PREVALENCE OF NEUROCOGNITIVE DISORDERS AND POTENTIAL CORRELATES IN THE PITT MEN'S STUDY COHORT

by

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ABSTRACT

Background: While people living with HIV (PLWH) are able to enjoy relatively good health due to the advent of combination antiretroviral therapy (cART), some aging HIV-positive individuals have demonstrated neurocognitive impairments which are not associated with other comorbidities. This condition, classified as HIV-associated neurocognitive disorder (HAND), has a spectrum of severity consisting of asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND), and HIV-associated dementia (HAD).

Objective: The purpose of this study is to investigate the prevalence of neurocognitive disorders within the Pitt Men's Study cohort, and identify correlating variables that could be potential risk factors for the disease.

Methods: The Pitt Men's Study is a sub-cohort of the Multicenter AIDS Cohort Study, and is a prospective study of gay and bisexual men. Neuropsychological impairment is diagnosed through the use of an algorithm developed by the HIV Neurobehavioral Research Center, which classifies disease based on an individual's scores in a series of neuropsychological function tests. SAS Statistical Software 9.4 was utilized for data analysis.

Results: There was no significant difference in frequency of neurocognitive disorders between HIV-negative and HIV-positive individuals. The rate of HAND in HIV-negative individuals was

31.89% while the rate in HIV-positive individuals was 31.82%. In individuals under 50 years old, ever having been infected with Hepatitis C virus was significantly higher in the neurocognitive disorder group than the normal group.

Conclusion: There is no evidence of HAND in the PMS cohort; rates of neurocognitive disorder are higher in the HIV-negative group than expected. The only significant risk factor for neurocognitive disorder found in the cohort was Hepatitis C virus infection in individuals under 50 years old.

Public Health Significance: Neurocognitive disorders have the potential to cause a reduction in quality of life. While there was no evidence of HAND in the PMS cohort, a large proportion of HIV-positive and HIV-negative MSM demonstrate neurocognitive disorders. This study may indicate a high prevalence of neurocognitive disorders in MSM due to an unknown risk factor. Further investigation is critical to identify risk factors of neurocognitive disorders.

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ACKNOWLEDGEMENTS

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ABBREVIATIONS

AIDS	Acquired immunodeficiency syndrome
ANI	Asymptomatic neurocognitive impairment
CHARTER	CNS HIV Antiretroviral Therapy Effects Research
CNS	Central nervous system
HAD	HIV-associated dementia
HAND	HIV-associated neurocognitive disorder
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
HNRC	HIV Neurobehavioral Research Center
IADL	Index of activities of daily living
MACS	Multicenter AIDS Cohort Study
MND	Mild neurocognitive disorder
MSM	Men who have sex with men
PMS	Pitt Men's Study
SD	Standard deviation

1.0 INTRODUCTION

Human Immunodeficiency Virus (HIV) and Acquired Immunodeficiency Syndrome (AIDS) are a global health concern. It is estimated that there are 36.9 million people living with HIV/AIDS(PLWH) worldwide, where individuals over 50 years old account for 3.6 million people ("AIDSinfo | UNAIDS," n.d.). ("HIV and Aging," n.d.). There are 1.2 million PLWH in the U.S, of which 21% are over 50 years old ("HIV Among People Aged 50 and Over | Age | HIV by Group | HIV/AIDS | CDC," n.d.). The use of combination antiretroviral therapy (cART) to treat HIV and prevent the development of AIDS has allowed PLWH to live into old age, and die from chronic diseases not related to HIV/AIDS(R K Heaton et al., 2010).

However, while PLWH are able to enjoy relatively good health, aging HIV-positive individuals have demonstrated neurocognitive impairments not associated with other comorbidities. This condition, classified as HIV-associated neurocognitive disorder (HAND), can be so mild that it does not impact daily life of patients, or it can develop into dementia. One study found that 32.7% of all HIV-positive individuals in the cohort had asymptomatic neurocognitive impairment (ANI), 11.7% had mild neurocognitive disorder (MND), and 2.4% had HIV-associated dementia (HAD)(R K Heaton et al., 2010). Due to the potential impacts of HAND on critical day-to-day activities, including employment, driving, and managing medications, the disorder is of great public health concern (Robert K. Heaton et al., 2011).

The purpose of this study is to investigate the prevalence of HAND within the Pitt Men's Study cohort, and investigate correlating variables that could be potential risk factors for the disease. Limited investigation has been performed in the Pitt Men's Study data set in regards to HAND. By investigating prevalence of cognitive impairment and any correlates, a door will be opened for other investigators to evaluate HAND and potential risk factors within the Pitt Men's Study data set.

2.0 BACKGROUND

2.1 HIV INFECTION OVERVIEW

Transmission of HIV occurs when the virus enters the blood stream through direct contact, such as injection, or when the virus permeates mucosal tissue after exposure to bodily fluids of an infected individual. HIV is frequently transmitted through vaginal and anal sex, as well as the sharing of contaminated needles for intravenous drug use.

Acute HIV infection often presents with flu-like symptoms, lasting for roughly 2 weeks. Seroconversion occurs between 3 to 6 weeks after initial infection (Nguyen & Holodniy, 2008). After acute infection, the chronic infection period can last as long as 10 to 15 years without treatment. Generally individuals in this phase of the infection are asymptomatic. The immune system is able to function properly, fighting off infections and controlling HIV replication (Nguyen & Holodniy, 2008). As the virus destroys CD4 cells, an individual will develop late stage HIV infection, also known as acquired immunodeficiency syndrome (AIDS). Without treatment, those who develop AIDS will die from complications of the disease within three years (Nguyen & Holodniy, 2008).

2.2 HIV AND NEUROCOGNITIVE DISORDERS

2.2.1 HIV and Mental Disorders

While it is well known that HIV/AIDS results in opportunistic infections and illnesses in individuals, the virus is also linked to higher rates of mental illness. HIV-infected older individuals have higher rates of depression, and poorer cognitive function, compared to HIV-negative controls. In addition to causing HAND, HIV infection is correlated with increased rates of active psychiatric disorders, such as bipolar disorder and mania, depression, psychosis, anxiety disorders, and substance abuse disorders (Nguyen & Holodniy, 2008). Nguyen & Holodniy reported that HIV-infected patients had a higher prevalence of alcohol/drug abuse and depression when compared to age-matched controls (Nguyen & Holodniy, 2008).

2.2.2 HAND Symptoms

Symptoms of HAND include impairment in dexterity, fine motor speed, aspects of memory and learning, speed of information processing, and several executive functioning domains. In addition, to a decrease in ability to concentrate, depression, motor dysfunction, frank dementia, and behavioral abnormalities (Nasi et al., 2014)(Ghafouri, Amini, Khalili, & Sawaya, 2006) (Giesbrecht et al., 2014). HAND also causes changes in personality, social withdrawal, and apathy. While the use of cART has reduced rates of HAD, those on medication are frequently diagnosed with ANI or MND (Ghafouri et al., 2006). HAND is not associated with AIDS, and can occur without any other symptoms of HIV infection or AIDS (Antinori et al., 2007). Older

HIV infected individuals are more likely to suffer from neurocognitive impairment, particularly if they have advanced disease progression (Woods et al., 2015)

2.2.3 HAND Diagnosis Definitions

In order to effectively classify cases of HAND and further evaluate the disease, the condition has been broken down into three classes. Impairment in six domains is evaluated in order to identify presence and severity of disease. These domains include executive function, attention and working memory, speed of information processing, learning, memory, and motor skills (Antinori et al., 2007). Acquired impairment in at least two domains, with no functional impairment, is classified as asymptomatic neurocognitive impairment (ANI). Mild cognitive disorder (MND) consists of acquired impairment in at least two domains, with some interference in functioning. This may be self-reported or observed as inefficiency at work or reduced mental acuity. HIV-associated dementia (HAD) consists of acquired impairment in at least two domains, with severe impairment in at least two domains, in addition to significant impairment in daily functioning, such as medication adherence, work, home life, or social activities (Manji, Jäger, & Winston, 2013). Early symptoms of HAD include apathy and depression, poor short-term memory, agitation and mania, poor concentration, and clumsiness. Late stage HAD manifests as global dementia, myelopathy, neuropathy, and seizures, amongst other features. (Manji et al., 2013). HAD is associated with severe, advanced immunosuppression, which can result in increased viral replication, possibly accelerating viral mutations in the CNS (Nightingale et al., 2015).

