliness increased the odds of worse performance on cognitive tests.

Study	Cognitive Impairment Variable		Social Connectedness Variable			Depression Variable	Other Variables	Relevant Associations/Findings
	Performance Based	Self-Report	Loneliness	Social Support	Other			
Eaton, 2020	Neurocognitive assessment battery adapted for low-literacy settings.	--	--	--	Living alone	15-item Geriatric depression scale (cut-off of 5/15)	Sociodemographic and clinical characteristics Instrumental activities of daily living (IADLs) Biomarkers: CD4+ cell count (current) Nadir CD4+ count	*Social variable* 16.6% lived alone *Cognitive/NP status (objective)* Participants were at a greater risk of having symptomatic HAND if they lived alone, were illiterate, or older at the time of HIV diagnosis.

Table 2.4: NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies

Criterion	Chan, 2007	Atkins, 2010	Han, 2017	Moore, 2018	Zhu, 2019	Subramanian, 2020
1. Research question clearly stated	Yes	Yes	Yes	Yes	Vague, no hypotheses	Vague, no hypotheses
2. Study population clearly specified and defined	No time period specified	No time period specified	Yes	Yes	Yes	No
3. Participation rate of eligible persons at least 50%	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
4. Groups recruited from the same population and uniform eligibility criteria	Yes	Yes	Pertinent analyses on subjects recruited in same population (HIV+)	Yes	Yes	No details given/not able to assess
5. Sample size justification	No	No	No	No	No	Yes
8. Different levels of the exposure of interest (categories or continuous)	Social support measured and operationalized as continuous variable	Social support measured as categorical, operationalized as binary (high vs low)	Loneliness measured and operationalized as continuous variable	Social support measured and operationalized as continuous variable	Social support measured and operationalized as continuous	Complete information not reported
9. Exposure measures and assessment clearly defined, reliable, valid	Social Provisions Scale not validated in study population	Social support question not validated	Modified Loneliness scale, not validated	Use of Duke Social Support Index not validated in study population	Use of AIDS-HAQ sub-scale not validated	Social Provisions Scale not validated in study population
11. Outcome measures and assessment clearly defined, reliable, valid	PAOFI not validated in study population; HKLLT not validated in HIV+	PAOFI validated; NP status, gold standard	NP status, gold standard	SCA includes PB testing	Subdomain of AIDS-HAQ, not validated and may be highly correlated with exposure	Subjective cognitive symptoms from a QoL scale, not validated
12. Blinding of outcome assessors	Not reported	Not reported	Not reported	Not Reported	Not reported	Not reported

Criterion	Chan, 2007	Atkins, 2010	Han, 2017	Moore, 2018	Zhu, 2019	Subramanian, 2020
14. Statistical analyses	Depression used as mediator; Age not in model; Assumptions for mediation not met.	Age not in final model	Depression variable not collected	Unknown, covariates not clearly listed	Use of same scale for both dependent and independent variable	Confounding not assessed; No effect sizes reported
Overall potential for bias	**High**	**Moderate**	**Low-Moderate**	**Moderate**	**High**	**High**

Note: Questions 6, 7, 10, & 13 omitted – N/A for cross sectional studies

Bias assessment framework presented in **Appendix 2.3**

Table 2.4: NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies *Continued*

Criterion	Harris, 2020	Eaton, 2020	Bourgeois, 2020	Wubetu, 2021	Han, 2021
1. Research question clearly stated	Yes	Yes	Yes	Yes	Yes
2. Study population clearly specified and defined	Yes	Yes	Published elsewhere	Yes	Yes
3. Participation rate of eligible persons at least 50%	Not reported	Rate 81.6%	Not reported	Not reported	Not Reported
4. Groups recruited from the same population and uniform eligibility criteria	Yes	Yes	Yes	Yes	Yes
5. Sample size justification	No	No	No	Yes	No
8. Different levels of the exposure of interest (categories or continuous)	Measured and operationalized as categorical variable	Measured as binary variable	Measured as continuous variable, operationalized as binary variable	Measured and operationalized as categorical variable	Measured and operationalized as continuous variable

Criterion	Harris, 2020	Eaton, 2020	Bourgeois, 2020	Wubetu, 2021	Han, 2021
9. Exposure measures and assessment clearly defined, reliable, valid	Loneliness measured not validated in study population	Measure of "Living alone" may not reliably reflect construct of social support	SPS and PHQ-9 validated in study population	Oslo- 3 item Social Support scale not validated in study population	Use of QoL sub-scale not validated
11. Outcome measures and assessment clearly defined, reliable, valid	B-CAM (NP testing) & PDQ unknown validity/reliability	NP testing, gold standard	MoCA, poor sensitivity	MMSE, poor sensitivity	Cognitive symptoms sub-domain of QoL scale, reliability/validity unknown
12. Blinding of outcome assessors	Not reported	Not reported	Not reported	Not Reported	Not Reported
14. Statistical analyses	Age not assessed; Hypotheses about antecedents/consequences cannot be assessed by cross-sectional data structure.	Depression not in final model.	Age and depression not in model.	Both age and depression in final model	Depression not in linear models, but included in SEM. Data does not meet assumptions for mediation.
Overall potential for bias	**Moderate**	**Low-Moderate**	**Moderate**	**Moderate**	**Moderate**

Note: Questions 6.7, 10, and 13 omitted – N/A for cross sectional

Bias assessment framework presented in **Appendix 2.3**

Table 2.5: Meta-Analysis of Studies (N=10)				
Model	N	I^2 [a]	Q-statistic, p-value [b]	Pooled d (95% CI) [c]
All studies	10	41.6	15.36, 0.081	0.365 (0.247, 0.482)
Sub-Analyses				
Self-Reported Cognitive Impairment [d]	5	85.3	27.90, 0.000	0.463 (0.175, 0.752)
Performance Based Impairment [e]	7	36.6	8.96, 0.176	0.374 (0.216, 0.532)
Loneliness [f]	3	59.7	5.18, 0.075	0.263 (-0.046, 0.571)
Social Isolation [g]	8	34.1	10.47, 0.163	0.380 (0.253, 0.507)

[a] Measure of inconsistency across the findings of the studies
[b] Q-statistic for test of homogeneity, threshold of $p<0.10$ used to account for small sample size
[c] Overall effect size and confidence interval
[d] Self-report cognitive impairment and either loneliness or social isolation
[e] Performance based cognitive impairment and either loneliness or social isolation
[f] Loneliness and either self-report or performance based cognitive impairment
[g] Social Isolation and either self-report or performance based cognitive impairment

Table 2.6: Random Effects Meta-Regression of All Studies (N=10)			
Explanatory Variables	Coefficient (95% CI)	*P*-value	I^2
Age ≥ 55 years [a]	-0.208 (-0.399, -0.018)	0.032	12.4%
Study Country/Location [b]			19.43%
USA	REF	n/a	
Canada	0.277 (0.015, 0.539)	0.038	
Africa	0.384 (0.037, 0.730)	0.030	
China	0.083 (-0.189, 0.357)	0.550	
Hong Kong			
CD4 cell count [c]	-0.127 (-.385, 0.131)	0.333	42.4%
Study quality/risk of bias [d]	0.265 (0.014, 0.515)	0.038	12.7%

[a] Mean age of study sample participants, <55 years is reference group
[b] Classified by Country (USA, Canada, Africa, India, China, and Hong Kong)
[c] Mean CD4 T-cell count of the sample, <400uL as reference group
[d] See Table 2.3 for risk of bias ratings/assessment

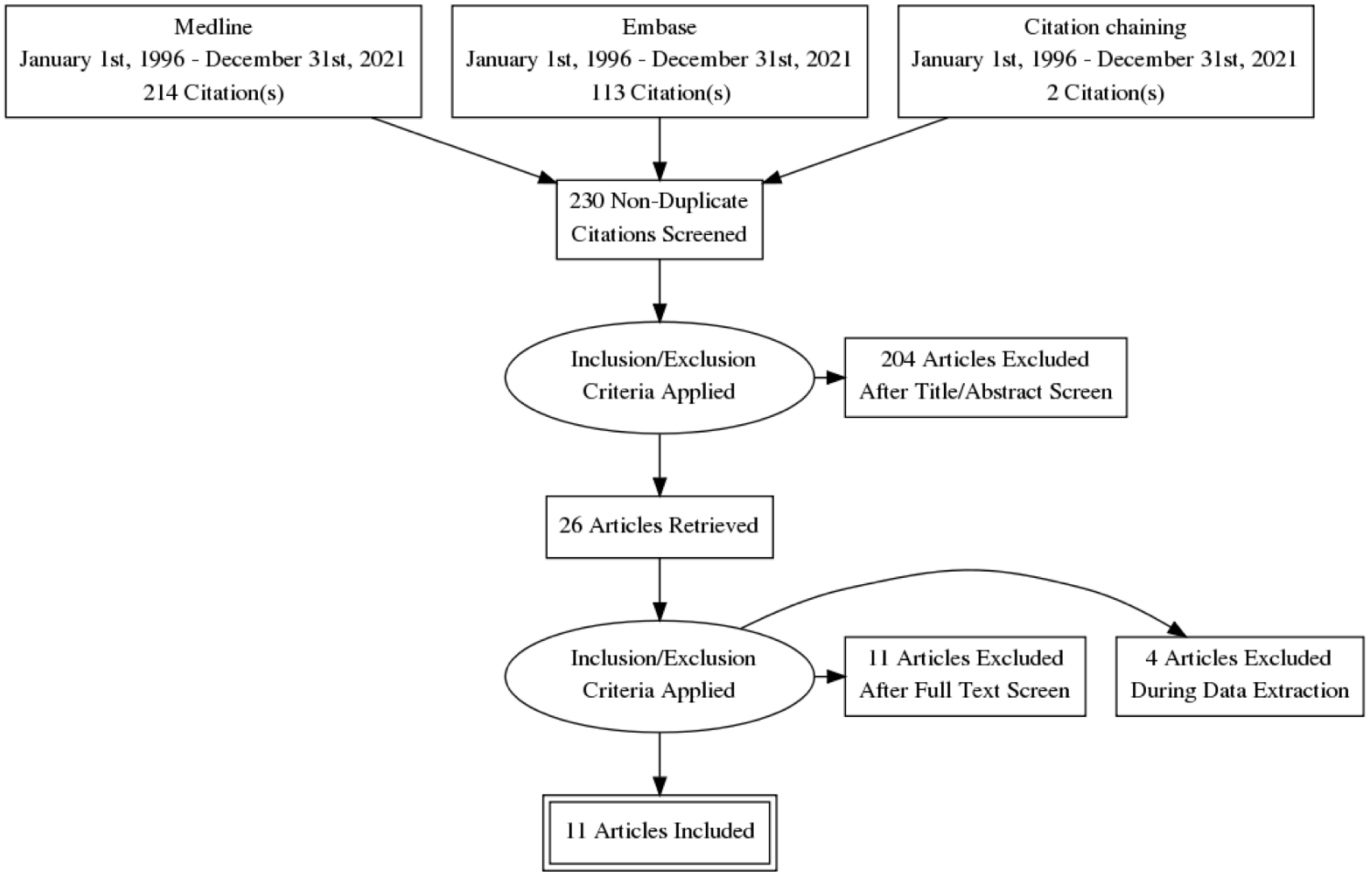

Figure 2.1: Preferred Reporting Items for Systematic Reviews (PRISMA) Flow Diagram

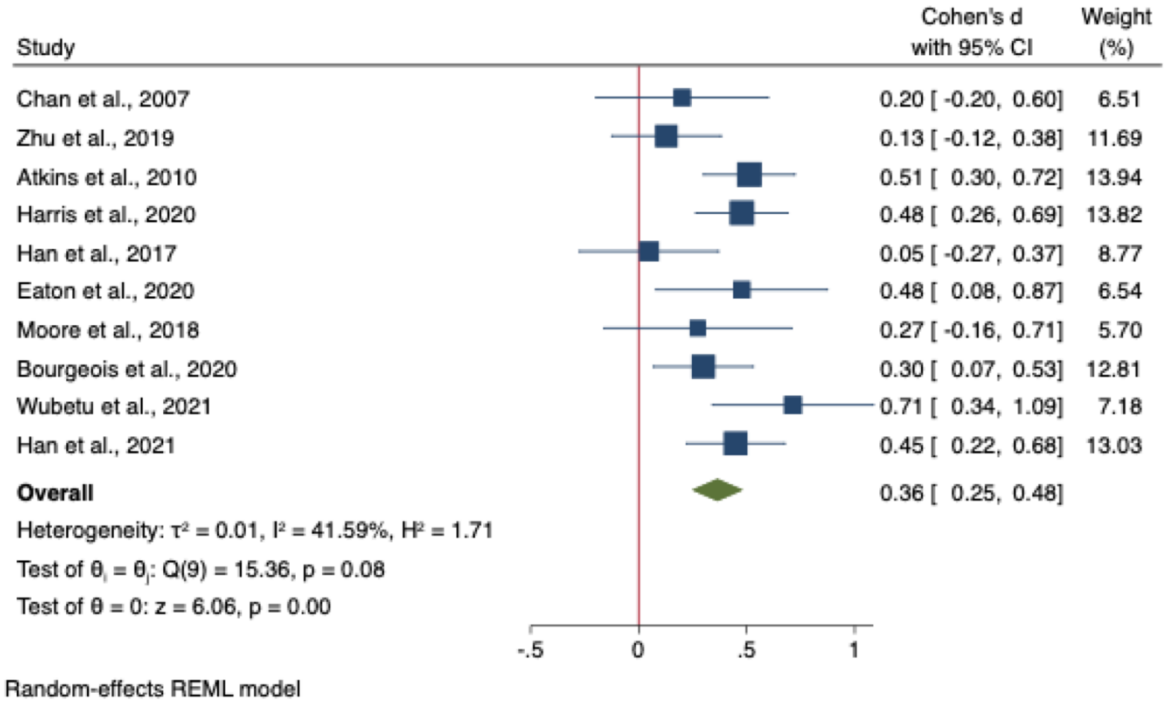

Figure 2.2: Forest plot for Association of Cognitive Impairment with Loneliness or Social Isolation among PLWH, All Studies

Forest plot of estimated effects (95% confidence intervals) of cognitive impairment effect size for each study. Center and width of diamond represents pooled estimates and 95% confidence intervals.

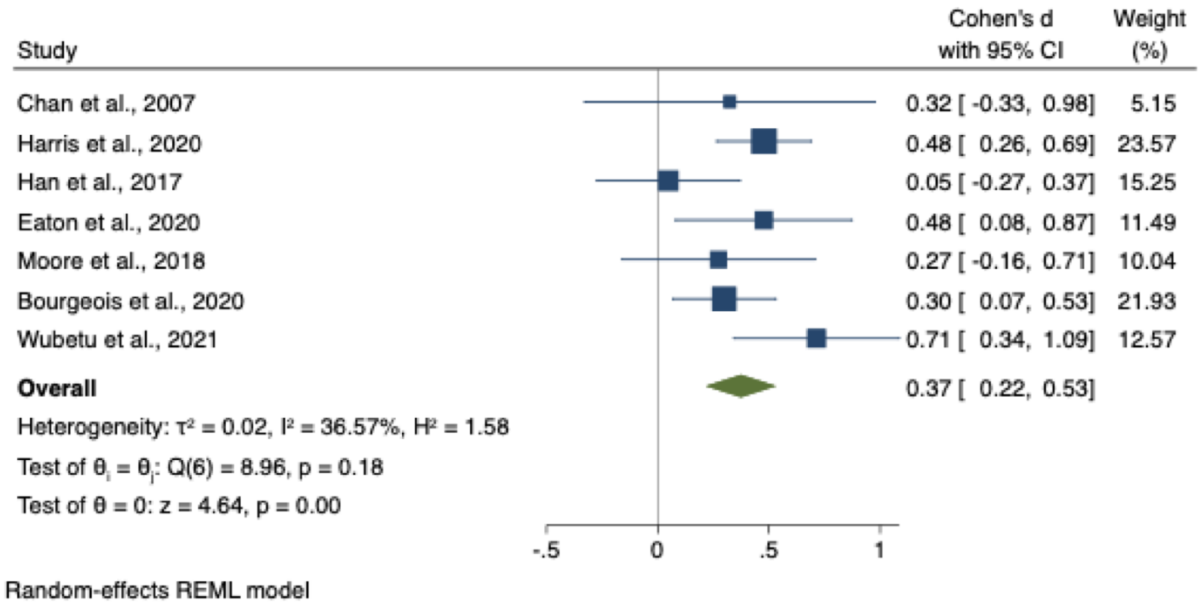

Figure 2.3: Forest plot for Association of Performance Based Cognitive Impairment with Loneliness or Social Isolation among PLWH

Forest plot of estimated effects (95% confidence intervals) of performance based cognitive impairment effect size for each study. Center and width of diamond represents pooled estimates and 95% confidence intervals. Excludes studies with self-reported measure of cognitive impairment.

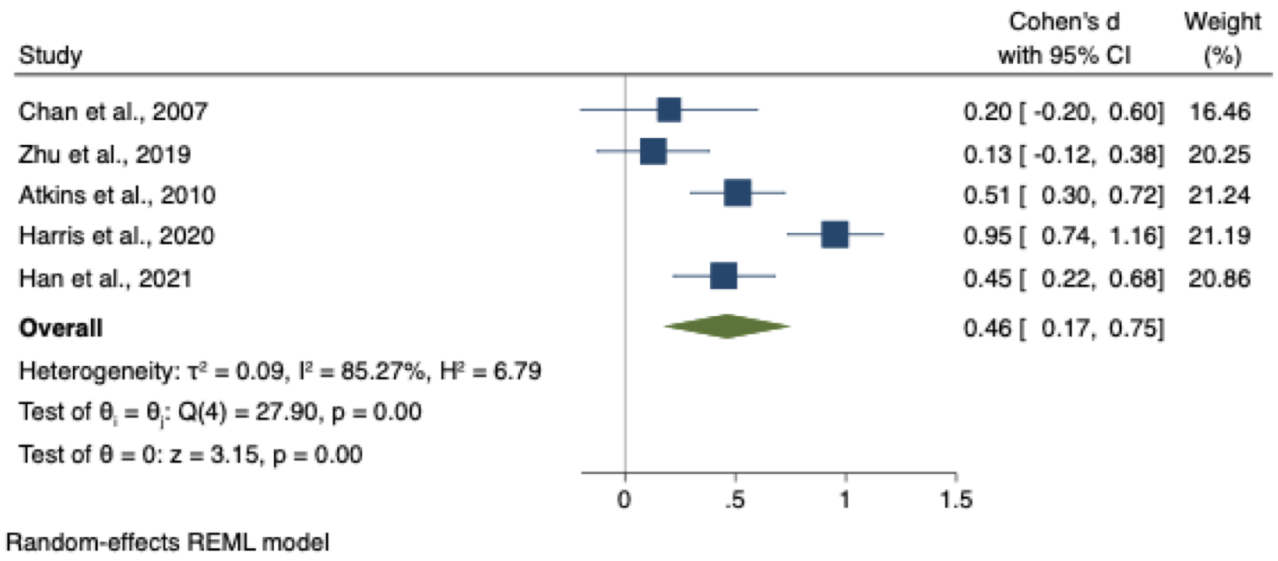

Figure 2.4: Forest plot for Association of Self-Reported Cognitive Impairment with Loneliness or Social Isolation among PLWH

Forest plot of estimated effects (95% confidence intervals) of self-reported cognitive impairment effect size for each study. Center and width of diamond represents pooled estimates and 95% confidence intervals. Excludes studies with performance-based measure of cognitive impairment.

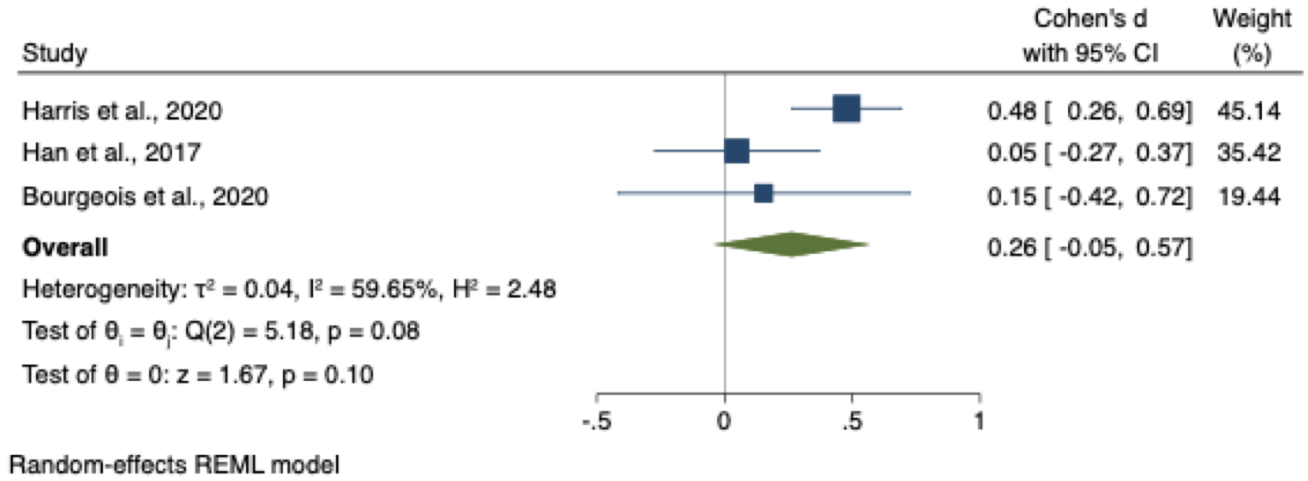

Figure 2.5: Forest Plot of Effect of Loneliness on Cognitive Impairment

Forest plot of estimated effects (95% confidence intervals) of loneliness on performance based *or* self-reported cognitive impairment for each study. Center and width of diamond represents pooled estimates and 95% confidence intervals. Excludes studies that measured social isolation.

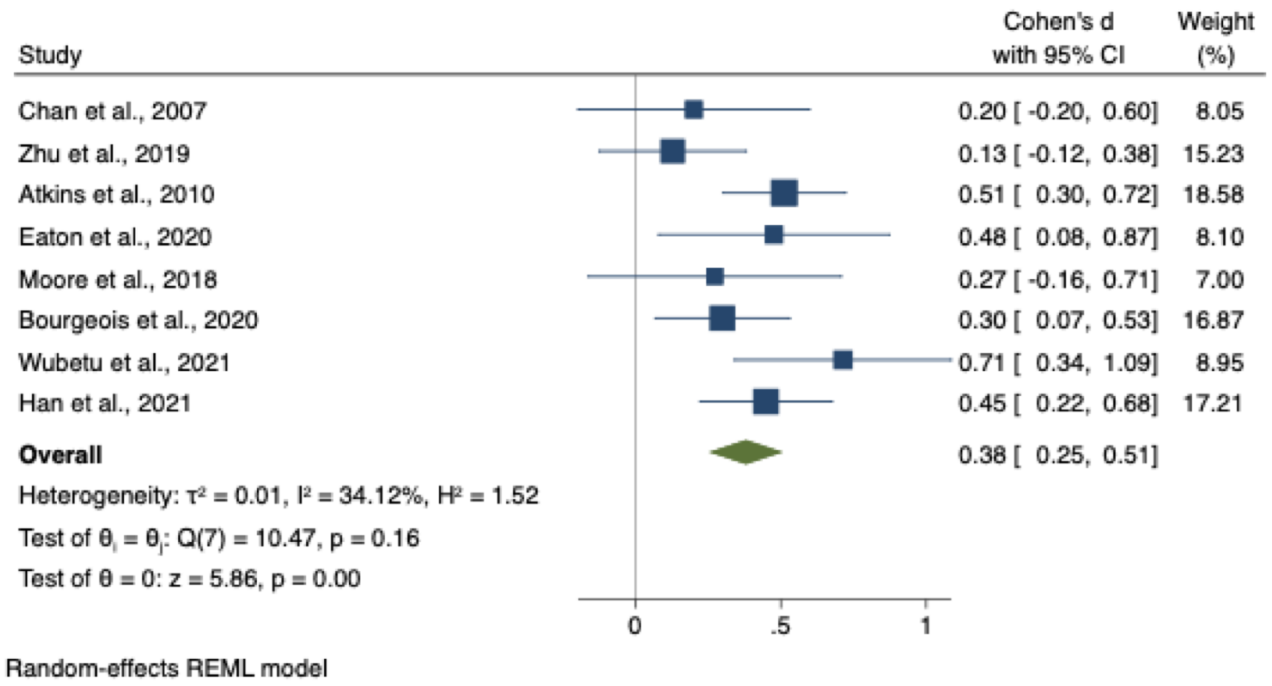

Figure 2.6: Forest Plot of Effect of Social Isolation on Cognitive Impairment

Forest plot of estimated effects (95% confidence intervals) of social isolation on performance based *or* self-reported cognitive impairment for each study. Center and width of diamond represents pooled estimates and 95% confidence intervals. Excludes studies that measured loneliness.

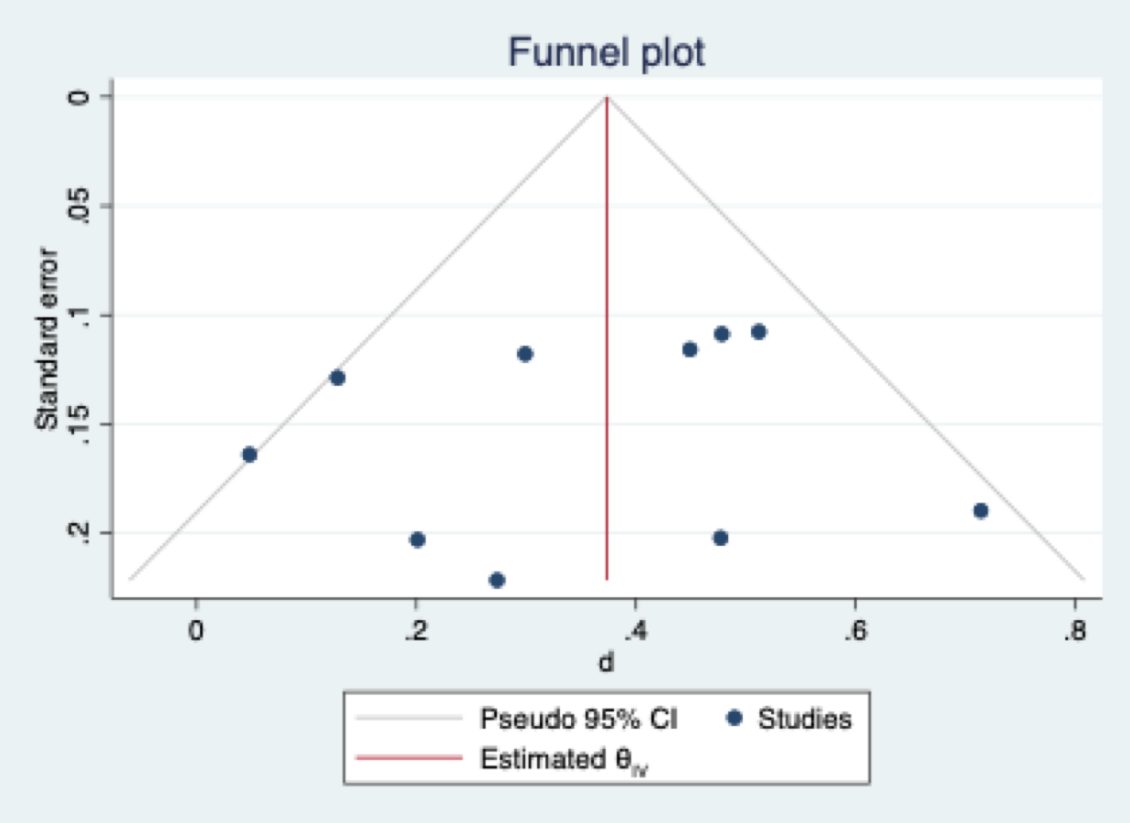

Figure 2.7: Funnel Plot for Publication Bias Assessment, All Studies

Effect estimates (*d*) are plotted against the standard error of the effect estimate. In the absence of both biases and heterogeneity, we expect that 95% of studies would be expected to lie inside the triangular region of the funnel.

Appendices

Appendix 2.A: Systematic Review Search Syntax

Medline:

(((((((HIV[Title/Abstract]) OR (human immunodeficiency virus[Title/Abstract])) OR (HIV- 1[Title/Abstract])) OR (HIV/AIDS[Title/Abstract])) OR ("acquired immune deficiency syndrome"[Title/Abstract])) OR (AIDS[Title/Abstract])) AND ((((((loneliness[Title/Abstract]) OR (lonely[Title/Abstract])) OR (social isolation[Title/Abstract])) OR (social connection[Title/Abstract])) OR (social support[Title/Abstract])) OR (social network[Title/Abstract]))) AND ((((((cognition[Title/Abstract]) OR (cognitive[Title/Abstract])) OR (cognitive impairment[Title/Abstract])) OR (hiv associated neurocognitive[Title/Abstract])) OR (cognitive aging[Title/Abstract])) OR (dementia[Title/Abstract]))) NOT ((hearing loss[Title/Abstract]) OR (hearing aid[Title/Abstract]))

Embase:

('social isolation':ab,ti OR 'social support':ab,ti OR 'social network':ab,ti OR 'loneliness':ab,ti OR 'lonely':ab,ti) AND ('human immunodeficiency virus':ab,ti OR 'human immunodeficiency virus infection':ab,ti OR 'acquired immune deficiency syndrome':ab,ti OR 'hiv':ab,ti OR 'hiv/aids':ab,ti) AND ('cognition' OR 'cognitive defect' OR 'cognitive function test' OR 'dementia' OR 'neurocognitive impairment' OR 'neurocognitive function' OR 'cognitive aging' OR (neurocognitive AND disorder) OR 'disorders of higher cerebral function')

Appendix 2.B Standardized Mean Difference (SMD) formulae for Meta-analysis

Table 2.7. Formulae Applied to Derive Effect Size and its Variability Based on Specific Parameters Available in the Selected Studies

Reported effect size parameter	**Conversion formula for Cohen's *d***
Odds ratio (OR)	$d = LogOR * \frac{\sqrt{3}}{\pi}$ where π is the mathematical constant ~3.14159 (Borenstein et al., 2011)
t-statistic	$d \approx \frac{2t}{\sqrt{n-2}}$ where *t* is the *t*-statistic and *n* is the total number of subjects (Thalheimer & Cook, 2002)
Correlation coefficient (*r*)	$d = \frac{2r}{\sqrt{1-r^2}}$ where *r* is the correlation coefficient (Friedman, 1968)

Appendix 2.C: NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies framework

Table 2.8: NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (2021)
Question 1. Research question
Did the authors describe their goal in conducting this research? Is it easy to understand what they were looking to find? This issue is important for any scientific paper of any type. Higher quality scientific research explicitly defines a research question.
Questions 2 and 3. Study population
Did the authors describe the group of people from which the study participants were selected or recruited, using demographics, location, and time period? If you were to conduct this study again, would you know who to recruit, from where, and from what time period? Is the cohort population free of the outcomes of interest at the time they were recruited? An example would be men over 40 years old with type 2 diabetes who began seeking medical care at Phoenix Good Samaritan Hospital between January 1, 1990 and December 31, 1994. In this example, the population is clearly described as: (1) who (men over 40 years old with type 2 diabetes); (2) where (Phoenix Good Samaritan Hospital); and (3) when (between January 1, 1990 and December 31, 1994). Another example is women ages 34 to 59 years of age in 1980 who were in the nursing profession and had no known coronary disease, stroke, cancer, hypercholesterolemia, or diabetes, and were recruited from the 11 most populous States, with contact information obtained from State nursing boards. In cohort studies, it is crucial that the population at baseline is free of the outcome of interest. For example, the nurses' population above would be an appropriate group in which to study incident coronary disease. This information is usually found either in descriptions of population recruitment, definitions of variables, or inclusion/exclusion criteria. You may need to look at prior papers on methods in order to make the assessment for this question. Those papers are usually in the reference list. If fewer than 50% of eligible persons participated in the study, then there is concern that the study population does not adequately represent the target population. This increases the risk of bias.
Question 4. Groups recruited from the same population and uniform eligibility criteria
Were the inclusion and exclusion criteria developed prior to recruitment or selection of the study population? Were the same underlying criteria used for all of the subjects involved? This issue is related to the description of the study population, above, and you may find the information for both of these questions in the same section of the paper. Most cohort studies begin with the selection of the cohort; participants in this cohort are then measured or evaluated to determine their exposure status. However, some cohort studies may recruit or select exposed participants in a different time or place than unexposed participants, especially retrospective cohort studies–which is when data are obtained from the past (retrospectively), but the analysis examines exposures prior to outcomes. For example, one research question could be whether diabetic men with clinical depression are at higher risk for cardiovascular disease than those without clinical depression. So, diabetic men with depression might be selected from a mental health clinic, while diabetic men without depression might be selected from an internal medicine or endocrinology clinic. This study recruits groups from different clinic populations, so this example would get a "no." However, the women nurses described in the question above were selected based on the same inclusion/exclusion criteria, so that example would get a "yes."

Table 2.8: NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (2021) *Continued*

Question 5. Sample size justification
Did the authors present their reasons for selecting or recruiting the number of people included or analyzed? Do they note or discuss the statistical power of the study? This question is about whether or not the study had enough participants to detect an association if one truly existed. A paragraph in the methods section of the article may explain the sample size needed to detect a hypothesized difference in outcomes. You may also find a discussion of power in the discussion section (such as the study had 85 percent power to detect a 20 percent increase in the rate of an outcome of interest, with a 2-sided alpha of 0.05). Sometimes estimates of variance and/or estimates of effect size are given, instead of sample size calculations. In any of these cases, the answer would be "yes." However, observational cohort studies often do not report anything about power or sample sizes because the analyses are exploratory in nature. In this case, the answer would be "no." This is not a "fatal flaw." It just may indicate that attention was not paid to whether the study was sufficiently sized to answer a prespecified question–i.e., it may have been an exploratory, hypothesis-generating study.
Question 6. Exposure assessed prior to outcome measurement
This question is important because, in order to determine whether an exposure causes an outcome, the exposure must come before the outcome. For some prospective cohort studies, the investigator enrolls the cohort and then determines the exposure status of various members of the cohort (large epidemiological studies like Framingham used this approach). However, for other cohort studies, the cohort is selected based on its exposure status, as in the example above of depressed diabetic men (the exposure being depression). Other examples include a cohort identified by its exposure to fluoridated drinking water and then compared to a cohort living in an area without fluoridated water, or a cohort of military personnel exposed to combat in the Gulf War compared to a cohort of military personnel not deployed in a combat zone. With either of these types of cohort studies, the cohort is followed forward in time (i.e., prospectively) to assess the outcomes that occurred in the exposed members compared to nonexposed members of the cohort. Therefore, you begin the study in the present by looking at groups that were exposed (or not) to some biological or behavioral factor, intervention, etc., and then you follow them forward in time to examine outcomes. If a cohort study is conducted properly, the answer to this question should be "yes," since the exposure status of members of the cohort was determined at the beginning of the study before the outcomes occurred. For retrospective cohort studies, the same principal applies. The difference is that, rather than identifying a cohort in the present and following them forward in time, the investigators go back in time (i.e., retrospectively) and select a cohort based on their exposure status in the past and then follow them forward to assess the outcomes that occurred in the exposed and nonexposed cohort members. Because in retrospective cohort studies the exposure and outcomes may have already occurred (it depends on how long they follow the cohort), it is important to make sure that the exposure preceded the outcome.Sometimes cross-sectional studies are conducted (or cross-sectional analyses of cohort-study data), where the exposures and outcomes are measured during the same timeframe. As a result, cross-sectional analyses provide weaker evidence than regular cohort studies regarding a potential causal relationship between exposures and outcomes. For cross-sectional analyses, the answer to Question 6 should be "no."

Table 2.8: NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (2021) *Continued*
Question 7. Sufficient timeframe to see an effect
Did the study allow enough time for a sufficient number of outcomes to occur or be observed, or enough time for an exposure to have a biological effect on an outcome? In the examples given above, if clinical depression has a biological effect on increasing risk for CVD, such an effect may take years. In the other example, if higher dietary sodium increases BP, a short timeframe may be sufficient to assess its association with BP, but a longer timeframe would be needed to examine its association with heart attacks. The issue of timeframe is important to enable meaningful analysis of the relationships between exposures and outcomes to be conducted. This often requires at least several years, especially when looking at health outcomes, but it depends on the research question and outcomes being examined. Cross-sectional analyses allow no time to see an effect, since the exposures and outcomes are assessed at the same time, so those would get a "no" response.
Question 8. Different levels of the exposure of interest
If the exposure can be defined as a range (examples: drug dosage, amount of physical activity, amount of sodium consumed), were multiple categories of that exposure assessed? (for example, for drugs: not on the medication, on a low dose, medium dose, high dose; for dietary sodium, higher than average U.S. consumption, lower than recommended consumption, between the two). Sometimes discrete categories of exposure are not used, but instead exposures are measured as continuous variables (for example, mg/day of dietary sodium or BP values). In any case, studying different levels of exposure (where possible) enables investigators to assess trends or dose-response relationships between exposures and outcomes–e.g., the higher the exposure, the greater the rate of the health outcome. The presence of trends or dose-response relationships lends credibility to the hypothesis of causality between exposure and outcome.For some exposures, however, this question may not be applicable (e.g., the exposure may be a dichotomous variable like living in a rural setting versus an urban setting, or vaccinated/not vaccinated with a one-time vaccine). If there are only two possible exposures (yes/no), then this question should be given an "NA," and it should not count negatively towards the quality rating.
Question 9. Exposure measures and assessment
Were the exposure measures defined in detail? Were the tools or methods used to measure exposure accurate and reliable–for example, have they been validated or are they objective? This issue is important as it influences confidence in the reported exposures. When exposures are measured with less accuracy or validity, it is harder to see an association between exposure and outcome even if one exists. Also as important is whether the exposures were assessed in the same manner within groups and between groups; if not, bias may result. For example, retrospective self-report of dietary salt intake is not as valid and reliable as prospectively using a standardized dietary log plus testing participants' urine for sodium content. Another example is measurement of BP, where there may be quite a difference between usual care, where clinicians measure BP however it is done in their practice setting (which can vary considerably), and use of trained BP assessors using standardized equipment (e.g., the same BP device which has been tested and calibrated) and a standardized protocol (e.g., patient is seated for 5 minutes with feet flat on the floor, BP is taken twice in each arm, and all four measurements are averaged). In each of these cases, the former would get a "no" and the latter a "yes." Here is a final example that illustrates the point about why it is important to assess exposures consistently across all groups: If people with higher BP (exposed cohort) are seen by their providers more frequently than those without elevated BP (nonexposed group), it also increases the chances of detecting and documenting changes in health outcomes, including CVD-related events. Therefore, it may lead to the conclusion that higher BP leads to more CVD events. This may be true, but it could also be due to the fact that the subjects with higher BP were seen more often; thus, more

CVD-related events were detected and documented simply because they had more encounters with the health care system. Thus, it could bias the results and lead to an erroneous conclusion.

Table 2.8: NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (2021) *Continued*

Question 10. Repeated exposure assessment

Was the exposure for each person measured more than once during the course of the study period? Multiple measurements with the same result increase our confidence that the exposure status was correctly classified. Also, multiple measurements enable investigators to look at changes in exposure over time, for example, people who ate high dietary sodium throughout the followup period, compared to those who started out high then reduced their intake, compared to those who ate low sodium throughout. Once again, this may not be applicable in all cases. In many older studies, exposure was measured only at baseline. However, multiple exposure measurements do result in a stronger study design.

Question 11. Outcome measures

Were the outcomes defined in detail? Were the tools or methods for measuring outcomes accurate and reliable–for example, have they been validated or are they objective? This issue is important because it influences confidence in the validity of study results. Also important is whether the outcomes were assessed in the same manner within groups and between groups. An example of an outcome measure that is objective, accurate, and reliable is death–the outcome measured with more accuracy than any other. But even with a measure as objective as death, there can be differences in the accuracy and reliability of how death was assessed by the investigators. Did they base it on an autopsy report, death certificate, death registry, or report from a family member? Another example is a study of whether dietary fat intake is related to blood cholesterol level (cholesterol level being the outcome), and the cholesterol level is measured from fasting blood samples that are all sent to the same laboratory. These examples would get a "yes." An example of a "no" would be self-report by subjects that they had a heart attack, or self-report of how much they weigh (if body weight is the outcome of interest). Similar to the example in Question 9, results may be biased if one group (e.g., people with high BP) is seen more frequently than another group (people with normal BP) because more frequent encounters with the health care system increases the chances of outcomes being detected and documented.

Question 12. Blinding of outcome assessors

Blinding means that outcome assessors did not know whether the participant was exposed or unexposed. It is also sometimes called "masking." The objective is to look for evidence in the article that the person(s) assessing the outcome(s) for the study (for example, examining medical records to determine the outcomes that occurred in the exposed and comparison groups) is masked to the exposure status of the participant. Sometimes the person measuring the exposure is the same person conducting the outcome assessment. In this case, the outcome assessor would most likely not be blinded to exposure status because they also took measurements of exposures. If so, make a note of that in the comments section. As you assess this criterion, think about whether it is likely that the person(s) doing the outcome assessment would know (or be able to figure out) the exposure status of the study participants. If the answer is no, then blinding is adequate. An example of adequate blinding of the outcome assessors is to create a separate committee, whose members were not involved in the care of the patient and had no information about the study participants' exposure status. The committee would then be provided with copies of participants' medical records, which had been stripped of any potential exposure information or personally identifiable information. The committee would then review the records for pre-specified outcomes according to the study protocol. If blinding was not possible, which is sometimes the case, mark "NA" and explain the potential for bias.

