The relationship between frailty and the development and progression of HIV-Associated Neurocognitive Disorder (HAND)

by

Kerry-Lee Clifton

Submitted in partial fulfilment of the requirements
for the degree of Master of Science

at

Dalhousie University
Halifax, Nova Scotia
January 2021

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABSTRACT

Background: Frailty is a concept that is increasingly considered in the context of aging with HIV. Frailty describes the variability in age-related health problems that arise from deterioration in various physiological systems. The objective of this study was to determine the relationship between frailty and the development and progression of HIV Associated Neurocognitive Disorder (HAND).

Methods: This study used data from the Ontario HIV Treatment Network (OHTN) Cohort Study (OCS). 1152 OCS participants were included in the study providing a total of 3496 study visits. The mean age of participants was 44.3 years (SD 10.6), and 22.7% of the participants identified as female. Neuropsychological testing was done annually from October 2007 to December 2014. HAND status was assigned according to Antinori et al. (2007) criteria. A Frailty Index was developed according to standardized methods by Searle et al. (2008). Frailty scores were categorized as 0 - 0.1 (no frailty), 0.1 - 0.2 (low frailty), 0.2 - 0.3 (moderate frailty), and 0.3+ (high frailty). Cox Proportional Hazards regression models were used to determine the association between frailty and the development of HAND. Transition matrices allowed for the calculation of a mobility measure to estimate progression between HAND states.

Results: At baseline 45.8% (n=528) of participants were characterized as neuropsychologically normal, 35.1% (n=404) had asymptomatic neurocognitive impairment, 14.8 (n = 171) had mild neurocognitive disorder, and 4.3% (n=49) were diagnosed with HIV-associated dementia. A total of 60 variables were included in the frailty index (FI). FI scores ranged from 0.00 to 0.54 at baseline with a mean of 0.22 (SD = 0.10) and were positively skewed. At baseline, 9.90% of participants were non-frail, 33.65% of participants had low frailty, 32.25% of participants had moderate frailty, and 24.19% of participants had high frailty (n=113, n=384, n=368, and n=276, respectively). Higher FI scores were associated with an increased risk of development of HAND (HR 1.68, 95% CI 1.00 – 2.87, p=0.048 for FI Scores 0.10 to 0.19; HR 1.75, 95% CI 1.04 – 2.92, p=0.034 for FI Score 0.20 to 0.29; and HR 2.27, 95% CI 1.36 – 3.81, p=0.002 for FI Score 0.30+). High frailty at baseline was associated with shorter time of progression to HAND. The Determinant Index matrix-based mobility measure demonstrated that non-frail and high frailty participants had significantly lower mobility between HAND states (0.91 and 0.95, respectively) than those with low and moderate frailty (0.98 and 0.97, respectively).

Conclusion: The frailty index was useful in predicting the development of HAND and the mobility between various HAND states. Measuring frailty could serve as a useful clinical intervention to decrease the risk of development and progression of HAND.

LIST OF ABBREVIATIONS USED

ANI	Asymptomatic Neurocognitive Impairment
cART	Combination Antiretroviral Therapy
HAART	Highly Active Antiretroviral Therapy
HAD	HIV-Associated Dementia
HANA	HIV-Associated non-AIDS
HAND	HIV-Associated Neurocognitive Disorder
MND	Mild Neurocognitive Disorder
OCS	OHTN Cohort Study
OHTN	Ontario HIV Treatment Network

ACKNOWLEDGEMENTS

I would like to express my deepest appreciation and gratitude to my supervisor, Dr. Susan Kirkland. Dr. Kirkland has been an incredible mentor and pillar of strength throughout this entire process. Without her continual encouragement, guidance, and expertise this thesis would not have been possible. Dr. Kirkland, I will forever be grateful that I have had the honour of having you as my supervisor. Thank you for your continual support, strength, and kindness - it has been an absolute honour and a privilege to work with you.

I would like to thank my committee members, Dr. Olga Theou and Dr. Pantelis Andreou. I have been so fortunate to have the guidance and expertise of Dr. Theou and Dr. Pantelis throughout this process. I know that this thesis would not have been possible without their continual guidance and support. I am so thankful to the both of you for agreeing to be on my committee. Thank you for helping to shape this work into what it is today. Your support and kindness has meant the world to me and I will forever be grateful to the both of you.

I would also like to thank my Community Advisory Committee. Their importance of their insight and contribution to this body of work is immeasurable. I am forever grateful to have worked with them and shaped this thesis with their guidance. Thank you for volunteering your time and effort throughout this process - your contributions have enriched my experience and this body of work. It has been an absolute pleasure to work with all of you. You have been an integral part of this process and I will always cherish the work we have accomplished together.