2.3 BURDEN OF HAND

Cognitive decline and psychiatric disorders present a major morbidity in aging HIV-infected individuals. While neurocognitive decline can occur independently of HIV, individuals who are HIV-positive tend to have significantly higher rates of neurocognitive impairment than their seronegative counterparts. One study found cognitive impairment prevalence to be significantly greater in an HIV-positive subjects than the control subjects. In this study by Pereda et al. 27% of the HIV-positive group had cognitive impairment while the controls had a rate of 3.2% (Pereda et al., 2000). This study also found the HIV-positive cohort scored significantly slower on a reaction time test when compared to negative controls, even when adjusted for age, depression, and educational level (Pereda et al., 2000). In a study of a female cohort, HIV-positive women had significantly slower visual scanning speed scores, and significant impairments in executive skills when compared to HIV-negative women who were matched by age, education, ethnicity, substance abuse, and other confounding factors (Giesbrecht et al., 2014). Additionally, a study of Chinese men infected by blood donation equipment demonstrated that 34% of the HIV-positive men had cognitive impairment, while only 13% of matched HIV-negative men displayed cognitive impairment. A follow-up study after one year found that 28% of the HIV-positive individuals demonstrated deteriorated cognitive function compared to 5% of the HIV-negative group (Giesbrecht et al., 2014).

While HAND can present clinically as similar to Alzheimer's disease, the increase in amyloid plaque deposition in the brain observed in Alzheimer's disease is not observed in cases of HAND, indicating it is in fact not the same disease (Clifford & Ances, 2013). High rates of mild neurocognitive impairment are observed in all stages of HIV infection, and HAND is an indicator of earlier mortality, independent of other morbidities (Robert K. Heaton et al., 2011).

While there has been a decrease in the incidence of diagnoses of HAD since the development of effective antiretrovirals, the prevalence of neurocognitive impairment due to HIV remains high (Antinori et al., 2007). The induction of the use of cART led to a reduction in the rate of HAD, however the rates of ANI and MND have remained constant. In 1993 it was estimated that 16% of HIV positive individuals suffered from HAD, which decreased to 5% by 2010 (Robert K. Heaton et al., 2011). However ANI and MND are quite common in the HIV-positive population. In the Hawaii Aging with HIV Cohort 30% of 37 patients who were previously neurocognitively normal had developed neurocognitive impairment within one year (Antinori et al., 2007). Another study found that ANI and MND impact up to half of the entire HIV-positive population, while another study suggested that 44% of individuals, with a mean age of 42.4 had some form of HAND (Oliveira et al., 2015)(R K Heaton et al., 2010). Interestingly, some evidence suggests that HAND is not concrete and severity can fluctuate over time. One study demonstrated that at least 20% of HIV-positive individuals have fluctuating neurological disease severity throughout their lives (Antinori et al., 2007). Studies demonstrate that cognitive disorders occur more frequently in older PLWH. Cognitive disorders are twice as likely in older HIV-positive people, than younger people who have had the infection for the same amount of time (Nasi et al., 2014).

While individuals who are classified as having ANI do not demonstrate severe impairment in cognitive testing, the disease classification is still associated with poor quality of life, low adherence to medications, poor driving ability, and unemployment (Nightingale et al., 2015). In addition, patients diagnosed with ANI in the CNS HIV Antiretroviral Therapy Effects Research (CHARTER) Study had a significantly higher risk of progressing into MND than individuals with normal cognitive function (Nightingale et al., 2015). While “asymptomatic

neurocognitive impairment" may sound like a disorder with little impact on quality of life, the mildest form of HAND has serious effects and implications.

2.4 HAND RISK FACTORS

Not all HIV-positive individuals develop HAND, and currently there is no clear predictor to whether or not an individual will develop HAND. Metabolic syndrome, Hepatitis C virus coinfection, older age, lower cognitive reserve, and lower nadir CD4 count are all factors that have been associated with a higher risk of HAND in previous studies (Cross, Önen, Gase, Overton, & Ances, 2013). Some studies suggest that the development, and degree of neurocognitive impairment depend on a variety of contributing factors, including irreversible brain injury caused by HIV infection prior to treatment with cART, and penetration of the blood-brain barrier by the virus without penetration by cART medications (Patel et al., 2013).

2.4.1 Nadir CD4

Nadir CD4 is the historically lowest CD4 count for an HIV-positive individual, and a particularly low nadir CD4 count has been demonstrated to be a risk factor of neurocognitive impairment(Patel et al., 2013). Extremely low nadir CD4 T cell counts may be indicative of irreversible damage to the CNS before treatment with cART, or of immune cell activation and inflammation which may persist even with treatment (Nightingale et al., 2015). Low Nadir CD4 is in fact a predictor of neurocognitive impairment, which has been demonstrated in several large studies within the United States as well as studies in other countries (Robert K. Heaton et al.,

2011). Brain atrophy in HIV positive men over 50 years old is correlated with lower CD4 count and cognitive impairment (Becker et al., 2011). The event of low nadir CD4 early in life impacting neurocognitive impairment later in life has been suggested to be a “legacy event”(R K Heaton et al., 2010). Studies suggest that the lowest rates of HAND are correlated with an absence of a history of severe immunosuppression (nadir CD4<200 cells/μl), in combination with a successful viral response to cART (Robert K. Heaton et al., 2011).

2.4.2 Drug Adherence and Viral Load

Substance abuse is linked to poor medication adherence, particularly with cocaine and methamphetamine use (Patel et al., 2013). However, illegal drug use with poor drug adherence is not the only potential risk factor that may affect viral load, it is estimated that of the entire HIV-positive population in the United States only 19% reach viral suppression in the blood. Viral suppression in the cerebrospinal fluid is even more difficult to achieve. Accessing HIV-specific health care, cART, and adhering to treatment are all potential areas where patients may have a barrier to the treatment they need (Nightingale et al., 2015). Some studies suggest that this failure to access and manage medications properly may put individuals at greater risk for poor health outcomes (Patel et al., 2013). Higher levels of HIV DNA, along with detectable viral load in peripheral blood are associated with neurocognitive impairment (Oliveira et al., 2015) (Giesbrecht et al., 2014). Patients who develop HAND while on cART tend to have near-normal or normal CD4 counts, and less elevated viral loads than what was observed in cases of pre-cART era HAND (Antinori et al., 2007). In older HIV positive cohorts, higher levels of HIV DNA in the blood are correlated with more severe neurocognitive impairment, especially in executive functions such as planning and cognitive flexibility. Interestingly, younger individuals

with similar HIV DNA levels do not demonstrate the same neurocognitive impairment. (Oliveira et al., 2015). In patients on cART who have not achieved viral suppression, higher levels of HIV DNA induce a persistent immune response in the brain and other tissues, which may contribute to neurodegeneration, and neurocognitive decline(Oliveira et al., 2015). However, while chronic detectable levels of HIV RNA in the cerebrospinal fluid could indicate CNS damage, evidence is not consistent in suggesting a correlation between HIV RNA concentration and cognitive impairment (Nightingale et al., 2015). In cases where cART is not used or in cases of poor adherence of cART, immunosuppression due to HIV may lead to higher viral loads as well as opportunistic infections that infect the central nervous system, such as cryptococcal meningitis, and toxoplasma encephalitis which may be difficult to differentiate from age-associated neurologic decline (Nguyen & Holodniy, 2008).

2.4.3 Neuroinflammation

Chronic, low-level inflammation occurs in HIV-positive patients even with proper treatment with cART. The failure of antiretrovirals to access cerebrospinal fluid may limit the ability of cART to inhibit HIV replication within the central nervous system (CNS). HIV replication within the CSF may induce neuroinflammation, which is a potential risk factor for HAND (Nightingale et al., 2015). Inflammation occurs when microglia, macrophages, and astrocytes detect infection and promote inflammation to induce infiltrating cells such as T and B lymphocytes, and macrophages to enter the central nervous system. Monocytes and macrophages are capable of crossing the blood-brain barrier, undergoing differentiation into resident macrophages and microglia. These cells are capable of carrying HIV infection to the central nervous system (Nasi

et al., 2014). It has been suggested that this influx of inflammatory cells and inflammation in the CNS can cause neurodegeneration and cognitive impairment (Nasi et al., 2014).

While neuroinflammation was expected in the pre-cART era, autopsies of HIV-positive individuals who were on cART also demonstrate high levels of neuroinflammation. However, pre-cART autopsies demonstrated inflammation in the basal ganglia, while individuals who were on cART exhibited inflammation in the hippocampi, and the entorhinal and temporal cortex (Manji et al., 2013). Chronic neuroinflammation is observed in HIV infection, but can also be induced by the build-up of endogenous factors which may be a normal condition of aging (Nasi et al., 2014).

Uncontrolled inflammation in the brain can occur from viral infection of the brain itself, or may be due to circulating inflammatory factors. Either condition may result in the formation of neurotoxic molecules that can exacerbate disease (Nasi et al., 2014). While neurons do not get infected by HIV, the neurotoxins produced in response to CNS infection can injure these cells. A correlation between HAND and systemic and CNS inflammation has been reported in some studies (Nasi et al., 2014).