Table 2.8: NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (2021) ***Continued***

Question 13. Follow-up rate
Higher overall follow-up rates are always better than lower follow-up rates, even though higher rates are expected in shorter studies, whereas lower overall follow-up rates are often seen in studies of longer duration. Usually, an acceptable overall follow-up rate is considered 80 percent or more of participants whose exposures were measured at baseline. However, this is just a general guideline. For example, a 6-month cohort study examining the relationship between dietary sodium intake and BP level may have over 90 percent follow-up, but a 20-year cohort study examining effects of sodium intake on stroke may have only a 65 percent follow-up rate.
Question 14. Statistical analyses
Were key potential confounding variables measured and adjusted for, such as by statistical adjustment for baseline differences? Logistic regression or other regression methods are often used to account for the influence of variables not of interest. This is a key issue in cohort studies, because statistical analyses need to control for potential confounders, in contrast to an RCT, where the randomization process controls for potential confounders. All key factors that may be associated both with the exposure of interest and the outcome–that are not of interest to the research question–should be controlled for in the analyses. For example, in a study of the relationship between cardiorespiratory fitness and CVD events (heart attacks and strokes), the study should control for age, BP, blood cholesterol, and body weight, because all of these factors are associated both with low fitness and with CVD events. Well-done cohort studies control for multiple potential confounders.
From: National Institutes of Health (NIH), Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies. (2021). Accessed from: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools

Chapter 3

The Association of Social Isolation and Loneliness with Cognitive Impairment among Older Adults Living with HIV and Symptomatic Neurocognitive Disorder

Sarah Dobbins

Abstract

More than half of the population of people living with HIV (PLWH) are 50 years and older, and cognitive impairment is prevalent among aging PLWH. PLWH experience more loneliness and social isolation than the general population, yet it is unknown if these factors are associated with cognitive impairment among older PLWH. The objective of our analysis was to examine the social network structure and to test the associations of loneliness and social isolation with degree of cognitive impairment among n=170 older PLWH age 55 and older with confirmed HIV-Associated Neurocognitive Disorders (HAND). Our results show that loneliness is correlated with mental health variables (depression, anxiety, and perceived stress) while social isolation is correlated with other marginalized conditions and socioeconomic factors (lower years of education, history of HCV, substance use disorder, and Black/African American race) and area-level socioeconomic environment. We also found that social isolation, but not loneliness or self-reported cognitive symptoms, was associated with higher odds of impairment in two cognitive domains (attention & working memory [ATT], and speed of processing [SPD]). These associations signal unique relationships between various aspects of social connectedness and neurocognitive disorders among older adults with HIV.

Introduction

Since the onset of the HIV epidemic, antiretroviral therapy (ART) has lengthened the lives of people living with HIV (PLWH). More than half of the population of PLWH are 50 years and older, and as the aging population of PLWH expands it is important to consider the factors that impact aging with HIV (Centers for Disease Control and Prevention, 2018). Literature indicates that, on average, PLWH experience more loneliness and social isolation than HIV-seronegative individuals (Greene et al., 2018; Grov et al., 2010; Poindexter & Shippy, 2008). An abundance of studies in seronegative populations show that measures of social connectedness such as isolation and loneliness are associated with poor physical, mental health, and cognitive outcomes in aging (Kuiper et al., 2015; Leigh-Hunt et al., 2017). However, these variables are understudied in the context of HIV-related health outcomes.

The manifestation of HIV-associated neurocognitive disorders (HAND), the term used for cognitive impairment in the setting of HIV, encompasses a wide range of emotional/affective changes, changes in both self-reported and observed attention and executive function, motor function, and memory (Winston & Spudich, 2020). It is estimated that about one third to one half of HIV-seropositive individuals have some degree of cognitive impairment (Heaton et al., 2010). These prevalence estimates vary based on population and assessment methods, and are likely lower in populations with sustained viral suppression (V. Valcour, personal communication, December 2018). Cognitive impairment in the setting of HIV is conceptualized as having a multifactorial etiology and progression (Winston & Spudich, 2020). Much is known about the biological basis and clinical risk for HAND, but less is known about the psychosocial factors involved in cognitive impairment among older PLWH.

Social isolation and loneliness are tightly linked to outcomes in geriatric medicine. However, these constructs are not always closely correlated with one another (Perissinotto & Covinsky, 2014), suggesting that social isolation and loneliness may reflect distinct experiences that affect brain health through different pathways. Loneliness has been described and defined in different ways, including “a debilitating psychological condition characterized by a deep sense of emptiness, worthlessness, lack of

control, and personal threat," (Cacioppo et al., 2014) stress caused by the discordance between actual and desired relationships (Leigh-Hunt et al., 2017), and a negative emotion, distinct from depression, produced by unmet social and intimacy-related needs (Peplau & Perlman, 1982). Likewise, social isolation has been defined as an objective description of a lack of interactions with others or with a wider community (Berkman et al., 2000). Despite the lack of definitional consensus for social isolation and loneliness, studies show that differing measures of loneliness and social isolation are associated with increased risk of all-cause mortality (Holt-Lunstad et al., 2010), and meta-analyses of longitudinal studies confirm that social connection and loneliness impact cognitive aging among the general population (Kuiper et al., 2015). Studies among PLWH indicate that loneliness, depression, social isolation, and stigma are highly interconnected (Grov et al., 2010; Poindexter & Shippy, 2008).

Although the influence of social isolation and loneliness on cognitive impairment in seronegative populations is well-established, these variables are understudied in the context of HIV-related health outcomes. A limited number of studies have examined correlations of loneliness or social isolation variables with cognitive impairment among PLWH and they show mixed findings (Atkins et al., 2010a; Harris et al., 2020; Moore et al., 2018). The approach to this paper is to examine the associations of loneliness and social isolation with cognitive impairment among older PLWH with symptomatic neurocognitive disorder. We used a cross-sectional, secondary data-analysis of a sample recruited at the UCSF Memory and Aging Center (MAC). First, we examined the social network structure of the sample. Second, we examined the clinical and sociodemographic correlates of social isolation and loneliness in the sample. Third, we examined the association of cognitive impairment measured by both performance based and self-report measures with loneliness and social isolation using multivariate models.

Methods

Sample

This study is a cross sectional, secondary data analysis of baseline data for N=170 individuals recruited in the San Francisco Bay Area for a Mindfulness Based Stress Reduction (MBSR) randomized control trial at the UCSF Memory and Aging Center. The study protocol and recruitment procedures have been published (Addington et al., 2020). This trial was approved by the Institutional Review Board at the University of California, San Francisco. The trial was conducted from March 2015 through September 2019.

Potential participants underwent a two-tiered screening process, with primary screen administered by phone to assess key exclusions (e.g. unsuppressed plasma viral load, not on ART) and to assure the presence of cognitive symptoms. Participants who passed the primary screen then completed a secondary screen including 90 minute neuropsychological testing conducted in person.

Inclusion criteria. Age ≥55 years, HIV-seropositive, undetectable plasma viral load, cognitively symptomatic and sufficient neuropsychological testing abnormality to be rated as having impairment by consensus conference due to HIV, but deficits in everyday functioning that would rate them as having no more than moderate disease. The first 122 participants were enrolled under the eligibility criteria of being 60 years or older, which was later changed to 55 years and older in order to improve generalizability. Assessment and testing data were reviewed at consensus conference, attended by a neurologist and neuropsychologist, who used utilize clinical acumen to determine the subject's cognitive diagnosis. Consensus conference diagnosis were guided by the 2007 Frascati criteria (Antinori et al., 2007). All participants were determined to have MND.

Exclusion criteria. Failure to attend two screening visits, unwillingness to participate in 8-week intervention, endorsement of illicit drug use in the past 6 months, current or extensive previous mindfulness practice, detectable plasma HIV RNA >100 copies/ml in the previous 6 months, the presence

of cognitive, neurological or psychiatric conditions where treatment options exist (e.g. obstructive sleep apnea, active hepatitis C, untreated depression), inability to provide informed consent, significant systemic medical illness such as cancer requiring chemotherapy or end-stage cardiac or renal insufficiency.

Confounding & contributing conditions. Following the Frascati criteria, individuals with substantial co-existing conditions that interfered with the interpretation of the neuropsychological data were considered to be confounded (Antinori et al., 2007). To improve generalizability of the results of the study, these individuals were allowed to enroll and, contrary to Frascati criteria, a HAND category was assigned based on interpretation of all data. Individuals with co-existing conditions that could have influenced testing but did not meet criteria for confounding were enrolled and provided HAND diagnosis with a qualifier of having potentially contributing conditions.

Determination of HAND status. When available, functioning was assessed by subject and proxy interview at screening, capturing impairment in memory, orientation, judgment, community affairs, home/hobbies, and personal care; the Katz & Lawton Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL) scales; and by an objective assessment of everyday functioning using the N:A:B, including objective measures of map reading, financial management, medication instructions, and employing judgment in decision-making. These functioning measurements help to ensure the correct outcome classification for HAND. The neurological examination is comprehensive (cranial nerves, strength, sensation, coordination, & extrapyramidal findings).

HAND classification requires consensus diagnosis with neuropsychologists who have expertise in applying such criteria within ethnically diverse populations. Data from the secondary screening visit were reviewed at consensus conference attended by a physician and neuropsychologist each trained in HAND (V.Valcour) who use clinical acumen to determine the participant's cognitive diagnosis. Consensus conference diagnoses for study participants were guided by the 2007 Frascati criteria (Antinori et al.,

2007). The Wide Range Achievement Test-4 (WRAT-4) was integrated into the consensus diagnosis to facilitate consideration of cultural and educational influence on test performance.

Statistical Analysis

Measures/Variables

Dependent variables. The primary dependent variables are degree of cognitive impairment based on standardized neuropsychological (NP) tests, summarized in **Table 3.1**, and self-reported cognitive symptoms on the Patients Assessment of Own Functioning Inventory (PAOFI). The PAOFI, a widely used instrument to assess self-reported cognitive functioning (Chelune et al., 1986), is a 41-item, multidimensional measurement tool in which higher scores indicate less cognitive impairment. NP performance variables are recorded in units of standard deviations (SD) and reflect the degree of cognitive impairment based on age-education-appropriate norms on standardized neuropsychological tests. The calculation of the Z-score is as follows,

$$z = \frac{x - \mu}{\sigma}$$

x = raw score
μ = mean
σ = standard deviation (std)

Mild-moderate cognitive symptoms include Z-scores ranging from $-1 \leq z > -2$ standard deviations below the mean, and severe symptoms include scores ≤ -2 SD below the mean. We compared those with mild-moderate symptoms to those with severe symptoms in five cognitive domains: 1) Attention and working memory (ATT), 2) Abstraction and executive function (ABS), 3) Speed of information processing (SPD), 4) Verbal Memory (VER), 5) Memory and Recall (MEM). Domain specific ORs are reported due to the phenomenon of "spotty impairments" in MND, in which cognitive domains may differ in degree of impairment in earlier phases of HAND.

Independent variables. The focal independent variables are loneliness and social isolation. Social isolation was measured with the Norbeck Social Support (NSS) scale (Norbeck et al., 1983). The NSS scale includes three domains: Total Functional Support (comprised of emotional support and

tangible support), Total Network Properties (comprised of the total number of people listed, duration known, and frequency of contact), and Total Loss (comprised of the number of people lost in the past year and amount of support they provided). This variable will be operationalized using scores reflecting total functional support and total network support, with higher scores indicating more support.

Loneliness was measured with the UCLA-20 item loneliness scale, with higher scores indicating more loneliness (Russell et al., 1980). Neither instrument has published, validated cutoff scores. Both social isolation and loneliness were divided into quartiles for our analysis to aid in the interpretability of regression parameters from the skewed variable distributions.

Covariates. Sociodemographic, clinical, and socioeconomic variables examined included age, gender, racial group, past drug and alcohol use meeting Diagnostic and Statistical Manual of Mental Disorders (DSM)-III criteria for either abuse or dependence, years of education, smoking (>100 cigarettes in lifetime), HIV clinical data (number of years living with HIV, nadir CD4 cell count, CD4/CD8 cell ratio, and past Hepatitis C infection), mental health measures (depression, anxiety, and stress), pharmacological treatment for depression, and area level measures of socioeconomic status. Depression was measured with the Geriatric Depression Scale (GDS) scale, with a cutoff score of > 9 indicating clinically significant depressive symptoms (Yesavage et al., 1982). Anxiety was measured with the State and Trait Anxiety Scales, with higher scores indicating more anxiety (Barnes et al., 2002). Perceived stress was measured with the Perceived Stress Scale (Cohen, 1988), with higher score indicating more stress. Depressive episode in the past two years and lifetime history of anxiety disorder were self-reported in a clinical interview. ZIP-code level socioeconomic data from the American Community Survey 2013-2017 census data for ZIP code was used to calculate area-level SEP variables (US Census Bureau, 2019). We examined the proportion of people in the participants' ZIP code living below poverty line, monthly median income, monthly median housing costs, and the proportion of residents with cost-burden (defined as paying more than 30% of income toward housing (Kimberlin, 2019)). Contributing and confounding

condition qualifiers, listed in **Figure 3.2**, contributing and confounding conditions, were collapsed into one variable for the purposes of bias analyses.

Statistical Methods

We first describe the social isolation and the social network of our sample and their degree of loneliness. We then examine these variables in terms of their association with sociodemographic, clinical, and socioeconomic variables using t-tests, rank sum tests for variables without normal distributions, and Pearson correlation coefficients with transformed variables where necessary. We investigated crude associations between loneliness, social isolation, and degree of cognitive impairment in the six cognitive domains and self-reported impairment. Domains that showed a statistically significant relationship (α=0.10) with loneliness or social isolation were subsequently examined with adjusted logistic regression using robust standard errors. In accordance with our findings and the current body of literature that indicate loneliness and social isolation reflect distinct constructs in terms of health and HIV, separate models for social isolation and loneliness were examined. Covariates for adjusted regression analyses were chosen *a priori* based on current evidence and taking into account the correlates of loneliness and social isolation from study Aim 1. To account for possible bias from confounding and contributing conditions, we adjusted for contributing conditions and also examined models that exclude all confounded participants.

Results

Sample Description

Our sample is described in **Table 3.2**. Participants were predominantly male (93%), white (72%), and had a mean age of 64.3 years (SD 5.3). More than half the sample reported living alone (54%) and the majority were able to live independently (96%). The mean CD4 cell count was 611.66 (SD 279.15). The sample participants had a mean 26 years (SD 6.8) living with HIV. Sixty-one (61.2%) had a nadir CD4 cell count less than 200 cells/μL. Less than one-fourth (23.5%) had a history of Hepatitis C. Over half

(57.1%) were current smokers and 48.2% had a history of substance use or dependence. The sample had a mean of 15.6 years of education (SD 2.3).

Psychometric instruments

In internal consistency of the instruments used in this study ranged from moderate to high (Tavakol & Dennick, 2011). The UCLA had a Cronbach's alpha of 0.8429, the GDS depression scale had an alpha of 0.8867, the PAOFI had an alpha of 0.9405, and the perceived stress scale had an alpha of 0.8636. The internal consistency of the dimensions of the NSS had an alpha of 0.9304.

Social Network Structure

The social networks of the participants are described in **Table 3.3** and **Figure 3.1**. A median of 7 people were listed in participants social networks (IQR 4 – 24) and 3% of the sample listed nobody in the social network. The NSS does not provide cut-offs or ranges for social network size, but in validation samples the mean network size ranged from 10.45 to 11.38 people (Gigliotti & Samuels, 2011). The most common sources listed in the social networks were: Friends (mean 4.8 listed), family (mean 2.9 listed), healthcare providers such as nurses or providers (mean 1.2 listed), partner or spouse (mean 1.0 listed), counselors/therapists (mean 1.4 listed), neighbors (mean 1.6 listed), work or school associates (mean 1.8 listed), and romantic partners (mean 1.2 listed) (**Figure 3.1**). Nearly a third (n=48, 31.8%) reported loss of an important relationship in the past year (**Table 3.3**).

Loneliness and Social Isolation

UCLA Loneliness and Norbeck Social Support (NSS) Scale scores are summarized in **Table 3.3**. Three participants did not fill out these measures and have missing data. The UCLA Loneliness scale had a mean score of 44.4 (SD 11.7). On the NSS Scale, Total Functional Support (median 116, IQR: 63 – 426) is comprised of emotional support and tangible support and Total Network Support (median 49.5, IQR: 28.5 – 167) is comprised of number of people listed, duration known, and frequency of contact.

Loneliness was correlated to both total network support and functional support (r=-0.37, p=0.000 and r=-0.43, p=0.00 respectively) such that increased loneliness is correlated with more social isolation. More loneliness, total network support, and total functional support were each significantly associated with living alone (t=-2.604, p= 0.010; z=2.119, p= 0.034, and z=2.249, p= 0.025, respectively). Increased loneliness was significantly associated with depressive episode in the last 2 years (t=-3.322, p=0.001), more depressive symptoms on the GDS (r=0.521, p=0.000), higher perceived stress (r=0.376, p=0.000), and higher state and trait anxiety scores (r=0.262, p=0.000 and r= 0.502, p=0.000, respectively) (**Table 3.4**).

Less total network support, indicated by lower NSS scores, was significantly associated with smoking (t=-1.945, p=0.026), fewer years of education (r=0.2763, p=0.0003), history of substance use (z=2.645, p= 0.0082), and the ZIP-code level proportion of people living in poverty (r=-0.222, p=0.006) and ratio of median monthly costs to median monthly income greater than 0.30 (z=2.527, p=0.012). Less functional social support was significantly associated with history of substance use disorder (z=2.322, p=0.020), fewer years of education (r=0.2697, p=0.0004), and ZIP-code level poverty rate (r=-0.206, p=0.010) and ratio of median monthly costs to median monthly income greater than 0.30 (z=2.043, p=0.041) (**Table 3.5**).

Self-Reported Cognitive Impairment

The mean PAOFI score was 143.46 (SD 25.03). We observed no significant correlation between self-reported cognitive impairment and loneliness or social isolation (**Table 3.4**). We did not observe significant differences in mean PAOFI score by degree of cognitive impairment, as measured by performance based testing, in any domain (**Table 3.6**). Furthermore, it did not appear that self-reported cognitive impairment (PAOFI) varied by contributing or confounding conditions.

Performance Based Cognitive Impairment

Thirty-nine percent (39%) of participants had a severe rating in the domain of attention and working memory (ATT), 25% had a severe score in the abstraction and executive function domain (ABS), and 27% had a severe score in the speed of processing domain (SPD). For cognitive domains with an apparent association with loneliness or social isolation in crude analyses (**Table 3.6**), we examined adjusted models for the association of loneliness and social isolation with cognitive impairment (**Appendix 1, Tables 3.8-3.23**). In adjusted regression analyses, we found that more functional social support was associated with lower odds of severe cognitive impairment in attention and working memory (AOR_{ATT}= 0.5756, 95% CI: [0.3917, 0.8460]). Similarly, more total network support was associated with lower odds of impairment in speed of processing (AOR_{SPD}= 0.702, 95% CI: [0.511, 0.965]). However, the association of functional social support and cognitive impairment in ATT, ABS, and SPD were not significant in adjusted models. We observed a relations between loneliness and verbal memory (AOR_{VER}=0.694, 95% CI: [0.472, 1.022]) but not with any other cognitive domain (**Summary Table 3.7**; **Appendix 1, Tables 3.8-3.23**).

Contributing & Confounding Conditions

To assess the impact of contributing and confounding conditions, we examined the association of social support and having one or more of these conditions. We saw a positive relationship between functional support as well as total network support increased with odds of having a confounding or contributing condition, but no significant association with loneliness. Therefore, in order to address statistical bias caused by having one or more contributing or confounding conditions, we report estimates adjusted for contributing conditions as well as models that exclude confounded participants (n=22) (**Table 3.7, Figure 3.3**).

Discussion

This study sought to investigate the relationship between cognitive impairment and two constructs of social connectedness: loneliness and social isolation. The results from our study helps to distinguish the constructs of social isolation and loneliness. Loneliness was closely linked to mental health variables, particularly depression, whereas social isolation was correlated to various factors reflecting socially patterned determinants of health, including years of education, hepatitis C history, history of a substance use disorder, black/African American race, area-level measures of socioeconomic status as well as impairment in certain cognitive domains. Among PLWH age 55 and older who have symptomatic HIV-associated neurocognitive disorder, increased total social support was associated with decreased odds of severe cognitive impairment (compared to mild-moderate impairment) in the cognitive domains of attention & working memory (ATT) and speed of information processing (SPD). However, loneliness and functional support alone were not associated with degree of impairment. Self-reported cognitive functioning on the PAOFI was not associated with social isolation nor loneliness. Taken together, these results suggest that social factors may impact brain health among older adults living with HIV through various pathways. This is an important distinction in the light of increased attention to the study of social connectedness and cognitive aging in aging populations.

The body of literature about loneliness, social support, and cognitive impairment among PLWH, though small, is expanding as the importance of social connectedness and cognition among PLWH is increasingly recognized. Loneliness, social support, and living alone continue to be recognized as distinct constructs among older adults with HIV (Perissinotto & Covinsky, 2014). Additionally, previous research suggests that older adults living with HIV have distinct social experiences that uniquely impact their health and wellbeing (Brennan-Ing et al., 2017; Shippy & Karpiak, 2005). This was also reflected in our sample. For example, 43.5% of participants listed a healthcare provider, distinct from a social worker or therapist, in their perceived social support networks. Any reported loss of a social support person in the past year, reported by nearly a third (32.2%) of the sample, corresponded to more social isolation but not

to loneliness. In the ROAH study, one of the most robust sources of information about social connectedness among aging PLWH, loss was characterized by some as part of the cost of social connections with other HIV-seropositive adults and contributes to the fragility of social networks in this community (Shippy & Karpiak, 2005). Additionally, the results from our first study aim, in which we saw that characteristics of the socioeconomic environment were correlated to social isolation, highlight social isolation as a construct aligned with marginalization, which disproportionately affect PLWH and may impact cognitive aging outcomes. However, there is little scientific study of these relationships among HIV seropositive populations. The various dimensions of social support among people aging with HIV, such as socioeconomic status, loss, and access to healthcare, could represent targets for improving cognitive outcomes in this population.

The current literature examining the relationship between social isolation and/or loneliness with cognitive functioning has mixed results. The only other study to date examining both loneliness and social isolation with cognitive status in the same sample showed that poor social support, but not loneliness, was associated with worse neuropsychiatric status when measured by the MoCA (Bourgeois et al., 2020). Similar to that study, our findings showed that social isolation, but not loneliness, was associated with higher odds of worse cognitive impairment status in some cognitive domains. Four other studies to date have examined social connectedness variables with cognitive status as measured by a full battery of NP tests (Atkins et al., 2010b; Han et al., 2017; Harris et al., 2020; Moore et al., 2018). In contrast to our results, one of these studies found a relationship between more loneliness and worse cognitive status (Harris et al., 2020). However, Harris et al. (2020) measured loneliness with a single item question from the OARS scale, which has not been validated and may therefore suffer from low construct validity and unknown reliability. Han et al. (2017) only found a relationship between cognitive impairment and loneliness when they looked at interaction by race, suggesting that our results may have been affected by having a predominantly White sample. Our study contributes to this literature through the use of validated instruments for social isolation and loneliness as well as use of a neuropsychological

test battery for cognitive status, which is the gold standard for measurement of cognitive impairment in this population.

Our study indicates that some cognitive domains may be more substantially affected by isolation than others. Among those with lower social support, there were decreased odds of impairment in attention and working memory and speed of processing, but not the other three cognitive domains. Even in stratified analysis, the there was a lower odds of impairment in attention and working memory among those with more total network support. Though lack of precision in the estimated odds ratios may have introduced bias in the stratified results, "spotty" impairments are a noted clinical manifestation in HAND. Future research about these relationships may benefit from examining the impact of social connectedness on both global cognitive changes as well as domain based changes.

The impact of confounding and contributing conditions to risk of HAND are important to consider in the association between social connection and cognitive outcomes. In one of the largest papers examining risk for HAND, those who had confounding conditions had a substantially higher probability of cognitive impairment (Heaton et al., 2010). These conditions, which include substance use, mental health, psychoactive medications, and other chronic health conditions reflect many of the health disparities/inequalities experienced by PLWH. The sample used in the present study included participants with these conditions to more closely reflect the population of PLWH. Further investigation is needed to discern the particular cognitive effects of social connectedness among those with contributing and confounding conditions.

Limitations

This study is limited in some ways. First, this is a cross-sectional secondary data analysis of a sample recruited for a mindfulness based randomized control trial to address symptoms of cognitive impairment. Therefore, no elements of causality or temporality could be assessed. Additionally, this may have introduced selection bias, which may limit external validity. However, the flexible enrollment

criteria regarding contributing and confounding conditions likely improved the overall generalizability of the sample. Additionally, Second, there may be issues with bias inherent in self-report instruments. Third, we noted a reduction in statistical power, and the precision of effect estimates, in our stratified analyses. This research merits replication in larger, more diverse cohorts.

Summary and Conclusions

In this study, we found that among older adults with HIV-associated neurocognitive disorders, loneliness and social isolation are constructs with different dimensions. Loneliness was correlated with mental health measures such as stress, anxiety, and depression. In contrast, social isolation was correlated with other conditions and experiences reflecting marginalization, such as history of substance use disorder, Hepatitis C, lower educational attainment, and area level poverty. Neither isolation nor loneliness were associated with self-reported cognitive symptoms. After adjustment for contributing and confounding conditions and other covariates, we found that social isolation was associated with worse impairment in two cognitive domains (ATT and SPD). Loneliness was not associated with cognitive impairment. These associations signal unique relationships between cognitive aging among PLWH and various aspects of social connectedness and social context. Nursing research should prioritize future research to examine the risk of social isolation and loneliness in neurocognitive and other health outcomes among aging PLWH.

References

Addington, E. L., Javandel, S., De Gruttola, V., Paul, R., Milanini, B., Ances, B. M., Moskowitz, J. T., & Valcour, V. (2020). Mindfulness-based stress reduction for HIV-associated neurocognitive disorder: Rationale and protocol for a randomized controlled trial in older adults. *Contemporary Clinical Trials*, *98*. https://doi.org/10.1016/j.cct.2020.106150

Antinori, A., Arendt, G., Becker, J. T., Brew, B. J., Byrd, D. A., Cherner, M., Clifford, D. B., Cinque, P., Epstein, L. G., Goodkin, K., Gisslen, M., Grant, I., Heaton, R. K., Joseph, J., Marder, K., Marra, C. M., McArthur, J. C., Nunn, M., Price, R. W., … Wojna, V. E. (2007). Updated research nosology for HIV-associated neurocognitive disorders. *Neurology*, *69*(18), 1789–1799. https://doi.org/10.1212/01.WNL.0000287431.88658.8b

Atkins, J. H., Rubenstein, S. L., Sota, T. L., Rueda, S., Fenta, H., Bacon, J., & Rourke, S. B. (2010a). Impact of social support on cognitive symptom burden in HIV/AIDS. *AIDS Care*, *22*(7), 793–802. https://doi.org/10.1080/09540120903482994

Atkins, J. H., Rubenstein, S. L., Sota, T. L., Rueda, S., Fenta, H., Bacon, J., & Rourke, S. B. (2010b). Impact of social support on cognitive symptom burden in HIV/AIDS. *AIDS Care*, *22*(7), 793–802. https://doi.org/10.1080/09540120903482994

Barnes, L. L. B., Harp, D., & Jung, W. S. (2002). Reliability Generalization of Scores on the Spielberger State-Trait Anxiety Inventory. *Educational and Psychological Measurement*, *62*(4), 603–618. https://doi.org/10.1177/0013164402062004005

Berkman, L. F., Glass, T., Brissette, I., & Seeman, T. E. (2000). From social integration to health: Durkheim in the new millennium. *Social Science & Medicine (1982)*, *51*(6), 843–857.

Bourgeois, J. A., John, M., Zepf, R., Greene, M., Frankel, S., & Hessol, N. A. (2020). Functional deficits and other psychiatric associations with abnormal scores on the Montreal Cognitive Assessment (MoCA) in older HIV-infected patients. *International Psychogeriatrics*, *32*(1), 105–118. Embase. https://doi.org/10.1017/S1041610219000413

Brennan-Ing, M., Seidel, L., & Karpiak, S. E. (2017). Social Support Systems and Social Network Characteristics of Older Adults with HIV. *HIV and Aging*, *42*, 159–172. https://doi.org/10.1159/000448561

Cacioppo, S., Capitanio, J. P., & Cacioppo, J. T. %J P. B. (2014). *Toward a neurology of loneliness*. *140*(6), 1464.

Centers for Disease Control and Prevention. (2018, September 18). *HIV Among People Aged 50 and Over*. https://www.cdc.gov/hiv/group/age/olderamericans/index.html

Chelune, G. J., Heaton, R. K., Lehman, R. A., & Goldstein, G. (1986). Advances in clinical neuropsychology. *US: Springer*, 95–126.

Cohen, S. (1988). *Perceived stress in a probability sample of the United States.*

Gigliotti, E., & Samuels, W. E. (2011). Use of averaged norbeck social support questionnaire scores. *ISRN Nursing*, *2011*, 567280. https://doi.org/10.5402/2011/567280

Greene, M., Hessol, N. A., Perissinotto, C., Zepf, R., Hutton Parrott, A., Foreman, C., Whirry, R., Gandhi, M., & John, M. (2018). Loneliness in Older Adults Living with HIV. *AIDS and Behavior*, *22*(5), 1475–1484. https://doi.org/10.1007/s10461-017-1985-1

Grov, C., Golub, S. A., Parsons, J. T., Brennan, M., & Karpiak, S. E. (2010). Loneliness and HIV-related stigma explain depression among older HIV-positive adults. *AIDS Care*, *22*(5), 630–639. https://doi.org/10.1080/09540120903280901

Han, S. D., Adeyemi, O., Wilson, R. S., Leurgans, S., Jimenez, A., Oullet, L., Shah, R., Landay, A., Bennett, D. A., & Barnes, L. L. (2017). Loneliness in Older Black Adults with Human Immunodeficiency Virus Is Associated with Poorer Cognition. *Gerontology*, *63*(3), 253–262. https://doi.org/10.1159/000455253

Harris, M., Brouillette, M.-J., Scott, S. C., Smaill, F., Smith, G., Thomas, R., Fellows, L. K., & Mayo, N. E. (2020). Impact of Loneliness on Brain Health and Quality of Life Among Adults Living With HIV in Canada. *Journal of Acquired Immune Deficiency Syndromes (1999)*, *84*(4), 336–344. Medline. https://doi.org/10.1097/QAI.0000000000002355

Heaton, R. K., Clifford, D. B., Franklin, D. R., Woods, S. P., Ake, C., Vaida, F., Ellis, R. J., Letendre, S. L., Marcotte, T. D., Atkinson, J. H., Rivera-Mindt, M., Vigil, O. R., Taylor, M. J., Collier, A. C., Marra, C. M., Gelman, B. B., McArthur, J. C., Morgello, S., Simpson, D. M., … Grant, I. (2010). HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy. *Neurology*, *75*(23), 2087. https://doi.org/10.1212/WNL.0b013e318200d727

Holt-Lunstad, J., Smith, T. B., & Layton, J. B. (2010). Social relationships and mortality risk: A meta-analytic review. *PLoS Medicine*, *7*(7), e1000316. https://doi.org/10.1371/journal.pmed.1000316

Kimberlin, S. (2019). *California's Housing Affordability Crisis Hits Renters and Households With the Lowest Incomes the Hardest*. 5.

Kuiper, J. S., Zuidersma, M., Oude Voshaar, R. C., Zuidema, S. U., van den Heuvel, E. R., Stolk, R. P., & Smidt, N. (2015). Social relationships and risk of dementia: A systematic review and meta-analysis of longitudinal cohort studies. *Ageing Research Reviews*, *22*, 39–57. https://doi.org/10.1016/j.arr.2015.04.006

Leigh-Hunt, N., Bagguley, D., Bash, K., Turner, V., Turnbull, S., Valtorta, N., & Caan, W. (2017). An overview of systematic reviews on the public health consequences of social isolation and loneliness. *Public Health*, *152*, 157–171. https://doi.org/10.1016/j.puhe.2017.07.035

Moore, D. J., Fazeli, P. L., Moore, R. C., Woods, S. P., Letendre, S. L., Jeste, D. V., & Grant, I. (2018). Positive Psychological Factors Are Linked to Successful Cognitive Aging Among Older Persons Living with HIV/AIDS. *AIDS and Behavior*, *22*(5), 1551–1561. https://doi.org/10.1007/s10461-017-2001-5

Norbeck, J. S., Lindsey, A. M., & Carrieri, V. L. (1983). Further development of the Norbeck Social Support Questionnaire: Normative data and validity testing. *Nurs Res*, *32*(1), 4–9.

Peplau, L. A., & Perlman, D. (1982). *Loneliness: A sourcebook of current theory, research, and therapy*. Wiley. http://ucsf.summon.serialssolutions.com/2.0.0/link/0/eLvHCXMwdV07C8IwED6kXbr5xDf-gUqbpsaMIoqDi6BIXUraJKMO4uC_9662oqJjCDmScHz3yH0XgIhNA_8LE3Ibouc8N4qrmHx

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Perissinotto, C. M., & Covinsky, K. E. (2014). Living alone, socially isolated or lonely—What are we measuring? *Journal of General Internal Medicine*, *29*(11), 1429–1431. https://doi.org/10.1007/s11606-014-2977-8

Poindexter, C., & Shippy, R. A. (2008). Networks of older New Yorkers with HIV: Fragility, resilience, and transformation. *AIDS Patient Care and STDs*, *22*(9), 723–733. https://doi.org/10.1089/apc.2007.0260

Russell, D., Peplau, L. A., & Cutrona, C. E. (1980). The revised UCLA Loneliness Scale: Concurrent and discriminant validity evidence. *Journal of Personality and Social Psychology*, *39*(3), 472–480.

Shippy, R. A., & Karpiak, S. E. (2005). The aging HIV/AIDS population: Fragile social networks. *Aging & Mental Health*, *9*(3), 246–254. https://doi.org/10.1080/13607860412331336850

Tavakol, M., & Dennick, R. (2011). Making sense of Cronbach's alpha. *International Journal of Medical Education*, *2*, 53–55. https://doi.org/10.5116/ijme.4dfb.8dfd

US Census Bureau, A. C. S. (2019). *2013-2017 American Community Survey 5-year estimates.* https://www.census.gov/acs/www/data/data-tables-and-tools/data-profiles/

Winston, A., & Spudich, S. (2020). Cognitive disorders in people living with HIV. *The Lancet HIV*, *7*(7), e504–e513. https://doi.org/10.1016/S2352-3018(20)30107-7

Yesavage, J. A., Brink, T. L., Rose, T. L., Lum, O., Huang, V., Adey, M., & Leirer, V. O. (1982). Development and validation of a geriatric depression screening scale: A preliminary report. *Journal of Psychiatric Research*, *17*(1), 37–49.

Table 3.1: UCSF HIV Neuropsychological Testing Battery	
Pre-morbid IQ	Wide Range Achievement Test (WRAT-4)
Learning and Memory	California Verbal Learning task (CVLT)-II sum of trials 1-5, Benson Figure Recall, 2-back
Executive Function	Trails B, STROOP Interference, Lexical Fluency (D words), Design Fluency
Visuospatial	Visual Object and Space Perception (VOSP), Benson Figure Copy
Psychomotor	Trails A, STROOP Color Naming
Motor/manual dexterity	Grooved Pegboard, Finger Tapping
Attention	CVLT trial 1, Digits Backward
Language	Boston Naming Test-15 item, Category Fluency (Animals OR Vegetables) +/- PASAT based on clinician acumen
Supplementary tests*	Paced Auditory Serial Addition Test (PASAT), Flanker task, PPVT-R, Verbal Agility, Logical Memory IA & IIA, Repetition, and/or Modified Trails.

* In the event the neuropsychologist determined that additional testing may be helpful to confirm cognitive status, supplementary cognitive tests were administered
From: Addington et al., 2020

Table 3.2: Sample Characteristics and Sociodemographic Information (n=170)	
Male (N, %)	158 (92.9)
Racial Group (N, %)	
white	123 (72.4%)
Black or African American	29 (17.1%)
Native Hawaiian or other Pacific Island	2 (1.2%)
Asian	6 (3.5%)
Other	10 (5.9%)
Age (Mean, SD)	64.3 (5.3)
Nadir CD4 cell count ≤200 (N, %)	104 (61.2%)
CD4/CD8 cell ratio	
Median (IQR Q1:Q3)	0.764 (0.549, 2.152)
Inverted (≤1.00) (N, %)	121 (71.18%)
Low (≤0.70) (N, %)	74 (43.79%)
Very Low (≤0.50) (N, %)	35 (20.71%)
Years Living with HIV (Mean, SD)	26 (6.8)
Years of Education (Mean, SD)	15.6 (2.3)
History of Substance use (abuse or dependence) (N, %)	82 (48.2%)
Currently Smoking (N, %)	97 (57.1%)
Years of Smoking (mean, SD)	
History of Hepatitis C (N, %)	40 (23.5%)
Depression	
Depressive episode in past 2 years (N, %)	87 (51.2%)
GDS >= 9 (N, %)	66 (38.8%)
GDS Score (Median, IQR Q1:Q3)	8 (0 – 24)
Perceived Stress Scale (Mean, SD)	14.2 (6.4)
Anxiety	
Lifetime History of Anxiety Disorder (N, %)	47 (27.7%)
State Anxiety (Median, IQR Q1:Q3)	33 (20 – 60)
Trait Anxiety (Median, IQR Q1:Q3)	37 (22 – 60)
Living Situation (N, %)	
Alone	91 (53.5%)
With spouse or partner	53 (31.2%)
With Friends	20 (11.8%)
With group	4 (2.4%)

Table 3.2: Sample Characteristics and Sociodemographic Information *Continued*	
Other	2 (1.2%)
Able to Live Independently (N, %)	163 (95.9%)
ZIP code Socioeconomic Variables	
Cost Burden (N, %)	56 (32.9%)
Poverty rate (Mean, SD)	13.4 (0.1)
Median monthly household income (USD) (Median, IQR Q1:Q3)	7362.66 (2796.00 – 11991.83)
Median monthly housing costs (USD) (Median, IQR Q1:Q3)	1823.5 (1005.00 – 2690.00)

Table 3.3: Measures of Loneliness and Social Isolation (n=167)

UCLA Loneliness Scale [a]	Mean (SD)
Total Loneliness	44.41 (11.67)
1st quantile	30.29 (3.82)
2nd quantile	39.63 (2.63)
3rd quantile	49.56 (2.89)
4th quantile	59.65 (4.31)
Norbeck Social Support Scale [b]	Median (IQR)
Total Functional Support [c]	115.5 (0 – 426)
Emotional support	85 (0 – 281)
Tangible support	28 (0 – 145)
1st quantile	37 (0 – 60)
2nd quantile	86 (67 – 107)
3rd quantile	141 (120 – 182)
4th quantile	267.5 (198 – 426)
Total Social Network [d]	49 (0 – 167)
Number people listed	7 (4 – 24)
Duration Known	24 (12 – 83)
Frequency of contact	18 (9 – 64)
1st quantile	16.5 (0 – 28)
2nd quantile	37.5 (29 – 49)
3rd quantile	62 (50 – 75)
4th quantile	95 (76 – 187)

[a] UCLA-20: Higher score indicates more loneliness
[b] NSS: Higher scores indicates more support / contact
[c] Sum of Emotional + Tangible support
[d] Sum of number people in network + Duration known + Contact frequency

Table 3.4: Correlates of Loneliness and Social Isolation			
	UCLA Loneliness Scale	Total Functional Support	Total Social Network
		Correlation Coefficient (*r*)	
Age	0.138	-0.057	-0.073
Years of Education	0.080	0.270*	0.276*
Nadir CD4 cell count	-0.061	-0.028	-0.023
CD4 cell count (Mean, SD)	0.019	-0.037	-0.052
CD4/CD8 cell ratio	0.0406	0.0277	0.0202
Years Living with HIV	-0.092	-0.143	-0.134
GDS Score	0.521*	0.062	-0.096
Perceived Stress Scale	0.376*	-0.094	-0.068
State Anxiety	0.262*	0.063	0.078
Trait Anxiety	0.502*	-0.013	-0.000
Patient's Own Assessment of Function Inventory	-0.0721	0.0985	0.0864
Area Level Characteristics			
% living below poverty line	0.068	-0.206*	-0.222*
Median monthly household income (USD)	-0.015	0.143	0.161*
Median monthly housing costs (USD)	-0.035	0.171*	0.191*
* $p < 0.05$			

Table 3.5: Between Group Differences for Measures of Social Connectedness (n=170)			
	Loneliness	Total Functional Support	Total Social Network
	Mean (SD)	Median Score (IQR Q1-Q3)	
Male	44.5 (11.8)	51 (29-167)	118 (63-426)
Racial Group			
White (Referent)	44.7 (11.9)	52 (32-153)	120 (75-380)
Black or African American	42.5 (9.0)	36 (21-88)**	86 (49-224)**
Native Hawaiian or Pacific Islander	37 (-)	45.5 (-)	132 (-)
Asian	42.3 (12.5)	55.5 (37-52)	131.5 (90-126)
Other	48.3 (15.7)	30 (17-36)**	62 (33-73)**
CD4/CD8 cell ratio			
Inverted (≤1.00)	44.48 (12.13)	49 (24.5-164)	113 (58-345)
Low (≤0.70)	44.5 (33-63)	49 (24-153)	110 (63-343)
Very Low (≤0.50)	40 (30-57)	60 (30-139)	135 (70-309)
History of substance abuse or dependence	45.5 (12.2)	41 (24-131)**	90 (52-345)**
History of Hepatitis C	44.4 (10.5)	39 (22-80)*	91.5 (51-223)*
Mental Health Measures			
Depressive episode in past 2 years	46.3 (11.3)*	44 (26-123)	106 (60-343)
GDS ≥ 9	50.4 (10.7)*	43 (24-95)*	105 (50-268)*
Lifetime History of Depression	46.25 (11.29)**	6.74 (5.05-8.43)	10.34 (7.75-13.30)
Lifetime History of Anxiety Disorder	47.2 (11.4)	45 (30-114)	115 (62-309)
Living Alone	46.6 (11.3)*	44.5 (24-139)**	100 (53-335)**
Cost Burdened	44.9 (11.6)	37 (17-137)**	90 (49.5-335)

Note: T-tests and rank sum tests used for tests of between-group differences with reference group. Significant results in bold face.
* $p < 0.10$ ** $p < 0.05$

Table 3.6: Unadjusted Estimates of the Association of Social Support and Loneliness and Moderate-Severe Impairment in Each Cognitive Domain and Self-Reported Cognitive Function

	Performance Based Cognitive Impairment [a]					Self-Reported [b]
	VER	MEM	ATT	ABS	SPD	POAFI
	Coefficient (95% Confidence Interval), *p*-value					
Total Network Social Support	0.844 (0.575, 1.237), 0.384	0.955 (0.709, 1.287), 0.761	**0.589 (0.436, 0.795), 0.001**	**0.725 (0.523, 1.000), 0.050**	**0.702 (0.511, 0.965), 0.029**	1.928 (-1.524, 5.380), 0.272
Total Functional Social Support	0.843 (0.577, 1.232), 0.379	0.996 (0.745, 1.334), 0.982	**0.664 (0.499, 0.885), 0.005**	**0.670 (0.483, 0.927), 0.016**	0.778 (0.573, 1.058), 0.110	2.599 (-0.762, 5.960), 0.129
Loneliness	**0.694 (0.472, 1.022), 0.065**	1.000 (0.740, 1.327), 0.951	0.925 (0.703, 1.217), 0.579	0.798 (0.582, 1.093) 0.161	0.832 (0.614, 1.127), 0.236	-1.867 (-5.241, 1.508), 0.276

[a] Unadjusted OR for severe domain-specific cognitive impairment (compared to mild-moderate impairment) for each increase in quantile of social isolation and loneliness scale scores. Domain specific ORs are reported due to the phenomenon of "spotty impairments" in MND, in which cognitive domains may differ in degree of impairment in earlier phases of HAND. Regression coefficient is Odds Ratio.