CHAPTER ONE: INTRODUCTION

Tremendous advances have been made in the treatment of HIV over the past few decades. Antiretroviral therapy has allowed those living with HIV/AIDS to effectively manage their disease and increase their life expectancy (Morgan et al., 2011). The introduction of combined antiretroviral therapy (cART) in the 1990's has transformed the diagnosis of HIV from what was once a terminal diagnosis to that of a chronic disease which can be managed by these antiretroviral therapies.

Despite advances in HIV treatment, cognitive impairment among individuals living with HIV/AIDS remains high (Saylor & Sacktor, 2016). This highlights a major gap in the treatment of HIV/AIDS and is becoming an increasing problem as individuals living with HIV age. Antiretroviral therapy, the HIV virus itself, co-morbid conditions, and the aging process have all been implicated in the development of cognitive impairment, however the exact mechanisms remain poorly understood.

It has been proposed (though also contested) that the process of aging is accelerated in those living with HIV/AIDS (Deeks, 2011; Desai & Landay, 2010). Both HIV status and the treatment of HIV with antiretroviral therapy may contribute to both HIV and non-HIV related comorbidities and multimorbidity, such as age-related diseases and frailty (Brown & Glesby, 2012; Orlando, 2006). The relationship between HIV, aging, frailty, multimorbidity, and cognitive impairment is complex and thus far not well understood or characterized.

Cognitive impairments have been reported to occur in up to fifty percent of individuals living with HIV/AIDS (Nightingale et al, 2014). These cognitive impairments can range from mild to severe and interfere not only with memory and executive function but can also impair everyday function in those affected (Hellmuth, Milanini, & Valcour, 2014). HIV-Associated Neurocognitive Disorder (HAND) is a term that encompasses the

spectrum of cognitive impairment in those living with HIV. HAND can interfere with many facets of an individual's life, and has been associated with lower medication adherence, a lower ability to perform every day complex tasks, difficulty obtaining employment, a lower quality of life, and shortened survival (Antinori, Arendt, Grant, Letendre, & Muñoz-Moreno, 2013). The cognitive deficits that are encompassed by HAND include psychomotor slowing, attention deficits, and memory impairments (Durvasula, Miller, Myers, & Wyatt, 2001).

Frailty is a concept that is increasingly being considered in the context of aging with HIV. Individuals that present as frail are more likely to have fluctuating disability, have an increased risk of falls, have longer hospital stays, have an increased risk of postoperative complications, respond poorly to vaccinations, and have an increased risk of functional decline and death (Clegg, Young, Iliffe, Rikkert, & Rockwood, 2013). The investigation of frailty among individuals with HIV serves as a useful tool in the identification of those more vulnerable to morbidity and mortality (Brothers et al., 2014). As the life expectancy for people living with HIV is increasing, the concept and measurement of frailty could provide us with useful information about those who may be vulnerable to HAND and therefore allow us to provide better care and treatment for those affected by HIV/AIDS (Brothers et al., 2014).

The aim of this study is to determine the prevalence of HAND as well as to determine the association between frailty and the development and progression of HIV-Associated Neurocognitive Disorder (HAND) among people living with HIV.

CHAPTER TWO: BACKGROUND AND RATIONALE

2.1 HIV & Aging

Advances in treatment of HIV such as the introduction of cART has extended the lifespan of those living with HIV and consequently the number of people that are living with and aging with HIV is growing (Chambers et al., 2013). An estimated 63,110 people are living with HIV/AIDS in Canada as of 2016 (a 5% increase over estimates from 2014), representing an estimated prevalence rate of 173 per 100,000 population (Public Health Agency of Canada, 2018). In Canada, the number of new cases of HIV has risen with an 8.2% increase in the number of new cases reported in 2018 over 2017 (a total of 2561 new cases in 2018, up from 2368 new cases in 2017) (Figure 1), representing a national diagnosis rate of 6.9% per 100,000 (up from 6.5% in 2017 and 6.4% in 2016) (Haddad, Li, Totten, & McGuire, 2018; Haddad et al., 2019). Ontario accounts for the highest number and proportion of HIV cases in Canada followed by Quebec, Alberta, and British Columbia (n=1003, 39.2%; n=766, 29.9%; n=249, 9.7%; n=199;7.8% respectively) (Haddad et al., 2019).