2.4.4 Stimulant Use or Dependence

Studies have demonstrated that history of methamphetamine use has a significant impact on cognitive function in PLWH who are over 50 years old, but not on HIV-positive individuals under 40 years old. Literature suggest this as another “legacy effect” (Woods et al., 2015). Studies have demonstrated the long term damage that methamphetamines can do to cognitive function, and the use of methamphetamines by HIV-positive individuals can exacerbate neurocognitive decline (Patel et al., 2013). It is not uncommon for older individuals who are

HIV-positive to have a history of substance use disorder, however active drug use in older individuals is quite rare (Woods et al., 2015). Methamphetamine is the most commonly used drug among HIV positive individuals (Ellis et al., 2003).

Studies have demonstrated that the use of methamphetamines, in conjunction with HIV infection, leads to more serious injury to the central nervous system. This includes more inflammation, higher viral loads, reduction in integrity and function of the blood-brain barrier, and neurodegeneration (Woods et al., 2015). HIV-positive individuals who have used methamphetamine have higher rates of neurocognitive impairment, primarily in the categories of memory, motor skills, learning, and attention (Woods et al., 2015). In the San Diego based CHARTER study, older HIV-positive individuals with a history of methamphetamine dependence in the past, had poorer performance in learning and memory when compared to all other groups in the study. These included combinations of individuals who were younger or older, HIV positive or negative, or individuals who did or did not have history of methamphetamine dependence. The same cohort of HIV-positive, older individuals with a history of methamphetamine dependence also had significantly lower scores for attention, and trending lower scores for motor skills, memory, and learning when compared to younger HIV-negative individuals with no history of methamphetamine use (Woods et al., 2015). In one study, 90% of the HIV-positive, history of methamphetamine dependence cohort were functionally dependent in at least one area of the Overall Functioning Composite Test, while 74 percent of the older, HIV-positive, no methamphetamine use, and 47% of the older HIV-negative, no methamphetamine use cohort had at least one area of functional impairment (Woods et al., 2015).

Being older, HIV-positive, and having a history of methamphetamine dependence have been identified as risk factors for functional impairment.

2.4.5 Hepatitis C Virus Coinfection

Hepatitis C virus (HCV) coinfection with HIV has been identified as another potential risk factor for HAND. It is estimated that 15-30% of the HIV-positive population has also been infected with HCV (Patel et al., 2013). HCV is also known to cause neurocognitive dysfunction alone, and some studies suggest that coinfection with HCV may have an additive, or even synergistic effect on cognition (Patel et al., 2013). While HCV infection has been demonstrated to be correlated with more severe cognitive impairment in people with HIV, HCV negative individuals do not demonstrate the same level of cognitive impairment, if any at all (Giesbrecht et al., 2014). HIV-positive individuals who are coinfected with HCV are demonstrated to have lower CD4 counts, higher viral loads, higher rates of AIDS, and more severe neurocognitive impairment. HIV/HCV coinfected individuals have higher prevalence of neurocognitive disorders when compared to individuals infected with HIV but not HCV. Additionally, symptomatic HAND was observed to be more severe in coinfected individuals (Vivithanaporn & Nelles, 2012). HCV proteins have been found in post-mortem brain tissue of HIV/HCV coinfected individuals, demonstrating the capability of the virus to infect the central nervous system, which may induce more severe or chronic inflammation (Vivithanaporn & Nelles, 2012).

2.4.6 Efavirenz Adverse Effects

While cART allows for HIV-positive individuals to live much healthier, longer lives than in the pre-cART era, there is potential for adverse effects from the chronic use of antiretrovirals to take place (Patel et al., 2013). Efavirenz, an antiretroviral medication is well known to cause side effects affecting the central nervous system, including headache, vivid dreams, and an assortment of neurological symptoms (Manji et al., 2013). Caution is recommended when using Efavirenz to treat elderly patients who have dementia, as well as patients with other cognitive or underlying psychiatric disorders, since the drug may exacerbate any cognitive dysfunctions of the patient (Nguyen & Holodniy, 2008).

2.4.7 APOε4 Allele

Some studies have demonstrated that the expression of apolipoprotein ε4 (APOε4) exacerbates brain connectivity and integrity in older HIV-positive subjects. However the evidence leans towards APOε4 having no impact on HIV status or neurocognitive impairment (Nasi et al., 2014). Apolipoproteins in the E class are known to control cholesterol metabolism, and the ε4 allele is observed in 14% of the population. This allele is found more frequently in individuals with impaired cognitive function, Alzheimer's disease, and atherosclerosis. The allele is also associated with coronary artery disease. While it has been hypothesized that the ε4 allele may play an important role in health in cognitive function in HIV-positive individuals, studies have demonstrated that this is not the case. One study found that having the ε4 allele had no associations with time to develop cognitive impairment, HIV infection, age, or death (Becker et al., 2015).

2.4.8 Aging and Metabolic Syndrome

It is unclear whether or not aging itself is a risk factor of HAND. It is quite possible that aging individuals are at risk of neurocognitive impairment due to expected, normal, age-related co-morbidities and immunosenescence, and not due to HIV infection (Patel et al., 2013). Additionally, older individuals have a greater risk of cerebrovascular or cardiovascular comorbidities, as well as a greater risk of metabolic dysregulation (Nasi et al., 2014). HIV infection is correlated with a higher prevalence of metabolic syndrome, resulting in increased insulin resistance and decreased glucose tolerance, high blood pressure, dyslipidemias, and abdominal obesity. Another study supported these findings, demonstrating that metabolic risk factors and cardiovascular risk factors were associated with HAND (Clifford & Ances, 2013). These conditions may be due to the long term use of HIV protease inhibitors, or may be due to the infection itself (Nguyen & Holodniy, 2008). HIV-positive individuals have greater rates of vascular disease than their HIV-negative counterparts. This includes coronary heart disease, hypertension, atherosclerosis, myocardial infarction, as well as diabetes and obesity. cART may be responsible for higher rates of vascular events and atherosclerosis (Patel et al., 2013). Additionally, vascular condition rates not only are higher for HIV positive individuals, but these conditions also correlate with neurocognitive impairments. Processing speed, executive function, learning and memory are associated with the vascular risks of diabetes, myocardial infarction, high cholesterol, and congestive heart failure (Patel et al., 2013).

2.4.9 Cognitive Reserve

Low cognitive reserve has been documented as a potential risk factor for neurocognitive impairment. The theory of cognitive reserve suggests that individuals whose brains function more efficiently, and are capable of utilizing alternate brain networks due to function demands may be protected from brain damage (Stern, 2003). Cognitive reserve capacity is indexed by educational attainment and intelligence, sometimes in conjunction with reading speed (Patel et al., 2013). HIV-positive individuals with fewer years of education and lower cognitive reserve appear to have a higher risk for HAND. It is possible that cognitive reserve capacity can be a good indicator to determine who will develop HAND (Patel et al., 2013). In one study, HIV-positive subjects with low cognitive reserve had more deficits in the areas of attention, memory, visuospatial ability, and executive functioning when compared to their high cognitive reserve counterparts and seronegative individuals of low and high cognitive reserve (Patel et al., 2013). However, it is possible that a high cognitive reserve may allow for individuals to have more resilience to neurocognitive disorders and dysfunction (Patel et al., 2013). A high cognitive reserve may allow individuals to bear more neurocognitive impairment before developing symptoms (Patel et al., 2013).

2.5 STUDY OBJECTIVES

The aim of this study is to evaluate HAND within the Pitt Men's Study cohort. The Pitt Men's Study contains a large amount of data that has not been analyzed in the scope of HAND. As a

longitudinal study with a variety of variables investigated in subjects who have been involved since as early as 1984, the study has the potential to give some insight into HAND.

The objective of this study is to answer two main questions;

1. What is the prevalence of HAND and the three different diagnoses of HAND within the Pitt Men's Study cohort?
2. Are there any correlating variables that may be associated with HAND, or could be potential risk factors for HAND?

3.0 METHODS

3.1 STUDY SUBJECTS

This study is a secondary analysis of data collected in the Pitt Men's Study (PMS). PMS is an ongoing prospective study, consisting of a cohort of homosexual and bisexual men, with or without HIV. This cohort is the Pittsburgh chapter of the larger Multicenter AIDS Cohort Study (MACS). Study participants visit the clinic every six months, where they undergo a physical exam, blood and other sample collection for lab testing, and a series of neuropsychological tests and functional assessments. An interview evaluates a variety of issues including, but not limited to, depression and behaviors such as sexual activities and illicit drug use.

3.2 IRB APPROVAL

This research was reviewed and approved by the University of Pittsburgh Institutional Review Board through the expedited review procedure. The study was determined to be minimal risk, and no clinical activities were performed in this study.