[b] Linear regression for POAFI score and quantiles of social isolation and loneliness. Higher POAFI score indicates better cognitive function. Regression coefficient is beta

Abbreviations OR: Odds Ratio, ATT: Attention and working memory, ABS: Abstraction and executive function, HAND: HIV-Associated Neurocognitive Disorders; SPD: Speed of Processing POAFI: Patient's Own Assessment of Functioning; MND: Mild Neurocognitive Disorder; MEM: Memory and Recall; VER: Verbal Memory

Table 3.7: Pooled and Stratified Estimates of the Association between Social Support and Loneliness and Moderate-Severe Impairment in Each Cognitive Domain

	Cognitive Domain					
Total Network Social Support [b]	ATT		ABS		SPD	
	AOR (95% Confidence Interval) [a] | *P*-value					
Pooled/adjusted, n=165	0.576 (0.392, 0.847)	0.005	0.729 (0.466, 1.139)	0.165	0.607 (0.401 0.919)	0.018
Pooled, excluding confounding conditions, n=143	0.636 (0.422, 0.960)	0.031	0.901 (0.554, 1.465)	0.674	0.603 (0.385, 0.945)	0.027
Total Functional Social Support [b]						
Pooled/adjusted	0.716 (0.504, 1.019)	0.064	0.719 (0.455, 1.137)	0.159	0.754 (0.514, 1.106)	0.149
Pooled, excluding confounding conditions	0.766 (0.523, 1.120)	0.170	0.879 (0.558, 1.384)	0.580	0.767 (0.508, 1.158)	0.208
Loneliness	MEM					
Pooled/adjusted	0.999 (0.695, 1.439)			0.999		
Pooled, excluding confounding conditions	0.726 (0.446, 1.182)			0.198		

[a] Adjusted Odds Ratio for severe domain-specific cognitive impairment (compared to mild-moderate impairment) for each increase in quantile of social isolation and loneliness scale scores.

[b] Model adjusted for GDS score, age, years of education, non-white racial group, years living with HIV, past substance use, and past Hepatitis C infection

Abbreviations: AOR: Adjusted Odds Ratio, ATT: Attention and working memory, ABS: Abstraction and executive function, HAND: HIV-Associated Neurocognitive Disorders; GDS: Geriatric Depression Scale; SPD: Speed of Processing POAFI: Patient's Own Assessment of Functioning; MEM: Memory and Recall

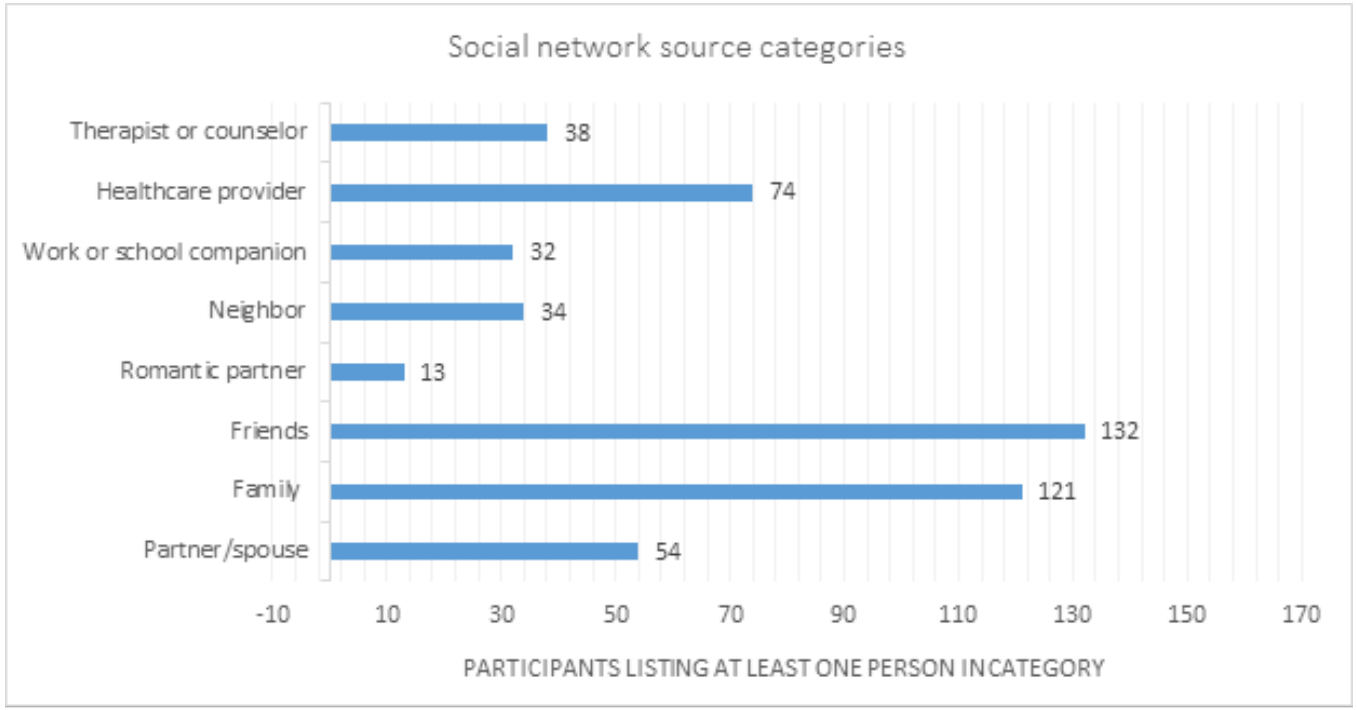

Figure 3.1: Social Support Network Categories and the Number of Study Participants who Reported at Least One Person in that Category

Categories of people who provide social support to the participant include Partner/spouse, family, friends, romantic partner, neighbor, work or school companion, healthcare provider, and therapist or counselor. Categories defined by the Norbeck Social Support Scale.

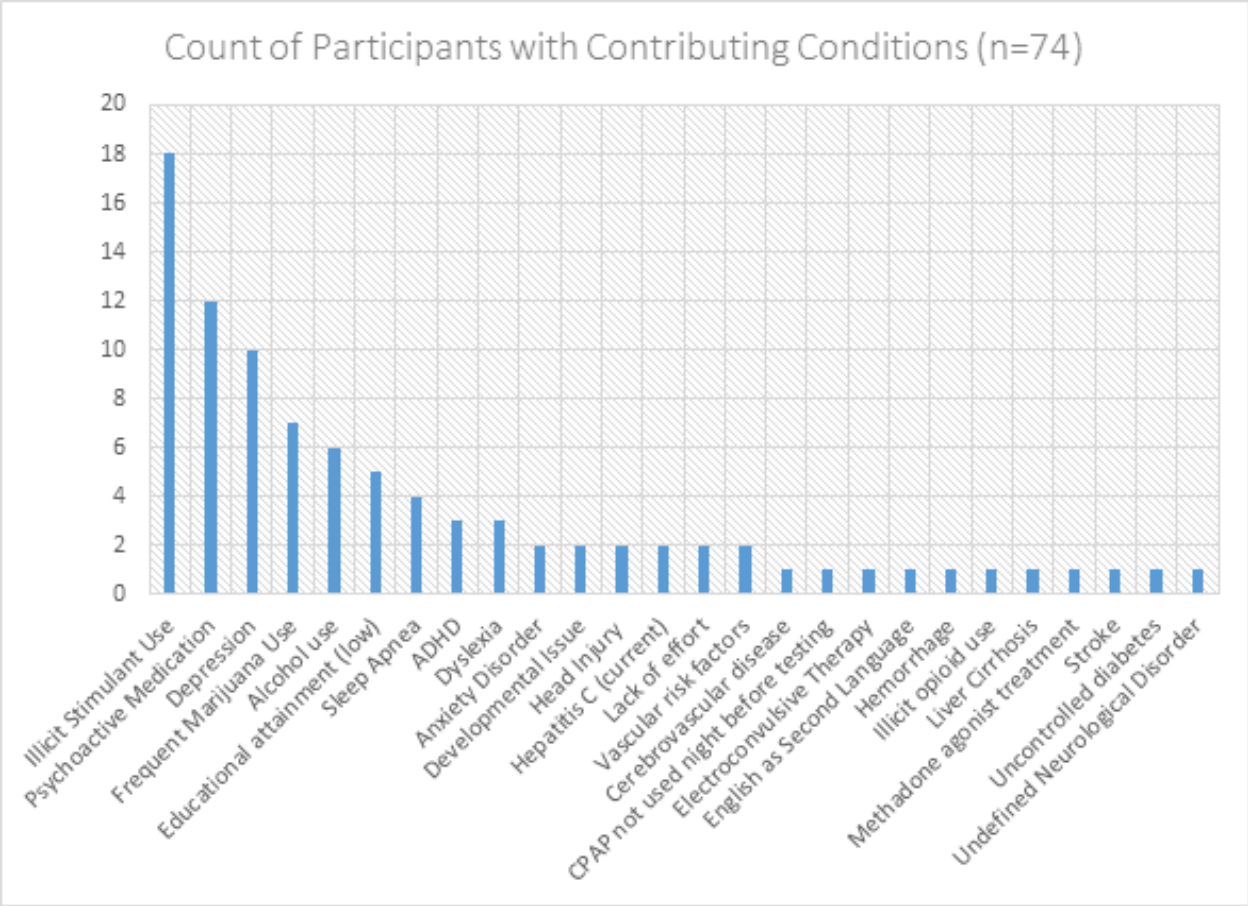

Figure 3.2: The Count of Participants with Each Contributing and/or Confounding Conditions

Following the Frascati criteria, individuals with substantial co-existing conditions that interfered with the interpretation of the neuropsychological data were considered to be confounded (Antinori et al., 2007). To improve generalizability of the results of the study, these individuals were allowed to enroll and, contrary to Frascati criteria, a HAND category was assigned based on interpretation of all data.

Appendices

Appendix 3.A: The Association of Social Isolation and Loneliness with Cognitive Domains, Full Models

Table 3.8: The Association of Total Social Network Support and Cognitive Impairment in Abstraction and Executive Function

	AOR [a]	95% Confidence Interval	*p*-value
Total Network Support (quartile)	0.729	0.466, 1.140	0.165
Depression (GDS ≥9)	0.722	0.293, 1.776	0.478
Years of Education	0.912	0.721, 1.153	0.442
Non-White Racial Group	2.341	0.872, 6.288	0.092
Years Living with HIV	0.951	0.884, 1.023	0.175
Age	0.879	0.798, 0.970	0.010
Past Substance Use Disorder	0.503	0.192, 1.321	0.163
Nadir CD4 cell count ≤200 cells/μL	1.223	0.463, 3.236	0.684
Contributing/Confounding Conditions	3.251	1.282, 8.243	0.013

[a] Adjusted Odds Ratio for severe domain-specific cognitive impairment (compared to mild-moderate impairment) for each increase in quantile of social isolation or loneliness scale scores.

Table 3.9: The Association of Total Social Network Support and Moderate-Severe Impairment in Speed of Processing

	AOR [a]	95% Confidence Interval		*p*-value
Total Network Support (quartile)	0.607	0.401	0.919	0.018
Depression (GDS ≥9)	0.691	0.297	1.607	0.391
Years of Education	1.124	0.911	1.386	0.276
Non-White Racial Group	1.954	0.772	4.943	0.157
Years Living with HIV	1.014	0.953	1.078	0.669
Age	0.942	0.867	1.024	0.164
Past Substance Use Disorder	0.634	0.263	1.531	0.311
Nadir CD4 cell count ≤200 cells/μL	0.78	0.332	1.837	0.57
Contributing/Confounding Conditions	1.177	0.491	2.821	0.715

[a] Adjusted Odds Ratio for severe domain-specific cognitive impairment (compared to mild-moderate impairment) for each increase in quantile of social isolation or loneliness scale scores.

Table 3.10: The Association of Total Social Network Support and Moderate-Severe Impairment in Attention and Working Memory

	AOR [a]	95% Confidence Interval		*p*-value
Total Network Support (quartile)	0.576	0.392	0.847	0.005
Depression (GDS ≥9)	0.834	0.381	1.825	0.649
Years of Education	0.841	0.695	1.017	0.075
Non-White Racial Group	2.447	1.017	5.887	0.046
Years Living with HIV	1.004	0.945	1.066	0.903
Age	0.934	0.863	1.01	0.086
Past Substance Use Disorder	0.905	0.401	2.044	0.81
Nadir CD4 cell count ≤200 cells/μL	0.755	0.336	1.693	0.495
Contributing/Confounding Conditions	0.882	0.396	1.967	0.759

[a] Adjusted Odds Ratio for severe domain-specific cognitive impairment (compared to mild-moderate impairment) for each increase in quantile of social isolation or loneliness scale scores.

Table 3.12: The Association of Total Social Network Support and Moderate-Severe Impairment in Memory and Recall				
	AOR [a]	**95% Confidence Interval**		***p*-value**
Total Network Support (quartile)	1.121	0.773	1.625	0.547
Depression (GDS ≥9)	1.296	0.599	2.804	0.51
Years of Education	0.917	0.763	1.102	0.355
Non-White Racial Group	3.063	1.048	8.948	0.041
Years Living with HIV	1.02	0.961	1.084	0.51
Age	0.99	0.92	1.066	0.798
Past Substance Use Disorder	2.008	0.881	4.576	0.097
Nadir CD4 cell count ≤200 cells/μL	0.718	0.311	1.659	0.438
Contributing/Confounding Conditions	1.384	0.625	3.065	0.423

[a] Adjusted Odds Ratio for severe domain-specific cognitive impairment (compared to mild-moderate impairment) for each increase in quantile of social isolation or loneliness scale scores.

Table 3.13: The Association of Total Social Network Support and Moderate-Severe Impairment in Verbal Memory			
	AOR [a]	**95% Confidence Interval**	***p*-value**
Total Network Support (quartile)	0.848	0.541, 1.329	0.472
Depression (GDS ≥9)	0.818	0.318, 2.107	0.678
Years of Education	0.873	0.698, 1.092	0.236
Non-White Racial Group	2.619	0.664, 10.324	0.169
Years Living with HIV	1.032	0.958, 1.112	0.401
Age	0.947	0.866, 1.036	0.235
Past Substance Use Disorder	1.054	0.385, 2.89	0.918
Nadir CD4 cell count ≤200 cells/μL	2.259	0.876, 5.825	0.092
Contributing/Confounding Conditions	0.536	0.203, 1.418	0.209

[a] Adjusted Odds Ratio for severe domain-specific cognitive impairment (compared to mild-moderate impairment) for each increase in quantile of social isolation or loneliness scale scores.

Table 3.14: The Association of Functional Social Network Support and Moderate-Severe Impairment in Attention and Working Memory

	AOR [a]	95% Confidence Interval	*p*-value
Functional Network Support (quartile)	0.716	0.504, 1.019	0.064
Depression (GDS ≥9)	0.839	0.393, 1.787	0.648
Years of Education	0.818	0.680, 0.983	0.032
Non-White Racial Group	1.893	0.822, 4.36	0.134
Years Living with HIV	1.012	0.955, 1.072	0.691
Age	0.954	0.885, 1.028	0.215
Past Substance Use Disorder	0.995	0.458, 2.164	0.991
Nadir CD4 cell count ≤200 cells/μL	0.757	0.347, 1.649	0.484
Contributing/Confounding Conditions	0.952	0.440, 2.058	0.901

[a] Adjusted Odds Ratio for severe domain-specific cognitive impairment (compared to mild-moderate impairment) for each increase in quantile of social isolation or loneliness scale scores.

Table 3.15: The Association of Functional Social Network Support and Moderate-Severe Impairment in Abstraction and Executive Function

	AOR[a]	95% Confidence Interval	*p*-value
Functional Network Support (quartile)	0.719	0.455, 1.137	0.159
Depression (GDS ≥9)	0.819	0.329, 2.039	0.667
Years of Education	0.919	0.730, 1.156	0.470
Non-White Racial Group	2.563	0.897, 7.318	0.079
Years Living with HIV	0.959	0.894, 1.027	0.232
Age	0.888	0.813, 0.97	0.008
Past Substance Use Disorder	0.611	0.257, 1.454	0.266
Nadir CD4 cell count ≤200 cells/μL	1.485	0.570, 3.873	0.418
Contributing/Confounding Conditions	2.940	1.188, 7.272	0.020

[a] Adjusted Odds Ratio for severe domain-specific cognitive impairment (compared to mild-moderate impairment) for each increase in quantile of social isolation or loneliness scale scores.

Table 3.16: The Association of Functional Social Network Support and Moderate-Severe Impairment in Speed of Processing			
	AOR [a]	**95% Confidence Interval**	***p*-value**
Functional Network Support (quartile)	0.754	0.514, 1.107	0.149
Depression (GDS ≥9)	0.835	0.368, 1.894	0.665
Years of Education	1.089	0.891, 1.331	0.404
Non-White Racial Group	2.050	0.844, 4.979	0.113
Years Living with HIV	1.018	0.959, 1.081	0.553
Age	0.962	0.888, 1.042	0.345
Past Substance Use Disorder	0.826	0.358, 1.905	0.654
Nadir CD4 cell count ≤200 cells/μL	0.899	0.390, 2.073	0.803
Contributing/Confounding Conditions	1.078	0.464, 2.505	0.862

[a] Adjusted Odds Ratio for severe domain-specific cognitive impairment (compared to mild-moderate impairment) for each increase in quantile of social isolation or loneliness scale scores.

Table 3.17: The Association of Functional Social Network Support and Moderate-Severe Impairment in Memory and Recall

	AOR [a]	95% Confidence Interval	*p*-value
Functional Network Support (quartile)	1.143	0.802, 1.627	0.460
Depression (GDS ≥9)	1.195	0.562, 2.539	0.644
Years of Education	0.914	0.765, 1.092	0.324
Non-White Racial Group	2.108	0.808, 5.503	0.128
Years Living with HIV	1.026	0.967, 1.089	0.392
Age	0.995	0.927, 1.069	0.892
Past Substance Use Disorder	1.846	0.837, 4.068	0.129
Nadir CD4 cell count ≤200 cells/μL	0.707	0.316, 1.583	0.399
Contributing/Confounding Conditions	1.556	0.715, 3.386	0.266

[a] Adjusted Odds Ratio for severe domain-specific cognitive impairment (compared to mild-moderate impairment) for each increase in quantile of social isolation or loneliness scale scores.

Table 3.18: The Association of Functional Social Network Support and Moderate-Severe Impairment in Verbal Memory

	AOR [a]	95% Confidence Interval	*p*-value
Functional Network Support (quartile)	0.852	0.542, 1.338	0.487
Depression (GDS ≥9)	0.814	0.317, 2.09	0.669
Years of Education	0.867	0.693, 1.084	0.211
Non-White Racial Group	2.686	0.687, 10.505	0.156
Years Living with HIV	1.033	0.959, 1.112	0.397
Age	0.949	0.870, 1.035	0.237
Past Substance Use Disorder	1.055	0.387, 2.874	0.917
Nadir CD4 cell count ≤200 cells/μL	2.189	0.850, 5.637	0.104
Contributing/Confounding Conditions	0.523	0.198, 1.38	0.191

[a] Adjusted Odds Ratio for severe domain-specific cognitive impairment (compared to mild-moderate impairment) for each increase in quantile of social isolation or loneliness scale scores.

Table 3.19: The Association of Loneliness and Moderate-Severe Impairment in Abstraction and Executive Function

	AOR [a]	95% Confidence Interval	*p*-value
Loneliness (quartile)	0.852	0.555, 1.309	0.465
Depression (GDS ≥9)	0.962	0.358, 2.59	0.940
Years of Education	0.857	0.687, 1.069	0.171
Non-White Racial Group	2.509	0.926, 6.795	0.070
Years Living with HIV	0.953	0.887, 1.025	0.197
Age	0.9	0.820, 0.989	0.028
Past Substance Use Disorder	0.649	0.256, 1.642	0.361
Nadir CD4 cell count ≤200 cells/μL	1.375	0.517, 3.658	0.524
Contributing/Confounding Conditions	3.357	1.329, 8.476	0.010

[a] Adjusted Odds Ratio for severe domain-specific cognitive impairment (compared to mild-moderate impairment) for each increase in quantile of social isolation or loneliness scale scores.

Table 3.20: The Association of Loneliness and Moderate-Severe Impairment in Speed of Processing			
	AOR [a]	**95% Confidence Interval**	***p*-value**
Loneliness (quartile)	0.903	0.610, 1.339	0.612
Depression (GDS ≥9)	0.932	0.372, 2.333	0.88
Years of Education	1.041	0.863, 1.256	0.671
Non-White Racial Group	2.016	0.807, 5.039	0.133
Years Living with HIV	1.016	0.957, 1.078	0.607
Age	0.973	0.899, 1.054	0.507
Past Substance Use Disorder	0.854	0.369, 1.975	0.712
Nadir CD4 cell count ≤200 cells/μL	0.849	0.366, 1.971	0.704
Contributing/Confounding Conditions	1.139	0.489, 2.658	0.763

[a] Adjusted Odds Ratio for severe domain-specific cognitive impairment (compared to mild-moderate impairment) for each increase in quantile of social isolation or loneliness scale scores.

Table 3.21: The Association of Loneliness and Moderate-Severe Impairment in Attention and Working Memory			
	AOR [a]	**95% Confidence Interval**	***p*-value**
Loneliness (quartile)	1.044	0.734, 1.485	0.811
Depression (GDS ≥9)	0.900	0.396, 2.045	0.801
Years of Education	0.781	0.654, 0.933	0.006
Non-White Racial Group	2.100	0.889, 4.961	0.091
Years Living with HIV	1.012	0.955, 1.072	0.684
Age	0.963	0.895, 1.037	0.316
Past Substance Use Disorder	1.107	0.514, 2.384	0.795
Nadir CD4 cell count ≤200 cells/μL	0.746	0.342, 1.629	0.462
Contributing/Confounding Conditions	0.841	0.385, 1.838	0.665

[a] Adjusted Odds Ratio for severe domain-specific cognitive impairment (compared to mild-moderate impairment) for each increase in quantile of social isolation or loneliness scale scores.

Table 3.22: The Association of Loneliness and Moderate-Severe Impairment in Verbal Memory			
	AOR [a]	**95% Confidence Interval**	***p*-value**
Loneliness (quartile)	0.701	0.434, 1.132	0.146
Depression (GDS ≥9)	1.265	0.427, 3.747	0.671
Years of Education	0.839	0.674, 1.044	0.115
Non-White Racial Group	2.73	0.693, 10.753	0.151
Years Living with HIV	1.03	0.955, 1.111	0.449
Age	0.974	0.890, 1.067	0.575
Past Substance Use Disorder	1.195	0.433, 3.296	0.731
Nadir CD4 cell count ≤200 cells/μL	2.479	0.935, 6.577	0.068
Contributing/Confounding Conditions	0.517	0.193, 1.383	0.189

[a] Adjusted Odds Ratio for severe domain-specific cognitive impairment (compared to mild-moderate impairment) for each increase in quantile of social isolation or loneliness scale scores.

Table 3.23: The Association of Loneliness and Moderate-Severe Impairment in Memory and Recall			
	AOR [a]	**95% Confidence Interval**	***p*-value**
Loneliness (quartile)	1.000	0.695, 1.439	0.999
Depression (GDS ≥9)	1.238	0.525, 2.92	0.625
Years of Education	0.922	0.775, 1.097	0.358
Non-White Racial Group	2.944	1.005, 8.621	0.049
Years Living with HIV	1.022	0.963, 1.085	0.476
Age	0.984	0.915, 1.059	0.672
Past Substance Use Disorder	1.839	0.825, 4.101	0.136
Nadir CD4 cell count ≤200 cells/μL	0.683	0.296, 1.576	0.372
Contributing/Confounding Conditions	1.353	0.613, 2.986	0.454

[a] Adjusted Odds Ratio for severe domain-specific cognitive impairment (compared to mild-moderate impairment) for each increase in quantile of social isolation or loneliness scale scores.

Appendix 3.B: The Relationship Between CD4/CD8 cell Ratio and Cognitive Impairment in Each Cognitive Domain

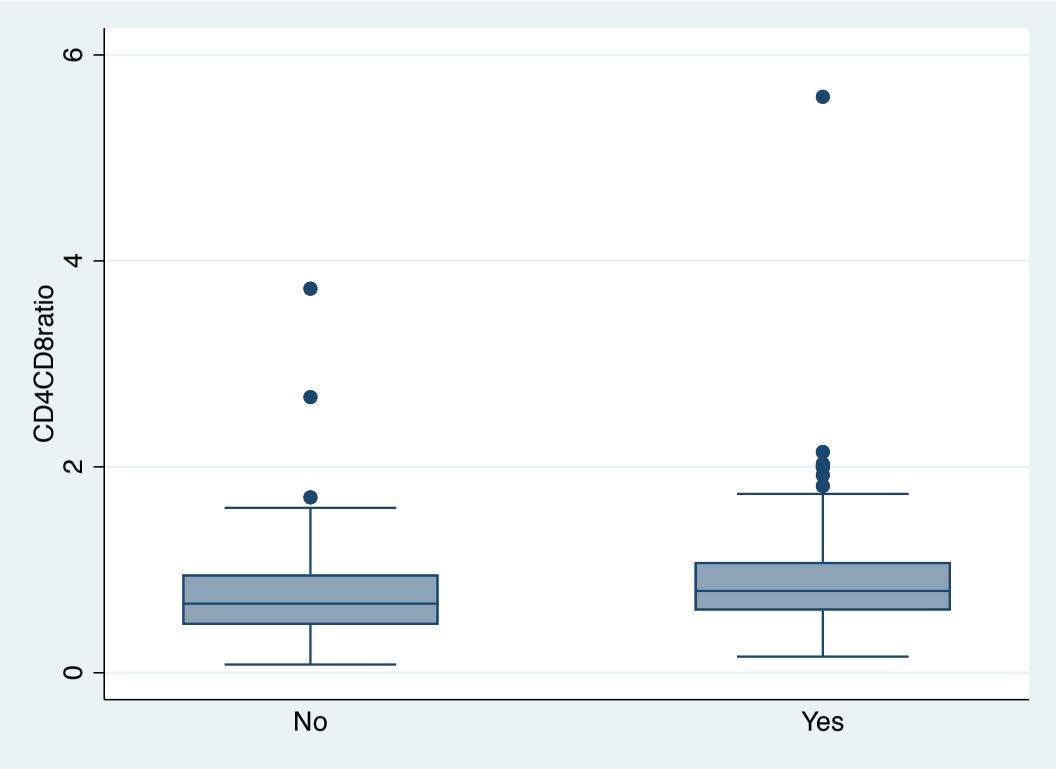

Figure 3.4: Box plot of CD4/CD8 cell ratio by moderate-severe impairment in the domain of Memory and Recall

No significant difference in the CD4/CD8 ratio by impairment in Memory and Recall

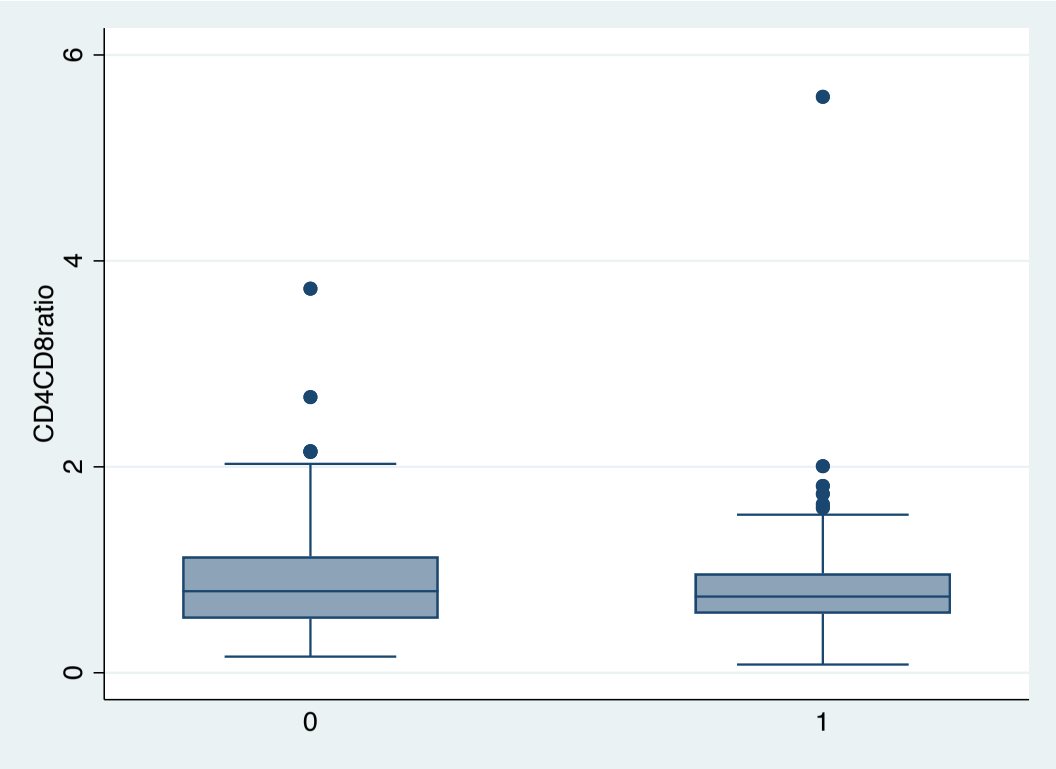

Figure 3.5: Box plot of CD4/CD8 cell ratio by moderate-severe impairment in the domain of Attention and Working Memory

No significant difference in the CD4/CD8 ratio by impairment in Attention and Working Memory

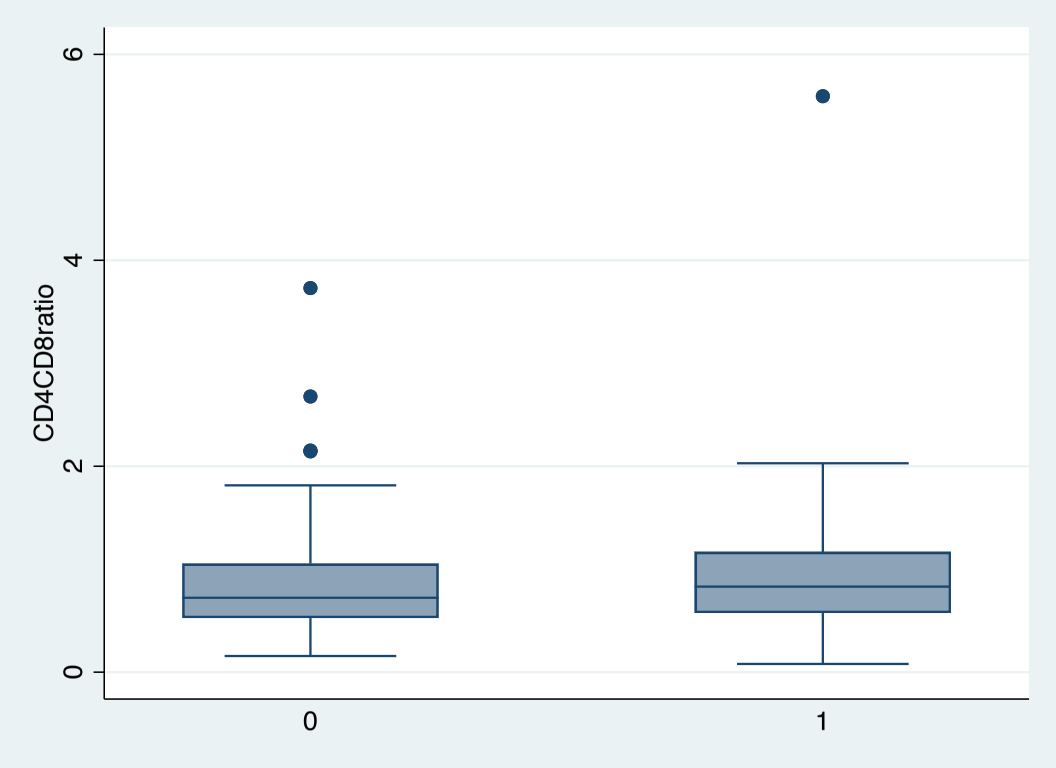

Figure 3.6: Box plot of CD4/CD8 cell ratio by moderate-severe impairment in the domain of Speed of Processing

No significant difference in the CD4/CD8 ratio by impairment in Speed of Processing

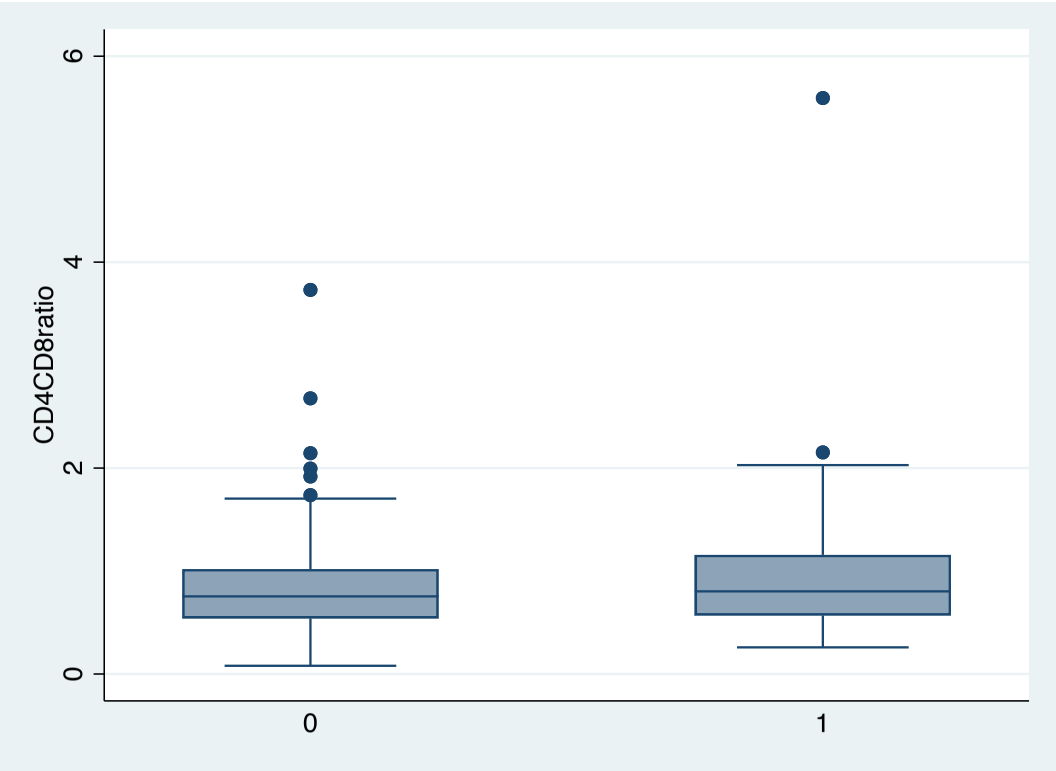

Figure 3.7: Box plot of CD4/CD8 cell ratio by moderate-severe impairment in the domain of Abstraction and Executive Function

No significant difference in the CD4/CD8 ratio by impairment in Abstraction and Executive Function

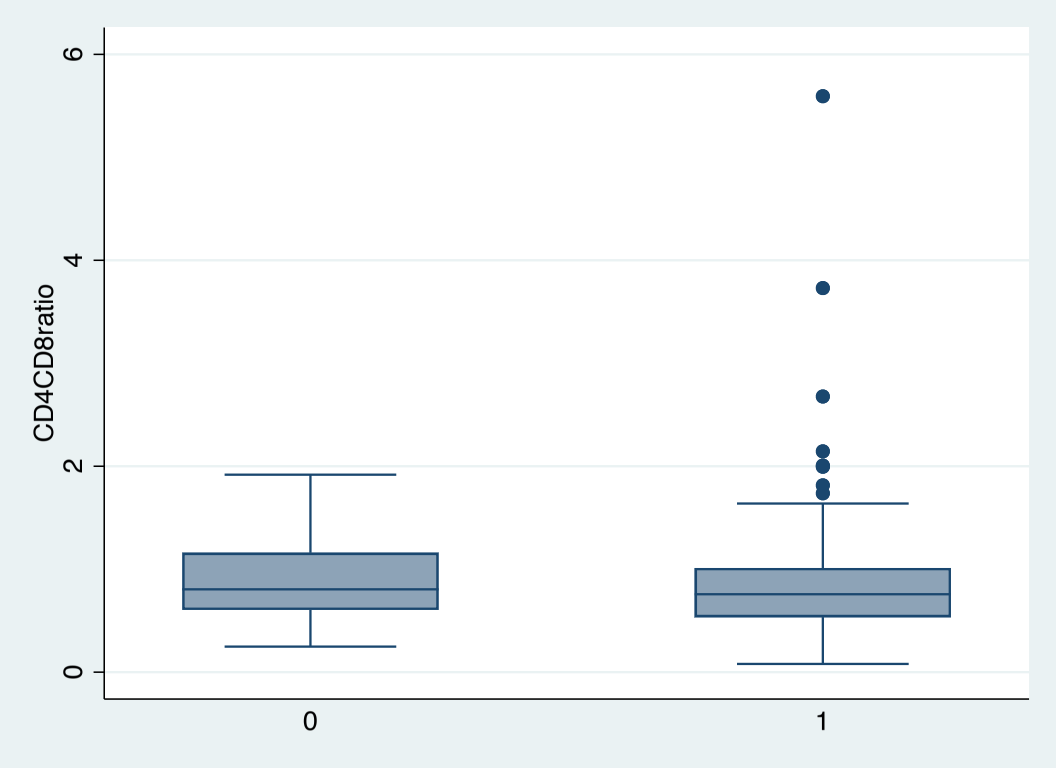

Figure 3.8: Box plot of CD4/CD8 cell ratio by moderate-severe impairment in the domain of Verbal Memory

No significant difference in the CD4/CD8 ratio by impairment in Verbal Memory

Chapter 4

An Exploratory Analysis of CD4/CD8 Cell Ratio among People Living with HIV 40 years and Older in the HAHCS

Sarah Dobbins

Abstract

Chronic inflammation in HIV has been linked to increased morbidity and mortality among PLWH. The CD4/CD8 ratio is an emerging biomarker of inflammation and immune dysregulation in HIV. Though CD4/CD8 ratio is thought to represent a marker of chronic inflammation, it has not been thoroughly investigated and debate remains as to the clinical and biological relevance of a low/inverted CD4/CD8. We explored the association of CD4/CD8 cell ratio with clinical characteristics and other biomarkers of inflammation associated with HIV infection (IL-1b, IL-6, IL-8. IL-10, CRP, INFγ , TNFα , MPO, SAA, and SAP, and monocyte subsets) through latent profile analysis and logistic regression. We found that low CD4/CD8 ratio was associated with Hepatitis C, years living with HIV, and low nadir CD4 T-cell count (≤200 cells/uL). Adjusted regression analysis showed that the lowest CD4/CD8 tertile was associated with high inflammation profile, as measured by established pro-inflammatory serum biomarkers (AOR=1.265, 95% CI: [-0.020, 2.551]). Additionally, the lowest CD4/CD8 tertile was associated with an expanded subset of mature monocytes compared to the highest tertile (β= 0.197, 95% CI: [0.010, 0.384]). The results of this study suggest a mechanistic link between CD4/CD8 ratio, chronic inflammation, and peripheral blood monocytes that may increase risk of HAND and other health outcomes in aging populations of PLWH.