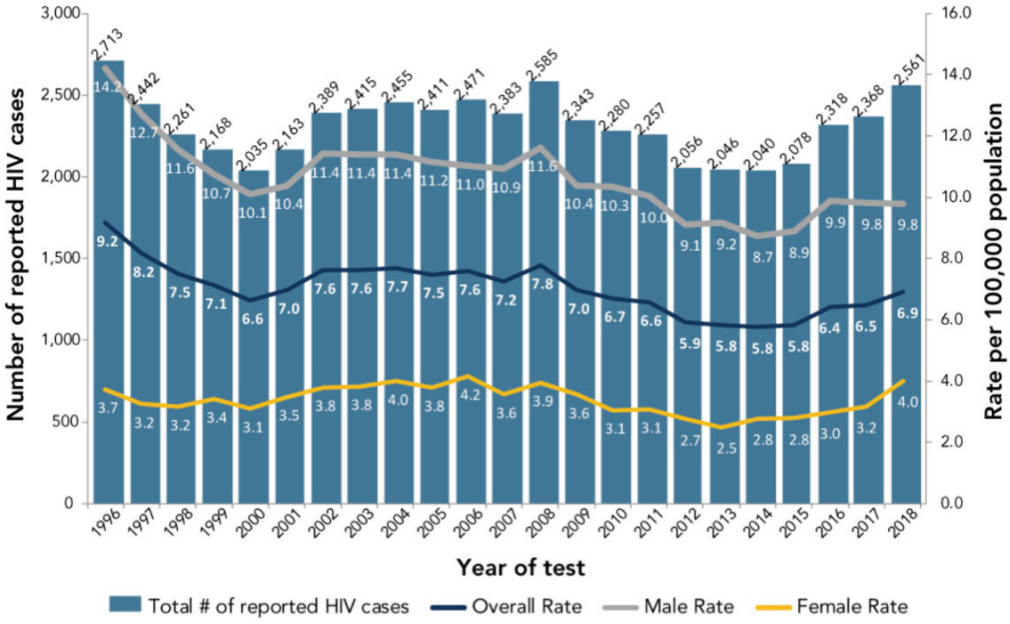
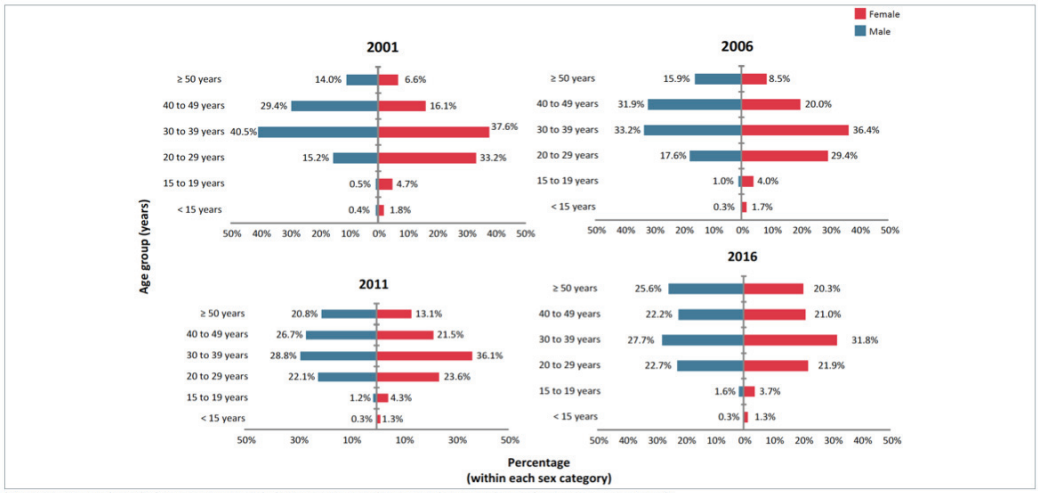


Figure 1. Number of reported cases of HIV and diagnosis rates overall, by sex and year, Canada, 1996-2018.
Note: Overall rate includes cases where sex is transgender, transsexual, not reported or unknown. From: "HIV in Canada - Surveillance Report, 2018" by Haddad N, Robert A, Weeks A, Popovic N, Siu W, Archibald C (2019). *Canadian Communicable Disease Report,* 45(12), pp. 304.

Adults aged 30-39 years of age account for the largest number of new HIV diagnoses in Canada, comprising 30.4% of the total new cases in 2018, followed by adults aged 50 and over and adults aged 20-29 years (each comprising 22.5% of total new cases), with the 40-49 age group comprising 21.9% of new cases (Haddad et al., 2019). The remainder of new HIV diagnoses in are within the 15-19 age group and under 15 years of age group (1.6% and 1.1% respectively). The 30-39 age group had the highest rate of new HIV cases in Canada in 2018 (15.4 per 100,000), followed by the 40-49 year age group (11.7 per 100,000 population) (Haddad et al., 2019). In 2018, 70.7% of new HIV cases were male and 29.3% were female, with the highest diagnosis rates in the 30-39 year age group for both males and females (20.5 and 10.1 per 100,000 population, respectively) (Haddad et al., 2018). Since 2001 there has been an increase in the proportion of cases in those

aged 50 and over, with males and females representing 25.6% and 20.3% of cases in 2016, respectively (Figure 2) (Bourgeois et al., 2017).