3.3 HAND DIAGNOSIS

Diagnosis of HAND was performed using the criteria developed by the HIV Neurobehavioral Research Center (HNRC) and an algorithm described by Antinori et al in 2007. Cases of HAND were diagnosed automatically through the algorithm in previous studies (Sacktor et al., 2015). Several components are required to classify HAND, including ruling out alternative neuropsychological diagnoses, cognitive testing, and an index of activities of daily living.

Classification of HAND with the HNRC criteria requires cognitive ability testing across 6 domains, including attention and working memory, verbal and language skills, sensory-perceptual ability, motor skills, and learning and recall memory (Antinori et al., 2007). For each ability domain, subjects were given a T score based on their testing score. If a subject had one or fewer domains with T scores 1 standard deviation (SD) or more below the mean, they were classified as within normal limits. If a subject had 2 or more domains with T scores 1 SD or more below the mean, they were classified as having minor cognitive impairment. If a subject had 2 or more ability domains with T scores 2 SDs or more below mean, or an ability domain T score 2.5 SDs or more below the mean, they were classified with moderate or severe cognitive impairment (Sacktor et al., 2015).

An index of activities of daily living (IADL) is also used as a component of HAND classification. Individuals answered a questionnaire in order to identify activities where abilities had declined. Individuals with minor decline on 2-3 questions were classified as having mild impairment. Major decline on 2 or more questions or major or minor decline on 4 or more questions was classified as severe impairment.

Subjects who were identified as having medical conditions which might confound with HAND diagnoses were excluded from HAND classification. Subjects who were not excluded

completed testing, and then were classified as normal, ANI, MND, or HAD based on IADL and cognitive ability diagnosis (Figure 1).

HAND classification		Instrumental Activities of Daily Living (IADL)		
		Normal	Mild impairment	Severe impairment
Cognitive classification	Within normal limits	Within normal limits	Within normal limits	Within normal limits
	Minor cognitive impairment	Asymptomatic neurocognitive impairment	Minor neurocognitive impairment	Minor neurocognitive impairment
	Moderate to severe cognitive impairment	Minor neurocognitive impairment	Minor neurocognitive impairment	HIV-associated dementia

Figure 1 Algorithm for Diagnosis of HAND within MACS

(Sacktor et al., 2015)

3.4 STATISTICAL ANALYSIS

Subjects underwent neuropsychological testing and were classified as Normal or having ANI, MND, or HAD. SAS 9.4 Statistical software was used to analyze data.

The frequency of HAND and the role of age, education, race, duration of infection, serostatus, nadir CD4, current CD4, viral load, hepatitis C virus coinfection, hypertension, diabetes, hypercholesterolemia, metabolic syndrome, binge drinking, and methamphetamine use on the development of HAND, frequencies between those without HAND, and those diagnosed

with HAND were assessed. Data analysis consisted of two-sample T-tests of unequal variances for continuous variables, and Chi-squared or Fisher's exact for categorical variables.

4.0 RESULTS

A total of 408 subjects were tested for HAND between 2007 and 2014, of which 254 were HIV-negative, and 154 were HIV-positive when they initially entered the study. Subjects were analyzed by the results of their most recent visit. There were 84 individuals who converted from HIV-negative to HIV-positive during the study, and were excluded from analysis of demographics overall. Due to the smaller HIV-positive population size they were included in analysis of the HIV-positive only group. Overall 278 subjects were found to have normal neurocognitive function, while 130 were diagnosed with neurocognitive dysfunction. The mean number of visits for the cohort is 2.85, with a standard deviation of 1.63. While not all PMS participants have been tested for HAND, the tested group accounts for 72.5% of the total active PMS cohort.

4.1 ANALYSIS OF RECRUITMENT COHORTS

The majority of the study subjects overall were recruited in 1984-85, although very few subjects in this cohort are HIV-positive (Figure 2). The majority of HIV-positive subjects are in the later cohorts of 2001-03 and 2010-14. There is a statistically significant difference in the frequencies of HIV among recruitment cohorts ($p<0.001$). This is likely due to a significant number of AIDS related deaths in the first two recruitment cohorts.

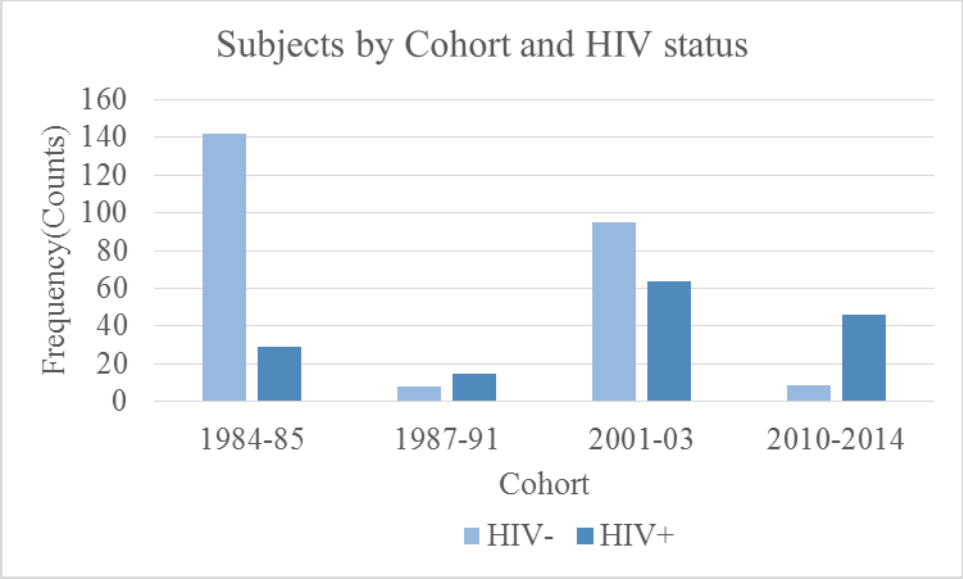

Figure 2 Subjects in each Recruitment Cohort by Serostatus, Counts

There was not a statistically significant difference in the frequency of neurocognitive disorder by cohort, regardless of HIV serostatus (Figure 3). Frequency of HAND diagnosis by serostatus within each recruitment cohort was analyzed. No individual cohort demonstrated significant differences in frequency of HAND diagnoses by serostatus (Figure 4).