Background

Even when HIV is well-managed, people living with HIV (PLWH) commonly develop aging-related conditions such as cardiovascular disease, cancers, liver disease, and HIV-Associated Neurocognitive Disorders (HAND) decades ahead of their HIV-negative counterparts, and their life expectancy is significantly reduced (Miller et al., 2014). It is thought that virally mediated changes in the immune system can lead to a compression of the aging process, resulting in earlier onset of age-related chronic disease and frailty (OAR Working Group on HIV and Aging, 2012). Additionally, HIV infection is associated with chronic, low-level inflammation throughout the body, which is in turn related to a number of health conditions (Deeks et al., 2013).

Inflammation in HIV-1 infection is marked by certain biomarkers that are activated by HIV-1 in the central nervous system (CNS) and in the periphery. A biomarker is defined by the Food and Drug Administration (FDA)/National Institutes of Health (NIH) Biomarker Working Group as "A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions. Molecular, histologic, radiographic, or physiologic characteristics are types of biomarkers but a biomarker is not an assessment of how an individual feels, functions, or survives." (FDA-NIH Biomarker Working Group, 2016). For example, middle to older adults (45–76 years of age) on combination ART have been found to have 40–60% higher concentrations of interleukin (IL)-6, a strongly pro-inflammatory cytokine, in circulation compared to age-matched controls (Neuhaus et al., 2010). The authors of this study also found that PLWH had increased high sensitivity C-reactive protein (hsCRP), which is another indicator of systemic inflammation (Deeks, 2011). Another example of biomarkers with links to disease in PLWH is the expansion of mature HIV-infected monocytes (CD14+ CD16+), which preferentially transmigrate across the blood-brain barrier and mediate neuroinflammation in the CNS, contributing to neurocognitive impairment (Veenstra et al., 2017).

The CD4/CD8 cell ratio is another emerging biomarker of chronic inflammation and immune dysfunction among people aging with HIV (Lu et al., 2015). Low CD4/CD8 cell ratio (≤ 1.0) is thought to reflect chronic inflammation in PLWH, even when HIV is treated with ART medications (Lu et al., 2015; McBride & Striker, 2017; Saracino et al., 2014; Serrano-Villar & Deeks, 2015). As the HIV virus infects and destroys CD4 T-cells, CD8 T-cells expand in response to the virus. If a person with HIV is treated with ART, they may restore/normalize their CD4 counts and CD8 count declines in response, leading to normalization of the CD4/CD8 cell ratio (Serrano-Villar & Deeks, 2015). For some, despite ART medications and viral suppression, CD8 cells remain elevated and the CD4/CD8 ratios fail to improve even when CD4 cell count has recovered (Cao et al., 2016) (**Figure 4.1**). Evidence demonstrates an overall increased risk of morbidity and mortality in HIV-positive individuals whose ratio fails to normalize (Mussini et al., 2015; Serrano-Villar et al., 2014). In a small number of studies, lower or inverted CD4/CD8 ratio was associated with the development of neurocognitive disorders (Correa et al., 2014; Grauer et al., 2015; Rawson et al., 2015; Vassallo et al., 2017).

Recent studies have identified the following factors may contribute to lower CD4/CD8 ratio: Older age, lower nadir CD4 cell count, detectable HIV viremia, cytomegalovirus (CMV) co-infection, duration of HIV viral suppression, and certain inflammatory biomarkers (hs-CRP, IL-6) (Mussini et al., 2015; Serrano-Villar et al., 2014; Lu et al., 2015). A better understanding of the relationship of this ratio to inflammation and other immunologic biomarkers as well as clinical characteristics will help to guide further research on the role of CD4/CD8 in HIV health outcomes in aging populations and possibly lead to targeted interventions.

In this study, we have three primary objectives: 1) Explore the clinical correlates of varying levels of CD4/CD8 T-cell ratio; 2) Explore the associations of CD4/CD8 T-cell ratio and established pro-inflammatory biomarkers (IL-1b, IL-6, IL-8, IL-10, CRP, INFy, TNFa, MPO, SAP, and SAA); and, 3) Examine the associations of CD4/CD8 T-cell ratio and peripheral blood monocyte concentration. We approach these objectives through an exploratory analysis of adults with HIV in the Public Dataset for the

Hawaii Aging with HIV Cardiovascular Study cohort (HAHCS-PDS), a natural history longitudinal study comprised of PLWH ages 40 and over. Key terms and concepts for this paper are summarized in the glossary (**Table 4.9**).

Methods

Sample

The HAHCS was designed to capture a representative set of individuals in Hawaii living with HIV-1. The sample used for this study aim is the HAHCS-PDS, which is restricted to the older age group (age 40+ years, n=103) from the baseline cohort of the HAHCS. This dataset was made publicly available by the authors at the University of Hawaii at Manoa (Shikuma & Chow, 2016). Participants had evaluations of their medical history, medication/adherence history, a Diagnostic and Statistical Manual of Mental Disorders (DSM)–IV-based substance abuse/dependence inventory, and immunologic and virologic laboratory tests. Recruitment, enrollment, and study procedures have been published in detail elsewhere (V. Valcour, Shikuma, Shiramizu, Watters, Poff, Selnes, Holck, et al., 2004; V. Valcour, Shikuma, Shiramizu, Watters, Poff, Selnes, Grove, et al., 2004).

Inclusion & exclusion criteria. This cohort includes participants living with HIV-1 in Hawaii, USA, age 40 and over and receiving stable antiretroviral therapy (ART) enrolled in 2009. All participants enrolled had demonstrated viral suppression for at least 3 consecutive months. Exclusion criteria include: 1) Diagnosed major psychiatric disorder including bipolar illness, schizophrenia, or active major depression, 2) Head injury with loss of consciousness greater than 1 hour, 3) Opportunistic brain infection, 4) Learning disability, and 5) Major neurologic disease such as multiple sclerosis, major stroke, or current delirium. Certain variables included in original study protocol are not included in the publicly available data (Shikuma & Chow, 2016).

Measures/Variables

Dependent variables. CD4 and CD8 T-cell lymphocyte counts were obtained by standard technique from a local certified reference laboratory. The CD4/CD8 ratio was calculated as the ratio of the absolute count of CD4 T-cells to CD8 T-cells measured at baseline. HIV literature has examined the CD4/CD8 in heterogeneous ways, and there is not yet definitive clinical or population health evidence as to what should be considered a "low ratio." Therefore, we first explored the clinical correlates of ratio cut-points ranging from 0.50 to 1.10. We then operationalized the CD4/CD8 ratio into teriles: 1st tertile was called "low ratio" (Range: 0.129-0.501), the 2nd tertile was called "middle/low ratio" (Range: 0.512-0.837), and the 3rd tertile was called "high/normalized" (Range: 0.838-2.041).

Independent variables. Inflammatory biomarker data is available for n=87 participants in the HAHCS-PDS. The inflammatory biomarkers in this analysis include acute phase reactants and cytokines that play a role in the complex process of inflammation in those with HIV. To measure these proteins, plasma was assayed for biomarkers of systemic inflammation including C-reactive protein (CRP), interleukin (IL)-6, IL-8, IL-10, IL-1*b*, tumor necrosis factor (TNF)-α, serum amyloid A (SAA), serum amyloid P (SAP), myeloperoxidase (MPO), interferon (IFN)-γ . Antibody-coated beads were used in a high sensitivity Milliplex Human cardiovascular disease biomarker panel (Millipore, Billerica, Massachusetts). The minimum detectable concentration of CRP of this assay is 0.001 ng/ml^{-1}. Samples were acquired on a Labscan 200 analyzer (Luminex, Austin, Texas) using Bio-Plex manager software (Bio-Rad, Hercules, California). The average coefficient of variation of all biomarker measurements was less than 10% (Shikuma & Chow, 2016).

Monocyte data was available for n=75 participants in the HAHCS-PDS. Monocytes were measured from frozen peripheral blood mononuclear cell (PBMCs) and then separated into monocyte and non-monocyte fractions, using the Human Monocyte Enrichment Kit without CD16 Depletion (StemCell Technologies, Vancouver, BC, Canada) as per manufacturer's guidelines, which is a negative selection, leaving the CD14 cells untouched. The CD14 monocyte fractions were then separated into CD16+

(activated) and CD16− (non-activated fractions). Activated monocytes (CD14+CD16+) were labeled with the alpha CD16-biotin antibody (BioLegend, San Diego, CA) and magnetically separated by streptavidin magnetic particles (Chemicell). Percentages of classical, intermediate, non-classical, and transitional monocyte subsets were determined based on CD14 and CD16 staining and absolute numbers of each subset were calculated from white blood cells and monocyte percent obtained from available clinical labs performed on each participant.

Covariates. Baseline sociodemographic and clinical variables were collected in a structured interview with each participant or from laboratory tests. Current or past substance dependence was defined as meeting DSM-IV criteria. Medical history was obtained through chart review and self-report. Current and past smoking status was taken from patient report as yes or no responses. Height, weight, systolic and diastolic blood pressure, waist and hip circumference were measured by trained staff. Hepatitis antibodies were tested via standard assays using peripheral blood draw. Duration of HIV infection was defined as elapsed time since first HIV positive test. Reporting of nadir CD4 lymphocyte count, date of first HIV positive test, and risk for HIV were obtained by a structured interview. Plasma viral loads were assessed using Amplicor HIV Monitor Ultrasensitive Assay (Roche Molecular System, Branchburg, NJ).

Statistical Analysis

Sociodemographic and clinical characteristics are reported to describe the cohort. Immunological biomarkers are described using the mean or median and interquartile range for continuous variables, depending on the skewedness of the distribution. Frequency in percentage is used to describe categorical variables. Prior to the proposed analyses, we explored the distribution of the data both qualitatively and statistically. Concentrations of all inflammatory biomarker and monocyte variables were significantly right skewed and violated assumptions of normality on Shapiro–Wilk tests and Q–Q plots. These skewed distributions were therefore transformed to create normally distributed data. Crude (unadjusted)

relationships between the dependent and independent variables were evaluated using chi-squared tests, t-tests, and rank sum tests as appropriate to the data structure. We used an alpha of 0.10 for this exploratory analysis (M. Rubin, 2017). Analyses were completed with Stata (StataCorp, 2017).

Latent Profile Analysis. The target markers for this analysis were those with prior evidence of an association with inflammation in chronic HIV infection and/or HAND (Appay & Sauce, 2008; Aratani, 2018; Deeks, 2011; Pedersen et al., 2013; Subramanian et al., 2012). Latent profile analysis (LPA) was used to examine latent subgroups among nine inflammatory biomarkers. This method provides a person-centered approach to mixture modeling to identify latent subgroups or profiles within a study sample based on patterns of responses to observed variables, or in our case inflammatory biomarkers (Weller et al., 2020). These groups are unobserved but inferred from a set of continuous variables and predictors. We reported on key aspects of our data that may influence power due to low sample size, and took steps to improve the solution and model selection. Using more indicators can help to improve model accuracy with sparse data (Wurpts & Geiser, 2014), therefore we included 10 indicators in the LPA. Furthermore, sample size has been shown to have little effect on the goodness of fit tests when the degree of separation between classes is high (Tein et al., 2013). We calculated and reported the degree of separation (Mahalanobis distance [*D]* and Entropy) in our data, which supports the validity of our findings.

We estimated latent profile groups using generalized structural equation modeling (GSEM) with three covariates: Undetectable viral load status, Hepatitis C antibody reactivity, and Hepatitis B antibody reactivity. These covariates were chosen because they may influence the degree of inflammation in the body. Additionally, simulation studies have shown that adding such predictors may improve the fit of the model because the covariates provide more information for the estimation process (Wurpts & Geiser, 2014).

LPA is based on a probabilistic model, which means that it models the probability of each participant belonging to a certain latent profile/class. The LPA model with the most parsimonious solution is chosen based on fit indicators of interest: the Akaike information criterion (AIC), the Bayesian

information criterion (BIC), entropy, and the likelihood ratio test (LRT) (Conley, 2017). AIC and BIC are indications of model fit, with smaller values indicating better fit. Some consider BIC to be the superior criterion (Nylund et al., 2007). The LRT is used to statistically compare the fit of the *k* cluster solution with that of the $k - 1$ class solution. When fit no longer statistically improves ($p > 0.05$) with the addition of a new class, the solution with the smaller number of classes is generally accepted. Entropy is an estimate of how distinct each profile is from one another. Entropy values over 0.8 indicate a good separate of the latent classes (Celeux & Soromenho, 1996). Though no preset criteria exist for deeming model fit acceptable, the cluster solution that provides the lowest AIC and BIC and the highest entropy value that also conforms to scientific theory is generally considered the best solution (Weller et al., 2020). After LPA model selection, using predicted marginal probabilities, each participant was assigned to one of the identified inflammation profiles.

Regression Analysis. The predicted profile groups from the LPA were used in logistic regression models to test the association of the identified profiles with CD4/CD8 cell ratio at given levels (0.50 - 1.10) while adjusting for covariates. At each level, the marginal probability of being in the high inflammation vs low inflammation group is reported.

We also examined the association between CD4/CD8 and concentration of four peripheral blood monocyte subsets: 1) Classical monocytes (CD14++CD16-), 2) Intermediate monocytes (CD14++CD16+), 3) "Transitional" monocytes (CD14dimCD16-); 4) Non-classical/mature monocytes (CD14low/+CD16++). We operationalized CD4/CD8 using the tertiles because we could not verify the assumptions for linear regression (treating both variables as continuous). For our regression analysis, we estimated the coefficient for change in log monocyte concentration using the highest (3^{rd}) tertile as the referent. Therefore, we report the following parameters: Lowest (1^{st}) *versus* highest/normalized *(*3^{rd}) tertile and middle (2^{nd}) v*ersus* highest/normalized (3^{rd}) tertile (**Figure 4.2**). We also report the marginal mean of the log monocyte subset concentration in each CD4/CD8 tertile.

Confounders for regression were chosen using a combination of *a priori* selection from current scientific evidence and selection based on bivariate analysis of our sample. For regression analysis of high and low inflammation profiles, confounders included age, male gender, and BMI. For regression analysis of monocyte concentration, confounders included age, years living with HIV, undetectable viral load status, male gender, and smoking status. We excluded nadir CD4 count as a covariate from regression models to avoid risk of bias from co-linearity, as nadir CD4 cell count has a strong correlation with current CD4 cell count in our data (r=0.56) and in extant literature (Lu et al., 2015). To address issues related to bias by HIV treatment era, we examined differences in CD4/CD8 ratio by era of HIV seroconversion. We found no differences in mean CD4 or CD8 cell count by treatment era (**Appendix 4.B, Figure 4.9-4.10**). Therefore, no adjustment was made for HIV treatment era in our final analyses.

Results

The average age of the sample was 51.5 years (SD 7.4), 85.5% were male and 58.65% were white. Eighty-four percent (84%) of the sample reported a substance use history, though substance use data was missing for nearly a third (31.1%) of the sample. The majority (72.46%) had been living with HIV for 10 or more years or longer, and 37.27% of data was missing for this variable. Though 64.1% reported ever smoking, only 24.3% reported current smoking. Almost 15% had a history of Hepatitis C infection and 66.4% had a nadir CD4 cell count below 200 cells/uL. Eighty-six percent (86.0%) had an undetectable viral load. Additional sample characteristics are summarized in **Table 4.1**.

Figure 4.3 shows the relationship between absolute CD4 and CD8 T-cells and log CD4/CD8 ratio, plotted as a quadratic function. The median CD4/CD8 cell count of the sample was 0.686, with an IQR of 0.471 to 1.742. Because there remains debate about what CD4/CD8 cut-points are clinically and/or biologically most relevant (Bruno et al., 2017), we explored sample characteristics using CD4/CD8 cut-points from 0.50 to 1.10 by tenths. In looking at **Figures 4.4 and 4.5** qualitatively, we saw little variation between cut-points in the mean age, proportion with an undetectable viral load, and proportion with history of Hepatitis C infection; However, did we did observe lower proportions of people who ever

smoked at CD4/CD8 ratio cut-points of 0.8 and above. Additionally, the proportion of people with a low nadir CD4 cell count (≤200 cells/uL) decreased as ratio cut-point increased (**Figures 4.4-4.5**).

We then explored clinical and sociodemographic variables with CD4/CD8 ratio by tertile, with the highest (3^{rd}) tertile as the referent group. CD4/CD8 ratio ranged from 0.129 to 0.501 in the lowest (1^{st}) tertile, 0.512 to 0.837 in the middle (2^{nd}) tertile, and 0.838 to 2.041 in the highest (3^{rd}) tertile (**Figure 4.2**). There was a higher odds of nadir CD4 cell count ≤200 cells/uL in the lowest compared to the highest tertile (OR: 1.803, 95% CI: [0.523, 3.082]). Additionally, those with CD4/CD8 ratio in the lowest (1^{st}) tertile had significantly more years living with HIV (β=5.407, 95% CI: [1.024, 9.791]). Notably, smoking status, past or current Hepatitis C, and viral load was not statistically significant between tertiles.

Latent Profiles of Inflammation

Results from the LPA supported the finding of two distinct profiles of inflammatory biomarkers among the HAHCS-PDS cohort. **Table 4.4** presents LPA model fit indices for different profile models. As shown in **Table 4.4**, the BIC and Entropy values suggested a two- profile solution provided the best fit. The AIC did not align with these indices, but because the BIC is considered a more reliable fit statistic in LPA, we selected a two-profile model. Furthermore, the Mahalanobis distance (D) for the three profile model suggested low degree of separation between classes 2 and 3 ($D_{2,3}$= 1.03; $D_{1,2=}$ 3.74). In contrast, the distance between the two-profile solution showed a very large degree of separation between profiles ($D_{1,2}$ = 2.133).

After we identified the best fitting solution as that with two-profiles, we then assigned each case to a specific profile based on their posterior profile membership probabilities. 23.2% of the sample was predicted to be in the first profile and the rest were in the second profile (**Table 4.5**). We then began to interpret the two profiles in the context of scientific theory. For each biomarker, higher values were noted to be in the second profile, which we named the "high-inflammation" profile. Likewise, the first profile was named the "low inflammation" profile to indicate the relatively lower values of each biomarker.

Figure 4.6 graphically represents the marginal means of each biomarker in the high and low profiles. In unadjusted analysis, we found that high inflammation profile was associated with older age, male gender, higher BMI, and higher CD8 T-Cell count. High inflammation was also associated with HCV history, however this was likely because HCV status used as a covariate for the LPA (**Table 4.3**).

We then began to explore the relationship of CD4/CD8 ratio to the inflammation profiles. **Figure 4.7** displays the proportion of the sample below each CD4/CD8 ratio threshold in the low and high inflammation profile groups. Among those in the high inflammation group, there is a consistently higher proportion of the sample below each CD4/CD8 cut-point. For example, 81.7% (CI: 69.6% - 89.6%) of those with high inflammation had an inverted ratio, whereas only 65.2% (CI: 44.0% - 81.8%) of those with low inflammation had an inverted ratio. Similarly, 61.7% (CI: 48.7%-73.2%) of those with high inflammation had a low ratio compared to just 26.1% (CI: 12.1% - 47.6%) of those with low inflammation. When we examined inflammation profiles by CD4/CD8 tertile, adjusting for age, gender, and BMI, we found increased odds of high inflammation among those in the (1st) tertile versus the highest (3^{rd}) tertile (AOR=1.248, 95% CI: -0.020, 2.551). There was not a significant difference in odds of high inflammation profile for those in the middle (2^{nd}) tertile versus the highest (3^{rd}) tertile (**Table 4.6**).

Peripheral Monocyte Subsets

We examined the change in monocyte concentration that corresponded to increasing CD4/CD8 ratio tertiles. In the lowest (1^{st}) compared to the highest (3^{rd}) tertile, there was a 0.197 higher log concentration of mature monocytes (95% CI: 0.010, 0.384). The difference in mature monocytes between the highest (3^{rd}) and middle (2^{nd}) tertile was not significant. We did not see significant differences by tertile in any other peripheral blood monocyte subsets **(Table 4.7).**

Discussion

This study was an exploratory analysis of CD4/CD8 in a cohort of PLWH ages 40 and over. We sought to investigate the association of CD4/CD8 with biomarkers of inflammation, monocytes subsets,

and other clinical characteristics and conditions. Adjusted regression analyses showed that participants in the lowest (1st) CD4/CD8 tertile (Median 0.3458, Range: 0.129 - 0.501) had increased odds of being in the high inflammation profile. Additionally, in this cohort, CD4/CD8 ratio the lowest (1st) tertile was associated with an expanded subset of mature monocytes. Markers of chronic inflammation in HIV have been linked to increased morbidity and mortality among PLWH (Serrano-Villar & Deeks, 2015) and is considered an accurate predictor of non-AIDS events (Bruno et al., 2017). Though CD4/CD8 is thought to represent a marker of chronic inflammation, this is still an emerging area of scientific investigation. Our study adds to the literature with the finding that low CD4/CD8 is associated with higher levels of soluble pro-inflammatory biomarkers and an expanded subset of mature monocytes in a cohort of PLWH ages 40 and over.

In the general population, inverted CD4/CD8 is considered a surrogate marker of immune senescence and is found in approximately 5% of the healthy, age-adjusted population (Amadori et al., 1995); However, among PLWH, an inverted CD4/CD8 (<1.0) is much more prevalent. This has led to an ongoing debate about whether there may be a more informative and/or clinically relevant threshold for CD4/CD8 among PLWH (Bruno et al., 2017; Saracino et al., 2014). For example, in a large prospective Canadian study, only 7.2% of participants achieved a normalized (>1.0) CD4/ CD8 ratio within a median of three years after ART initiation (Leung et al., 2013). In our analysis of middle-aged and older adults who had been living with HIV for a mean of 14.9 years, CD4/CD8 was operationalized into tertiles to explore the clinical correlates of this biomarker. We found low (1st tertile) CD4/CD8 ratio, which ranged from 0.129 to 0.501, was associated with more years living with HIV and low nadir CD4 T-cell count; however, those in the middle tertile, which ranged from 0.512 to 0.837, did not show this association. Similarly, we saw that the lowest (1st) tertile, but not the middle (2nd) tertile, to be associated with higher concentration of mature monocyte as well as increased odds of having a high inflammation profile. Taken together, this evidence suggests that CD4/CD8 ratio less than 0.50 may provide additional clinically relevant information about risk of health outcomes among middle-aged adults living with HIV.

In this study, we used LPA to assess soluble biomarkers of inflammation and found that our sample fell into two distinct profiles: those with lower and higher levels of inflammatory biomarkers. These inflammation profiles reflect the concentration of peripheral pro-inflammatory cytokines, with particularly high concentrations of SAP, SAA, and CRP. Additionally, when we looked at these biomarkers in single, pairwise analyses we saw that TNFα, MPO, and SAP were significantly associated with CD4/CD8 cell ratio (**Appendix 4.A, Table 4.10**). These findings link a higher inflammation profile among middle-aged and older PLWH to certain cytokines with a known role in the etiology of HAND. TNFα has been implicated in risk for HAND due to its role in neuronal cell death (Bortolato et al., 2015; Brabers & Nottet, 2006). Additionally, TNFα co-operates with several other pro-inflammatory mediators to enhance toxic effects and enhances permeability if the blood brain barrier (Brabers & Nottet, 2006). Serum amyloid A (SAA, serum amyloid P (SAP) and CRP are considered acute phase reactants and markers of active inflammation (Lau et al., 2006). While serum amyloid has not been extensively studied in connection neuroinflammation in HIV, CRP has been linked to HIV-associated cognitive impairment (Rubin et al., 2018). One study (Rubin 2020) examined the peripheral immune responses implicated in neuroinflammatory processes among women living with HIV. They identified IL-6 and SAA (among others) in a neuroinflammatory profile, characterized by leukocyte recruitment to the brain, while CRP and IL-10 (among others) was linked to T-cell recruitment to the brain. This study determined that a leukocyte migration immune profile may be a major contributor to immune dysfunction in HIV, and is known to contribute to chronic neuroinflammation during HIV infection despite viral suppression with ART . (Rubin 2020)

We found that higher inflammation profile was associated with increased age, male gender, higher BMI, and the lowest CD4/CD8 ratio tertile. In a study by Saracino et al. (2014), CD4/CD8 cell ratio <0.90 was not associated with chronic inflammation measured by IL-6, high-sensitivity (hs)CRP, and D-dimer levels. These authors state that their chosen biomarkers may not accurately reflect the concept of inflammation. Furthermore, Saracino et al. (2014) suggest that lower cutoffs, such as those

used in the present study, may be more discriminative in the population of PLWH. Our study examined IL-6, CRP, and several other markers of inflammation in pairwise analyses (**Appendix 4.A, Table 4.10, Figure 4.8**), and found that only TNFα and SAP were correlated on CD4/CD8 ratio. In this study, when biomarkers were examined as latent profiles, rather than stand-alone cytokines, the lowest tertile of CD4/CD8 ratio was associated with a profile signaling higher peripheral inflammation. While certain biomarkers may have driven this relationship, the use of LPA shows that inflammation may be seen as a complex and dynamic system, and the CD4/CD8 ratio may be a useful indicator of the overall state of these inflammatory biomarkers.

In PLWH, monocytes are composed of three distinct phenotypic subsets based on CD14 and CD16 expression: Classical (CD14++CD16−), Intermediate (CD14++CD16+), and mature/non-classical (CD14+CD16++ and CD14+CD16+) subsets. Classical monocytes are the first subset to appear in peripheral blood, followed by intermediate, and then they develop into non-classical and mature monocytes (Valcour et al., 2010). Monocytes are noted to be chronically activated during HIV infection. Mature HIV-infected monocytes (CD14+ CD16+) preferentially transmigrate across the blood-brain barrier. These mature monocytes mediate neuroinflammation in the CNS and can cause neuronal damage, contributing to neurocognitive impairment regardless of ART status (Veenstra et al., 2017). The current body of evidence has established that activated monocytes in HIV infection are some of the main factors in the development of cardiovascular disease, neurocognitive disorders, and overall aging of the innate immune system. Specifically, a previous study in the HAHCS cohort found mature monocytes were associated with neurocognitive deficits (Valcour, Shikuma, Watters, & Sacktor, 2004).

A small number of studies have linked the CD4/CD8 ratio biomarker to risk of HAND (Correa et al., 2014; Grauer et al., 2015; Rawson et al., 2015; Vassallo et al., 2017), but none have provided specific evidence about potential biological pathways or mechanisms for this risk. Our study suggests a link between CD4/CD8 ratio and systemic inflammation—particularly with inflammatory biomarkers that are associated with neurocognitive disorders, such as TNFα and mature monocytes. The results of this study

suggest a mechanistic link between CD4/CD8 ratio, chronic inflammation, and PBMCs that may increase risk of HAND.

Limitations

Limitations to the internal validity of this study include the use of secondary data, in which the data collection was not designed to answer our particular research questions. Additionally, the data do not allow us to estimate causal relationships. Data on the relationship of inflammation and cognition could not be tested because there were no neurocognitive variables included in the PDS. The validity of the statistical conclusions in this study were impacted by the sample size. We may have low power due to the sample size for our latent profile analysis; However, we report on key aspects of our data that may influence power and take steps to improve the solution and model selection. We calculated and reported the degree of separation in our data, which supports the validity of our findings. We were not able to control for the effect of CMV exposure or genetic factors on the CD4/CD8 ratio, therefore this should be explored in future research. The external validity of this study may be limited, as this sample excluded those diagnosed major psychiatric disorder and anyone who was not virally suppressed. Additionally, 65.4% of the sample was diagnosed in the pre-ART era. We examined the possibility of bias by ART-era in the dependent variable in a bias analysis, and found this to be less likely.

Summary and Conclusions

CD4/CD8 ratio likely reflects a complex phenotype, and more information is needed about how and why CD4/CD8 impacts risk for morbidity and mortality in aging and HIV. Our exploratory analysis examined the association of the CD4/CD8 ratio with inflammation profile and monocyte subsets among adults living with HIV 40 and older. We found that CD4/CD8 ratio in the lowest tertile (range: 0.129 to 0.501), but not the middle tertile, was associated with a higher inflammation profile and expanded subset of peripheral mature monocytes. The results of this study suggest a mechanistic link between CD4/CD8 ratio, chronic inflammation, and peripheral blood monocytes that may increase risk of HAND and other

health outcomes in aging populations of PLWH. We concluded that the relationships between these biomarkers of inflammation remains an important subject for further investigation, and the particular utility of low CD4/CD8 ratio (≤0.50) should be considered for future clinical and population health research.

References

Amadori, A., Zamarchi, R., Silvestro, G. D., Forza, G., Cavatton, G., Danieli, G. A., Clementi, M., & Chieco-Bianchi, L. (1995). Genetic control of the CD4/CD8 T-cell ratio in humans. *Nature Medicine*, *1*(12), 1279. https://doi.org/10.1038/nm1295-1279

Appay, V., & Sauce, D. (2008). Immune activation and inflammation in HIV-1 infection: Causes and consequences. *The Journal of Pathology*, *214*(2), 231–241. https://doi.org/10.1002/path.2276

Aratani, Y. (2018). Myeloperoxidase: Its role for host defense, inflammation, and neutrophil function. *Archives of Biochemistry and Biophysics*, *640*, 47–52. https://doi.org/10.1016/j.abb.2018.01.004

Bortolato, B., Carvalho, A. F., Soczynska, J. K., Perini, G. I., & McIntyre, R. S. (2015). The involvement of TNF-α in cognitive dysfunction associated with major depressive disorder: An opportunity for domain specific treatments. *Current Neuropharmacology*, *13*(5), 558–576. PsycINFO. https://doi.org/10.2174/1570159X13666150630171433

Brabers, N. a. C. H., & Nottet, H. S. L. M. (2006). Role of the pro-inflammatory cytokines TNF-alpha and IL-1beta in HIV-associated dementia. *European Journal of Clinical Investigation*, *36*(7), 447–458. https://doi.org/10.1111/j.1365-2362.2006.01657.x

Bruno, G., Saracino, A., Monno, L., & Angarano, G. (2017). The Revival of an "Old" Marker: CD4/CD8 Ratio. *AIDS Reviews*, *19*(2), 81–88.

Cao, W., Mehraj, V., Kaufmann, D. E., Li, T., & Routy, J.-P. (2016). Elevation and persistence of CD8 T-cells in HIV infection: The Achilles heel in the ART era. *Journal of the International AIDS Society*, *19*(1), 20697. https://doi.org/10.7448/IAS.19.1.20697

Conley, S. (2017). Symptom Cluster Research with Biomarkers and Genetics Using Latent Class Analysis. *Western Journal of Nursing Research*, *39*(12), 1639–1653. https://doi.org/10.1177/0193945916679812

Correa, B. L., Ornaghi, A. P., Muller, G. C., Engroff, P., Lopes, R. P., Filho, I. G. da S., Bosch, J. A., Bonorino, C., & Bauer, M. E. (2014). The Inverted CD4:CD8 Ratio Is Associated with

Cytomegalovirus, Poor Cognitive and Functional States in Older Adults. *Neuroimmunomodulation*, *21*(4), 206–212. https://doi.org/10.1159/000356827

Deeks, S. G. (2011). HIV Infection, Inflammation, Immunosenescence, and Aging. *Annual Review of Medicine*, *62*(1), 141–155. https://doi.org/10.1146/annurev-med-042909-093756

Deeks, S. G., Tracy, R., & Douek, D. C. (2013). Systemic Effects of Inflammation on Health during Chronic HIV Infection. *Immunity*, *39*(4), 633–645. https://doi.org/10.1016/j.immuni.2013.10.001

FDA-NIH Biomarker Working Group. (2016). *BEST (Biomarkers, EndpointS, and other Tools) Resource*. Food and Drug Administration (US). http://www.ncbi.nlm.nih.gov/books/NBK326791/

Grauer, O. M., Reichelt, D., Grüneberg, U., Lohmann, H., Schneider-Hohendorf, T., Schulte-Mecklenbeck, A., Gross, C. C., Meuth, S. G., Wiendl, H., & Husstedt, I. W. (2015). Neurocognitive decline in HIV patients is associated with ongoing T-cell activation in the cerebrospinal fluid. *Annals of Clinical and Translational Neurology*, *2*(9), 906–919.

Lau, B., Sharrett, A. R., Kingsley, L. A., Post, W., Palella, F. J., Visscher, B., & Gange, S. J. (2006). C-Reactive Protein Is a Marker for Human Immunodeficiency Virus Disease Progression. *Archives of Internal Medicine*, *166*(1), 64–70. https://doi.org/10.1001/archinte.166.1.64

Leung, V., Gillis, J., Raboud, J., Cooper, C., Hogg, R. S., Loutfy, M. R., Machouf, N., Montaner, J. S. G., Rourke, S. B., Tsoukas, C., Klein, M. B., & CANOC Collaboration. (2013). Predictors of CD4:CD8 ratio normalization and its effect on health outcomes in the era of combination antiretroviral therapy. *PloS One*, *8*(10), e77665. https://doi.org/10.1371/journal.pone.0077665

Lu, W., Mehraj, V., Vyboh, K., Cao, W., Li, T., & Routy, J.-P. (2015). CD4:CD8 ratio as a frontier marker for clinical outcome, immune dysfunction and viral reservoir size in virologically suppressed HIV-positive patients. *Journal of the International AIDS Society*, *18*(1), 20052. https://doi.org/10.7448/IAS.18.1.20052

McBride, J. A., & Striker, R. (2017). Imbalance in the game of T cells: What can the CD4/CD8 T-cell ratio tell us about HIV and health? *PLOS Pathogens*, *13*(11), e1006624. https://doi.org/10.1371/journal.ppat.1006624

Miller, C. J., Baker, J. V., Bormann, A. M., Erlandson, K. M., Huppler Hullsiek, K., Justice, A. C., Neuhaus, J., Paredes, R., Petoumenos, K., & Wentworth, D. (2014). Adjudicated morbidity and mortality outcomes by age among individuals with HIV infection on suppressive antiretroviral therapy. *PloS One*, *9*(4), e95061.

Mussini, C., Lorenzini, P., Cozzi-Lepri, A., Lapadula, G., Marchetti, G., Nicastri, E., Cingolani, A., Lichtner, M., Antinori, A., Gori, A., & Monforte, A. d'Arminio. (2015). CD4/CD8 ratio normalisation and non-AIDS-related events in individuals with HIV who achieve viral load suppression with antiretroviral therapy: An observational cohort study. *The Lancet HIV*, *2*(3), e98–e106. https://doi.org/10.1016/S2352-3018(15)00006-5

Neuhaus, J., Jacobs, D. R., Baker, J. V., Calmy, A., Duprez, D., La Rosa, A., Kuller, L. H., Pett, S. L., Ristola, M., Ross, M. J., Shlipak, M. G., Tracy, R., & Neaton, J. D. (2010). Markers of inflammation, coagulation, and renal function are elevated in adults with HIV infection. *The Journal of Infectious Diseases*, *201*(12), 1788–1795. https://doi.org/10.1086/652749

OAR Working Group on HIV and Aging. (2012). HIV and Aging: State of Knowledge and Areas of Critical Need for Research. *Journal of Acquired Immune Deficiency Syndromes (1999)*, *60*(Suppl 1), S1-18. https://doi.org/10.1097/QAI.0b013e31825a3668

Pedersen, K. K., Pedersen, M., Gaardbo, J. C., Ronit, A., Hartling, H. J., Bruunsgaard, H., Gerstoft, J., Ullum, H., & Nielsen, S. D. (2013). Persisting inflammation and chronic immune activation but intact cognitive function in HIV-infected patients after long-term treatment with combination antiretroviral therapy. *J Acquir Immune Defic Syndr*, *63*(3), 272–279. https://doi.org/10.1097/QAI.0b013e318289bced

Rawson, T. M., Dubb, S., Pozniak, A., Kelleher, W. P., Mandalia, S., Gazzard, B., & Barber, T. J. (2015). Assessing the role of peripheral CD8 T cells in neurocognitive impairment in HIV-infected men

who have sex with men: Data from the MSM Neurocog Study. *Int J STD AIDS*, *26*(2), 128–132. https://doi.org/10.1177/0956462414531934

Rubin, L. H., Benning, L., Keating, S. M., Norris, P. J., Burke-Miller, J., Savarese, A., Kumanan, K. N., Awadalla, S., Springer, G., Anastos, K., Young, M., Milam, J., Valcour, V. G., Weber, K. M., & Maki, P. M. (2018). Variability in C-reactive protein is associated with cognitive impairment in women living with and without HIV: A longitudinal study. *Journal of Neurovirology*, *24*(1), 41–51. https://doi.org/10.1007/s13365-017-0590-4

Rubin, M. (2017). Do p Values Lose Their Meaning in Exploratory Analyses? It Depends How You Define the Familywise Error Rate. *Review of General Psychology*, *21*(3), 269–275. https://doi.org/10.1037/gpr0000123

Saracino, A., Bruno, G., Scudeller, L., Volpe, A., Caricato, P., Ladisa, N., Monno, L., & Angarano, G. (2014). Chronic Inflammation in a Long-Term Cohort of HIV-Infected Patients According to the Normalization of the CD4:CD8 Ratio. *AIDS Research and Human Retroviruses*, *30*(12), 1178–1184. https://doi.org/10.1089/aid.2014.0080

Serrano-Villar, S., & Deeks, S. G. (2015). CD4/CD8 ratio: An emerging biomarker for HIV. *The Lancet HIV*, *2*(3), e76–e77. https://doi.org/10.1016/S2352-3018(15)00018-1

Serrano-Villar, S., Sainz, T., Lee, S. A., Hunt, P. W., Sinclair, E., Shacklett, B. L., Ferre, A. L., Hayes, T. L., Somsouk, M., Hsue, P. Y., Natta, M. L. V., Meinert, C. L., Lederman, M. M., Hatano, H., Jain, V., Huang, Y., Hecht, F. M., Martin, J. N., McCune, J. M., … Deeks, S. G. (2014). HIV-Infected Individuals with Low CD4/CD8 Ratio despite Effective Antiretroviral Therapy Exhibit Altered T Cell Subsets, Heightened CD8+ T Cell Activation, and Increased Risk of Non-AIDS Morbidity and Mortality. *PLOS Pathogens*, *10*(5), e1004078. https://doi.org/10.1371/journal.ppat.1004078

Shikuma, C., & Chow, D. (2016). *Hawaii Aging with HIV Cardiovascular Study, 2009-2014*. Inter-university Consortium for Political and Social Research [distributor]. https://doi.org/10.3886/ICPSR36389.v1

StataCorp. (2017). *Stata Statistical Software: Release 15.* StataCorp LLC.

Subramanian, S., Tawakol, A., Burdo, T. H., Abbara, S., Wei, J., Vijayakumar, J., Corsini, E., Abdelbaky, A., Zanni, M. V., Hoffmann, U., Williams, K. C., Lo, J., & Grinspoon, S. K. (2012). Arterial Inflammation in Patients With HIV. *JAMA*, *308*(4), 379–386. https://doi.org/10.1001/jama.2012.6698

Valcour, V. G., Shikuma, C. M., Watters, M. R., & Sacktor, N. C. (2004). Cognitive impairment in older HIV-1-seropositive individuals: Prevalence and potential mechanisms. *AIDS (London, England)*, *18 Suppl 1*, S79-86.

Valcour, V. G., Shiramizu, B. T., & Shikuma, C. M. (2010). HIV DNA in circulating monocytes as a mechanism to dementia and other HIV complications. *Journal of Leukocyte Biology*, *87*(4), 621–626. https://doi.org/10.1189/jlb.0809571

Valcour, V., Shikuma, C., Shiramizu, B., Watters, M., Poff, P., Selnes, O. A., Grove, J., Liu, Y., Abdul-Majid, K.-B., Gartner, S., & Sacktor, N. (2004). Age, apolipoprotein E4, and the risk of HIV dementia: The Hawaii Aging with HIV Cohort. *Journal of Neuroimmunology*, *157*(1–2), 197–202. https://doi.org/10.1016/j.jneuroim.2004.08.029

Valcour, V., Shikuma, C., Shiramizu, B., Watters, M., Poff, P., Selnes, O., Holck, P., Grove, J., & Sacktor, N. (2004). Higher frequency of dementia in older HIV-1 individuals: The Hawaii Aging with HIV-1 Cohort. *Neurology*, *63*(5), 822–827.