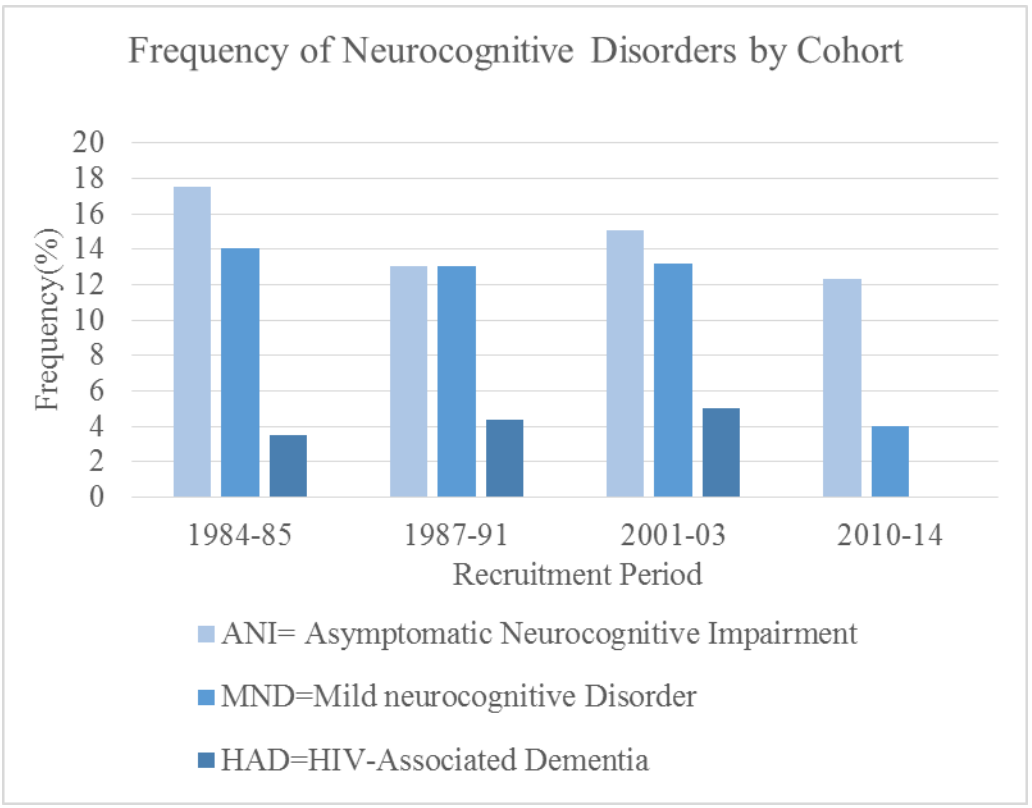

Figure 3 Frequency of Neurocognitive Disorder Diagnoses in Each Cohort, Percent

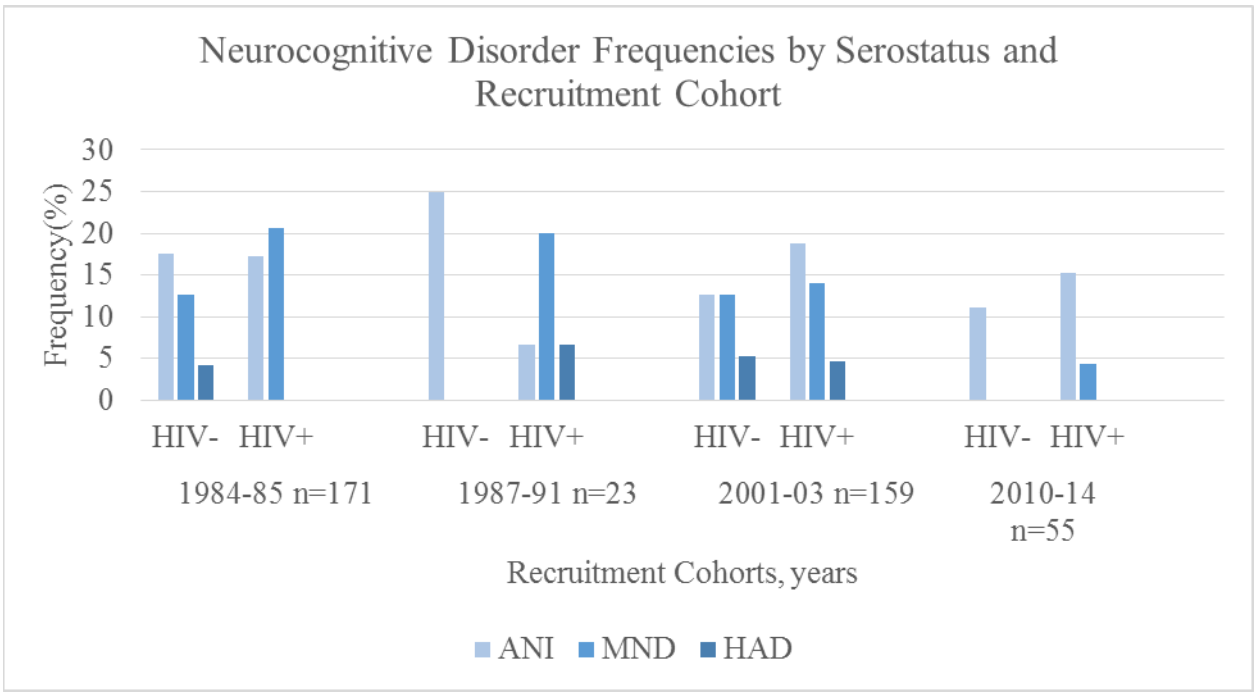

Figure 4 Frequency of Neurocognitive Disorder Diagnoses by Serostatus and Recruitment Cohort, Percent

4.2 PREVALENCE OF HAND

Interestingly, the prevalence of neurocognitive impairment was not significantly different between the HIV-positive and HIV-negative cohorts, where 31.89% of HIV-negative subjects and 31.82% of HIV-positive subjects were diagnosed with some degree of neurocognitive disorder (Table 1, Figure 5). There was no statistically significant variance by serostatus and severity of neurocognitive impairment. The cohort was separated by HAND diagnosis without considering serostatus, as either having normal cognitive function (N=278) or having neurocognitive disorder (n=130). It is important to recognize that individuals who are classified as having HAND or HAD while they are HIV-negative have neurocognitive disorder, though it is not due to HIV.

Subjects were stratified by age, where 255 subjects were equal to or over 50 years old (Figure 6), while 153 were under 50 years old (Figure 7). Stratifying subjects into groups by age did not demonstrate any significant difference in neurocognitive disorder prevalence. Due to the very similar rates of neurocognitive disorder between these groups, it is not possible to distinguish HAND from some other neurocognitive disorder that would appear without the virus being present. For this reason, analysis of potential correlates was performed on the population without separating into groups by serostatus to seek out risk factors for neurocognitive disorder in the cohort.

Table 1 Frequency of Neurocognitive Disorder (Any) by Serostatus, Percent

Diagnosis	HIV-	HIV+
Normal	68.11	68.18
ANI	15.75	16.23
MND	11.81	12.99
HAD	4.33	2.6

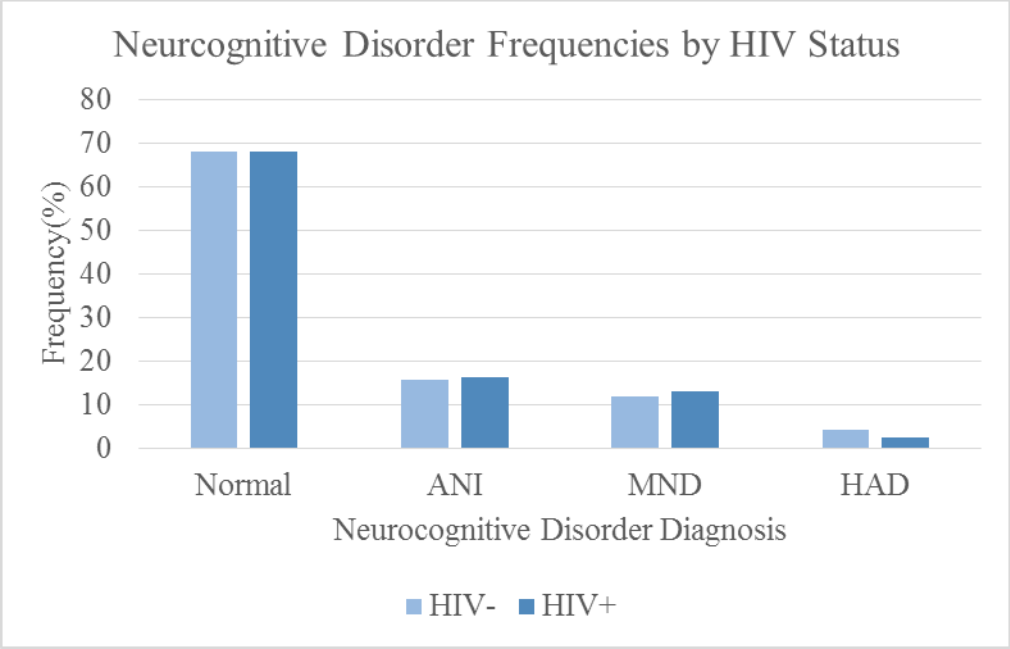

Figure 5 Frequency of Neurocognitive Disorder by Diagnosis and Serostatus

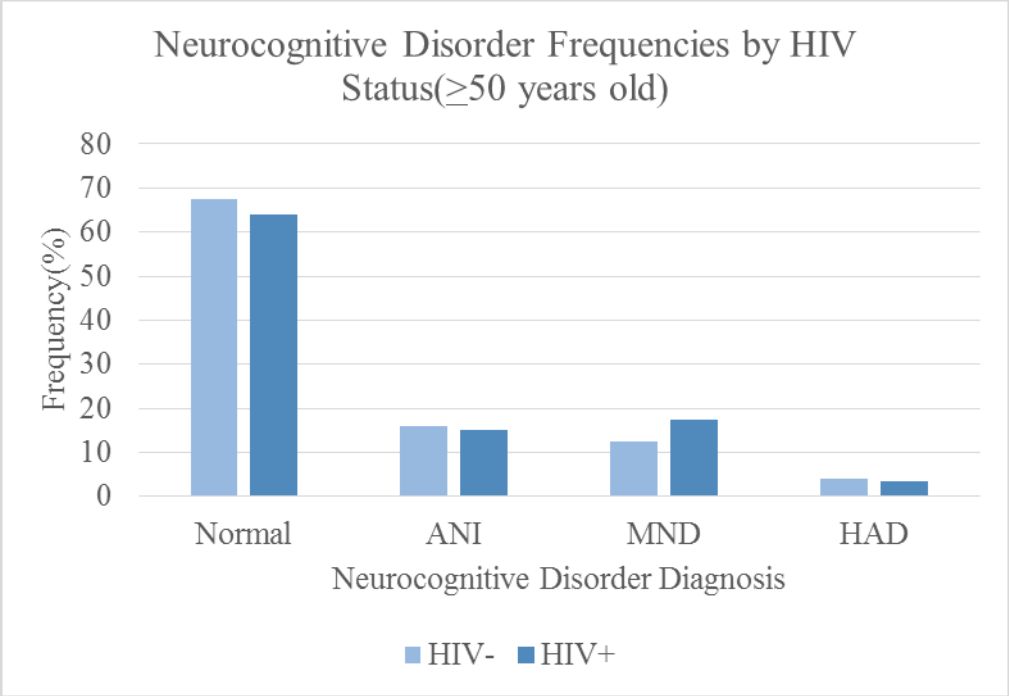

Figure 6 Frequency of Neurocognitive Disorder in Subjects 50 Years old or Older by Diagnosis and Serostatus

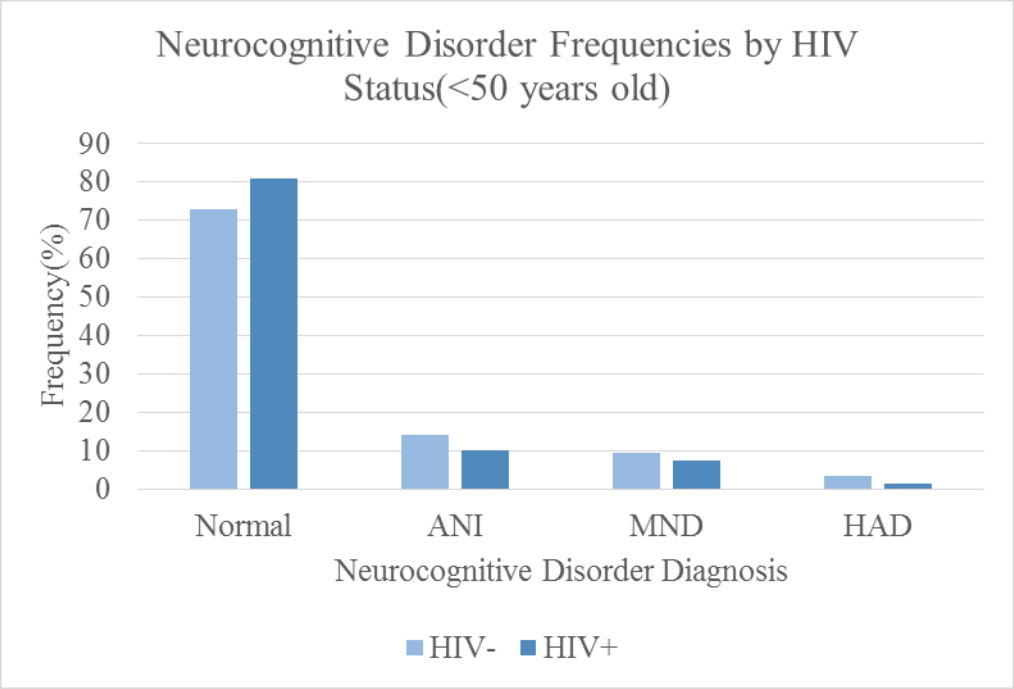

Figure 7 Frequency of Neurocognitive Disorder in Subjects Under 50 Years Old by Diagnosis and Serostatus

4.3 DEMOGRAPHICS, REGARDLESS OF SEROSTATUS

Demographics of the population were analyzed and there were no statistically significant differences between the Normal and HAND groups regarding mean age, race, education, hepatitis C coinfection, hypertension, diabetes, metabolic syndrome, methamphetamine use, drinking habit, or serostatus (Table 2).

Table 2 Demographics of Individuals in PMS

Characteristic	Normal(278)	HAND(130)	p Value
Age, y, mean(SD)	51.15(12.37)	52.69(13.46)	0.2562
Caucasian, %	76.26	73.85	0.6637
Education, y, mean(SD)	15.32(2.47)	14.81(2.51)	0.0518
Hepatitis C Infection-ever antibody positive, %	7.56	17.07	0.0517
Hypertension, %	18.77	25.38	0.126
Diabetes, %	7.91	8.46	0.9977
Metabolic Syndrome, %	24.46	20.77	0.6302
Hypercholesterolemia, %	58.27	48.46	0.3054
Methamphetamine/Uppers use, y, mean(SD)	0.01(0.06)	0.02(0.14)	0.6026
Methamphetamine/Uppers use ever, %	20.86	25.38	0.3067
Binge Drinking since last visit, %	14.8	15.75	0.0673
HIV-Positive %	37.77	37.69	0.988

Table 3 Demographics of Individuals Less Than 50 Years Old in PMS

Characteristic	Normal(109)	HAND(44)	p Value
Age, y, mean(SD)	38.51(8.00)	37.54(7.14)	0.4875
Caucasian, %	70.64	56.82	0.3426
Education, y, mean(SD)	14.79(2.49)	14.11(2.59)	0.1302
Hepatitis C Infection-ever antibody positive, %	2.75	11.37	**0.0358**
Hypertension, %	10.09	11.36	0.7776
Diabetes, %	5.50	2.27	0.9528
Metabolic Syndrome, %	22.02	11.36	0.2287
Hypercholesterolemia, %	46.79	45.45	0.9782
Methamphetamine/Uppers use, y, mean(SD)	0.01(0.05)	0.002(0.01)	0.0935
Methamphetamine/Uppers use ever, %	17.43	18.18	0.9122
Binge Drinking since last visit, %	23.85	20.45	0.7341
HIV-Positive %	45.87	40.91	0.5761

Subjects who were diagnosed with HAND and were less than 50 years of age had a significantly higher rate for history of Hepatitis C Infection (p=0.0358), although no other demographic variables were found to have significant differences (Table 3). In subjects 50 years of age or older there were no statistically significant differences observed in the data analysis regarding

age, race, education, hepatitis C infection, hypertension, diabetes, metabolic syndrome, hypercholesterolemia, methamphetamine use, binge drinking, or HIV serostatus (Table 4).

Table 4 Demographics of Individuals 50 Years of Age or Older in PMS

Characteristic (over 50)	Normal(169)	HAND(86)	p Value
Age, y, mean(SD)	59.30(6.38)	60.43(8.36)	0.2711
Caucasian, %	79.88	82.56	0.8999
Education, y, mean(SD)	15.67(2.40)	15.16(2.40)	0.1165
Hepatitis C Infection-ever antibody positive, %	10.60	12.70	0.3235
Hypertension, %	24.40	32.56	0.1668
Diabetes, %	9.47	11.63	0.9211
Metabolic Syndrome, %	26.04	25.58	0.9573
Hypercholesterolemia, %	65.68	50.00	0.0592
Methamphetamine/Uppers use, y, mean(SD)	0.01(0.06)	0.03(0.17)	0.4612
Methamphetamine/Uppers use ever, %	23.08	29.07	0.2967
Binge Drinking since last visit, %	8.93	13.25	0.0589
HIV-Positive %	32.54	36.05	0.576

4.4 PREVALENCE IN HIV-POSITIVE SUBJECTS

A total of 238 HIV-positive individuals, including seroconverters, have undergone testing for HAND in the PMS cohort. A total of 82 HIV-positive subjects were diagnosed with some form of HAND, and 156 subjects were within the normal limits of neuropsychological function (Table 5).

Table 5. Frequency of HAND in HIV-positive Individuals, including seroconverters

HAND Diagnosis	Frequency	Percent
Normal	156	65.55
ANI	47	19.75
MND	27	11.34
HAD	8	3.36

Overall, 34.45% of the HIV-positive population, including seroconverters were diagnosed with HAND. Analysis of frequency of testing over time was performed using two-year intervals. The frequency of testing increased slightly with each time period (Figure 8). Frequency by disease severity also varied slightly by testing period, but this was not statistically significant.

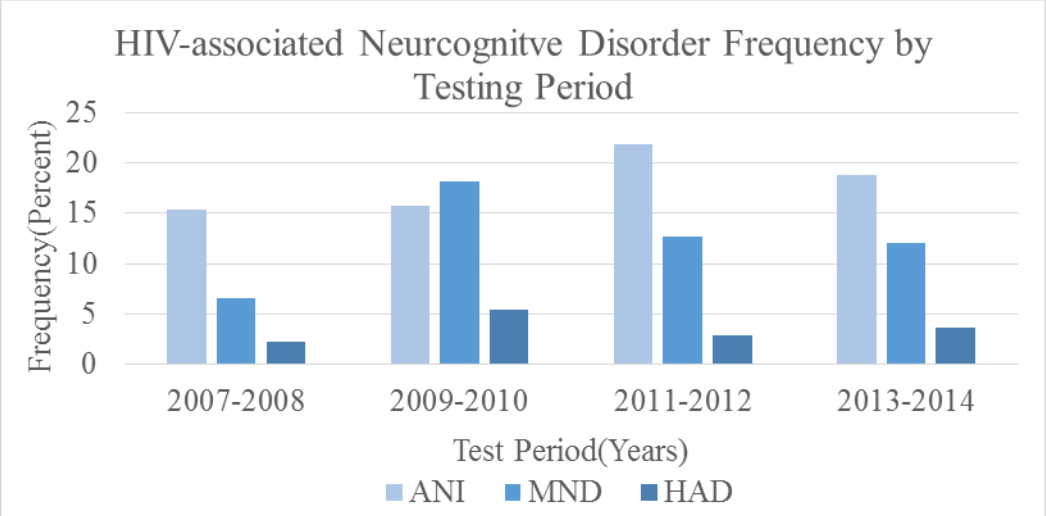

Figure 8 Frequency of HAND Diagnoses in HIV-Positive Individuals Only by Testing Period, Percent