Vassallo, M., Fabre, R., Durant, J., Lebrun-Frenay, C., Joly, H., Ticchioni, M., DeSalvador, F., Harvey-Langton, A., Dunais, B., Laffon, M., Cottalorda, J., Dellamonica, P., & Pradier, C. (2017). A decreasing CD4/CD8 ratio over time and lower CSF-penetrating antiretroviral regimens are associated with a higher risk of neurocognitive deterioration, independently of viral replication. *J Neurovirol*, *23*(2), 216–225. https://doi.org/10.1007/s13365-016-0490-z

Veenstra, M., Williams, D. W., Calderon, T. M., Anastos, K., Morgello, S., & Berman, J. W. (2017). Frontline Science: CXCR7 mediates CD14(+)CD16(+) monocyte transmigration across the blood

brain barrier: A potential therapeutic target for NeuroAIDS. *J Leukoc Biol*, *102*(5), 1173–1185. https://doi.org/10.1189/jlb.3HI0517-167R

Weller, B. E., Bowen, N. K., & Faubert, S. J. (2020). Latent Class Analysis: A Guide to Best Practice. In *Journal of Black Psychology* (Vol. 46, Issue 4, pp. 287–311). https://journals.sagepub.com/doi/abs/10.1177/0095798420930932

Wurpts, I. C., & Geiser, C. (2014). Is adding more indicators to a latent class analysis beneficial or detrimental? Results of a Monte-Carlo study. *Frontiers in Psychology*, *5*, 920. https://doi.org/10.3389/fpsyg.2014.00920

Table 4.1: Sociodemographic Characteristics (n=103)	
	Mean (SD) or n (%)
Age, mean (SD)	51.55 (7.4)
Gender, n (%)	
Male	77 (85.5%)
Female	13 (14.4%)
Non-white racial group, n (%)	43 (41.4%)
Racial Group, n (%)	
White	61 (58.65%)
Black/African American	4 (3.85%)
Native American/Native Alaskan	2 (1.92%)
Native Hawaiian/Pacific Islander	9 (8.65%)
Asian	4 (3.85%)
More than one race	14 (13.46%)
Unknown	8 (7.69%)
Missing	2 (1.92%)
Substance Use History, n (%)	71 (64.55%)
Missing	35 (31.82%)
Years living with HIV, n (%)	
1-5 years	8 (11.59%)
5-10 years	11 (15.94%)
10+ years	50 (72.46%)
Missing	41 (37.27%)
HIV Diagnosis prior to 1996, n (%)	51 (65.4%)
Smoking, n (%)	
Smoking ever	66 (64.1%)
Smoking currently	25 (24.3%)
BMI	
BMI (score), mean (SD)	26.23 (3.9)
High BMI (>= 25), n (%)	65 (59.09%)
Metabolic Syndrome, n (%)	19 (18.3%)
History of Diabetes, n (%)	11 (10.6%)
History of HCV Infection, n (%)	15 (14.6%)
History of HBV Infection, n (%)	29 (28.2%)
Low Nadir CD4 cell count (≤ 200 cells/uL), n (%)	69 (66.4%)
CD4 T-cell lymphocytes, mean (SD)	505.99 (236.77)
CD8 T-cell lymphocytes, median (IQR)	693 (693- 1431)

	Mean (SD) or n (%)
Undetectable viral load, n (%)	89 (85.6%)
CD4/CD8 cell ratio, median (IQR)	
Overall	0.6857 (0.471 - 1.7421)
1st Tertile	0.32301 (0.2460, 0.4901)
2nd Tertile	0.6966377 (0.6006 - 0.8051)
3rd Tertile	1.1428 (0.9724 - 1.7421)
Serum Cytokines (n=87), median (IQR)	
IL-1 beta	0.305 (0.275 - 0.610)
IL-6	1.63 (0.97 - 7.46)
IL-8	3.58 (2.81 - 9.94)
IL-10	2.22 (0.70 - 16.79)
CRP	8158.04 (3359.78 - 266488.00)
INF-gamma	0.70 (0.39 - 4.07)
TNF-alpha	1.144 (0.641 - 2.154)
SAA	11599.2 (3232.59- 1000000.00)
MPO	15.76 (10.5 - 51.67)
Monocyte subsets (n=75), mean (SD)	
cd14++cd16- (Classical)	8.491 (0.141)
cd14++cd16+ (Intermediate)	6.730 (0.515)
cd14+cd16- (Transitional)	7.781 (0.232)
cd14+cd16+ cd14-cd16+ (Non-classical)	7.379 (0.286)

Table 4.2: Sociodemographic and Clinical characteristics by CD4/CD8 Ratio Tertile (n=89)				
	CD4/CD8 Tertiles			
	Low (n=30)	Middle (n=30)	High/Normalized (n=29)	
	N (%) or mean (SD)/median (IQR)			*P*-value
Age	52.0 (7.3)	52.2 (7.0)	51.9 (8.3)	0.945
Male Gender	27 (90%)	25 (83.3%)	24 (82.8%)	0.679
Racial Group				0.140
White	15 (50%)	22 (73.3%)	16 (55.2%)	
Black/African American	4 (13.3%)	0 (0%)	0 (0%)	
Native American/Native Alaskan	1 (3.3%)	0 (0%)	0 (0%)	
Native Hawaiian/Pacific Islander	2 (6.7%)	1 (3.3%)	3 (10.3%)	
Asian	0 (0%)	2 (6.7%)	2 (6.9%)	
More than one race	4 (13.3%)	3 (10.0%)	4 (13.7%)	
Unknown	4 (13.3%)	2 (6.7%)	4 (13.7%)	
Non-white racial group	15 (50%)	8 (26.67%)	13 (44.8%)	0.155
Substance Use History	20 (100%)	18 (90%)	18 (90%)	0.343
Smoking, n (%)				
Smoking Ever	20 (66.7%)	16 (55.2%)	18 (62.1%)	0.660
Smoking Currently	7 (23.3%)	6 (20.7%)	8 (27.6%)	0.824
BMI (score)	26.60 (4.25)	25.38 (3.68)	26.32 (4.6918)	0.794
High BMI (≥ 25)	20 (66.67%)	16 (53.33%)	17 (58.62%)	0.570
Metabolic Syndrome	5 (16.7%)	8 (26.6%)	5 (17.2%)	0.558
History of HCV infection	4 (13.3%)	1 (3.5%)	7 (24.1%)	0.100
History of HBV infection	9 (30%)	9 (31.0%)	9 (31.0%)	0.995
History of Diabetes	2 (6.7%)	4 (13.3%)	4 (13.8%)	0.622
Low Nadir CD4 count (≤ 200)	22 (86.7%)	17 (56.7%)	15 (51.7%)	0.009
Undetectable viral load	25 (83.3%)	26 (86.7%)	27 (93.1%)	0.512
Years Living with HIV	18.2 (6.2)	14.1 (7.2)	12.8 (7.1)	0.015
Lipoatrophy	3 (15%)	6 (30%)	2 (10%)	0.235

Table 4.3: Sociodemographic Characteristics by Inflammation Group (n=89)			
	Inflammation Profile		
	Low (n=23)	High (n=75)	
	N (%) or mean (SD)/median (IQR)		*P*-value
Age	49 (5.4)	52.2 (7.8)	0.068
Male Gender	60.9%	94.7%	0.000
Racial Group			0.739
White	13 (56.5%)	43 (57.3%)	
Black/African American	0 (0%)	4 (5.3%)	
Native American/Native Alaskan	1 (4.4%)	1 (1.3%)	
Native Hawaiian/Pacific Islander	2 (8.7%)	6 (8%)	
Asian	1 (4.4%)	3 (4%)	
More than one race	2 (8.7%)	12 (16%)	
Unknown	4 (17.4%)	6 (8%)	
Non-white racial group	10 (43.5%)	32 (42.7%)	0.945
Substance Use History	11 (84.6%)	54 (96.%)	0.101
Smoking Ever	13 (56.5%)	50 (67.6%)	0.332
Smoking Currently	6 (26.1%)	18 (24.3%)	0.864
BMI (score)	24.62 (3.57)	26.60 (3.9)	0.034
High BMI (>= 25)	40 (60.61%)	22 (68.75%)	0.433
Metabolic Syndrome	4 (17.4%)	12 (16.0%)	0.875
History of HCV infection *	0 (0%)	15 (20.3%)	0.019
History of HBV infection *	7 (30.4%)	16 (21.6%)	0.385
History of Diabetes	2 (8.7%)	7 (9.3%)	0.926
Nadir CD4 count ≤ 200	13 (56.5%)	54 (69.3%)	0.163
CD4 T-cell lymphocytes	557.22 (268.13)	490.27 (232.96)	0.248
CD8 T-cell lymphocytes	650.174 (261.33)	832.5 (451.06)	0.072
CD4/CD8 Ratio	0.84 (0.47 - 1.58)	0.60 (0.23 - 1.39)	0.170
Undetectable viral load *	21 (91.3%)	64 (85.3%)	0.460
Years Living with HIV	14.32 (7.33)	15.43 (7.11)	0.673
Lipoatrophy	2 (15.4%)	11 (19.6%)	0.724
* Inflammation profile predictions conditioned on exposure to Hep C, Hep B, and most recent HIV viral load			

Table 4.4: Statistical Criteria for Model Selection in the Latent Profile Analysis

	LRT [a]	AIC [b]	BIC [b]	Smallest Posterior Probability in Profile	Entropy
1-class	--	1721.520	1762.750	--	--
2-class	**0.0000**	**1679.200**	**1752.495**	**23.2%**	**0.8810**
3-class	0.0001	1659.437	1762.508	21.0%	0.8171
4-class	0.0000	1639.847	1772.694	4.6%	0.7401

Note: LRT, entropy, and D not applicable for one class.

[a] LRT *p*-values are for the *k* vs. *k*-1 model

[b] Akaike information criterion (AIC) and Bayesian information criterion (BIC) are indications of model fit. Smaller values indicates better fit; Some consider BIC to be the superior IC (Nylund et al., 2007)

[c] Entropy is an estimate of how distinct each profile is from one another. Entropy values over 0.8 indicate a good separate of the latent classes (Celeux & Soromenho, 1996)

Table 4.5: Predicted Probability of Membership in Two-Profile Solution

	Probability (95% CI)
Group 1	0.767 (0.662, 0.848)
Group 2	0.232 (0.152, 0.338)

Table 4.6: Odds of Being in High Inflammation Profile by CD4/CD8 Ratio Tertile

	Low vs High CD4/CD8 Tertile [a]			Medium vs High CD4/CD8 Tertile [a]		
	AOR | 95% Confidence Interval | P-value					
High Inflammation profile [b]	1.265	-0.020, 2.551	0.054	1.013	-0.345, 2.370	0.144
Age (years)	-0.001	-0.080, 0.078	0.985	0.008	-0.069, 0.086	0.830
Male Gender	0.288	-1.315, 1..892	0.725	-0.322	-1.800, 1.156	0.669
BMI > 25	0.328	-0.768, 1.424	0.558	0.073	-1.084, 1.230	0.901

[a] Highest CD4/CD8 tertile is referent group

Table 4.7: Log Concertation of Peripheral Monocyte Subsets by CD4/CD8 Ratio Tertile

	Low CD4/CD8 Tertile [a]		Medium CD4/CD8 Tertile [a]	
Monocyte Subset	Coefficient (95% Confidence Interval) | P-value			
Classical	-0.037 (-0.132, 0.056)	0.422	-0.021 (-0.113, 0.070)	0.640
Intermediate	-0.213 (-0.572, 0.146)	0.239	-0.032 (-0.400, 0.334)	0.859
Transitional	0.015 (-0.166, 0.135)	0.838	0.0258 (-0.128, 0.179)	0.738
Non-classical/mature	0.197 (0.010, 0.384)	0.039	-0.096 (-0.279, 0.086)	0.296

[a] Highest tertile is referent group

Table 4.8: Predicted Marginal Mean of Log-Transformed Peripheral Monocyte Concentration by CD4/CD8 Tertile

	1st Tertile (Low)	2nd Tertile (Medium)	3rd Tertile (Highest/Normalized)
Subset		Marginal Mean (95% CI)	
Classical	8.504 (8.440, 8.569)	8.483 (8.420, 8.546)	8.466 (8.403, 8.529)
Intermediate	6.806 (6.554, 7.058)	6.593 (6.347, 6.839)	6.773 (6.527, 7.019)
Transitional	7.793 (7.687, 7.898)	7.777 (7.674, 7.881)	7.818 (7.715, 7.922)
Non-classical/mature	7.479 (7.345, 7.613)	7.383 (7.282, 7.484)	7.282 (7.126, 7.438)

Table 4.9: Glossary of Paper Terms	
Cytomegalovirus (CMV)	Cytomegalovirus is a common virus. A healthy person's immune system typically keeps the virus from causing illness. It is estimated that more than 50% of US adults have been infected with CMV by age 40 (CDC, 2020).
Detectable HIV viremia	When viral load is detectable, this indicates that HIV is replicating in the body. This is defined as having an HIV viral load of 59 copies/mL.
C-Reactive Protein (CRP)	CRP is an acute-phase proteins recognized as an indicator of inflammatory conditions. Levels of CRP change in response to the proinflammatory cytokines, IL-1 and IL-6. CRP levels have been shown to associate with HIV disease progression, independent of CD4 count and viral load (Lau et al., 2006). CRP has been linked to HIV-associated cognitive impairment (Rubin et al., 2018)
HIV-Associated Neurocognitive Disorders (HAND)	The manifestation of HIV-associated neurocognitive disorders (HAND), the term used for cognitive impairment in the setting of HIV, encompasses a wide range of emotional/affective changes, changes in both self-reported and observed attention and executive function, motor function, and memory (Winston & Spudich, 2020). It is estimated that about one third to one half of HIV-seropositive individuals have some degree of cognitive impairment (Heaton et al., 2010). These prevalence estimates vary based on population and assessment methods, and are likely lower in populations with sustained viral suppression (V. Valcour, personal communication, December 2018). Cognitive impairment in the setting of HIV is conceptualized as having a multifactorial etiology and progression (Winston & Spudich, 2020).
Hepatitis C / B antibody reactivity	Variables determined by the questions: Do you have hepatitis B? yes/no Do you have hepatitis C? Yes/no; Then confirmed with antibodies tests via standard assays using peripheral blood draw. Indicates past or present infection.
Interleukins (IL)	Interleukins are cytokines with complex roles in immune function. HIV infection results in upregulation and secretion of many ILs (Kedzierska & Crowe, 2001).
Interleukin (IL)-1β	IL-1β is a proinflammatory cytokine produced predominantly by macrophages in response to infections and inflammation. HIV results in upregulation and secretion of IL-1β, which is suppressed during ART (Kedzierska & Crowe, 2001).

Table 4.9: Glossary of Paper Terms *Continued*

Interleukin (IL)-6	IL-6 is a proinflammatory cytokine produced by a variety of cells, including T cells, B cells, macrophages, fibroblasts and endothelial cells. It has a wide spectrum of activities including B-cell stimulation and monocyte differentiation (Kedzierska & Crowe, 2001).
Interleukin (IL)-8	IL-8 is a proinflammatory cytokine produced by macrophages, T cells, neutrophils and endothelial cells in acute and chronic inflammatory states. It induces T-cells, Natural Killer cells, neutrophils and basophils (Kedzierska & Crowe, 2001).
Interleukin (IL)-10	IL-10 is a anti-inflammatory cytokine produced by activated T- and B-cells, monocytes, macrophages and keratinocytes. It inhibits T-cell proliferation, predominantly by suppressing synthesis of Th1 cytokines and inhibits macrophage activation and secretion of pro-inflammatory cytokines (IL-1, IL-6, IL-8, IL-12, TNF-α) (Kedzierska & Crowe, 2001).
Interferon (INF)γ	Interferons have a variety of antiviral and immunomodulatory effects and they are capable of inhibiting viral infection in a non-specific manner (Kedzierska & Crowe, 2001).
Latent profile analysis (LPA)	A statistical method that a person-centered approach to mixture modeling. LPA identifies latent subgroups or profiles within a study sample based on patterns of responses to observed variables (Weller et al., 2020). These profiles are unobserved but inferred from a set of continuous variables and predictors.
Neuroinflammation	There is evidence that the inflammatory process following HIV infection of the central nervous system (CNS) persist despite effective control of HIV RNA with ART medications. Neuroinflammation has therefore been suggested to be a major contributing factor for HIV-associated brain disease (Valcour et al., 2011).
Nadir CD4 cell count	The person's lowest CD4 count ever. Date of nadir and CD4 count are often obtained by self-report. CD4 nadir is a predictor of HIV neurocognitive impairment in the era of combination antiretroviral therapy (Ellis et al., 2011).
Peripheral Monocytes	In PLWH, monocytes are composed of three distinct phenotypic subsets based on CD14 and CD16 expression: Classical (CD14++CD16−), Intermediate (CD14++CD16+), and mature/non-classical (CD14+CD16++ and CD14+CD16+) subsets. Classical monocytes are the first subset to appear in peripheral blood, followed by intermediate, and then they develop into non-classical and mature monocytes (Valcour et al., 2010). Monocytes are noted to be chronically activated during HIV infection. Mature HIV-infected monocytes (CD14+ CD16+) preferentially transmigrate across the blood-brain barrier. These mature monocytes mediate neuroinflammation in the CNS and can cause neuronal damage, contributing to neurocognitive impairment regardless of ART status (Veenstra et al., 2017).

Table 4.9: Glossary of Paper Terms *Continued*

Myeloperoxidase (MPO)	Myeloperoxidase (MPO) is a proinflammatory enzyme released by activated neutrophils. Serum levels of MPO have been shown to be high in PLWH, and correlate with CRP.
Serum amyloid A (SAA) & Serum amyloid P (SAP)	Serum amyloid A (SAA) and serum amyloid P (SAP) are acute phase reactants and markers of active inflammation. Elevated SAA has been seen to associate with chronic inflammation in PLWH. Serum amyloid has not been extensively studied in connection neuroinflammation in HIV.
Tumor Necrosis Factor-*α*	TNFα is a proinflammatory cytokine produced by a wide variety of cells, including monocytes, macrophages, T cells, B cells, NK cells, neutrophils and microglia cells. It mediates a spectrum of inflammatory and immune responses (Kedzierska & Crowe, 2001). TNFα co-operates with several other pro-inflammatory mediators to enhance toxic effects and enhances permeability if the blood brain barrier (Brabers & Nottet, 2006).

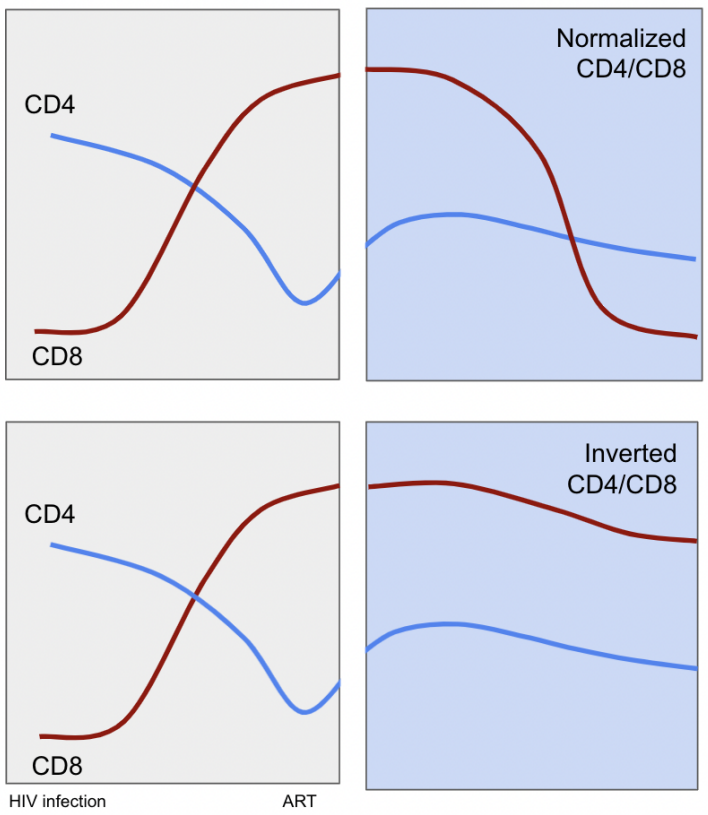

Figure 4.1: Visual Depiction of a Normalized and Inverted CD4/CD8 Cell Ratio in HIV Infection

Upon HIV seroconversion, HIV virus infects human CD4 T-cells (line in blue). As HIV kills CD4 T-cells, CD8 T-cells (line in red), which are a key part of the cellular immune response, simultaneously expand in response to the virus. If a person with HIV is treated with HAART medications, they may restore/normalize their CD4 counts and CD8 count will decline, leading to normalization of the CD4/CD8 cell ratio (upper panel). For some, despite HAART medications and viral suppression, CD4/CD8 ratios fail to improve even when CD4 cell count has recovered (lower panel) (Cao et al., 2016).

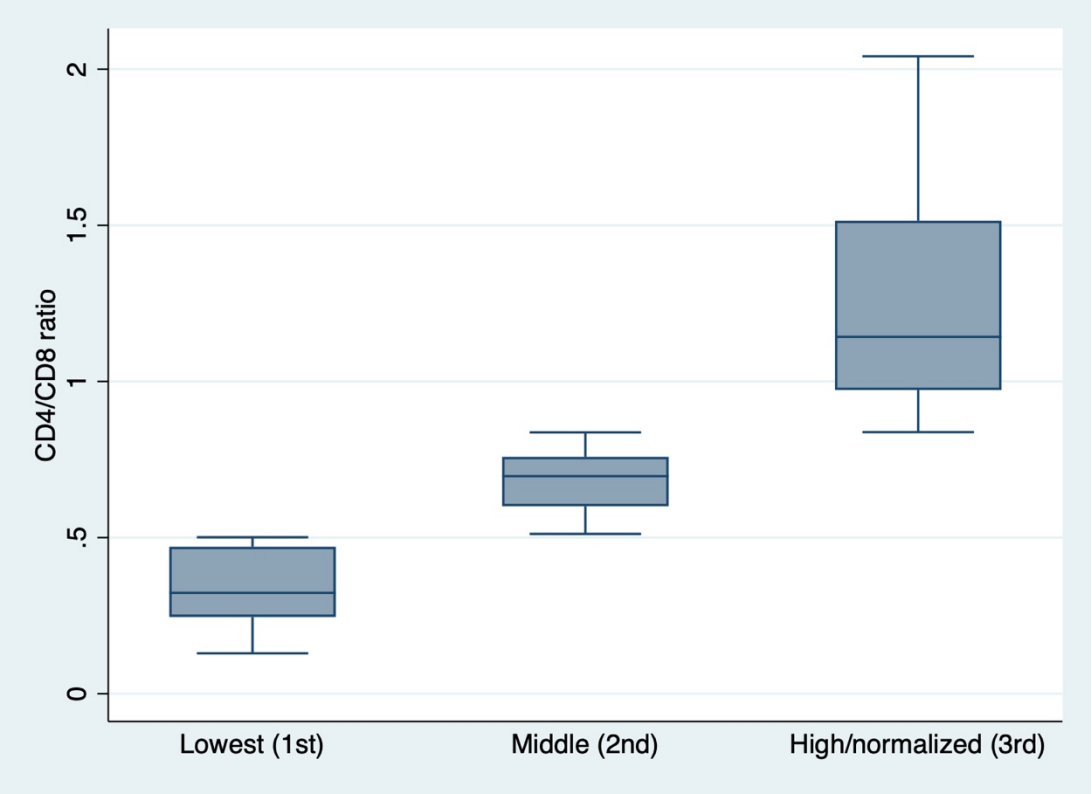

Figure 4.2: Range and Mean of CD4/CD8 Ratio in Each Tertile

Low/first tertile ranges from 0.129 to 0.501 (Mean 0.346). Middle/second tertile ranges from 0.512 to 0.837 (mean 0.681). Normalized/third tertile ranges from 0.838 to 2.041 (mean 1.243717, median 1.143)

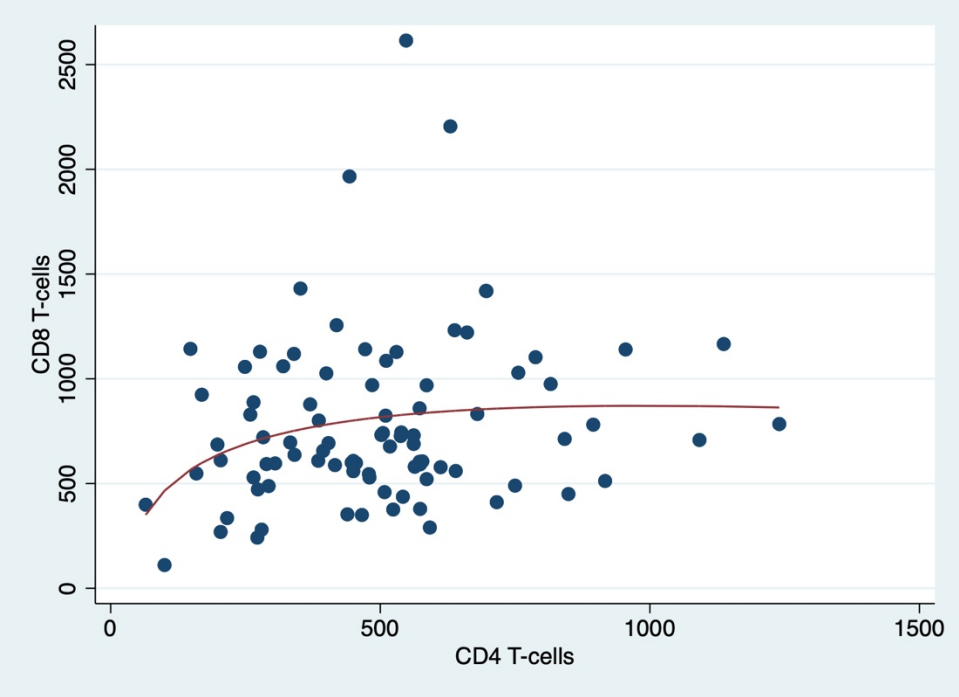

Figure 4.3: Relationship Between Absolute CD4 and CD8 Cell Count

Fitted line is plotted as a quadratic function, as the relationship between these two cell types is non-linear

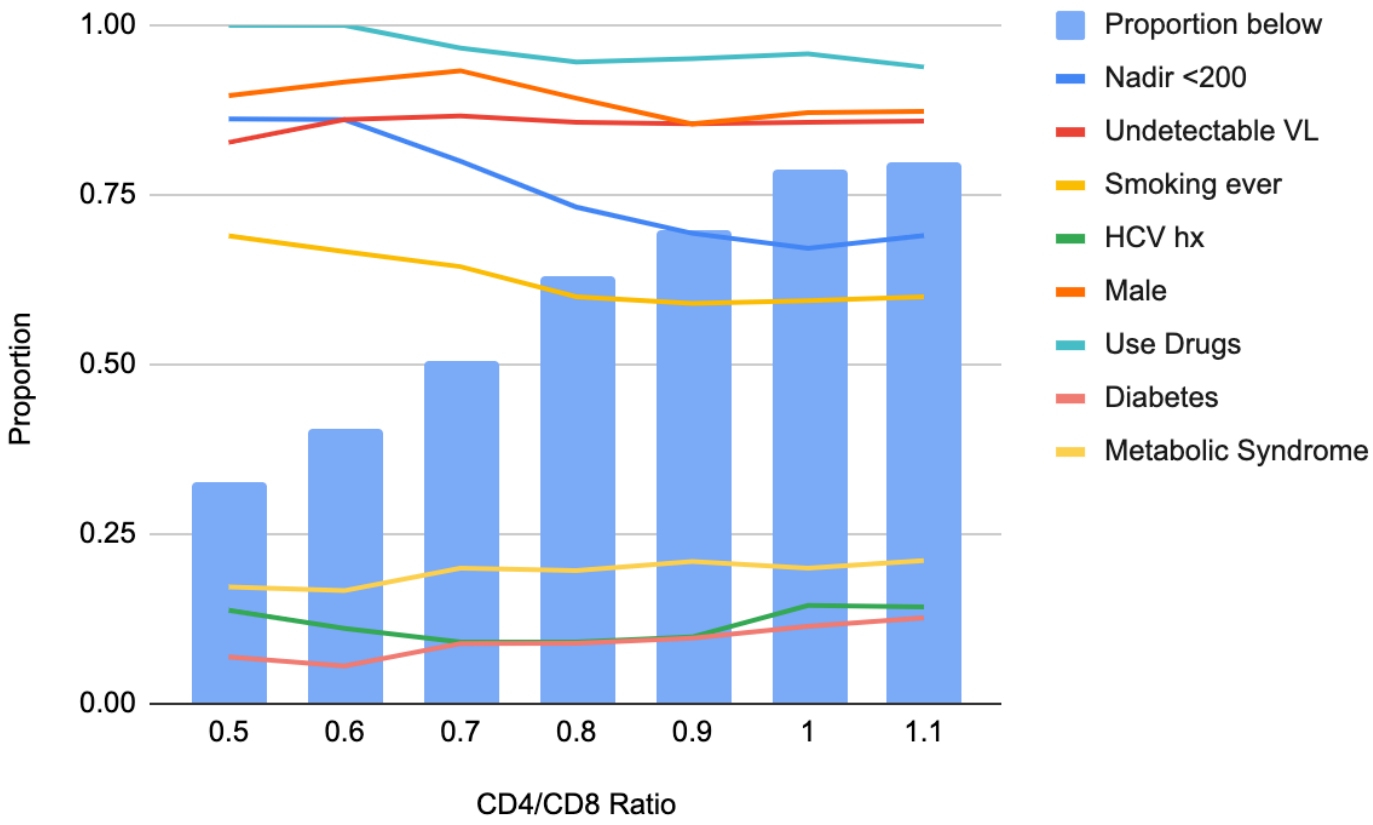

Figure 4.4: CD4/CD8 Cell Ratio Cut-points (0.50 – 1.10) and Proportion of Clinical characteristics

The proportion below each cut-point threshold (blue) is plotted against the proportion of those with each of the following characteristics: Low nadir CD4 T-cell count, undetectable viral load, past or current smoking, history of hepatitis C, Male gender, drug use history, diabetes, and metabolic syndrome.

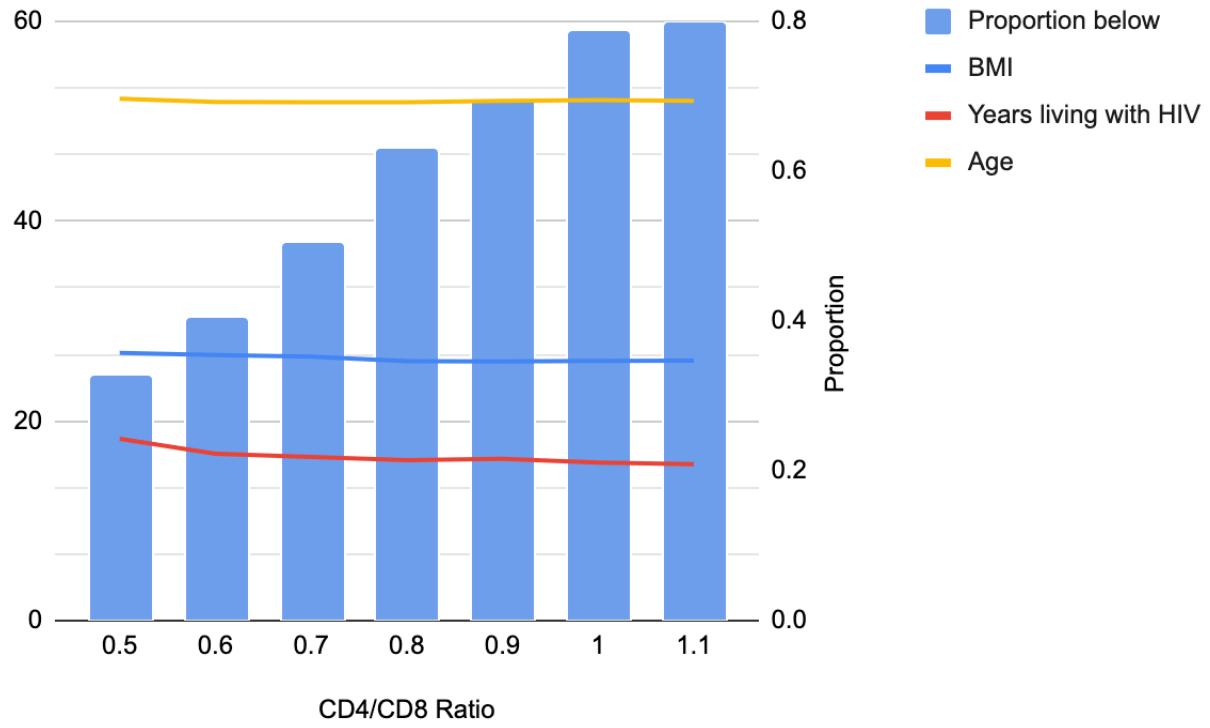

Figure 4.5: CD4/CD8 Cell Ratio Cut-points (0.50 – 1.10) and Mean Age, BMI, and Years Living with HIV

The proportion below each cut-point threshold (blue) is plotted against the mean of the following variables: Age (years), BMI (score), and number of years living with HIV

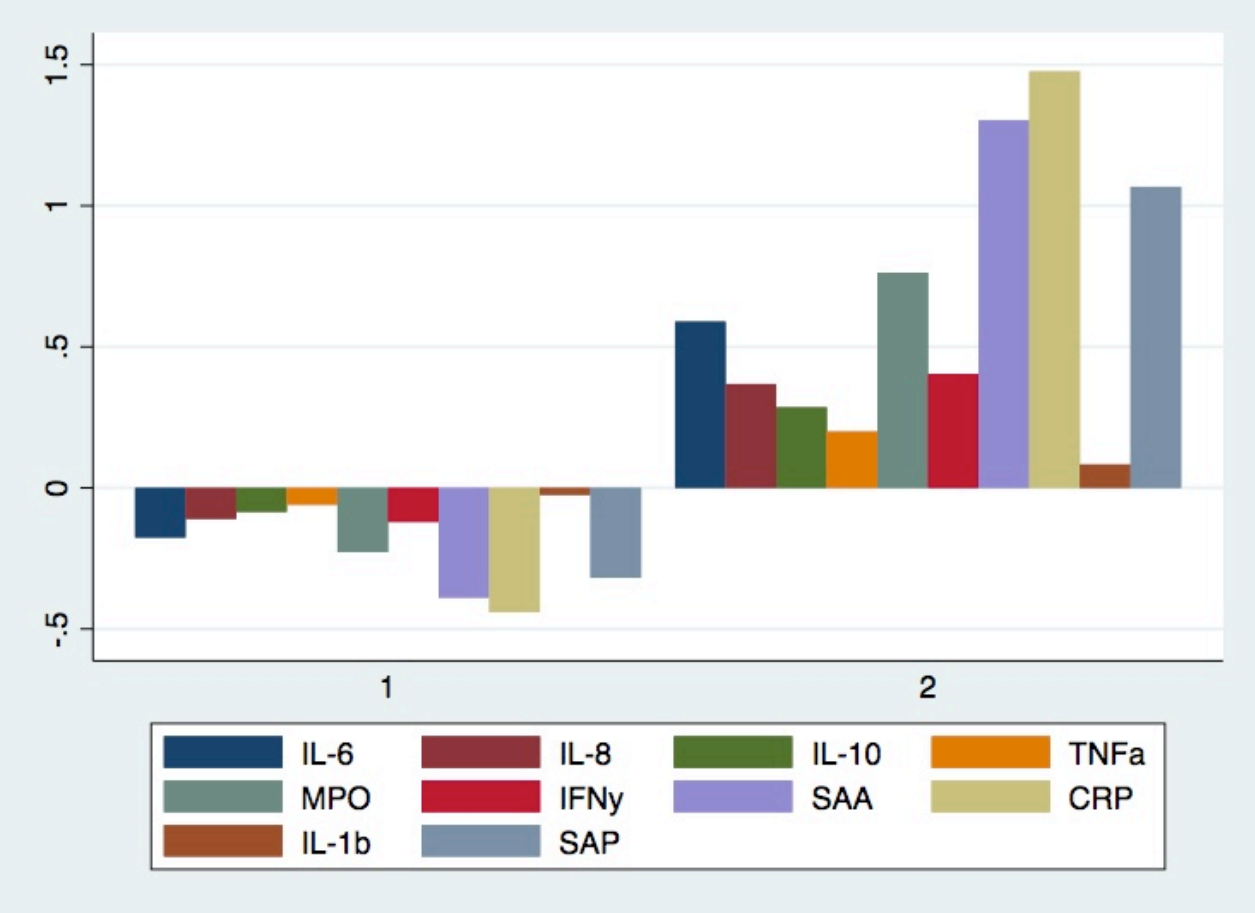

Figure 4.6: Mean Values of Inflammatory Markers in Each Profile

Log transformed biomarkers reported on standardized scale. Abbreviations: C-reactive protein (CRP), interleukin (IL), tumor necrosis factor (TNF), serum amyloid A (SAA), serum amyloid P (SAP), myeloperoxidase (MPO).

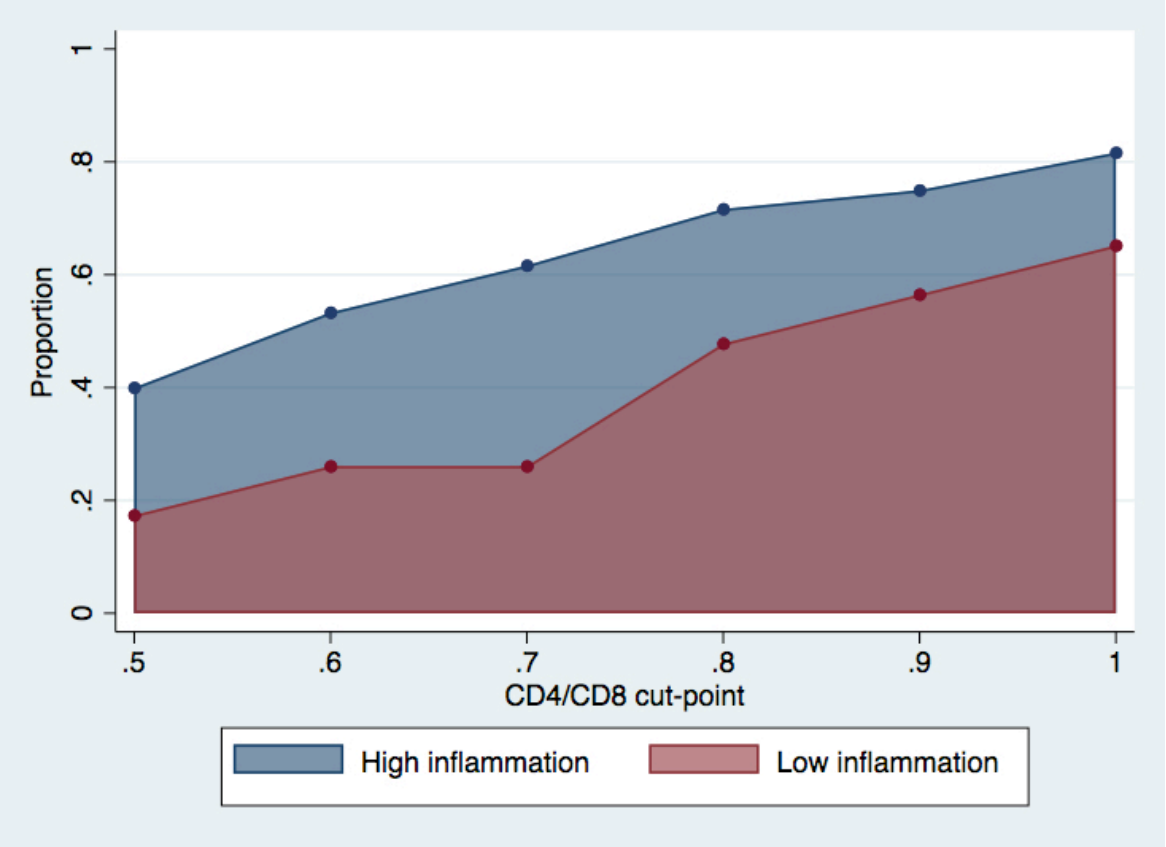

Figure 4.7: Proportion of Sample Below CD4/CD8 Cutoff Points by Inflammation Profile

The proportion of the sample in the low and high inflammation profiles with a CD4/CD8 ratio below cut-points ranging from 0.50 – 1.0. Among those in the high inflammation group, there is a consistently higher proportion of the sample below each CD4/CD8 cut-point. 81.7% (95% CI: 69.6% - 89.6%) of those with high inflammation had an inverted ratio at the cut-off of 1.0 compared to 65.2% (95% CI: 44.0% - 81.8%) of those with low inflammation. Similarly, 61.7% (95% CI: 48.7%-73.2%) of those with high inflammation had ratio < 0.70 compared to just 26.1% (95% CI: 12.1% - 47.6%) of those with low inflammation.