Table 6 Frequency of HAND in HIV-Positive Individuals Only, Counts

Diagnosis	2007-2008	2009-2010	2011-2012	2013-2014
Normal	69	100	109	146
ANI	14	26	38	42
MND	6	30	22	27
HAD	2	9	5	8
Total	145	165	174	223

4.5 DEMOGRAPHICS OF HIV-POSITIVE SUBJECTS

Demographic factors were analyzed independently, by each subject's most recent HAND diagnosis. The mean age for those with normal cognitive function was 49.66, while the mean age for those with HAND was 50.34. There were three low outliers for age in the HAND group, which were not significant. There was no significant difference in the age, race, education, duration of HIV infection, current CD4 count, nadir CD4 count, HIV RNA level, rates of hepatitis C virus infection, hypertension, diabetes, metabolic syndrome, hypercholesterolemia, methamphetamine use, or binge drinking, between HIV-positive subjects with HAND and individuals with normal cognitive function. This is similar to the results for all individuals, regardless of serostatus.

Table 7. Demographics of HIV-Positive Individuals Only

Characteristic	Normal(n=156)	HAND(n=82)	p Value
Age, y, mean(SD)	49.66(11.92)	50.34(9.91)	0.638
Caucasian, n (%)	78.85	76.83	0.529
Education, y, mean (SD)	14.90(2.190)	14.83(2.37)	0.809
Duration of HIV infection, y, mean (SD)	12.82(9.99)	14.61(9.81)	0.188
CD4 Nadir, mean (SD)	378.8(196.8)	343.3(204.3)	0.195
CD4 Count Current	734.1(288.4)	729.4(340.0)	0.915
Plasma HIV RNA <50 copies/mL, %	87.12	89.03	0.519
Hepatitis C Coinfection-ever antibody positive, %	4.48	12.19	0.118
Hypertension, %	14.1	19.51	0.352
Diabetes, %	10.26	8.64	0.0794
Metabolic Syndrome, %	30.13	24.39	0.1125
Hypercholesterolemia, %	75	78.12	0.069
Methamphetamine/Uppers use, y, mean (SD)	0.136(1.267)	0.0687(0.407)	0.547
Binge Drinking since last visit, %	12.82	20.25	0.065

5.0 DISCUSSION

5.1 PREVALENCE OF NEUROCOGNITIVE IMPAIRMENT REGARDLESS OF SEROSTATUS

The near-equality of the rates of neurocognitive disorders in the seropositive and seronegative groups does not represent previous findings in other cohorts (Giesbrecht et al., 2014; Pereda et al., 2000). The rate of HAND in the HIV-positive population is similar to published results, while the rate of neurocognitive disorder in the HIV-negative population appears higher than expected. Previous studies report rates of neurocognitive disorder in HIV-negative populations as quite low, ranging from 3.2% to 13%, although these studies do not investigate cohorts of MSM (Giesbrecht et al., 2014; Pereda et al., 2000). However, frequencies of neurocognitive disorders in the MACS cohort reported by Becker et al. were quite similar to the frequencies discovered in this data analysis, where 26.42% of active HIV-negative subjects and 29.01% of HIV-positive subjects were diagnosed with mild or severe neurocognitive dysfunction (Becker et al., 2015). The PMS cohort was included in this analysis, along with the cohorts in Washington D.C./Baltimore, Chicago, and Los Angeles.

Becker et al reported that the HIV-positive cohort had significantly higher rates of cognitive abnormality than the HIV-negative cohort, in men recruited between 1984 and 1991, but no difference in rates of cognitive abnormality in the cohort recruited between 2001-2003

(Becker et al., 2015). The analysis of cases of HAND overall and by recruitment cohort in this study did not find a significant difference in HAND diagnoses. The results of this study of the PMS cohort cannot come to the same conclusion as Becker et al. based on the simple analysis performed.

Similar frequencies of neurocognitive disorder between HIV-positive and negative MSM were found in a study originating in the United Kingdom, however the reported rates were still lower than the observed frequencies in the PMS cohort (McDonnell et al., 2014). McDonnell et al reported that 21.0% of HIV-positive subjects were diagnosed with HAND using the Frascati criteria, while 28.9% of the HIV-negative subjects were diagnosed with neurocognitive disorders, where the difference in frequencies was not significant (McDonnell et al., 2014). The lack of a significant difference in neurocognitive disorder rates is consistent with the results in this study.

The acronym HAND suggests that individuals who are HIV-positive are at risk of developing neurocognitive disorders based solely on the fact that they are infected with HIV. This statement is not supported by the frequencies of neurocognitive disorder observed in the PMS cohort, or by McDonnell et al. The results demonstrated in this study suggest that neurocognitive disorder in the cohort is not due to HIV, but is due to an unknown factor, which was not investigated here. The findings on prevalence of neurocognitive disorder introduce several questions, particularly regarding whether HAND is a true issue HIV-positive individuals suffer from, or if HIV is being blamed when another risk factor is the cause. More case-control studies of MSM need to be performed to investigate the rate of neurocognitive disorder, and to continue evaluation of potential risk factors. It is also quite possible that the algorithm used to

diagnose HAND is not sensitive or accurate enough to truly identify cases of HAND. In addition, the HNRC algorithm needs to be evaluated, and possibly refined.

5.2 NEUROCOGNITIVE DISORDER RISK FACTORS

Hepatitis C virus infection was found to be statistically significant in subjects under 50 years old. Subjects with neurocognitive dysfunction had a significantly higher rate of HCV infection than individuals without neurocognitive disorder ($p=0.0358$). The rate of HCV in the neurocognitive disorder cohort was 11.37 while the rate in the normal group was 2.75. HCV infection is a known cause of neurocognitive disorder on its own (Patel et al., 2013). This is far from a complete explanation for the rates of neurocognitive disorder observed.

No other risk factors analyzed were found to be statistically significant, when analyzing both HIV-positive and negative individuals, or when analyzing HIV-positive individuals alone. Additionally, no other risk factors besides Hepatitis C infection were found to be significant when the cohort was stratified by being over or under 50 years old. The demographic variables were chosen based on previous evidence, suggesting that they could be risk factors for HAND. While it was not possible to determine if HAND actually exists in this cohort from this study, the data analysis performed demonstrates that age, race, education level, diabetes, metabolic syndrome, and hypercholesterolemia do not appear to be risk factors for neurocognitive disorder in the PMS cohort. In addition, duration of HIV infection, current CD4 count, and HIV RNA level are not risk factors for neurocognitive disorder within the HIV-positive group.

5.3 LIMITATIONS

The first limitation of this analysis is the use of a single method for diagnosing HAND. While the HNRC criteria and corresponding algorithm is quite comprehensive, the developers do report it is a working criteria. Rates of neurocognitive disorder vary across different cohorts and studies, and it is possible cases of HAND are being missed, or individuals are being misdiagnosed when they have a different cause for neurocognitive dysfunction. Analysis by each cognitive ability may provide more specificity.

Another limitation is that this study includes a cohort of men who are homosexual or bisexual. This study therefore has limited generalizability. The results from this population can be compared appropriately to other MSM cohorts, however they cannot be accurately compared to cohorts who do not represent MSM due to the differences in behaviors and drug use, as well as the variance in other demographic variables. It is important to take into account the differences among demographic variables and behaviors, particularly when the direct cause of a condition such as neurocognitive impairment is unknown.

A third limitation is that subjects were evaluated based on their most recent session of neuropsychological testing and HAND diagnosis. The progression of severity or changing of HAND diagnosis for each subject was not analyzed. Many studies demonstrate that subjects who are diagnosed with HAND will develop more severe forms of the disorder, or they can revert back to a normal cognitive function diagnosis.

6.0 CONCLUSION

The results of this study demonstrate an inability to discriminate between HAND and other neurocognitive disorders within the PMS cohort. Frequencies of neurocognitive disorders were the same for the HIV-negative and HIV-positive groups, inhibiting the analysis of neurocognitive disorder due exclusively to HIV. Rates of neurocognitive disorder were higher than expected in the HIV-negative group, and were within the expected range for the HIV-positive group. There are limited published results with similar conclusions, indicating the importance of investigating and comparing neurocognitive dysfunction among HIV-positive and HIV-negative MSM.