Appendices

Appendix 4.A: Correlation Between Individual Biomarkers and Log CD4/CD8 Ratio

Table 4.10 Correlations Between Individual Biomarkers and Log CD4/CD8 Ratio

Variables	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)
(1) CD4/CD8 ratio	1.000										
(2) CRP	-0.166	1.000									
(3) SAA	-0.163	0.829*	1.000								
(4) MPO	**-0.209***	0.416*	0.482*	1.000							
(5) IFNy	-0.015	0.180*	0.257*	0.158	1.000						
(6) SAP	**-0.230***	0.637*	0.631*	0.390*	0.215*	1.000					
(7) TNFa	**-0.319***	0.122	0.137	0.053	0.039	-0.177	1.000				
(8) IL-10	-0.091	0.145	0.179*	0.231*	0.134	0.051	0.302*	1.000			
(9) IL-8	0.034	0.350*	0.382*	0.240*	-0.041	0.155	0.215*	0.254*	1.000		
(10) IL-6	-0.031	0.426*	0.435*	0.335*	0.026	0.185*	0.333*	0.318*	0.509*	1.000	
(11) IL-1b	0.008	0.042	0.023	0.074	0.075	0.144	0.172	0.162	0.243*	0.113	1.000

Note: Variables transformed to meet criteria for normal distribution

*** *p<0.01*, ** *p<0.05*, * *p<0.1*

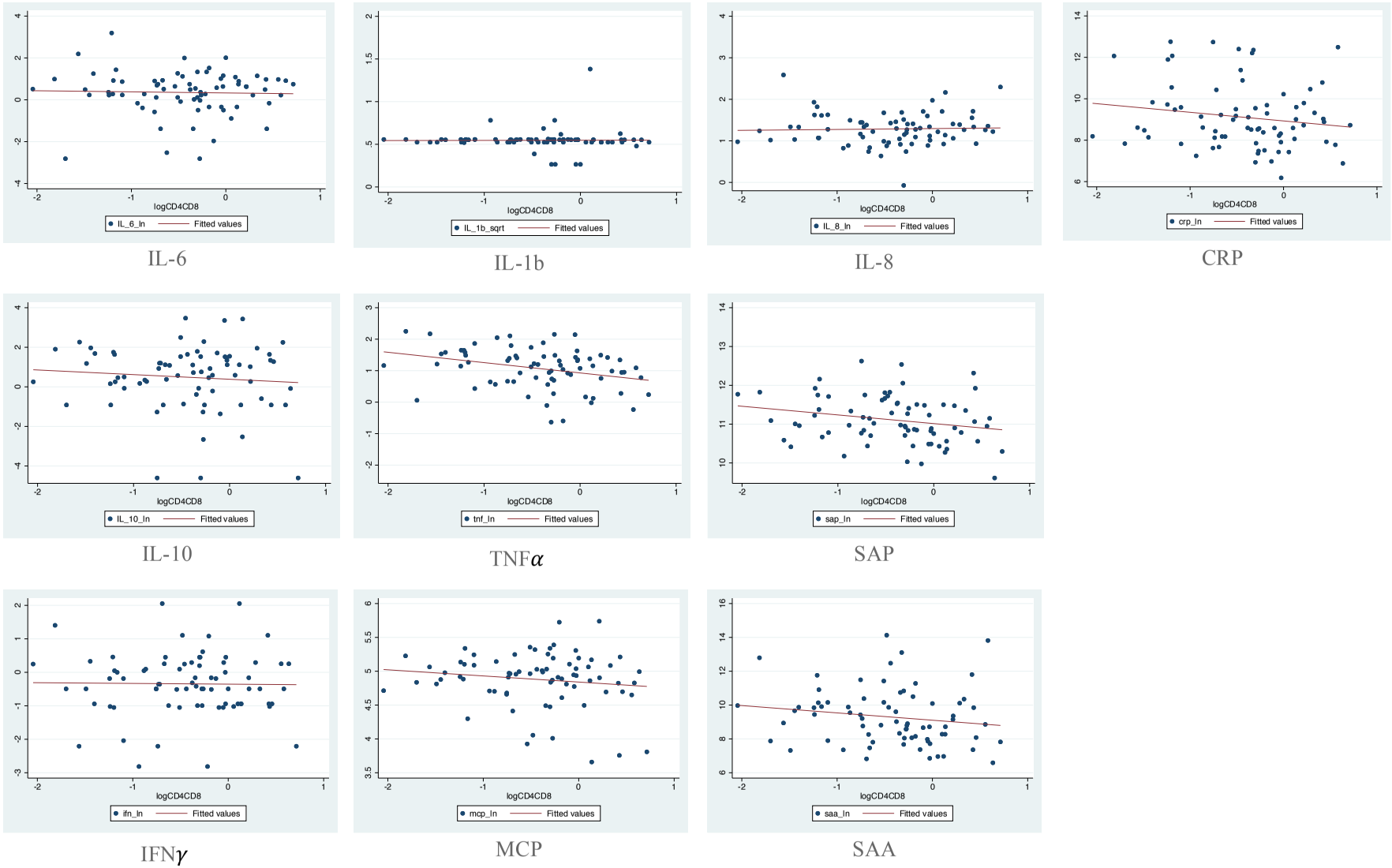

Figure 4.8: Correlation Between Inflammatory Biomarkers and Log CD4/CD8 Ratio

Appendix 4.B: Bias Analysis for CD4/CD8 Ratio by HIV Treatment Era

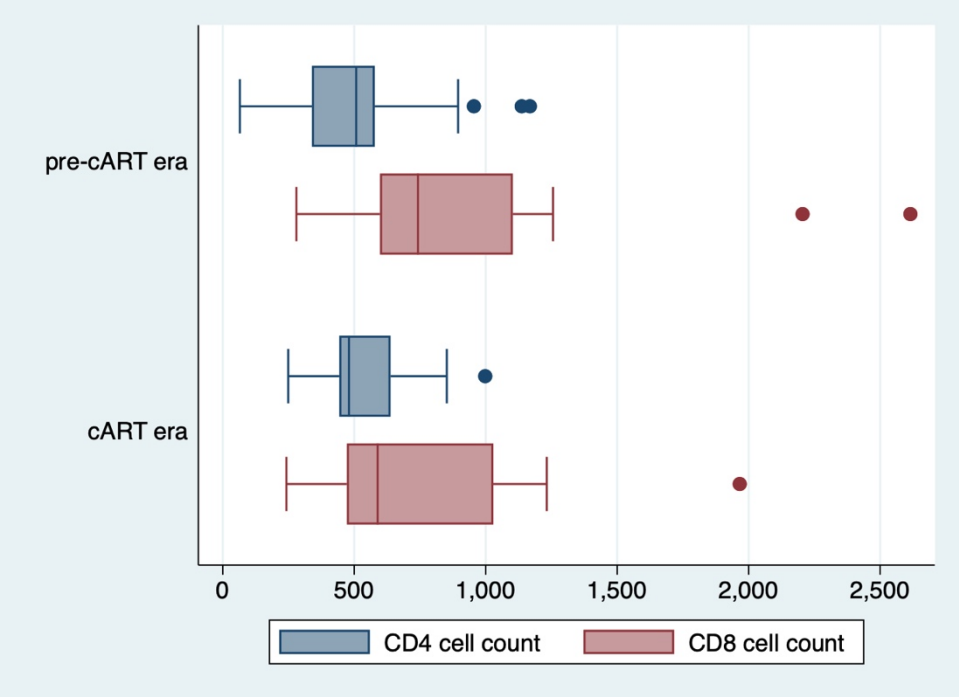

Figure 4.9: Absolute CD4 and CD8 T-cell Count by ART Era

Non-significant differences in CD4 cell count, CD8 cell count, and CD4/CD8 by HIV treatment era. cART era defined as 1996 or later.

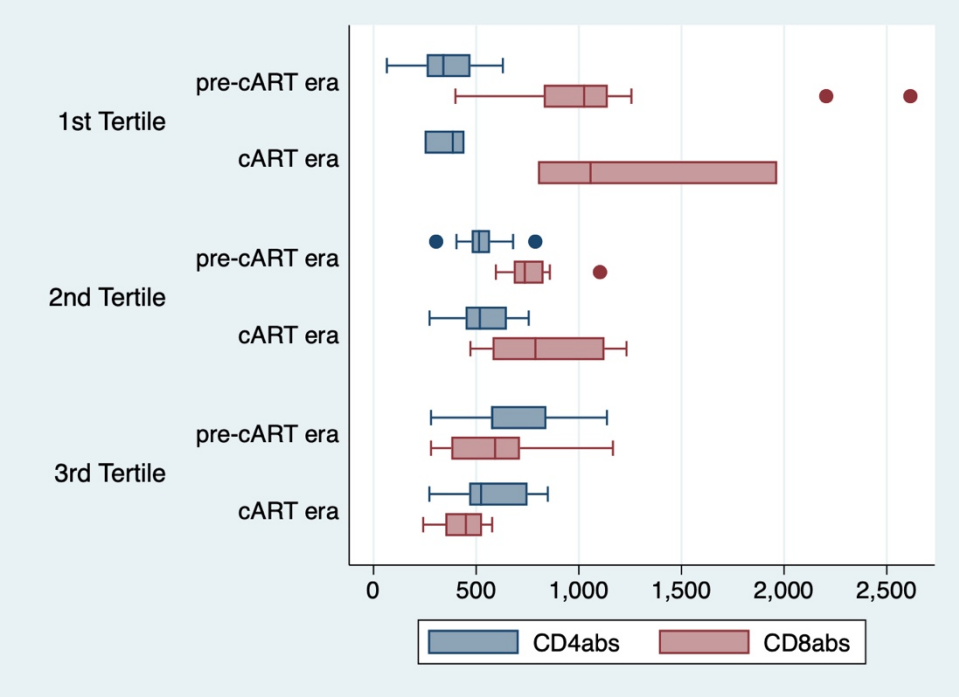

Figure 4.10: Absolute CD4 and CD8 T-cell Count in Each CD4/CD8 Ratio Tertile, by cART Era

Non-significant differences in CD4 cell count, CD8 cell count within CD4/CD8 tertile, by HIV treatment era. cART era defined as 1996 or later.

Chapter 5

Variability and Correlates of CD4/CD8 Cell Ratio Over 10 Years Among Women Living with HIV

Sarah Dobbins

Abstract

Inverted CD4/CD8 ratio (≤1.0) is a marker of chronic inflammation in people living with HIV (PLWH). To date, there is little known about the individual-level characteristics and correlates of CD4/CD8 cell ratio among PLWH. The aim of this study is to examine the intra-individual variability and determinants of CD4/CD8 cell ratio over 10 years among women living with HIV in the WIHS study. **Methods**: We estimated the intra-individual variability and change in CD4/CD8 ratio among HIV+ women over 10 years with linear mixed effects regression models. Subsequently, we examined the average associations of CD4/CD8 ratio with HIV-related variables, sociodemographic characteristics, and health conditions over 10 years of follow-up time. We operationalized CD4/CD8 ratio in two ways: 1) "Low" CD4/CD8 ratio (≤ 0.70 *versus* >0.70), and 2) "Inverted" CD4/CD8 ratio (≤1.00 *versus* >1.00). We used random-effects logistic regression, and all models were weighed for inverse probability of censoring to account for potential bias. **Results**: When we examined the intra-individual variability in log CD4/CD8 ratio over 10 years (n=1,462), there was no significant time trend and the ratio was relatively stable over the study period (ICC=0.895). Log CD4/CD8 ratio decreased with age, and detectable viral load and increased with ART adherence. Both inverted and low CD4/CD8 ratio were associated with detectable viral load and years of educational attainment. In a follow-up analysis to examine "very low" CD4/CD8 ratio (≤0.50 *versus* >0.50), this variable was associated with age, detectable viral load, Hepatitis C, and lower educational attainment. **Conclusion**: Among women with HIV, CD4/CD8 ratio is associated with both individual and sociodemographic factors, many of which are also implicated in age-related conditions among PLWH.

Background

Even when HIV is well-managed, people living with HIV (PLWH) commonly develop aging-related conditions such as cardiovascular disease, cancers, liver disease, and HIV Associated Neurocognitive Disorders (HAND) decades ahead of their HIV-negative counterparts, and their life expectancy is significantly reduced (Miller et al., 2014). It is thought that virally mediated changes in the immune system can lead to a compression of the aging process, resulting in earlier onset of age-related chronic disease and frailty (OAR Working Group on HIV and Aging, 2012). Low CD4/CD8 cell ratio is thought to be a biomarker of chronic inflammation and aging of the immune system (Lu et al., 2015; McBride & Striker, 2017; Saracino et al., 2014; Serrano-Villar & Deeks, 2015) (**Figure 5.1**). Studies have identified the factors that may be associated with low CD4/CD8 ratio among PLWH: Older age, lower nadir CD4 cell count, detectable HIV viremia, cytomegalovirus (CMV) co-infection, duration of HIV viral suppression, and certain inflammatory biomarkers (hs-CRP, IL-6) (Lu et al., 2015; Serrano-Villar & Deeks, 2015). The precise threshold for what to consider a low CD4/CD8 cell ratio among PLWH is still debated and there is a paucity of studies that confirm the clinical and population health relevance of this biomarker at various cut-points. Similarly, there is little information about clinical and sociodemographic factors associated with CD4/CD8 cell ratio, and the subject-specific variability of this ratio over time has not yet been established in the HIV literature.

Study Rationale and Objectives

The overall objective of this study is to examine the CD4/CD8 ratio over 10 years among women living with HIV. The aims of this study are: 1) Examine intra-individual variability in the CD4/CD8 ratio change over time, and investigate which sociodemographic and clinical characteristics are associated with this variability; and, 2) Examine the sociodemographic and clinical characteristics associated with low and inverted CD4/CD8 ratio among a population of women living with HIV.

Methods

Sample

In this study, to examine the intra-individual variability of CD4/CD8 ratio as well as the association of sociodemographic and clinical characteristics low CD4/CD8 ratio, we designed a secondary data analysis for a 10-year window of the Women's Interagency HIV Study Public Data Set cohort (WIHS-PDS). The Women's Interagency HIV Study (WIHS) is a multicenter longitudinal cohort study comprised of both HIV-infected women and at-risk HIV-uninfected women (Barkan et al., 1998). There are six WIHS consortia, each made up of multiple clinical subsites, located in Bronx/Manhattan, NY; Brooklyn, NY; Los Angeles/Southern California/Hawaii; San Francisco/Bay Area, CA; Chicago, IL; and Washington, DC. Each consortium represents the population of HIV+ women in its metropolitan area. A detailed account of the cohort, recruitment ,and retention have been published (Adimora et al., 2018; Bacon et al., 2005). The WIHS Public Data Set (WIHS-PDS) provides de-identified data meeting HIPAA criteria. Data from HIV-seropositive and HIV-seronegative women are made publicly available by the Johns Hopkins School of Public Health. Our data time frame covers the 10 years between 10/01/1998 (visit 9) through 09/30/2008. We chose this narrow time frame to 10 years to avoid excessive bias from cohort effects, while allowing enough time for potential changes in the CD4/CD8 ratio to manifest. All participants in the final sample reported seroconversion in the pre-ART era, defined as 1996 or earlier. The study sample selection is described in **Figure 5.2**.

WIHS Inclusion and Exclusion Criteria

At the time of the original WIHS recruitment, there were few inclusion and exclusion criteria. Adult women able and willing to consent to participation in the study, complete the interview in English or Spanish, travel to the research site for an interview and physical examination every six months, and have blood drawn for laboratory testing by venous or arterial access were enrolled into one of two groups: HIV positive or HIV negative. Women are never withdrawn from the study due to missed visits.

Abbreviated visits were conducted over the phone for ill or incarcerated participants, with data collection limited to the participant's medical and therapeutic history for the preceding 6 months and less than 1.0% (n=69) were done as abbreviated visits. A detailed description of the original recruitment was published elsewhere (Barkan et al., 1998).

Measures and Variables

The WIHS is structured with a 6-calendar-month period for visit windows. Centrally scripted interviews were conducted at each 6-month WIHS visit. Self-reported data include general medical history, antiretroviral therapy, use of drugs, alcohol, and cigarettes, and psychological status. To ensure the highest-quality data, centralized training was conducted for all study interviewers at the start of the WIHS and again prior to its expansion. A designated interviewer from each consortium completed additional training that enabled them to orient new staff and evaluate all interviewers at their sites on an annual basis. Additionally, question-by-question guidance forms are distributed at the start of each visit to assist interviewers with new questions and their abilities to objectively prompt participants to clarify answers when needed. All WIHS participants had blood, and urine specimens taken at each 6-month visit. Sociodemographic data was collected through interviewer assessment. Clinical variables were collected from serum blood draw or from medical record review.

Dependent Variable. The dependent variable is the CD4/CD8 cell ratio. CD lymphocyte subsets were quantified with standard flow cytometric methods in laboratories participating in the National Institutes of Health/National Institute of Allergy and Infectious Disease Flow Cytometry Quality Assessment Program. The CD4/CD8 cell ratio is created by taking the ratio of absolute counts of plasma CD lymphocytes at each study time point. This variable is available for participants at all time points. We examine the CD4/CD8 cell ratio as a continuous, log transformed variable in our analysis of intra-individual variability. In subsequent analyses of the correlates of CD4/CD8 ratio, we operationalized the variable as binary using three separate cut-points: a) Inverted ratio (CD4/CD8 between 0 to 1.0,

inclusive); b) Inverted/Low ratio (CD4/CD8 between 0 to 0.70, inclusive); and, c) Inverted/Very low ratio (CD4/CD8 between 0 to 0.50, inclusive).

Independent Variables. Reporting of cytomegalovirus (CMV) infection, and date of first HIV positive test were obtained by a structured interview and confirmed by medical record review, when available (Barkan et al., 1998). The HIV RNA viral load in plasma was measured with the isothermal nucleic acid sequence–based amplification (Nuclisens) method (bioMérieux, Boxtel, Netherlands). Viral load levels less than 80 copies/mL were reported as undetectable. Years living with HIV was obtained by self-report. Among those in the HIV+ WIHS-PDS cohort at our baseline (visit 9), n=66 (5.1%) did not know when their first seropositive test date was. For these participants, the year of the last negative HIV test was used in lieu of the first HIV+ test. ART adherence of participants was classified according to whether they reported taking all drugs as prescribed at least 95% of the time since the previous 6-month visit. This adherence measure was introduced to WIHS instruments in October 1998 (visit 9). On the basis of these self-reports, a covariate, measured biannually, that reflected those taking ART 95% of the time in the past 6 months was created. We chose to exclude the variable of nadir CD4 cell count due to the high amount of missing data, which was only available for 489 (33.44%) participants.

Participants were asked about smoking habits, and anyone reporting smoking since the last study visit (i.e. the past 6 months) was considered a current smoker. Participants self-reporting having smoked at least 100 cigarettes in their lifetime were considered positive for lifetime smoking status. A positive response to any illicit substance use (cocaine/crack, hallucinogen, speed/methamphetamine, or opioids [heroin or non-prescription methadone]) since the last study visit was recorded.

Certain sociodemographic variables were collected at study baseline (visit 1) only: Monthly average income, years of education attained, mother's educational attainment, and residential status. Monthly average income was measured using a response card and the question: "What is the current average monthly income, before taxes, of your household. Remember, your household includes family members or other people who live with you and depend on that money. Include pay or money from all

sources such as wages, salaries, tips, Social Security, Aid for Dependent Children (AFDC), pension or retirement, and any other kind of support." Years education and mother's years of education was recorded during patient interview. This was categorized as no school, grades 1-6, grades 7-11, high school or equivalent, some college, 4 years of college, and some/complete graduate school. Residential status was categorized as living in one's own residence, marginally housed (living with family or someone else's home, residential treatment or boarding house, jail) and homeless (living in a shelter, single room occupancy [SRO]/ "welfare hotel", or on the street).

Social support was measured using the following three yes or no questions: 1) "At times people may need help with caring for children, getting a ride somewhere or we may need to borrow something. Within the past month did you get this kind of help from family, friends and/or your partner?" 2) "Within the past month, have family, friends, and/or your partner given you comfort and encouragement?" 3) "During the past month, did family, friends, and/or your partner listen and/or try to understand your concerns (worries/troubles)?" The available answers were yes (1), and no (0). These three questions were asked yearly from visit 10-20. Thus, the social support scores used for this analysis range from 0-3, with higher scores indicating more support. This variable was operationalized as an ordinal variable (0=low support, 1=moderate-low support, 2= moderate-high support, and 3=high support). This is not a validated scale.

Depression was represented by a validated measure of depressive symptomology, the CES-D scale (González et al., 2017; Long Foley et al., 2002; Zhang et al., 2012). The CES-D is a short scale of 20 self-report items intended to measure the level of depressive symptomatology in the past week. Response options vary from 0 to 3 and refer to frequency of the symptoms, with higher scores indicating more severe symptoms. The CES-D literacy level has been defined as easy, and it takes between 2 and 5 minutes to complete. This scale has been validated in diverse populations (Mueses-Marín et al., 2019). Among PLWH, the CES-D is a validated instrument, and when the cut-off score of $\geq$16 is used to define depression the scale has a sensitivity of 72.7%-79.8% and a specificity of 78.5%-83.0% in different

studies (Ranganathan & Pramesh, 2012). In this analysis, we examined CES-D as both a continuous variable and as a binary variable using a cutoff score of ≥16.

Statistical Methods

All analyses in the WIHS-PDS are restricted to the HIV+ serostatus group (n=3,685). Those who started the study as HIV-seronegative but subsequently seroconverted (n=24) were excluded. Those with self-reported past CMV infection (n=11) were excluded from the analyses of CD4/CD8 ratio because of its well-established, strong effect on the CD4/CD8 ratio (Caby et al., 2016). Because the ART adherence measure was not introduced until visit 9 (three years after baseline), we defined visit 9 as our analytic baseline. Thus, for this analysis, we include data from the WIHS-PDS (version P15), collected from visit 9 (10/01/1998) through visit 28 (09/30/2008) (N=1,462) (**Figure 5.2**). We present the distribution of variables at study baseline (visit 1) in the Supplemental Information section. Analyses were conducted in Stata (StataCorp, 2017). While we defined alpha at a threshold of 0.05. Other guidance that *p*-values alone should not be used to summarily reject hypotheses (Gelman & Stern, 2006; Greenland et al., 2016; Wasserstein & Lazar, 2016), led us to considered the threshold of alpha of 0.10 as indicating potentially important relationships between variables.

We first examine the independent and dependent variables. Sample sociodemographic and clinical characteristics were described with means and standard deviations or median and interquartile range for continuous variables, and frequency in percentage for binary and categorical variables (**Tables 5.1-5.2**). Shapiro–Wilk test, Q–Q plot, and box plot were used to test the data normality. CD lymphocyte subsets and CD4/CD8 cell ratio were described using standard deviations or median and interquartile range for continuous variables. Shapiro–Wilk test, Q–Q plot, and box plot were used to test the data normality, and non-symmetrically distributed variables were transformed. The internal consistency and reliability of the CES-D scale is examined using Cronbach's alpha, which relies on internal consistency to evaluate reliability (Tavakol & Dennick, 2011). We then examined the differences in sociodemographic and clinical characteristics by inverted and low CD4/CD8 ratio (**Table 5.3**).

To address study aim 1, we examine the intra-individual variability in CD4/CD8 ratio among HIV+ women and the effects of co-variates on CD4/CD8 ratio variation over time. We used the log-transformed CD4/CD8 ratio as a dependent variable in linear mixed effects models with both random intercepts and random slopes with an exchangeable covariance structure. This method uses all available data for follow-up and takes into account the fact that repeated measures on the same individual are correlated with each other. When both the intercept and the slope are fitted as random effects, it allows individuals to have different CD4/CD8 ratio at baseline and different rates of change over the follow-up period. We then added independent variables as covariates if they were significant in unadjusted analyses or previously established factors in CD4/CD8 ratio, and we report both fixed and random effects of the model (**Table 5.4**). Time-invariant covariates in the final model include: Age at recruitment, lifetime smoking status, and years living with HIV at recruitment. Time-varying covariates include: Detectable viral load, ART adherence, Hepatitis C, and any illicit substance use. Time-varying covariates reflect exposures the prior 6-month period of time. To exclude outliers, the values at the highest and lowest 2.5% of the distribution of the log CD4/CD8 were truncated to create the trimmed distribution (**Figure 5.5**). We parallel test the full distribution of log CD4/CD8 ratio and an outlier-excluded distribution of log CD4/CD8 ratio to avoid bias from extreme values/outliers (Laird & Ware, 1982) (**Table 5.4**). In **Table 5.4**, we report results that are weighted for censoring bias (unweighted results are reported in Appendix B **(Table 5.8**).

To address study aim 2, we examined the average association of low and inverted CD4/CD8 ratio with independent variables over 10 years of follow-up time. We first tested the crude, unadjusted and unweighted relationships of low and inverted CD4/CD8 ratio with independent variables using logistic regression with random effects for repeated measures in individuals. Second, we selected independent variables that were significant in crude analyses to be entered into adjusted and weighted logistic regression models. These results are presented in **Table 5.5**. Third, we perform a follow-up analysis to examine "inverted/very-low" CD4/CD8 ratio, defined using the cut-off of CD4/CD8 $\leq$0.50, as the

dependent variable (**Table 5.6**). This follow-up analysis was developed after examining the distribution of the CD4/CD8 in the sample. In **Tables 5.5-5.6,** we report unadjusted results that are weighted for censoring bias. Unweighted results are reported in Appendix B (**Table 5.9**).

Censoring Bias. Bias due to selective mortality and attrition is a potential concern in longitudinal studies and is especially relevant in HIV research because HIV predicts subsequent mortality, and it is difficult to anticipate the magnitude of bias (Ranganathan & Pramesh, 2012). We assess censorship bias through stratification of independent variables by censoring during study period (Appendix C, **Table 5.10**) and examining differences in CD4/CD8 ratio by censorship while adjusting for independent variables. We determined that bias due to censorship was likely a threat to the validity of the analysis, so we constructed a censoring weight using inverse probability weighting methods (Austin & Stuart, 2015). The inverse probability of censoring weight (IPCW) was conditioned on age, detectable viral load, ART adherence, Hepatitis C, CES-D depression score, smoking status, white racial group, residential status, and monthly income. The weight was then trimmed to the central 95% of its distribution to minimize issue from very large weights (**Figure 5.6**). We used the trimmed IPCW in our fully adjusted models examining the intra-variability in CD4/CD8 ratio over time and low and inverted CD4/CD8 cell ratio, and unweighted models are reported in supplemental information (Austin & Stuart, 2015).

Results

All participants were cis-female (n=1,462). The mean age at time of recruitment was 36.18 years (SD 7.82) and the majority of the sample (56.40%) was Black or African American and 24.81% reported Latinx ethnicity. In the baseline sample, 70.43% had a detectable viral load and 53.75% reported ART adherence of 95% or better in the past 6 months. The mean number of years living with HIV at recruitment was 3.68 (SD 2.66). Approximately two-thirds (73.02%) of the sample endorsed illicit substance use in the past 6 months and 56.05% had smoked cigarettes in last 6 months. A larger proportion (73.02%) reported smoking more than 100 cigarettes in their lifetime. At baseline, forty-one percent (41.17%) had serum antibodies to hepatitis C, and less than one percent (0.68%) reported

exposure to CMV in the past. The largest proportion of the sample reported less than high school education (31.73%), followed by high school completion (31.34%) and some college (28.4%). The largest portion of the sample reported their mother's education was high school completion (36.96%), followed by grades 7-11 (21.67%); however, about a third (29.64%) of people had missing data for this variable. The majority reported an average monthly income of 501$ to $1000 dollars per month (28.87%), followed by 500$/month or less (22.52%). At recruitment, 69.2% of the sample was housed in their own residence, 26.3% was marginally or transitionally housed, and 4.02% was homeless (Table 1).

The mean baseline CD4 T-cell count was 404 (SD 268) and the median baseline CD8 cell count was 785 (IQR 528-3791). The median baseline CD4/CD8 cell ratio was 0.45 (IQR: 0.25-0.70). A large majority (83.44%) of the sample had an inverted CD4/CD8 cell ratio (≤ 1.0) while 69.04% had a low CD4/CD8 cell ratio (≤ 0.70). Social isolation in the sample was high, with 61.1% of the sample reporting high isolation, and 23.87% reporting moderate-high isolation. Similarly, depressive symptoms were prevalent in the sample. Fifty-nine percent (59%) has a CES-D score ≥16 and the mean baseline score was 19.21 (7.80). The internal consistency (Cronbach's alpha) of the CES-D scale was 92.0%.

Censoring Bias. A total of 400 (27.35%) participants in the study sample died during the 10-year follow-up period. None disenrolled during the 10 period of our analysis. There were differences in the proportion of those who were censored during the study period due to death by CD4/CD8 ratio, detectable viral load, ART adherence, hepatitis C, age, racial group, lifetime smoking, depressive symptom score, baseline monthly income, and baseline residential status (Appendices C, **Table 5.10**). After adjusting for covariates, censorship was still associated with increased odds of low and inverted CD4/CD8 ratio by censorship (Appendix D, **Tables 5.11-5.12**). Therefore, we included a censoring weight all our mixed effects models account for possible bias from censoring in the data.

Change in CD4/CD8 over time. We examined the change of the log CD4/CD8 ratio over 10 years of follow-up time. We examined both the full distribution of CD4/CD8 ratio as well as an outlier-excluded distribution of log CD4/CD8 ratio, which we included to avoid potential bias from the influence

of extreme outliers. The slope for time had a non-significant coefficient of β=0.0041 (95% CI:[-0.001, 0.009]) when censoring weight outliers at the top and bottom 2.5% of the distribution were excluded. The intra-class correlation coefficient (ICC) was 0.826 (95% CI: 0.755, 0.880) in the full distribution IPCW model and 0.895 (95% CI: [0.881, 0.908]) in the trimmed IPCW model. We found that CD4/CD8 ratio decreased as age increased (β=-0.006, 95% CI: [-0.012, 0.000]). CD4/CD8 ratio was higher when ART adherence was reported to be 95% or better in the past 6 months (β=0.056, 95% CI:[0.037, 0.076]). CD4/CD8 ratio was lower when there was a detectable viral load (β=-0.229, 95% CI:[-0.251, -0.208]).

Average Association with Low and Inverted CD4/CD8. We tested the average association of low and inverted CD4/CD8 ratio with clinical and sociodemographic variables over time. In unadjusted analyses that were weighted to account for censoring bias, inverted CD4/CD8 was associated with higher odds of detectable viral load, past 6-month illicit drug use, lifetime smoking, and higher depressive symptom score. Inverted CD4/CD8 was associated with lower odds of ART adherence and White racial group (versus all other racial groups). Odds of inverted CD4/CD8 decreased as age increased and as education level increased.

In unadjusted analyses that were weighted to account for censoring bias, inverted CD4/CD8 ratio was associated with higher odds of detectable viral load (OR=4.764, 95% CI: [4.438, 5.116]), serum HCV antibodies (OR=1.867, 95% CI: [1.515, 2.302]), past 6-month drug use (OR=1.490, 95% CI: [1.342, 1.654]), and lifetime smoking (OR=1.392, 95% CI: 1.050, 1.844). Inverted CD4/CD8 ratio was associated with lower odds of ART adherence (OR=0.399, 95% CI: [0.377, 0.421]) and white (vs non-white) racial group (OR=0.361, 95% CI: [0.233, 0.560]). For each year increase in age, there was a 0.987 lower odds of inverted CD4/CD8 cell ratio (95% CI: [0.977, 0.996]). For each increase in level of educational attainment, there was a 0.809 decreased odds of inverted CD4/CD8 ratio (95% CI: [0.736, 0.889]).

In unadjusted analyses that were weighted to account for censoring bias, detectable viral load (OR=4.814, 95% CI: [4.482, 5.171]), serum HCV antibodies (OR=2.447, 95% CI: [1.984, 3.018]), past 6-month drug use (OR=1.428, 95% CI: [1.304, 1.564]), and lifetime smoking (OR=1.668, 95% CI: [1.223,

2.275]) were associated with higher odds of having low CD4/CD8 ratio. White (versus all non-white) racial group (OR=0.293, 95% CI: [0.198, 0.433]) and ART adherence (OR=0.399, 95% CI: [0.377, 0.421]) were associated with lower odds of low CD4/CD8 ratio. For each increase in level of educational attainment, there was a 0.796 decrease in odds of inverted CD4/CD8 ratio (95% CI: [0.720, 0.881]).

In fully adjusted analyses that were weighted to account for censoring bias, detectable viral load remained associated with higher odds of inverted (AOR=4.276, 95% CI: [3.245, 5.634]) and low (AOR=5.146, 95% CI: [4.186, 6.328]) CD4/CD8 ratio. Increasing level of educational attainment also remained significantly associated with inverted (AOR=0.830, 95% CI: [0.716, 0.962]) and low (AOR=0.702, 95% CI: [0.599, 0.823]) CD4/CD8 ratio (**Figure 5.7**).

Based on these results, a subsequent analysis was performed to examine a "very-low" CD4/CD8 ratio at the cut-off of ≤0.50. Over ¾ of the sample ever had a CD4/CD8 ≤0.50 in the study period (n=1184, 81.71%) and more than half (n=682, 57.65%) had a ratio ≤0.50 at baseline (visit 9) (**Figure 5.3**). In our analysis of very low ratio as the dependent variable, we found that detectable viral load (AOR=7.898, 95% CI: [6.340, 9.835]), HCV serum antibodies (AOR=1.584, 95% CI: [1.093, 2.296]), age (AOR=1.068, 95% CI:1.043, 1.093), and educational attainment (AOR=0.740, 95% CI: [0.632, 0.865]) were each associated with very low CD4/CD8 ratio (**Table 5.6, Figure 5.7**).

Discussion

The results obtained from this study links intra-individual changes over 10 years in CD4/CD8 ratio, an emerging biomarker of chronic inflammation and mortality risk, with related health indicators including age, ART adherence and detectable viral load, and years of educational attainment among women with HIV. There was not a significant effect of time on CD4/CD8 ratio. The ICC, which represents that proportion of the total variance in CD4/CD8 ratio that is accounted for by the clustering at the individual level, was 0.895 (95% CI: 0.881, 0.908). Rather, we found that clinical and sociodemographic characteristics were associated with intra-individual change.

Over 10 years of observation, inverted and low CD4/CD8 ratio were associated with detectable viral load and years of educational attainment. We also chose to examine "very low" CD4/CD8 ratio because over half of the WIHS-PDS cohort had a "very low" CD4/CD8 ratio of ≤0.50 at baseline, and the sample had median CD4/CD8 ratio of 0.45 (IQR: 0.25 - 0.70) at baseline. When "very low" CD4/CD8 ratio of ≤0.50 was used as the dependent variable, detectable viral load and educational attainment remained significant. Additionally, age and Hepatitis C were associated very low CD4/CD8 ratio. Furthermore, white racial group showed itself as a variable of interest in this analysis though it was not statistically significant.

Though CD4/CD8 is thought to represent a marker of chronic inflammation, this is still an emerging area of scientific investigation. Indeed, there is an ongoing debate about what threshold for the CD4/CD8 is most informative and clinically relevant. Pertinent to this debate is the intra-individual variability of the CD4/CD8, which no published studies have examined to date. Pertinent to the discussion of the CD4/CD8 threshold are our results for the population average associations of inverted, low, and very low CD4/CD8 ratio. Both inverted (≤1.0) and low (≤0.70) thresholds had similar results, with detectable viral load and years of educational attainment remaining significant in fully adjusted and weighted analyses. In follow-up analysis of very low ratio (<=0.50) the additional variables of age and Hepatitis C were associated very low CD4/CD8 ratio. Taken together, these results suggest that CD4/CD8 ratio values less than 0.50 may reflect a population experiencing more marginalization and/or racial disparities. If we continue to use a threshold of 1.0 to apprise risks associated with CD4/CD8, we may be missing important information about health risks in marginalized populations and people experiencing marginalized conditions.

HIV is a marginalized condition and PLWH experience substantial health disparities and inequities(Farmer et al., 2006; Rhodes et al., 2005). Therefore, it is important to understand the environmental and psychosocial impacts on aging with HIV. The WIHS cohort is especially unique in its racial/ethnic diversity and inclusion of large numbers of women of color and

women of lower socioeconomic status, which mirrors HIV prevalence in the US. The WHIS cohort is comprised of women living with HIV who have experienced, on average, more social marginalization than other samples of PLWH. For example, 73.3% of the sample reported an average monthly income of less than $1,000, and only 69.4% reported having their own home at baseline. Additionally, prior to 1996, HAART exposure was limited to early clinical trials, therefore many enrollees were naıve to HAART and many had already been diagnosed with an AIDS-defining illness. Therefore, this sample represents a representative population of PLWH with a high risk of HAND and other poor health outcomes in aging. As such, the evaluation of low and very low CD4/CD8 ratios is particularly relevant in this sample and strengthens the generalizability of our results.

Our study included variables to indicate socioeconomic position, including monthly income, educational attainment, residential status, and social support. At all CD4/CD8 thresholds tested in adjusted analyses, educational attainment emerged as a significant variable. Education can be conceptualized as a social determinant of health and one aspect of the domain of environment. In their conceptual framework of the SDOH, the WHO position education as a component of both socioeconomic position and socioeconomic/political context (World Health Organization, 2010). As the WHO states, "Circumstances in early life are seen as the initial stage in the pathway to adult health but with an indirect effect, influencing adult health through social trajectories, such as restricting educational opportunities, thus influencing socioeconomic circumstances and health in later life... People attain different positions in the social hierarchy according, mainly, to their social class, occupational status, educational achievement and income level." (WHO, 2010, pp. 18-28). Our study adds to a growing body of evidence on the correlates of CD4/CD8 ratio in adults living with HIV and indicates a potential link between educational attainment, a social determinant of health, and CD4/CD8 ratio.

Past evidence has suggested a link between CD4/CD8 ratio and aging among PLWH, including risk for neurocognitive disorders in the setting of HIV. These disorders are known to have a multifactorial etiology and progression (Winston & Spudich, 2020). In addition to established clinical imaging studies

and neuropsychiatric testing that aid in the diagnosis of neurocognitive disorders, immune dysfunction and inflammation are thought to be a core component of HAND etiology (Chan et al., 2016; Kusao et al., 2012; Valcour et al., 2011). Although the CD4/CD8 cell ratio has been studied in connection to HAND (Lu et al., 2015), this area of inquiry is still nascent as only four studies have looked at the relationship between HAND and CD4/CD8 cell ratio (Correa et al., 2014; Grauer et al., 2015; Rawson et al., 2015; Vassallo et al., 2017). Although our study did not examine this association, we did find notable results suggesting inverted, low, and very low CD4/CD8 ratio is associated with educational attainment. It is well established that level of education contributes to risk of cognitive impairment among both seropositive (De Ronchi et al., 2002; Foley et al., 2012) and seronegative populations (Glymour et al., 2012; Weuve et al., 2018). Indeed, it has been shown that education may serve as a critical mediator of racial inequities and risk of cognitive impairment. Notably, our models indicate a potentially important relationship between white racial group and very low CD4/CD8 ratio, which may reflect racial disparities and inequities in education and/or other factors impacting CD4/CD8 ratio among HIV+ women.

Our study found evidence that detectable viral load is strongly associated with inverted, low, and very low CD4/CD8 ratio, which aligns with the current literature (Lu et al., 2015). The expansion of CD8 cells caused by increased viral load can manifest in lower CD4/CD8 cell ratios (**Figure 5.1**), therefore this finding is not surprising. It is important to note that HIV viremia is also a well-known component of the etiology of HAND, which suggests potential utility of CD4/CD8 as a biomarker of HAND risk. Lastly, Hepatitis C exposure and age were associated with very low CD4/CD8 in our analysis. Hepatitis C is considered a contributing condition for HAND and confers increased risk of cognitive impairment, as does age (Heaton et al., 2010). Taken together, our results suggest that CD4/CD8 ratio, depending on threshold used, may reflects a constellation of factors that impact risk of cognitive impairment among PLWH at both the biological level and also the environmental level.

Limitations

Limitations to this study include the use of secondary data, in which the data collection was not designed to answer our particular research questions. Additionally, the data do not allow us to estimate causal relationships. Other limitations include possible bias in health status, as participants in clinical trials and other studies sometimes experience improved outcomes compared with non-participants due to better care, behavioral changes and/or possibly other unknown factors. IPCWs can only address confounding caused by measured covariates and are equally prone to bias due to unmeasured confounders. Lastly, this dataset did not contain data about CMV serostatus, which is known to influence CD4/CD8. Although we excluded all participants with a known history of CMV infection, this is likely an under-representation of the true CMV seroprevalence.

Summary and Conclusions

Our study did not confirm an independent effect of time on intra-individual changes in CD4/CD8 among HIV+ women over 10 years, and the CD4.CD8 showed relatively mild variability over time. Variables impacting intra-individual change in CD4/CD8 over time were: Age, ART adherence, detectable viral load, and years of educational attainment. Over 10 years of observation, inverted and low CD4/CD8 ratio were associated with detectable viral load and years of educational attainment. Additionally, very low CD4/CD8 ratio, which we defined as ≤0.50, was associated with detectable viral load, educational attainment, age, and Hepatitis C exposure. Our results suggest that CD4/CD8 ratio, depending on threshold used, reflects both individual and environmental factors in age-related conditions among PLWH.

References

Adimora, A. A., Ramirez, C., Benning, L., Greenblatt, R. M., Kempf, M.-C., Tien, P. C., Kassaye, S. G., Anastos, K., Cohen, M., Minkoff, H., Wingood, G., Ofotokun, I., Fischl, M. A., & Gange, S. (2018). Cohort Profile: The Women's Interagency HIV Study (WIHS). *International Journal of Epidemiology*, *47*(2), 393–394i. https://doi.org/10.1093/ije/dyy021

Austin, P. C., & Stuart, E. A. (2015). Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. *Statistics in Medicine*, *34*(28), 3661–3679. https://doi.org/10.1002/sim.6607

Bacon, M. C., von Wyl, V., Alden, C., Sharp, G., Robison, E., Hessol, N., Gange, S., Barranday, Y., Holman, S., Weber, K., & Young, M. A. (2005). The Women's Interagency HIV Study: An Observational Cohort Brings Clinical Sciences to the Bench. *Clinical and Diagnostic Laboratory Immunology*, *12*(9), 1013–1019. https://doi.org/10.1128/CDLI.12.9.1013-1019.2005

Barkan, S. E., Melnick, S. L., Preston-Martin, S., Weber, K., Kalish, L. A., Miotti, P., Young, M., Greenblatt, R., Sacks, H., & Feldman, J. (1998). The Women's Interagency HIV Study. WIHS Collaborative Study Group. *Epidemiology (Cambridge, Mass.)*, *9*(2), 117–125.

Caby, F., Guihot, A., Lambert-Niclot, S., Guiguet, M., Boutolleau, D., Agher, R., Valantin, M.-A., Tubiana, R., Calvez, V., Marcelin, A.-G., Carcelain, G., Autran, B., Costagliola, D., & Katlama, C. (2016). Determinants of a Low CD4/CD8 Ratio in HIV-1-Infected Individuals Despite Long-term Viral Suppression. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America*, *62*(10), 1297–1303. https://doi.org/10.1093/cid/ciw076

Chan, P., Hellmuth, J., Spudich, S., & Valcour, V. (2016). Cognitive Impairment and Persistent CNS Injury in Treated HIV. *Current HIV/AIDS Reports*, *13*(4), 209–217. PubMed. https://doi.org/10.1007/s11904-016-0319-7

Correa, B. L., Ornaghi, A. P., Muller, G. C., Engroff, P., Lopes, R. P., Filho, I. G. da S., Bosch, J. A., Bonorino, C., & Bauer, M. E. (2014). The Inverted CD4:CD8 Ratio Is Associated with Cytomegalovirus, Poor Cognitive and Functional States in Older Adults. *Neuroimmunomodulation*, *21*(4), 206–212. https://doi.org/10.1159/000356827

De Ronchi, D., Faranca, I., Berardi, D., Scudellari, P., Borderi, M., Manfredi, R., & Fratiglioni, L. (2002). Risk Factors for Cognitive Impairment in HIV-1–Infected Persons With Different Risk Behaviors. *Archives of Neurology*, *59*(5), 812–818. https://doi.org/10.1001/archneur.59.5.812

Farmer, P. E., Nizeye, B., Stulac, S., & Keshavjee, S. (2006). Structural Violence and Clinical Medicine. *PLoS Medicine*, *3*(10). https://doi.org/10.1371/journal.pmed.0030449

Foley, J. M., Ettenhofer, M. L., Kim, M. S., Behdin, N., Castellon, S. A., & Hinkin, C. H. (2012). Cognitive reserve as a protective factor in older HIV-positive patients at risk for cognitive decline. *Appl Neuropsychol Adult*, *19*(1), 16–25. https://doi.org/10.1080/09084282.2011.595601

Gelman, A., & Stern, H. (2006). The Difference Between "Significant" and "Not Significant" Is Not Itself Statistically Significant. *The American Statistician*, *60*, 328–331.

Glymour, M. M., Tzourio, C., & Dufouil, C. (2012). Is Cognitive Aging Predicted by One's Own or One's Parents' Educational Level? Results From the Three-City Study. *American Journal of Epidemiology*, *175*(8), 750–759. https://doi.org/10.1093/aje/kwr509

González, P., Nuñez, A., Merz, E., Brintz, C., Weitzman, O., Navas, E. L., Camacho, A., Buelna, C., Penedo, F. J., Wassertheil-Smoller, S., Perreira, K., Isasi, C. R., Choca, J., Talavera, G. A., & Gallo, L. C. (2017). Measurement properties of the Center for Epidemiologic Studies

Depression Scale (CES-D 10): Findings from HCHS/SOL. *Psychological Assessment*, *29*(4), 372–381. https://doi.org/10.1037/pas0000330

Grauer, O. M., Reichelt, D., Grüneberg, U., Lohmann, H., Schneider-Hohendorf, T., Schulte-Mecklenbeck, A., Gross, C. C., Meuth, S. G., Wiendl, H., & Husstedt, I. W. (2015). Neurocognitive decline in HIV patients is associated with ongoing T-cell activation in the cerebrospinal fluid. *Annals of Clinical and Translational Neurology*, *2*(9), 906–919.

Greenland, S., Senn, S. J., Rothman, K. J., Carlin, J. B., Poole, C., Goodman, S. N., & Altman, D. G. (2016). Statistical tests, P values, confidence intervals, and power: A guide to misinterpretations. *European Journal of Epidemiology*, *31*, 337–350. https://doi.org/10.1007/s10654-016-0149-3

Kusao, I., Shiramizu, B., Liang, C. Y., Grove, J., Agsalda, M., Troelstrup, D., Velasco, V. N., Marshall, A., Whitenack, N., Shikuma, C., & Valcour, V. (2012). Cognitive performance related to HIV-1-infected monocytes. *J Neuropsychiatry Clin Neurosci*, *24*(1), 71–80. https://doi.org/10.1176/appi.neuropsych.11050109

Laird, N. M., & Ware, J. H. (1982). Random-effects models for longitudinal data. *Biometrics*, *38*(4), 963–974.

Long Foley, K., Reed, P. S., Mutran, E. J., & DeVellis, R. F. (2002). Measurement adequacy of the CES-D among a sample of older African–Americans. *Psychiatry Research*, *109*(1), 61–69. https://doi.org/10.1016/S0165-1781(01)00360-2

Lu, W., Mehraj, V., Vyboh, K., Cao, W., Li, T., & Routy, J.-P. (2015). CD4:CD8 ratio as a frontier marker for clinical outcome, immune dysfunction and viral reservoir size in virologically suppressed HIV-positive patients. *Journal of the International AIDS Society*, *18*(1), 20052. https://doi.org/10.7448/IAS.18.1.20052

McBride, J. A., & Striker, R. (2017). Imbalance in the game of T cells: What can the CD4/CD8 T-cell ratio tell us about HIV and health? *PLOS Pathogens*, *13*(11), e1006624. https://doi.org/10.1371/journal.ppat.1006624

Miller, C. J., Baker, J. V., Bormann, A. M., Erlandson, K. M., Huppler Hullsiek, K., Justice, A. C., Neuhaus, J., Paredes, R., Petoumenos, K., & Wentworth, D. (2014). Adjudicated morbidity and mortality outcomes by age among individuals with HIV infection on suppressive antiretroviral therapy. *PloS One*, *9*(4), e95061.

Mueses-Marín, H., Montaño, D., Galindo, J., Alvarado-Llano, B., Martínez-Cajas, J., Mueses-Marín, H., Montaño, D., Galindo, J., Alvarado-Llano, B., & Martínez-Cajas, J. (2019). Psychometric properties and validity of the Center for Epidemiological Studies Depression Scale (CES-D) in a population attending an HIV clinic in Cali,Colombia. *Biomédica*, *39*(1), 33–45. https://doi.org/10.7705/biomedica.v39i1.3843

OAR Working Group on HIV and Aging. (2012). HIV and Aging: State of Knowledge and Areas of Critical Need for Research. *Journal of Acquired Immune Deficiency Syndromes (1999)*, *60*(Suppl 1), S1-18. https://doi.org/10.1097/QAI.0b013e31825a3668

Radloff, L. S. (1977). The CES-D Scale: A self-report depression scale for research in the general population. *Applied Psychological Measurement*, *1*(3), 385–401. https://doi.org/10.1177/014662167700100306

Ranganathan, P., & Pramesh, C. S. (2012). Censoring in survival analysis: Potential for bias. *Perspectives in Clinical Research*, *3*(1), 40. https://doi.org/10.4103/2229-3485.92307

Rawson, T. M., Dubb, S., Pozniak, A., Kelleher, W. P., Mandalia, S., Gazzard, B., & Barber, T. J. (2015). Assessing the role of peripheral CD8 T cells in neurocognitive impairment in HIV-infected men who have sex with men: Data from the MSM Neurocog Study. *Int J STD AIDS*, *26*(2), 128–132. https://doi.org/10.1177/0956462414531934

Rhodes, T., Singer, M., Bourgois, P., Friedman, S. R., & Strathdee, S. A. (2005). The social structural production of HIV risk among injecting drug users. *Social Science & Medicine (1982)*, *61*(5), 1026–1044. https://doi.org/10.1016/j.socscimed.2004.12.024

Saracino, A., Bruno, G., Scudeller, L., Volpe, A., Caricato, P., Ladisa, N., Monno, L., & Angarano, G. (2014). Chronic Inflammation in a Long-Term Cohort of HIV-Infected Patients According to the Normalization of the CD4:CD8 Ratio. *AIDS Research and Human Retroviruses*, *30*(12), 1178–1184. https://doi.org/10.1089/aid.2014.0080

Serrano-Villar, S., & Deeks, S. G. (2015). CD4/CD8 ratio: An emerging biomarker for HIV. *The Lancet HIV*, *2*(3), e76–e77. https://doi.org/10.1016/S2352-3018(15)00018-1

StataCorp. (2017). *Stata Statistical Software: Release 15.* StataCorp LLC.

Tavakol, M., & Dennick, R. (2011). Making sense of Cronbach's alpha. *International Journal of Medical Education*, *2*, 53–55. https://doi.org/10.5116/ijme.4dfb.8dfd

Valcour, V., Sithinamsuwan, P., Letendre, S., & Ances, B. (2011). Pathogenesis of HIV in the central nervous system. *Current HIV/AIDS Reports*, *8*(1), 54–61. https://doi.org/10.1007/s11904-010-0070-4

Vassallo, M., Fabre, R., Durant, J., Lebrun-Frenay, C., Joly, H., Ticchioni, M., DeSalvador, F., Harvey-Langton, A., Dunais, B., Laffon, M., Cottalorda, J., Dellamonica, P., & Pradier, C. (2017). A decreasing CD4/CD8 ratio over time and lower CSF-penetrating antiretroviral regimens are associated with a higher risk of neurocognitive deterioration, independently of viral replication. *J Neurovirol*, *23*(2), 216–225. https://doi.org/10.1007/s13365-016-0490-z

Wasserstein, R. L., & Lazar, N. A. (2016). The ASA Statement on p-Values: Context, Process, and Purpose. *The American Statistician*, *70*(2), 129–133. https://doi.org/10.1080/00031305.2016.1154108

Weuve, J., Barnes, L. L., Mendes de Leon, C. F., Rajan, K. B., Beck, T., Aggarwal, N. T., Hebert, L. E., Bennett, D. A., Wilson, R. S., & Evans, D. A. (2018). Cognitive Aging in Black and

White Americans: Cognition, Cognitive Decline, and Incidence of Alzheimer Disease Dementia. *Epidemiology*, *29*(1), 151. https://doi.org/10.1097/EDE.0000000000000747

Winston, A., & Spudich, S. (2020). Cognitive disorders in people living with HIV. *The Lancet HIV*, *7*(7), e504–e513. https://doi.org/10.1016/S2352-3018(20)30107-7

World Health Organization. (2010). *A conceptual framework for action on the social determinants of health: Debates, policy & practice, case studies.* http://apps.who.int/iris/bitstream/10665/44489/1/9789241500852_eng.pdf

Zhang, W., O'Brien, N., Forrest, J. I., Salters, K. A., Patterson, T. L., Montaner, J. S., Hogg, R. S., & Lima, V. D. (2012). Validating a shortened depression scale (10 item CES-D) among HIV-positive people in British Columbia, Canada. *PloS One*, *7*(7), e40793.

Table 5.1: Baseline (visit 9) Sample Characteristics Among HIV+ WIHS-PDS Cohort (n=1,492)	
CD4/CD8 cell ratio	
Absolute CD4/CD8 (median, IQR)	0.45 (0.25 - 0.70)
Inverted Ratio (< 1.0), (n %)	1078 (83.44%)
Inverted Ratio (< 0.70), (n %)	892 (69.04%)
Inverted Ratio (< 0.50), (n %)	688 (57.67%)
CD4 T-cell lymphocytes, (mean, SD)	404 (268)
CD8 T-cell lymphocytes, (median, IQR)	785 (528 - 3791)
Detectable viral load, (n %)	874 (70.43%)
ART adherence ≥ 95% *	888 (53.75%)
Years living with HIV at recruitment, (mean, SD)	3.68 (2.66)
Hepatitis C antibodies, (n %)	506 (41.17%)
CMV exposure, (n %)	8 (0.62%)
Age, (mean, SD)	36.18 (7.82)
Racial group, (n %)	
White	237 (18.40%)
Black/African American	727 (56.40%)
Asian	13 (1.01%)
Native American/Alaska Native	99 (7.68%)
Native Hawaiian / Other Pacific Islander	303 (23.52%)
Latinx Ethnicity, (n %)	320 (24.81%)
Illicit drug use, (n %)	942 (73.02%)
Smoking, (n %)	
Smoked ≥100 cigarettes in lifetime	942 (73.02%)
Smoked in past 6 months	709 (56.05%)
Education Level, (n %)	
No school	9 (0.71%)
Grades 1-6	52 (4.09%)
Grade 7-11	403 (31.73%)
High School	398 (31.34%)
Some college	315 (24.80%)
4 years college	65 (5.12%)
Some/Complete Grad School	28 (2.20%)

Table 5.1: Baseline (visit 9) Sample Characteristics Among HIV+ WIHS-PDS Cohort (n=1,492) ***Continued***	
Mother's Education Level, (n %)	
No school	33 (3.63%)
Grades 1-6	149 (16.39%)
Grade 7-11	197 (21.67%)
High School	336 (36.96%)
Some college	96 (10.56%)
4 years college	75 (8.25%)
Some/Complete Grad School	23 (2.53%)
Missing	383 (29.64%)
CES-D Score, (Mean SD)	21.32 (8.96)
CES-D ≥ 16, (n %)	869 (68.86%)
Social Isolation, (n %)	
3 Low	115 (9.15%)
2 Moderate - Low	74 (5.89%)
1 Moderate - High	300 (23.87%)
0 High	768 (61.10%)
Average monthly income, (n %)	
$500 or less	291 (22.52%)
$501-$1000	373 (28.87%)
$1001-$1500	151 (11.69%)
$1501-$2000	104 (8.05%)
$2001-$2500	61 (4.72%)
$2501-$3000	45 (3.48%)
$3001-$6250	69 (5.34%)
> $6250	19 (1.47%)
Residential Status	
Own house/apartment	894 (69.20%)
Marginal or Transitional Residence	340 (26.32%)
Homeless	52 (4.02%)
n=1,281 in baseline sample	

Table 5.2: Baseline (visit 9) Sample Characteristics by Low and Inverted CD4/CD8 Cell Ratio		
	Inverted Ratio (≤1.0) (n=1,069)	Low Ratio (≤0.70) (n=883)
CD4/CD8 cell ratio, (median, IQR)	0.404 (0.234 - 0.617)	0.348 (0.214 - 0.490)
CD4 T-cell lymphocytes, (mean, SD)	369.30 (237.93)	327.27 (217.21)
CD8 T-cell lymphocytes, (median, IQR)	833.5 (548 - 1125)	872 (570 - 1181.5)
Detectable viral load, (n %)	788 (73.78%)	683 (77.35%)
Past 6-month ART adherence ≥ 95%	760 (71.09%)	629 (71.23%)
Years living with HIV, (mean, SD) [a]	3.72 (2.66)	3.70 (2.65)
Hepatitis C antibodies, (n %)	419 (40.37%)	356 (41.54%)
Age, (mean, SD) [a]	36.12 (7.79)	36.27 (7.82)
Racial group, (n %) [a]		
White	197 (18.33%)	150 (16.87%)
Black/African American	610 (56.69%)	520 (58.43%)
Asian	10 (0.93%)	10 (1.12%)
Native American/Alaska Native	79 (7.34%)	59 (6.63%)
Native Hawaiian / Other Pacific Islander	252 (23.44%)	206 (23.17%)
Hispanic Ethnicity, (n %) [a]	141 (23.66%)	117 (24.84%)
Past 6-month illicit drug use, (n %)	87 (8.07%)	74 (8.30%)
Smoking (n %)		
Smoked ≥100 cigarettes in lifetime [a]	778 (72.30%)	634 (71.24%)
Smoked in last 6 months	590 (75.84%)	496 (78.23%)
Education Level, (n %) [a]		
No school	8 (0.74%)	6 (0.67%)
Grades 1-6	45 (4.18%)	36 (4.04%)
Grade 7-11	340 (31.57%)	281 (31.54%)
High School	340 (31.57%)	292 (32.77%)
Some college	265 (24.61%)	216 (24.24%)
4 years college	55 (5.11%0	41 (4.60%)
Some/Complete Grad School	24 (2.23%)	19 (2.13%)
Mother's Education Level, (n %) [a]		
No school	84 (3.60%)	81 (3.98%)
Grades 1-6	302 (12.93%)	275 (13.52%)
Grade 7-11	508 (21.75%)	444 (21.83%)

	Inverted Ratio (≤1.0) (n=1,069)	Low Ratio (≤0.70) (n=883)
High School	888 (38.01%)	753 (37.02%)
Some college	266 (11.39%)	229 (11.26%)
4 years college	217 (9.29%)	194 (9.54%)
Some/Complete Grad School	71 (3.04%)	58 (2.85%)
CES-D score, (mean, SD)	21.11 (8.90)	21.34 (9.06)
CES-D ≥ 16, (n %)	730 (68.22%)	609 (68.81%)
Social Support, (n %)		
3 High	662 (62.16%)	547 (62.09%)
2 Moderate -High	247 (23.19%)	205 (23.27%)
1 Moderate - Low	63 (5.92%)	50 (5.68%)
0 Low	93 (8.73%)	79 (8.97%)
Average monthly income [a]		
$500 or less	420 (27.04%)	399 (26.94%)
$501-$1000	533 (34.32%)	512 (34.57%)
$1001-$1500	206 (13.26%)	201 (13.57%)
$1501-$2000	131 (8.44%)	122 (8.24%)
$2001-$2500	85 (5.47%)	77 (5.20%)
$2501-$3000	66 (4.25%)	64 (4.32%)
$3001-$6250	87 (5.60%)	83 (5.60%)
> $6250	25 (1.61%)	23 (1.55%)
Residential Status [a]		
Own house/apartment	1183 (68.78%)	1234 (68.33%)
Marginal or Transitional Residence	464 (26.98%)	494 (27.35%)
Homeless	73 (4.24%)	78 (4.32%)

[a] Measured once at baseline

Table 5.3: Unadjusted Associations of Low and Inverted CD4/CD8 Characteristics with Sample Characteristics over 10 Years				
	Inverted Ratio (≤1.0)		Low Ratio (≤0.70)	
	Coefficient (95% CI)	*P*-value	Coefficient (95% CI)	*P*-value
Detectable viral load	4.764 (4.438, 5.116)	0.000	4.814 (4.482, 5.171)	0.000
ART adherence	0.399 (0.377, 0.421)	0.000	0.399 (0.377, 0.421)	0.000
Years living with HIV	0.993 (0.969, 1.016)	0.540	0.989 (0.966, 1.013)	0.378
Hepatitis C antibodies	1.867 (1.515, 2.302)	0.000	2.447 (1.984, 3.018)	0.000
Age	0.987 (0.977, 0.996)	0.007	0.993 (0.983, 1.003)	0.191
Racial group				
White	0.361 (0.233, 0.560)	0.001	0.293 (0.198, 0.433)	0.000
Black/African American	1.006 (0.798, 1.268)	0.961	0.999 (0.793, 1.260)	0.996
Asian	0.272 (0.064, 1.146)	0.076	0.362 (0.095, 1.384)	0.138
Native American/Alaska Native	0.976 (0.706, 1.350)	0.885	0.923 (0.667, 1.275)	0.625
Native Hawaiian / Other Pacific Islander	0.840 (0.534, 1.322)	0.452	0.854 (0.554, 1.316)	0.474
Hispanic Ethnicity	1.031 (0.663, 1.604)	0.891	1.162 (0.758, 1.781)	0.491
Past 6-month illicit drug use	1.490 (1.342, 1.654)	0.000	1.428 (1.304, 1.564)	0.000
Smoking				
Smoked ≥100 cigarettes in lifetime	1.392 (1.050, 1.844)	0.021	1.668 (1.223, 2.275)	0.001
Past 6-mothing smoking	1.091 (0.772, 1.540)	0.621	0.833 (0.602, 1.1507)	0.267
Education Level	0.809 (0.736, 0.889)	0.000	0.796 (0.720, 0.881)	0.000
Mother's Education Level	0.622 (0.538, 0.719)	0.000	0.660 (0.576, 0.756)	0.000
CES-D score	1.004 (0.996, 1.012)	0.362	1.008 (1.001, 1.015)	0.028
CES-D ≥ 16	1.007 (0.889, 1.139)	0.918	1.091 (0.974, 1.224)	0.133
Social Isolation	1.009 (0.919, 1.108)	0.850	1.055 (0.954, 1.166)	0.296
Residence				
Own house/apartment	REF		REF	
Marginal or Transitional Residence	1.160 (0.884, 1.520)	0.284	1.169 (0.873, 1.564)	0.294
Homeless	1.083 (0.592, 1.981)	0.796	1.262 (0.659, 2.420)	0.483

Table 5.4: Fixed and Random Effects of Sociodemographic and Clinical Characteristics on Log CD4/CD8 Ratio Over 10 Years, Weighted for Censoring Bias

	Full Distribution CD4/CD8 [a] (n=1,328)			Outlier-excluded CD4/CD8 distribution [a,d] (n=1,274)		
	Coefficient	95% Confidence Interval	P-value	Coefficient	95% Confidence Interval	P-value
Fixed Effects [b]						
Time (months)	-0.017	-0.024, -0.008	0.000	-0.002	-0.008, 0.003	0.437
Age	-0.009	-0.016, -0.001	0.029	-0.006	-0.012, 0.000	0.066
Years Living with HIV	-0.028	-0.051, -0.005	0.019	-0.014	-0.032, 0.003	0.115
Detectable Viral Load	-0.267	-0.293, -0.242	0.000	-0.229	-0.251, -0.208	0.000
Hepatitis C	0.009	-0.120, 0.137	0.895	-0.032	-0.135, 0.071	0.544
ART Adherence	0.091	0.064, 0.119	0.000	0.056	0.037, 0.076	0.000
Smoked ≥100 cigarettes in lifetime	0.026	-0.010, 0.062	0.157	0.027	-0.001, 0.056	0.058
Illicit Drug Use	0.001	-0.019, 0.020	0.931	-0.001	-0.017, 0.016	0.948
Depressive symptoms (CES-D)	-0.001	-0.002, 0.001	0.381	-0.001	-0.002, 0.000	0.184
Education level	0.032	-0.018, 0.083	0.211	0.018	-0.022, 0.057	0.381
Random Effects [c]						
Variance	0.088	0.073, 0.106	-	0.060	0.056, 0.063	-
Intercept	0.419	0.303, 0.579	-	0.510	0.452, 0.575	-
Slope	0.001	0.001, 0.002	-	0.001	0.001, 0.001	-
Intraclass Correlation Coefficient (ICC)	0.826	0.755, 0.880	-	0.895	0.881, 0.908	-
Model Selection Criteria						
AIC	19562.66			8155.592		
BIC	19652.71			8244.96		
Log Likelihood	-9769.33			-4065.80		
Censoring weights [d]			Mean *SD* (Min/Max)			
	1.576 *1.397* (1.021, 9.758)					

[a] Log transformed CD4/CD8 ratio
[b] Fixed effect estimates of the relationship between independent variables and CD4/CD8 within individuals

[c] Random effects estimates are estimated variances and can be interpreted as the magnitude of the variability of intra-individual coefficients from the mean fixed effects coefficient. The ICC is the proportion of the total variance in the outcome that is accounted for by clustering; It can be interpreted as the correlation among observations within the same cluster.
[d] Trimmed to central 95% of values to avoid bias from very large and very small weights

Table 5.5: Odds of Inverted [a] or Low [b] CD4/CD8 cell ratio Among Women Living with HIV

	Inverted CD4/CD8 ratio [a, c]		Low CD4/CD8 ratio [b, c]	
	AOR (95% CI) | *P*-value			
Depressive Symptom Score (CESD)	0.996 (0.982, 1.010)	0.595	1.006 (0.993, 1.019)	0.365
Age	1.007 (0.986, 1.029)	0.495	1.017 (0.994, 1.041)	0.152
Detectable Viral Load	4.276 (3.245, 5.634)	0.000	5.146 (4.186, 6.328)	0.000
ART adherence	0.894 (0.696, 1.148)	0.379	0.838 (0.682, 1.029)	0.091
Smoked ≥100 cigarettes in lifetime	1.291 (0.898, 1.857)	0.168	1.297 (0.885, 1.901)	0.183
Illicit Drug Use	1.025 (0.894, 1.176)	0.723	0.908 (0.785, 1.049)	0.190
Hepatitis C	0.922 (0.658, 1.293)	0.639	0.991 (0.683, 1.438)	0.962
White Racial Group	1.078 (0.719, 1.615)	0.716	0.741 (0.479, 1.147)	0.179
Education Level	0.830 (0.716, 0.962)	0.013	0.702 (0.599, 0.823)	0.000

[a] Defined as (CD4/CD8 ≤ 1.00)
[b] Defined as (CD4/CD8 ≤ 0.70)
[c] Weighted with trimmed IPCW

Table 5.6: Odds of Very Low [a] CD4/CD8 Cell Ratio among Women Living with HIV		
	AOR (95% CI) [b]	*P*-value
Detectable Viral Load	7.898 (6.340, 9.835)	0.000
ART adherence	0.840 (0.676, 1.045)	0.117
Hepatitis C	1.584 (1.093, 2.296)	0.015
White Racial Group	0.676 (0.423, 1.080)	0.102
Illicit Drug Use	0.912 (0.742, 1.120)	0.379
Smoked ≥100 Cigarettes in Lifetime	1.162 (0.789, 1.712)	0.447
Depressive Symptom Score (CES-D)	1.008 (0.997, 1.019)	0.139
Education Level	0.740 (0.632, 0.865)	0.000
Age	1.068 (1.043, 1.093)	0.000

[a] Defined as (CD4/CD8 ≤ 0.50)
[b] Weighted with trimmed IPCW

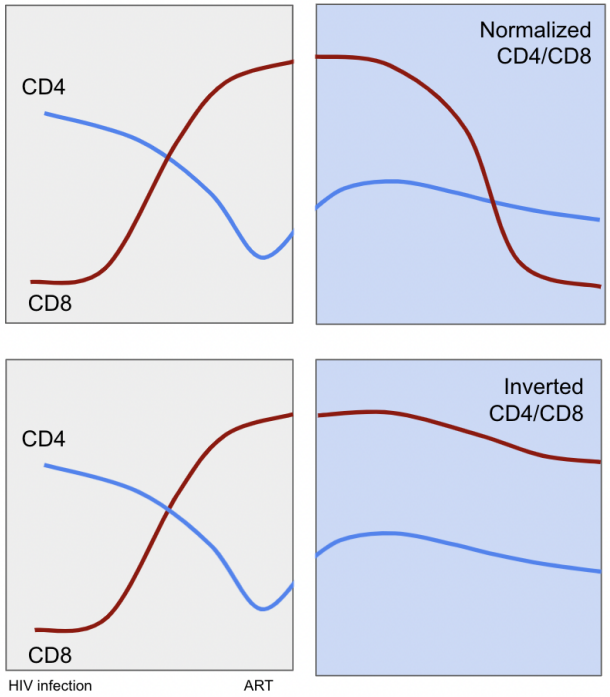

Figure 5.1: Visual Depiction of a Normalized and Inverted CD4/CD8 Cell Ratio in HIV Infection

Upon HIV seroconversion, HIV virus infects human CD4 T-cells (line in blue). As HIV kills CD4 T-cells, CD8 T-cells (line in red), which are a key part of the cellular immune response, simultaneously expand in response to the virus. If a person with HIV is treated with HAART medications, they may restore/normalize their CD4 counts and CD8 count will decline, leading to normalization of the CD4/CD8 cell ratio (upper panel). For some, despite HAART medications and viral suppression, CD4/CD8 ratios fail to improve even when CD4 cell count has recovered (lower panel) (Cao et al., 2016).

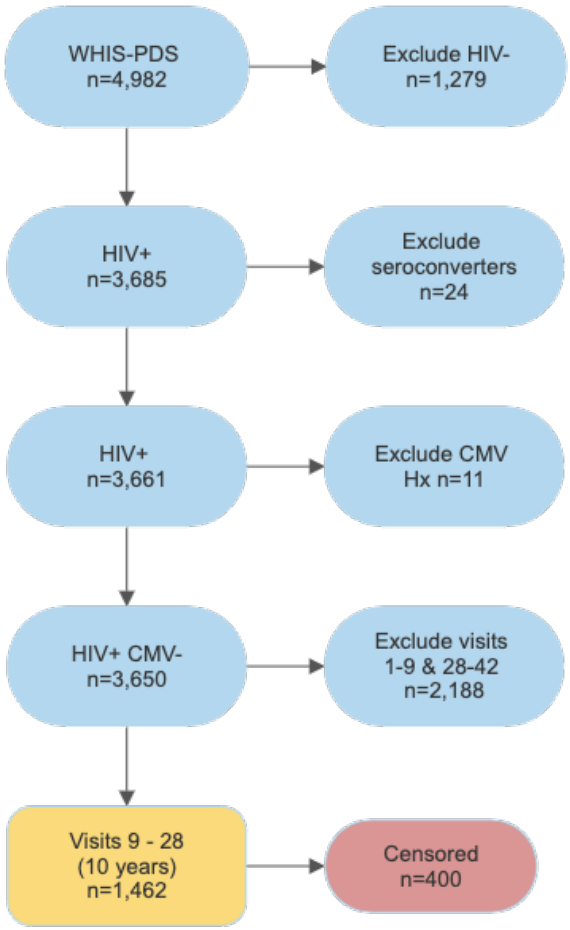

Figure 5.2: Flow Diagram of Participant Inclusion in Study Sample

The final study sample includes n=1,462 participants, 400 (27.4%) of whom were censored by death or disenrollment before the end of the study period

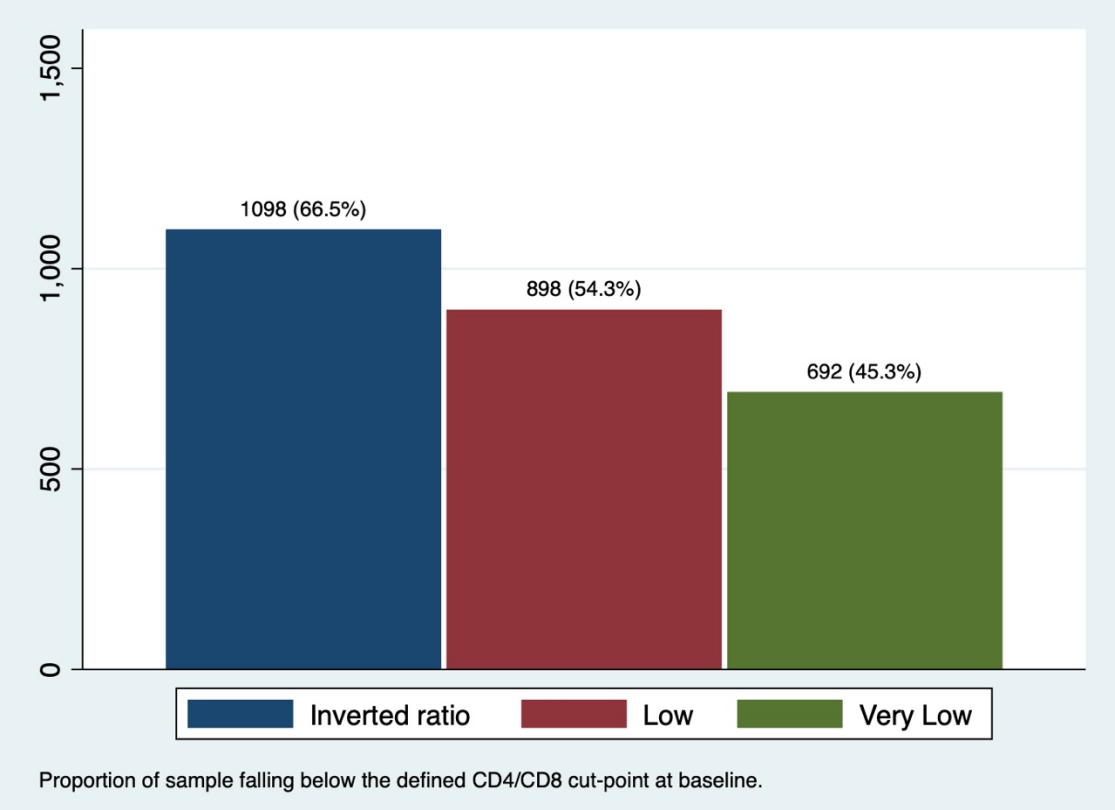

Figure 5.3: Proportion of HIV+ Women with Inverted, Low, and Very Low CD4/CD8 at Baseline

Inverted CD4/CD8 ratio (below 1.0), low ratio (below 0.70), and very low ratio (below 0.50). Total sample=1,527.

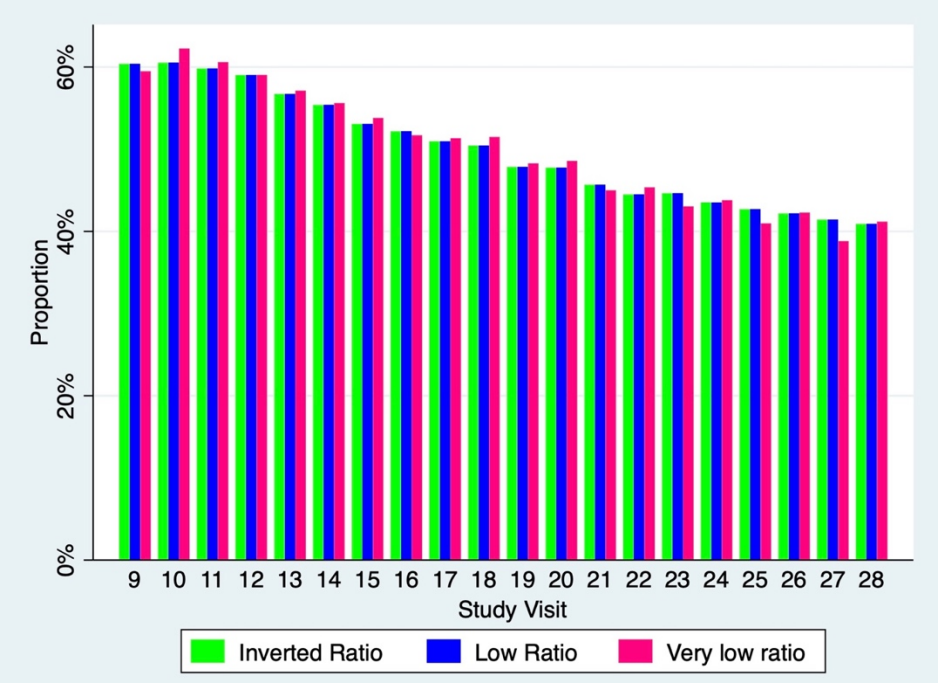

Figure 5.4: Proportion of HIV+ Women with Inverted, Low, and Very low CD4/CD8 at Each Study Visit

Inverted CD4/CD8 ratio (below 1.0), low ratio (below 0.70), and very low ratio (below 0.50).

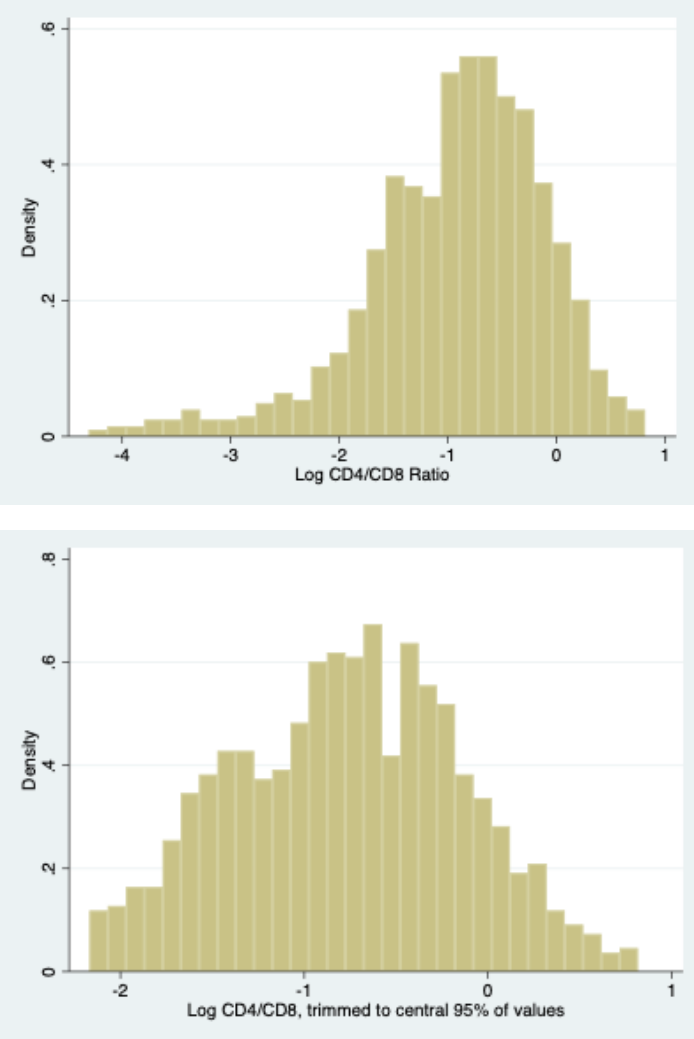

Figure 5.5: Baseline Distribution of Log CD4/CD8 ratio

The top plot shows the full distribution, including outlier values, and the bottom plot shows the trimmed distribution, which excludes the top and bottom 2.5% of distribution (extreme outliers).