The variables of HIV status, age, education level, race, hypertension, diabetes, metabolic syndrome, hypercholesterolemia, methamphetamine use, and binge drinking were not found to be correlated with HAND diagnosis in the entire cohort, or in HIV-positive individuals. In further analysis of HIV-positive individuals the duration of HIV infection, current CD4 count, nadir CD4 count, HIV RNA level, and HCV infection rate were not correlated with HAND diagnosis. History of HCV infection in subjects less than 50 years old with HAND was the only statistically significant correlating variable in this data analysis. HCV infection is reported to cause neurocognitive dysfunction, without HIV coinfection, suggesting that neurocognitive dysfunction may not be due to HAND. Due to the lack of evidence of potential risk factors for

neurocognitive disorders in this study, further investigation is essential to identify the source of the disorder in the PMS cohort.

6.1 PUBLIC HEALTH SIGNIFICANCE

With millions of people living with HIV worldwide, and new cases of HIV occurring every day, the infection and subsequent disease is not disappearing any time soon. The use of antiretrovirals has significantly extended life expectancy for persons diagnosed as HIV-positive. In cases where cART is in use, PLWH can live to old age, and have such successful viral suppression that they do not die from AIDS, but from old age or chronic non-infectious diseases. However, these individuals may experience poorer quality of life due to complications from HIV, or the medications used to suppress it. The chronic conditions that PLWH experience are a public health concern.

Neurocognitive disorders can inhibit a person's ability to work, maintain relationships, and live independently. Such issues lead to a drop in quality of life, and added expense to taxpayers. Whether it is in fact a condition unique to HIV-positive individuals, or that the thorough investigation through MACS has enabled researchers to identify neurocognitive disorders with an uncertain cause in MSM, it is critical to investigate methods to better identify, and in the future prevent neurocognitive decline within the population.

BIBLIOGRAPHY

Antinori, A., Arendt, G., Becker, J. T., Brew, B. J., Byrd, D. A., Cherner, M., … Wojna, V. E. (2007). Updated research nosology for HIV-associated neurocognitive disorders. *Neurology*, *69*(18), 1789–99. http://doi.org/10.1212/01.WNL.0000287431.88658.8b

Becker, J. T., Kingsley, L. A., Molsberry, S., Reynolds, S., Aronow, A., Levine, A. J., … Selnes, O. A. (2015). Cohort Profile: Recruitment cohorts in the neuropsychological substudy of the Multicenter AIDS Cohort Study. *International Journal of Epidemiology*, *44*(5), 1506–1516. http://doi.org/10.1093/ije/dyu092

Becker, J. T., Sanders, J., Madsen, S. K., Ragin, A., Kingsley, L., Maruca, V., … Thompson, P. M. (2011). Subcortical brain atrophy persists even in HAART-regulated HIV disease. *Brain Imaging and Behavior*, *5*(2), 77–85. http://doi.org/10.1007/s11682-011-9113-8

Clifford, D. B., & Ances, B. M. (2013). HIV-associated neurocognitive disorder. *The Lancet. Infectious Diseases*, *13*(11), 976–86. http://doi.org/10.1016/S1473-3099(13)70269-X

Cross, S., Önen, N., Gase, A., Overton, E. T., & Ances, B. M. (2013). Identifying risk factors for HIV-associated neurocognitive disorders using the international HIV dementia scale. *Journal of Neuroimmune Pharmacology : The Official Journal of the Society on NeuroImmune Pharmacology*, *8*(5), 1114–22. http://doi.org/10.1007/s11481-013-9505-1

Ghafouri, M., Amini, S., Khalili, K., & Sawaya, B. E. (2006). HIV-1 associated dementia: symptoms and causes. *Retrovirology*, *3*(1), 28. http://doi.org/10.1186/1742-4690-3-28

Giesbrecht, C. J., Thornton, A. E., Hall-Patch, C., Maan, E. J., Côté, H. C. F., Money, D. M., … Pick, N. (2014). Select neurocognitive impairment in HIV-infected women: associations with HIV viral load, hepatitis C virus, and depression, but not leukocyte telomere length. *PloS One*, *9*(3), e89556. http://doi.org/10.1371/journal.pone.0089556

Heaton, R. K., Clifford, D. B., Franklin, D. R., Woods, S. P., Ake, C., Vaida, F., … Grant, I. (2010). HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER Study. *Neurology*, *75*(23), 2087–96. http://doi.org/10.1212/WNL.0b013e318200d727

Heaton, R. K., Franklin, D. R., Ellis, R. J., McCutchan, J. A., Letendre, S. L., LeBlanc, S., … Grant, I. (2011). HIV-associated neurocognitive disorders before and during the era of combination antiretroviral therapy: differences in rates, nature, and predictors. *Journal of NeuroVirology*, *17*(1), 3–16. http://doi.org/10.1007/s13365-010-0006-1

HIV and Aging. (n.d.). Retrieved January 5, 2016, from http://www.unaids.org/sites/default/files/media_asset/20131101_JC2563_hiv-and-aging_en_0.pdf

Manji, H., Jäger, H. R., & Winston, A. (2013). HIV, dementia and antiretroviral drugs: 30 years of an epidemic. *Journal of Neurology, Neurosurgery, and Psychiatry*, *84*(10), 1126–37. http://doi.org/10.1136/jnnp-2012-304022

McDonnell, J., Haddow, L., Daskalopoulou, M., Lampe, F., Speakman, A., Gilson, R., … Rodger, A. (2014). Minimal Cognitive Impairment in UK HIV Positive Men Who Have Sex with Men: Effect of Case Definitions, and Comparison with the General Population and HIV Negative Men. *Journal of Acquired Immune Deficiency Syndromes (1999)*, *67*(2), 120–127. http://doi.org/10.1097/QAI.0000000000000273

Nasi, M., Pinti, M., De Biasi, S., Gibellini, L., Ferraro, D., Mussini, C., & Cossarizza, A. (2014). Aging with HIV infection: A journey to the center of inflammAIDS, immunosenescence and neuroHIV. *Immunology Letters*, *162*(1), 329–333. http://doi.org/10.1016/j.imlet.2014.06.012

Nguyen, N., & Holodniy, M. (2008). HIV infection in the elderly. *Clinical Interventions in Aging*, *3*(3), 453–72. Retrieved from http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2682378&tool=pmcentrez&rendertype=abstract

Nightingale, S., Winsto, A., Letendre, S., Michael, B. D., Mcarthur, J. C., Khoo, S., & Solomon, T. (2015). Controversies in HIV-associated neurocognitive disorders, *13*(11), 1139–1151. http://doi.org/10.1016/S1474-4422(14)70137-1.Controversies

Oliveira, M. F. de, Murrel, B., Pérez-Santiago, J., Vargas, M., Ellis, R. J., Letendre, S., … Gianella, S. (2015). Circulating HIV DNA Correlates With Neurocognitive Impairment in Older HIV-infected Adults on Suppressive ART. *Scientific Reports*, *5*(October), 17094. http://doi.org/10.1038/srep17094

Patel, S., Thames, A., Arbid, N., Panos, S., Castellon, S., & Hinkin, C. (2013). The Aggregate Effects of Multiple Comorbid Risk Factors on Cognition Among HIV-infected Individuals. *J Clin Exp Neuropsychol*, *35*(4), 421–434. http://doi.org/10.1080/13803395.2013.783000

Pereda, M., Ayuso-Mateos, J. L., Gómez Del Barrio, a, Echevarria, S., Farinas, M. C., García Palomo, D., … Vázquez-Barquero, J. L. (2000). Factors associated with neuropsychological performance in HIV-seropositive subjects without AIDS. *Psychological Medicine*, *30*(1), 205–17. http://doi.org/10.1017/S0033291799001348

Sacktor, N., Skolasky, R. L., Seaberg, E., Munro, C., Becker, J. T., Martin, E., … Miller, E. (2015). Prevalence of HIV-associated neurocognitive disorders in the Multicenter AIDS Cohort Study. *Neurology*, WNL.0000000000002277–. http://doi.org/10.1212/WNL.0000000000002277

Stern, Y. (2003). The concept of cognitive reserve: a catalyst for research. *Journal of Clinical and Experimental Neuropsychology*, *25*(5), 589–593. http://doi.org/10.1016/j.jns.2009.02.069

Vivithanaporn, P., & Nelles, K. (2012). Hepatitis C virus co-infection increases neurocognitive impairment severity and risk of death in treated HIV/AIDS. *Journal of the …*, *312*(1-2), 45–51. http://doi.org/10.1016/j.jns.2011.08.025

Woods, S. P., Translational, T., & Aids, M. (2015). Younger HIV + Adults : Evidence for a Legacy Effect ?, *20*(1), 85–98. http://doi.org/10.1007/s13365-014-0233-y.Detrimental