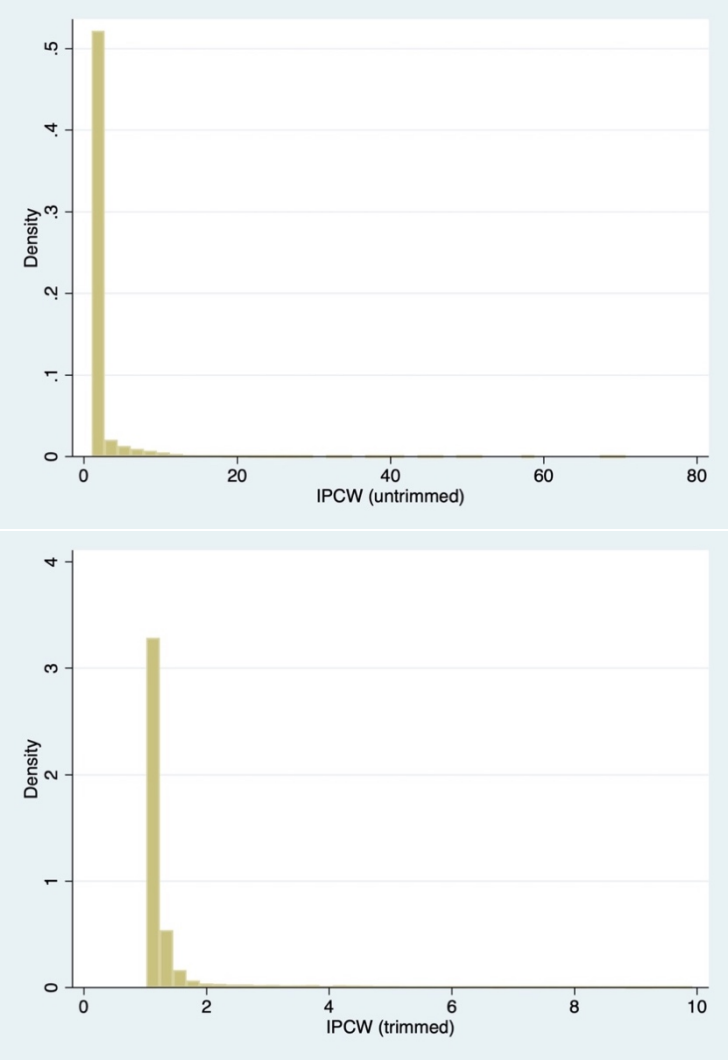

Figure 5.6: Distribution of Inverse Probability of Censoring Weights

The top plot shows the full distribution of IPCWs and the bottom plot shows the trimmed distribution of IPCWs, which excludes very large and very small weights

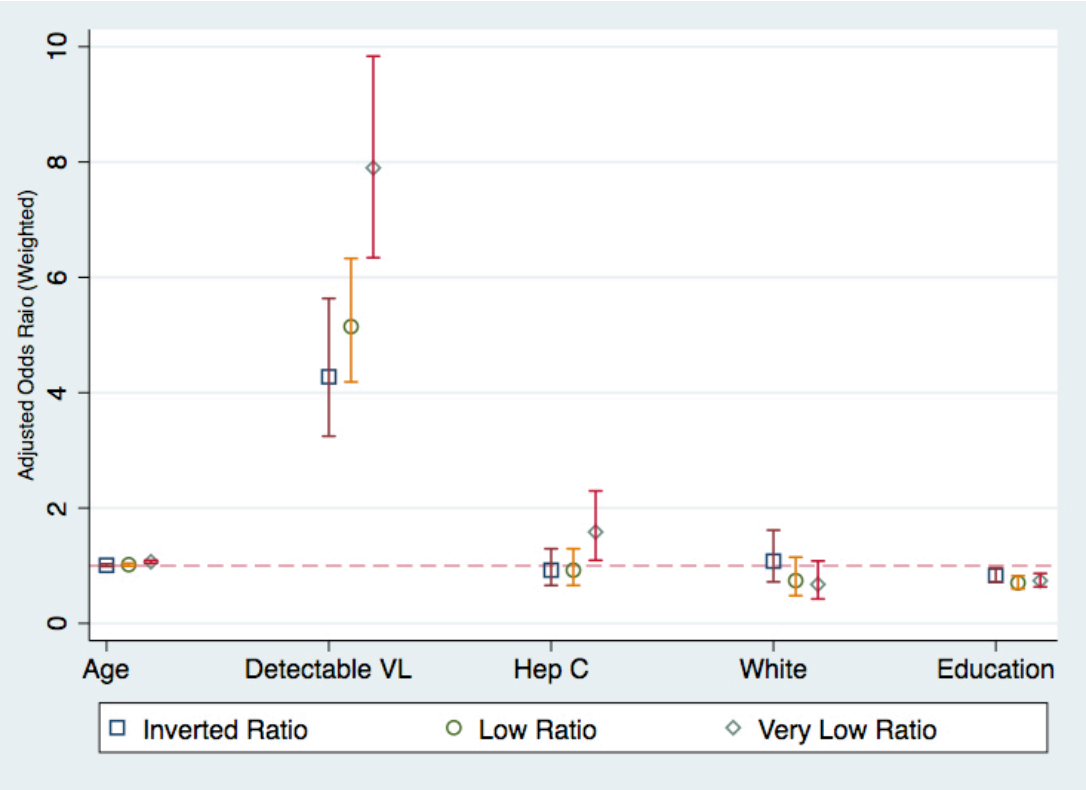

Figure 5.7: Adjusted Odds Ratio of Inverted, Low, and Very Low Cd4/CD8 Ratio by Independent Variables

Inverted CD4/CD8 ratio (≤1.0) (square), low ratio (≤0.70) (circle), and very low ratio (≤ 0.50) (diamond). Reference line for Odds Ratio=1.0

Appendices

Appendix 5.A: Comparison of Sample Characteristics at the Analytic Baseline and Study Baseline

Table 5.7: Sample Characteristics Among HIV+ WIHS-PDS Cohort at Study Baseline (visit 1) and Analysis Baseline (visit 9)		
	Visit 1 (n=2,053)	Visit 9 (n=1,292)
CD4/CD8 cell ratio		
Absolute CD4/CD8 (median, IQR)	0.34 (0.21, 2.38)	0.45 (0.25 – 0.70)
Inverted Ratio (< 1.0), (n %)	1,816 (88.46%)	1078 (83.44%)
Inverted Ratio (< 0.70), (n %)	1,566 (76.28%)	892 (69.04%)
CD4 T-cell lymphocytes, (mean, SD)	376.53 (283.83)	404 (268)
CD8 T-cell lymphocytes, (median, IQR)	772 (527.5 – 1102)	785 (528 – 3791)
Detectable viral load, (n %)	1,902 (94.72%)	874 (70.43%)
Past 6-month ART adherence ≥ 95% *	--	888 (53.75%)
Years living w/ HIV at recruitment, (mean, SD)	3.76 (2.76)	3.68 (2.66)
Hepatitis C, (n %)	859 (43.17%)	506 (41.17%)
CMV exposure, (n %)	10 (0.49%)	8 (0.62%)
Age, (mean, SD)	36.32 (7.85)	36.18 (7.82)
Racial group, (n %)		
White	404 (19.68%)	237 (18.40%)
Black/African American	1,160 (56.50%)	727 (56.40%)
Asian	14 (0.68%)	13 (1.01%)
Native American/Alaska Native	128 (6.23%)	99 (7.68%)
Native Hawaiian / Other Pacific Islander	450 (21.92%)	303 (23.52%)
Latinx Ethnicity, (n %)	482 (23.51%)	320 (24.81%)
Ever used illicit drugs, (n %)	1,439 (70.09%)	1,403 (68.34%)
Past 6-month illicit drug use	--	942 (73.02%)
Smoking, (n %)		
Smoked ≥100 cigarettes in lifetime	1,499 (73.26%)	709 (56.05%)
Current smoker	1,141 (76.07%)	709 (54.88%)
CES-D score, (mean, SD)	23.57 (9.63)	21.32 (8.96)

	Visit 1 (n=2,053)	Visit 9 (n=1,292)
CES-D ≥ 16, (n %)	1,575 (77.82%)	869 (68.86%)
Education Level, (n %)		
No school	12 (0.59%)	9 (0.71%)
Grades 1-6	83 (4.05%)	52 (4.09%)
Grade 7-11	668 (32.57%)	403 (31.73%)
High School	644 (31.40%)	398 (31.34%)
Some college	502 (24.48%)	315 (24.80%)
4 years college	98 (4.78%)	65 (5.12%)
Some/Complete Grad School	44 (2.15%)	28 (2.20%)
Missing	2 (0.10%)	22 (1.70%)
Mother's Education Level, (n %)		
No school	48 (3.27%)	33 (3.63%)
Grades 1-6	224 (15.26%)	149 (16.39%)
Grade 7-11	311 (21.19%)	197 (21.67%)
High School	552 (37.60%)	336 (36.96%)
Some college	172 (11.72%)	96 (10.56%)
4 years college	122 (8.31%)	75 (8.25%)
Some/Complete Grad School	39 (2.66%)	23 (2.53%)
Missing	585 (28.49%)	383 (29.64%)
Social Support, (n %)		
3=High	1,314 (64.95%)	768 (61.10%)
2=Moderate – high	445 (22.00%)	300 (23.87%)
1=Moderate – low	135 (6.67%)	74 (5.89%)
0=low	129 (6.38%)	115 (9.15%)
Average monthly income, (n %)		
$500 or less	458 (26.11%)	291 (22.52%)
$501-$1000	605 (34.49%)	373 (28.87%)
$1001-$1500	229 (13.06%)	151 (11.69%)
$1501-$2000	152 (8.67%)	104 (8.05%)
$2001-$2500	102 (5.82%)	61 (4.72%)
$2501-$3000	74 (4.22%)	45 (3.48%)
$3001-$6250	102 (5.82%)	69 (5.34%)
> $6250	32 (1.82%)	19 (1.47%)

Residential Status, (n %)		
	Visit 1 (n=2,053)	Visit 9 (n=1,292)
Own house/apartment	1,395 (68.18%)	894 (69.20%)
Marginal or Transitional Residence	564 (27.57%)	340 (26.32%)
Homeless	87 (4.25%)	52 (4.02%)

Appendix 5.B: Unweighted Models

Table 5.8: Fixed and Random Effects of Sociodemographic and Clinical Characteristics on Log CD4/CD8 Ratio Over 10 years (Unweighted)

	Full Distribution CD4/CD8 [a] (n=1,372)			Outlier-excluded CD4/CD8 distribution [a,d] (n=1,293)		
	Coefficient	95% Confidence Interval	P-value	Coefficient	95% Confidence Interval	P-value
Fixed Effects [b]						
Time (months)	-0.011	-0.017, -0.005	0.000	0.001	-0.004, 0.005	0.787
Age	-0.007	-0.001, -0.001	0.021	-0.007	-0.012, -0.001	0.014
Years Living with HIV	-0.023	-0.043, -0.004	0.021	-0.015	-0.0314, 0.000	0.052
Detectable Viral Load	-0.281	-0.304, -0.259	0.000	-0.246	-0.267, -0.227	0.000
Hepatitis C	0.036	-0.078, 0.150	0.539	-0.009	-0.099, 0.082	0.852
ART Adherence	0.081	0.062, 0.100	0.000	0.054	0.038, 0.070	0.000
Smoked ≥100 cigarettes in lifetime	0.219	0.092, 0.344	0.001	0.138	0.040, 0.235	0.006
Illicit Drug Use	0.004	-0.012, 0.022	0.579	0.009	-0.006, 0.023	0.262
Depressive symptoms (CES-D score)	-0.001	-0.001, 0.001	0.377	-0.000	-0.001, 0.001	0.524
Education level	0.043	-0.002, 0.088	0.062	0.024	-0.013, 0.060	0.200
Random Effects [c]						
Variance	0.108	0.098, 0.119	--	0.068	0.064, 0.072	--
Intercept	0.707	0.629, 0.793	--	0.444	0.401, 0.491	--
Slope	0.002	0.001, 0.002	--	0.000	0.001, 0.001	--
Intraclass Correlation Coefficient (ICC)	0.867	0.848, 0.884	--	0.867	0.852, 0.881	--
Model Selection Criteria						
AIC	16371.00			9182.082		
BIC	16476.84			9287.083		
Log Likelihood	-8171.501			-4577.041		

[a] Log transformed CD4/CD8 ratio
[b] Fixed effect estimates of the relationship between independent variables and CD4/CD8 within individuals
[c] Random effects estimates are estimated variances and can be interpreted as the magnitude of the variability of intra-individual coefficients from the mean fixed effects coefficient. The ICC is the proportion of the total variance in the outcome that is accounted for by clustering; It can be interpreted as the correlation among observations within the same cluster.

[d] Trimmed to central 95% of values to avoid bias from very large and very small weights

Table 5.9: Odds of Inverted [a] or Low [b] CD4/CD8 Cell Ratio among Women Living with HIV (Unweighted)				
	Inverted CD4/CD8 ratio [a] (n=946)		Low CD4/CD8 ratio [b] (n=946)	
	AOR (95% CI) | *P*-value			
Depressive Symptom Score (CESD)	0.993 (0.982, 1.004)	0.194	1.003 (0.994, 1.012)	0.541
Age	1.002 (0.976, 1.030)	0.864	1.014 (0.988, 1.041)	0.295
Detectable Viral Load	4.073 (3.347, 4.956)	0.000	5.075 (4.346, 5.926)	0.000
ART adherence	0.921 (0.771, 1.101)	0.367	0.870 (0.753, 1.005)	0.058
Smoked ≥100 Cigarettes in Lifetime	1.358 (0.877, 1.102)	0.170	1.265 (0.826, 1.937)	0.280
Illicit Drug Use	0.998 (0.852, 1.168)	0.976	0.937 (0.827, 1.061)	0.302
Hepatitis C	0.861 (0.558, 1.328)	0.498	0.975 (0.640, 1.484)	0.904
White Racial Group	1.084 (0.648, 1.811)	0.759	0.771 (0.468, 1.271)	0.308
Education Level	0.832 (0.692, 0.999)	0.049	0.718 (0.600, 0.860)	0.000

[a] Defined as (CD4/CD8 ≤ 1.00)
[b] Defined as (CD4/CD8 ≤ 0.70)

Appendix 5.C: Bias analysis: Stratification of independent and dependent variables by censorship

Table 5.10: Censorship Through Mortality or Attrition During Study Period by Baseline Sample Characteristics		
	Censored (n=400)	Not Censored (n=1,003)
	n (%) or Mean (SD)	
CD4/CD8 cell ratio		
Log CD4/CD8	-1.39 (0.99)	-0.76 (0.71)
Inverted Ratio (< 1.0)	297 (85.59%)	772 (82.66%)
Low Ratio (< 0.70)	270 (77.81%)	613 (65.63%)
Detectable viral load	269 (82.77%)	598 (66.08%)
ART adherence	215 (61.96%)	661 (70.77%)
Years living with HIV	3.97 (2.88)	3.57 (2.56)
Hepatitis C	194 (59.33%)	307 (34.38%)
Age	38.58 (7.82)	35.27 (7.66)
Racial group		
White	47 (13.54%)	186 (19.98%)
Black/African American	225 (64.84%)	498 (53.43%)
Asian	9 (0.97%)	4 (1.15%)
Native American/Alaska Native	95 (10.19%)	2 (0.58%)
Native Hawaiian / Other Pacific Islander	69 (19.88%)	232 (24.92%)
Latinx Ethnicity	73 (21.04%)	246 (26.39%)
Past 6-month Illicit drug use	253 (63.25%)	760 (77.75%)
Smoking		
Smoked at least 100 cigarettes/life	283 (81.79%)	651 (69.70%)
Smoked in past 6 months	239 (71.77%)	464 (50.38%)
Education Level		
No school	2 (0.59%)	7 (0.76%)
Grades 1-6	11 (3.26%)	41 (4.45%)
Grade 7-11	127 (37.69%)	276 (29.93%)
High School	109 (32.34%)	284 (30.80%)
Some college	76 (22.55%)	234 (25.38%)
4 years college	8 (2.37%)	57 (6.18%)

Table 5.10: Censorship Through Mortality or Attrition During Study Period by Baseline Sample Characteristics ***Continued***		
Some/Complete Grad School	4 (1.19%)	23 (2.49%)
CES-D score	23.90 (10.05)	20.37 (8.35)
CES-D ≥ 16	612 (66.59%)	248 (74.70%)
Social Support		
3 High	44 (13.25%)	70 (7.66%)
2 Moderate – High	23 (6.93%)	50 (5.47%)
1 Moderate – Low	65 (19.58%)	233 (25.49%)
0 Low	200 (60.24%)	561 (61.38%)
Average monthly income		
$500 or less	91 (32.16%)	199 (24.27%)
$501-$1000	105 (37.10%)	264 (32.20%)
$1001-$1500	40 (14.13%)	109 (13.29%)
$1501-$2000	20 (7.07%)	84 (10.24%)
$2001-$2500	12 (4.24%)	47 (5.73%)
$2501-$3000	4 (1.41%)	41 (5.00%)
$3001-$6250	7 (2.47%)	62 (7.56%)
> $6250	4 (1.41%)	14 (1.71%)
Residential Status		
Own house/apartment	210 (60.52%)	676 (72.38%)
Marginal or Transitional Residence	114 (32.85%)	224 (23.98%)
Homeless	21 (6.05%)	31 (3.32%)

Appendix 5.D: Bias analysis: Association of Inverted and Low Ratio with censorship, adjusted for Independent Variables

Table 5.11: Association of Inverted CD4/CD8 Cell Ratio with Censorship, Adjusted for Key Independent Variables			
		AOR (95% CI)	*P*-value
Censoring	1.265	(0.479, 3.342)	0.636
Detectable Viral Load	4.306	(3.555, 5.215)	0
ART Adherence	0.935	(0.787, 1.111)	0.443
Hepatitis C	0.8	(0.512, 1.25)	0.327
White Racial Group	1.052	(0.633, 1.748)	0.845
Illicit Drug Use	1.025	(0.885, 1.187)	0.741
Lifetime Smoking	1.373	(0.886, 2.128)	0.157
Depression (CES-D score)	0.992	(0.981, 1.002)	0.124
Education	0.813	(0.678, 0.975)	0.026
Age	1	(0.973, 1.027)	0.973
Residential Status			
Own Housing		REF	
Marginal Housing	1.104	(0.697, 1.748)	0.673
Homeless	0.737	(0.25, 2.175)	0.58

Table 5.12: Association of Low CD4/CD8 Cell Ratio with Censorship, Adjusted for Key Independent Variables			
		AOR (95% CI)	*P*-value
Censoring	1.356	(0.557, 3.304)	0.502
Detectable Viral Load	5.299	(4.563, 6.153)	0.000
ART Adherence	0.873	(0.760, 1.003)	0.055
Hepatitis C	0.922	(0.599, 1.419)	0.711
White Racial Group	0.803	(0.491, 1.313)	0.381
Illicit Drug Use	0.964	(0.858, 1.083)	0.535
Lifetime Smoking	1.283	(0.837, 1.966)	0.253
Depression (CES-D score)	1.000	(0.991, 1.009)	0.933
Education	0.711	(0.596, 0.849)	0.000
Age	1.013	(0.987, 1.039)	0.323
Residential Status			
Own Housing		REF	
Marginal Housing	1.015	(0.653, 1.578)	0.947
Homeless	0.621	(0.216, 1.786)	0.377

Chaper 6

Synthesis of Papers

The purpose of the synthesis of papers is to summarize and tie together the dissertation results. First, each of the study results will be summarized and discussed within the theoretical context of the dissertation work. Second, key themes and implications for nursing praxis that emerged across studies will be synthesized. Third, the overall limitations and directions for future research are discussed.

In seronegative populations, cognitive impairment and dementia is consistently associated with aspects of social connectedness—particularly loneliness, social isolation/support, and social networks (Kuiper et al., 2015). This association has not been firmly established among PLWH, although on average PLWH experience more loneliness and isolation than the general population. The 2nd chapter of this dissertation systematically examined the current body of quantitative literature examining the relationship between cognitive impairment, loneliness, and social isolation among adults living with HIV. This study used meta-analysis and meta-regression to summarize the associations of these variables in the literature. Overall, eleven (11) studies were reviewed, but were limited by the use of un-validated scales and measures of loneliness and social support as well as heterogeneous measures of cognitive symptoms and cognitive status. Across studies reviewed, increased cognitive impairment was associated with increased social isolation or loneliness. We found moderate heterogeneity for the pooled model, and there was not substantial publication bias. Meta-regression showed moderation by study quality, older age (≥55 years), and study country but not by CD4 cell count.

Current literature shows poor concordance between self-reported cognitive symptoms and performance based cognitive impairment measured by neuropsychological testing. This is seen in the general population (Brailean et al., 2019; Caracciolo et al., 2012; Reid et al., 2012; Slavin et al., 2010) as well as HIV-seropositive populations (Laverick et al., 2017; Thames et al., 2011). Because of this delineation between self-reported cognitive issues (symptoms) and cognitive performance (signs), we chose to examine four sub-group analyses in the meta-analysis. In these sub-group analyses, there was a significant positive association between a) self-reported cognitive impairment and loneliness or social isolation, b) performance based cognitive impairment and either loneliness or social isolation, and c)

social isolation and either self-report or performance based cognitive impairment. These sub-group analyses reflect distinctions between symptom and sign as well as various dimensions of social connectedness. Further research in this area is needed to more fully understand these complex relationships.

Chapter 3 examined the association of loneliness and social isolation with cognitive impairment among older adults (55 years and older) with confirmed HAND. Cognitive impairment was assessed with performance-based testing (NP testing battery) as well as a measure of subjective cognitive complaints (POAFI). The results of this study revealed that loneliness was correlated with mental health variables (depression, anxiety, and perceived stress) while social isolation was correlated with other marginalized conditions (history of HCV and history of substance use disorder) and socioeconomic factors (less education and area-level socioeconomic environment). This study also found that social isolation, but not loneliness, was associated with higher odds of impairment in certain cognitive domains (ATT and SPD).

Chapters 2 and 3 help elucidate aspects of social connectedness as a risk for cognitive impairment among PLWH. In chapter 2, across studies reviewed, increased cognitive impairment was associated with increased social isolation and loneliness. When examined separately, social isolation—but not loneliness—was associated with increased cognitive imapirment. In chapter 3, social isolation was associated with history of HCV, history of substance use disorders, lower years of education, area-level socioeconomic environment, and more severe cognitive impairment in two domains. In contrast, loneliness more closely aligned with psychosocial experiences and mental health symptoms and did not have a clear association with neurocognitive disorders among those with HIV. Using our theoretical model to interpret these results in concert, I surmise that social isolation is a particular pathway of embodiment, reflecting experiences of marginality that could have an impact on risk of HIV-associated cognitive impairment.

Chapter 4 was an exploratory analysis of biomarkers with clinical and sociodemographic characteristics among middle-aged and older adults 40 years and older living with HIV. In this paper, I

focused on the relationships between CD4/CD8 and pro-inflammatory serum biomarkers, including cytokines and monocyte subsets. I found that the lowest CD4/CD8 ratio tertile was associated with Hepatitis C, years living with HIV, and low nadir CD4 T-cell count (≤200 cells/uL). Adjusted regression analysis showed that the lowest CD4/CD8 tertile was associated with the higher inflammation profile, as measured by pro-inflammatory serum biomarkers. Additionally, the lowest CD4/CD8 tertile was associated with an expanded subset of mature monocytes. These findings suggest that lower CD4/CD8 ratios (<0.50) may provide clinically relevant information about chronic inflammation, which may impact risk for neurocognitive impairment and other health conditions among aging PLWH.

As Nancy Krieger states, embodiment is all at once an abstract idea, a concrete reality, and a process that is "contingent upon bodily existence" (Krieger, 2005, p.351). Using our modified theoretical model, I therefore view the CD4/CD8 as an embodied biomarker, shaped by the existence and "story" of the body living with HIV. Among middle aged adults with HIV, keys parts of this story were revealed in chapter 4. I found that Hepatitis C, the number of years living with HIV, and having a low nadir CD4 T-cell count (≤200 cells/uL) were associated with CD4/CD8 ratio. The link between these factors and HAND have been previously established in the literature (Winston & Spudich, 2020). Although we were not able to test the specific relationship of CD4/CD8 ratio with neurocognitive impairment in this study, our evidence suggests that CD4/CD8 ratio reflects systemic inflammation and the expansion of mature monocytes that can cross the blood brain barrier and produce neuroinflammation, all of which could impact brain health among those aging with HIV. Therefore low CD4/CD8 ratio should be further investigated as a biomarker of risk for cognitive impairment among PLWH.

In chapter 5, I incorporated findings from chapter 4 to develop additional research questions about the CD4/CD8 ratio in a representative sample of women living with HIV (n=1,462). This study examined the intra-individual variability of the CD4/CD8 ratio over 10 years as well as the clinical and sociodemographic correlates of inverted (≤1.0) and low (≤0.70) CD4/CD8 ratio among women living with HIV. The results showed that, over 10 years, CD4/CD8 ratio was relatively stable (ICC=89.5%) and

there was no significant trend for time. CD4/CD8 ratio decreased with age and detectable viral load and increased with ART adherence. Inverted ratio (≤1.0) and low ratio (≤0.70) CD4/CD8 ratio were associated with detectable viral load and fewer years of educational attainment. Because much of (81.71%) the WIHS sample ever had a CD4/CD8 ratio that was below 0.50, in addition to findings from chapter 4 that indicate CD4/CD8 ratio less than 0.501 is associated with inflammation, I performed a follow-up analysis on the binary variable of "very low" CD4/CD8 ratio (≤0.50 *versus* > 0.50). I saw that very low CD4/CD8 ratio was associated with increased age, detectable viral load, past or present Hepatitis C, white (versus non-white) racial group, and lower educational attainment. Notably, I did not see an association between social support and CD4/CD8 ratio at any threshold, though the validity and reliability of the social support measure is unknown. Overall, this study suggests that, among women with HIV, the CD4/CD8 ratio is associated with both individual and environmental factors, many of which are also implicated in cognitive impairment among PLWH.

In chapter 5, I found additional evidence to suggest that the CD4/CD8 biomarker covaried with certain sociodemographic and clinical characteristics. I also found that lower educational attainment, a fundamental/root cause of poor health, was associated with low as well as very low CD4/CD8 ratio. This reflects a key aspect of the embodiment construct—that the environment and root causes actively shape living beings, and are then in turn expressed in biological characteristics (Kreiger, 2005, p. 351). In HIV-seronegative populations, low educational attainment is a strong predictor of cognitive impairment and dementia (Glymour et al., 2008, 2012; Glymour & Manly, 2008; Weuve et al., 2018). Educational attainment is also known to be a racialized exposure in America society, which is to say that there are racial inequities and disparities in nearly all facets of the United States' education systems and educational outcomes. In linking CD4/CD8 ratio to lower educational attainment, chapter 5 implicates immune function and inflammation as embodied pathways by which root causes may impact risk of cognitive impairment. Although I was not able to test the specific relationship of educational attainment

and CD4/CD8 ratio with cognitive impairment in this study, this biomarker appears to be shaped by the existence and "stories" of the body living with HIV that impact on brain health in aging.

Another key finding in this dissertation research is the distinction between CD4/CD8 ratio cut-points and what may be considered clinically relevant for aging PLWH and risk of cognitive impairment. Bruno et al. (2017) states that there is still debate about thresholds for CD4/CD8 ratio among PLWH. In one prospective study of 4,206 PLWH, CD4/CD8 ratio only normalized (>1.0) in 7.2% of subjects after a median of 3 years (Leung et al., 2013). Though this was a cohort with relatively low nadir CD4 cell counts, it agrees with findings from the study by Mussini et al. (2015), which showed that in a sample of 3,236 PLWH only 12% achieved normalization after 2 years. Additionally, in a study with 15 years of follow-up, the authors showed that only 37% eventually achieved CD4/CD8 normalization despite most showing recovered CD4 T-cell counts (Saracino et al., 2014). Overall, CD4/CD8 ratio normalization to 1.0, appears to occur in relatively few PLWH and is commonly associated with ART and HIV viral suppression, nadir CD4 cell count, and age (Bruno et al., 2017). In each of the papers in this dissertation, when "very low"/first tertile (<0.50) CD4/CD8 ratio was examined, key relationships emerged that were not appreciated when higher thresholds under 1.0 were used. The results of these studies suggest that very low CD4/CD8 ratio may be conceptualized as an embodied pathway, reflecting both social and biological risks that have established links to cognitive impairment.

Limitations and Directions for Future Research

Although the particular limitations of each study are outlined in the respective limitation sections, there are important limitations of the overall dissertation. These overall limitations will be discussed below in terms of four types of validity outlines by Shadish, Cook, and Campbell (Shadish et al., 2002): Internal validity, statistical conclusion validity, construct validity, and external validity. *Validity* refers to the "approximate truth" of an inference made on the basis of scientific evidence (Shadish et al., 2002, p.34). A *threat* to validly is a reason why our inference or conclusion may be partially or completely wrong (Shadish et al., 2002, p.39).

Internal Validity

Internal validity refers to the question of whether the independent and dependent variables covary and whether other explanations for the covariation may have been excluded or accounted for. According to Shadish, Cook & Campbell, interval validity is not simply a matter of reproducibility or the notion of "measuring what one thinks they are measuring." Rather, it is about whether a "complex and inevitability multivariate treatment [exposure] caused a difference to some variable-as-it-was-measured within the particular setting, time frames, and kinds of units that were sampled in the study" (p.54). The studies in chapters 2, 3 and 4 were all cross sectional, which necessitates the threat of ambiguous temporal precedence. The study in chapter 5 examined a series of cross-sectional associations, averaged over time, and therefore cannot claim to have established temporal precedence. Therefore, this dissertation is limited in any inference about causality. Other threats to internal validity include possible issues of attrition/loss-to-follow-up or additive and interactive effects. Wherever possible, these threats were evaluated and accounted for in our data analyses.

Selection, or systematic differences of respondents, is also a threat to the internal validity of these studies. The characteristics of the three samples in chapters 3-5 were different in key ways, including gender, age, and co-occurring marginalized conditions. Additionally, the sample used in chapter 3 and many samples in chapter 2 excluded participants with a current substance use disorder or untreated/undertreated psychiatric disorders, which is a common exclusion criteria in studies of cognitive impairment. Overall, these sample differences may lead to selection bias and limit our ability to consider these studies in concert. Rather, we must acknowledge that the validity of the results is particular to the population from which the sample was drawn.

Another threat to the internal validity in this body of research is that of history, wherein events occurring concurrently with an exposure could cause an observed effect (p.55). For example, both cognitive impairment and CD4/CD8 ratio are known to be highly influenced by HIV viral suppression, nadir CD4 cell count, and ART treatment (Serrano-Villar & Deeks, 2015; Valcour et al., 2011). All of

these are impacted by community access to HIV screening, prevention, and treatment. Historical events that restrict or increase community access to screening prevention efforts commonly occur at the local and federal levels. Additionally, funding for access to healthcare and ART for PLWH, as well as changes to HIV standards of care, have continued to change since the onset of the HIV epidemic (CDC, 2020). As such, historical or cohort effects may cause bias in these studies (CDC, 2020).

Statistical Conclusion Validity

Statistical conclusion validity refers to the appropriateness of statistics to infer what the independent and dependent variables convey. In this dissertation, threats to statistical conclusion validity include low statistical power in some key analyses, including sub-group comparisons in the meta-analysis and a small number of studies included meta-regression in chapter 2, and small sample sizes in our exploratory analyses and latent profile analyses in chapter 4. The secondary data analysis approach threatens internal validity due to the increased likelihood of unmeasured confounding. Some have criticized statistical approaches that separately examine cognitive domains, as I did in chapter 3, as artificially inflating statistical significance; However, alternative approaches to analysis are not yet recommended, and many suggest that cognitive domains are not so similar as to produce multiple testing error (Gelman et al., 2012). A major threat to statistical conclusion validity in the extant literature was revealed in chapter 2—the use of heterogeneous, un-validated measures of social isolation, loneliness, and cognitive impairment. I aimed to minimize measurement error in chapter 3 with the use of a validated measures of loneliness and social isolation as well as use of NP test battery for cognitive impairment, which is considered gold-standard in determination of HAND. Lastly, I could not control for the effect of CMV exposure in any study, as this data was not available.

Construct Validity

Construct validity refers to the generalizability of study constructs, both in our understanding of them and measurement of them (Shadish, Cook, and Campbell, 2002, p.65). The constructs used in this

research are particularly important to our final results and conclusions. In chapters 2 and 3, the constructs of loneliness and social isolation are thought to be distinct and were measured and analyzed in different ways. Chapter 2 revealed substantial heterogeneity in the construct of social connectedness, with varied measures and interpretations of social isolation and loneliness among the studies. This chapter in particular may suffer from threat due to the inadequate explication of constructs across the studies reviewed. In chapter 3, the experience of loneliness, when measured with the UCLA, was more reflective of other mental health constructs (anxiety, depression, and stress). In contrast, the experience of social isolation, when measured with the NSS, reflected other marginalized conditions (hepatitis C, substance use disorder) as well as environmental measures of SEP. Our confidence in the validity of these constructs in chapter 3 is increased by a) use of validated measures for loneliness and social isolation, and b) the distinction between social isolation and loneliness in chapter 3 generally aligned with the findings from chapter 2. In chapter 5, social isolation was measured with an un-validated scale, which may have impacted by the validity of the findings. Because chapters 2, 3, and 5 rely on several self-report instruments, the results of these studies may be impacted by self-report changes, in which participants change their response on self-report instruments due to extraneous factors, reactivity to other elements of being the study, or expectancies of the interviewer/assessor. However, these threats to validity are unlikely to be consistent across our studies, which all used different recruitment methods, sampling strategies, and study procedures.

External Validity

External validity refers to the question of generalizability—of whether relationships are consistent across populations, settings, treatments, and variables (Shadish, Cook, and Campbell, 2002, p.83). One threat to the external validity of these findings is that relationships seen in the study samples may not hold if other populations had been studied. For example, as mentioned above, it is common practice to exclude people with active substance use disorders from research on neurocognitive conditions. Because substance use disproportionately impacts PLWH, the relationships seen in chapters 2

and 3 may not hold true in other populations of PLWH, such as the population from which the sample in chapter 5 was drawn. Similarly, the samples in chapters 3 and 4 were majority white (72.4% and 58.6%, respectively) and male (92.9% and 87.5%, respectively), therefore the results from these studies may not be generalizable to those from chapter 5 (18.4% white and 100% female). Additionally, there may be bias from interactive or additive effects by HIV treatment era in the external validly of our studies about the CD4/CD8 ratio.

Directions for Future Research

This dissertation research should be used to inform future nursing research in representative samples of PLWH as further evidence will help to clarify the relationships between biomarkers, environmental factors, and cognitive impairment among people aging with HIV. Inclusion of PEMC in studies about HAND and self-reported cognitive impairment will improve generalizability of results. The use of validated scales for measuring the distinct concepts of loneliness and social isolation will help to elucidate unique risk factors for HAND that are attributable to these experiences. Furthermore, social isolation among PLWH may be considered an area of interest for future nursing interventions.

Literature about the concept of the CD4/CD8 ratio biomarker is continuing to emerge, though this ratio is not commonly examined in clinical nursing practice. In general, CD4/CD8 ratio below 1.0 is thought to reflect risk of morbidity and mortality; however, the studies in this dissertation studies suggest that much lower thresholds should also be considered for translational and clinical nursing research. The CD4/CD8 ratio should continue to be explored as a biomarker as a risk factor for hand. Lower CD4/CD8 ($\leq$0.50) may reveal an embodied endophenotype that indicates increased screening for HAND in clinical practice, particularly among people who experienced HIV and other marginalized conditions.

Though research in marginalized populations is often approach from a disease-specific lens, it is important to recognize that PLWH have intersecting experiences environments and health conditions that interact and amplify risk of cognitive impairment. Kreiger states that the construct of embodiment stands

in contrast to “disembodied notions of ‘behaviours’ and ‘exposures’” (Kreiger, 2005, p. 350). The challenge for future research in this area is to engage with the meaning of embodiment in the intersecting domains of nursing science.

References

Brailean, A., Steptoe, A., Batty, G. D., Zaninotto, P., & Llewellyn, D. J. (2019). Are subjective memory complaints indicative of objective cognitive decline or depressive symptoms? Findings from the English Longitudinal Study of Ageing. *Journal of Psychiatric Research*, *110*, 143–151. https://doi.org/10.1016/j.jpsychires.2018.12.005

Bruno, G., Saracino, A., Monno, L., & Angarano, G. (2017). The Revival of an "Old" Marker: CD4/CD8 Ratio. *AIDS Reviews*, *19*(2), 81–88.

Caracciolo, B., Gatz, M., Xu, W., Pedersen, N. L., & Fratiglioni, L. (2012). Differential distribution of subjective and objective cognitive impairment in the population: A nation-wide twin-study. *Journal of Alzheimer's Disease: JAD*, *29*(2), 393–403. https://doi.org/10.3233/JAD-2011-111904

CDC. (n.d.). *HIV and AIDS Timeline*. Retrieved March 23, 2022, from https://npin.cdc.gov/pages/hiv-and-aids-timeline#1980

Gelman, A., Hill, J., & Yajima, M. (2012). Why We (Usually) Don't Have to Worry About Multiple Comparisons. *Journal of Research on Educational Effectiveness*, *5*(2), 189–211. https://doi.org/10.1080/19345747.2011.618213

Glymour, M. M., Kawachi, I., Jencks, C. S., & Berkman, L. F. (2008). Does childhood schooling affect old age memory or mental status? Using state schooling laws as natural experiments. *Journal of Epidemiology and Community Health*, *62*(6), 532–537. https://doi.org/10.1136/jech.2006.059469

Glymour, M. M., & Manly, J. J. (2008). Lifecourse social conditions and racial and ethnic patterns of cognitive aging. *Neuropsychology Review*, *18*(3), 223–254. https://doi.org/10.1007/s11065-008-9064-z

Glymour, M. M., Tzourio, C., & Dufouil, C. (2012). Is Cognitive Aging Predicted by One's Own or One's Parents' Educational Level? Results From the Three-City Study. *American Journal of Epidemiology*, *175*(8), 750–759. https://doi.org/10.1093/aje/kwr509

Krieger, N. (2005). Embodiment: A conceptual glossary for epidemiology. *Journal of Epidemiology & Community Health*, *59*(5), 350–355. https://doi.org/10.1136/jech.2004.024562

Kuiper, J. S., Zuidersma, M., Oude Voshaar, R. C., Zuidema, S. U., van den Heuvel, E. R., Stolk, R. P., & Smidt, N. (2015). Social relationships and risk of dementia: A systematic review and meta-analysis of longitudinal cohort studies. *Ageing Research Reviews*, *22*, 39–57. https://doi.org/10.1016/j.arr.2015.04.006

Laverick, R., Haddow, L., Daskalopoulou, M., Lampe, F., Gilson, R., Speakman, A., Antinori, A., Bruun, T., Vassilenko, A., Collins, S., & Rodger, A. (2017). Self-Reported Decline in Everyday Function, Cognitive Symptoms, and Cognitive Function in People With HIV. *J Acquir Immune Defic Syndr*, *76*(3), e74–e83. https://doi.org/10.1097/qai.0000000000001468

Leung, V., Gillis, J., Raboud, J., Cooper, C., Hogg, R. S., Loutfy, M. R., Machouf, N., Montaner, J. S. G., Rourke, S. B., Tsoukas, C., Klein, M. B., & CANOC Collaboration. (2013). Predictors of CD4:CD8 ratio normalization and its effect on health outcomes in the era of combination antiretroviral therapy. *PloS One*, *8*(10), e77665. https://doi.org/10.1371/journal.pone.0077665

Mussini, C., Lorenzini, P., Cozzi-Lepri, A., Lapadula, G., Marchetti, G., Nicastri, E., Cingolani, A., Lichtner, M., Antinori, A., Gori, A., & Monforte, A. d'Arminio. (2015). CD4/CD8 ratio normalisation and non-AIDS-related events in individuals with HIV who achieve viral load suppression with antiretroviral therapy: An observational cohort study. *The Lancet HIV*, *2*(3), e98–e106. https://doi.org/10.1016/S2352-3018(15)00006-5

Reid, M., Parkinson, L., Gibson, R., Schofield, P., D'Este, C., Attia, J., Tavener, M., & Byles, J. (2012). Memory Complaint Questionnaire performed poorly as screening tool: Validation against psychometric tests and affective measures. *Journal of Clinical Epidemiology*, *65*(2), 199–205. https://doi.org/10.1016/j.jclinepi.2011.06.006

Saracino, A., Bruno, G., Scudeller, L., Volpe, A., Caricato, P., Ladisa, N., Monno, L., & Angarano, G. (2014). Chronic Inflammation in a Long-Term Cohort of HIV-Infected Patients According to the Normalization of the CD4:CD8 Ratio. *AIDS Research and Human Retroviruses*, *30*(12), 1178–1184. https://doi.org/10.1089/aid.2014.0080

Serrano-Villar, S., & Deeks, S. G. (2015). CD4/CD8 ratio: An emerging biomarker for HIV. *The Lancet HIV*, *2*(3), e76–e77. https://doi.org/10.1016/S2352-3018(15)00018-1

Shadish, W. R., Cook, T. D., & Campbell, D. T. (2002). *Experimental and quasi-experimental designs for generalized causal inference*. Houghton, Mifflin and Company.

Slavin, M. J., Brodaty, H., Kochan, N. A., Crawford, J. D., Trollor, J. N., Draper, B., & Sachdev, P. S. (2010). Prevalence and Predictors of "Subjective Cognitive Complaints" in the Sydney Memory and Ageing Study. *The American Journal of Geriatric Psychiatry*, *18*(8), 701–710. https://doi.org/10.1097/JGP.0b013e3181df49fb

Thames, A. D., Kim, M. S., Becker, B. W., Foley, J. M., Hines, L. J., Singer, E. J., Heaton, R. K., Castellon, S. A., & Hinkin, C. H. (2011). Medication and finance management among HIV-infected adults: The impact of age and cognition. *J Clin Exp Neuropsychol*, *33*(2), 200–209. https://doi.org/10.1080/13803395.2010.499357

Valcour, V., Sithinamsuwan, P., Letendre, S., & Ances, B. (2011). Pathogenesis of HIV in the central nervous system. *Current HIV/AIDS Reports*, *8*(1), 54–61. https://doi.org/10.1007/s11904-010-0070-4

Weuve, J., Barnes, L. L., Mendes de Leon, C. F., Rajan, K. B., Beck, T., Aggarwal, N. T., Hebert, L. E., Bennett, D. A., Wilson, R. S., & Evans, D. A. (2018). Cognitive Aging in Black and White Americans: Cognition, Cognitive Decline, and Incidence of Alzheimer Disease Dementia. *Epidemiology*, *29*(1), 151. https://doi.org/10.1097/EDE.0000000000000747

Winston, A., & Spudich, S. (2020). Cognitive disorders in people living with HIV. *The Lancet HIV*, *7*(7), e504–e513. https://doi.org/10.1016/S2352-3018(20)30107-7

Table 6.1: Dissertation Papers Summary

	Sample & Population	Dependent Variables	Independent Variable	Analysis Approach	Findings
Paper 1	N=11 studies concerning social isolation/social support, and loneliness are associated with cognitive impairment in adults living with HIV	Cognitive impairment: 1) Self-reported symptoms 2) Performance based tests	Social connectedness: 1) Loneliness 2) Social Isolation	*Approach*: Systematic Review; Meta-analysis / meta-regression with sub-group analyses *Methods*: Random-effects (RE) pooled meta-analysis, RE meta-regression	Studies were limited by the use of un-validated measures of loneliness/social support and heterogeneous measures of cognitive symptoms/ cognitive performance. Increased cognitive impairment was associated with increased social isolation or loneliness. There was moderate heterogeneity and no substantial publication bias. Meta-regression showed moderation by study quality, older age (≥55 years), and study country but not by CD4 cell count.
Paper 2	N=171, individuals recruited in the San Francisco Bay Area for a Mindfulness Based Stress Reduction (MBSR) randomized control trial. PLWH with confirmed HAND, ages 55 and over	Degree of HIV-Associated Neurocognitive Disorder (Mild-moderate impairment versus severe impairment)	1) Loneliness (UCLA-20 item scale) 2) Social isolation (Norbeck Social Support scale)	*Approach*: Secondary data analysis *Method*: Regression analysis	Loneliness was correlated with mental health variables (depression, anxiety, and perceived stress) while social isolation was correlated with other marginalized conditions (history of HCV and history of substance use disorder) and socioeconomic factors (lower years of education, and Black/African American race, and area-level socioeconomic environment). Social isolation, but not loneliness, was associated with higher odds of impairment in two cognitive domains (ATT and SPD).

	Sample & Population	Dependent Variables	Independent Variable	Analysis Approach	Findings
Paper 3	N=103, the Hawaii Aging with HIV Cardiovascular Study (HAHCS) cohort-Public Data Set (HAHCS-PDS), age 40+ years from the baseline cohort of the HAHCS	CD4/CD8 ratio	Sociodemographic and clinical characteristics (n=103); Inflammatory biomarkers (n=87); Monocyte subsets (n= 75)	*Approach*: Secondary data analysis of HAHCS- PDS cohort *Methods*: Latent Profile Analysis and Regression analysis	The lowest CD4/CD8 ratio tertile was associated with Hepatitis C, years living with HIV, and low nadir CD4 T-cell count (≤200 cells/uL). When compared to the highest CD4/CD8 tertile, the lowest tertile of CD4/CD8 was associated with having a high inflammation profile and an expanded subset of mature monocytes
Paper 4	N=1,462 HIV+ women in Women's Interagency HIV Study Public Data Set (WIHS-PDS)	CD4/CD8 ratio	Sociodemographic & clinical characteristics, social support, and depression (N=1,462)	*Approach*: Secondary data analysis of WIHS-PDS cohort, 10 years in pre-ART era *Method*: Mixed-effect models to examine intra-individual variability; Random-effects logistic regression for longitudinal data, using IPCWs for censoring bias	Over 10 years, CD4/CD8 ratio decreased with age and detectable viral load while it increased with >95% ART adherence. Inverted ratio (≤1.0 *vs* > 1.0) and low ratio (≤0.70 *vs* > 0.70) ratio were associated with detectable viral load and fewer years of educational attainment. In follow-up analyses, "very low" ratio (≤0.50 *vs* > 0.50) was associated with increased age, detectable viral load, past or present Hepatitis C, white (*vs* non-white) racial group, and lower educational attainment.

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