In the United States the largest percentage of those living with HIV are aged 50-54 years, which comprises 15% of the 1,040,352 people living with HIV by year-end 2018 (CDC, 2018). The largest increase in rates between 2014 and 2018 was seen in those aged 65 years and older, with an increase of 51% (CDC, 2018). These groups represent a vast amount of people living and aging with HIV who would benefit from early and targeted interventions in the prevention of frailty and HAND.



[1] Denominators used to calculate percentages exclude "sex not reported/transsexual/transgender" and "age group not reported"

Figure 2. Age group distribution of reported HIV cases by sex in Canada - 2016. Note: Denominators used to calculate percentages exclude "sex not reported/transsexual/ transgender" and "age group not reported". From: "HIV in Canada - Surveillance Report, 2016" by Bourgeois AC, Edmunds M, Awan A, Jonah L, Varsaneux O, Siu W. (2017). *Canadian Communicable Disease Report,* 43(12), pp. 251.

Cognitive impairment among older adults aging with HIV is common, with older adults living with HIV experiencing cognitive impairment at a rate twice that of their younger counterparts (Saylor & Sacktor, 2016). Cognitive impairment also occurs at an earlier age in individuals living with HIV, versus those not living with HIV (Saylor & Sacktor, 2016). Clinical factors that may increase the vulnerability of older adults with HIV

include a longer duration of infection, longer duration of antiretroviral exposure, increased risk of exposure to older and more toxic antiretrovirals, and age-related comorbidities (Wendelken & Valcour, 2012). Delayed diagnosis of HIV is also more common in older adults resulting in an increase of the duration of exposure to high levels of the HIV virus in the body and subsequent immunosuppression - both factors which can lead to an increased risk of HIV-Associated Dementia (Wendelken & Valcour, 2012).

The HIV virus enters the central nervous system via infected macrophages early in infection (Dupont & Sattentau; Kaul, Garden, & Lipton, 2001). Once the virus has entered the CNS it establishes infection in the macrophages and microglia (macrophages of the CNS which are triggered in response to immune damage). The infected macrophages and microglia are able to activate uninfected macrophages and microglia through the release of inflammatory cytokines and HIV-derived proteins, a process which leads to the accumulation of microglia around areas of necrosis, forming microglial nodules and multinucleated giant cells (Kaul, Garden, & Lipton, 2001; Nebuloni et al., 2000). The release of neurotoxic substances from the immune activated HIV-infected macrophages and microglia is thought to play a major role in the pathogenesis of HIV-associated dementia and cognitive decline (Kaul, Garden, & Lipton, 2001).

Neurological damage from HIV occurs as a result of direct factors, such as the effect of the HIV virus on the brain structure and function via a reduction in cortical matter and grey matter, as well as indirect factors such as the increased risk of cardiovascular disease seen in those living with HIV (Cohen, Seider, & Navia, 2015). Structural brain changes are seen in the normal aging process, however in individuals living with HIV there is both premature and accelerated age-related brain atrophy seen in subcortical regions, both of which have been proposed to contribute to cognitive related deficits (Chang, Holt, Yakupov, Jiang, & Ernst, 2013; Holt, Kraft-Terry, Chang, 2012). cART has led to improvements in cognitive functioning and reduced the incidence of neurological damage in those living with HIV (Cohen, Seider, & Navia, 2015). However approximately 30%

to 50% of those living with HIV still experience symptoms of HAND (Cohen et al., 2015). A study by Seider et al. (2014) demonstrated that HIV is associated with accelerated cognitive aging to the extent that individuals in their 50's and 60's living with HIV are more cognitively similar to 70 and 80 year old individuals living without HIV.

Several mechanisms have been proposed to explain the cognitive decline in those living with HIV. It is important to note that while some mechanisms of cognitive aging in HAND might be similar to that of Alzheimer's disease (a neurodegenerative disorder in which the mechanisms of action are perhaps more well studied) there are several important differences with regards to how HIV and Alzheimer's disease affect both the brain and cognition (Cohen et al., 2015). For example, while the presence of abnormal beta-amyloid (Aβ) protein may be implicated in both Alzheimer's disease and HAND, the exact dispersion and accumulation patterns of Aβ in the brain differ between the two disorders (Cohen et al., 2015). Pathology results have shown different patterns of amyloid deposition between Alzheimer's and HIV+ brains, with Alzheimer's brains showing extracellular neuritic amyloid plaques and HIV+ brains showing a more diffuse, non-neuritic, and intra-neuronal pattern of amyloid plaques (Sacktor & Saylor, 2014). There are also conflicting findings with regards to apolipoprotein E4 (or, ApoE4, the APOE gene allele associated with an increased risk of Alzheimer's), with some studies suggesting an increased risk of HAND, others finding no association, and other studies concluding that age modulates the association (Hellmuth, Milanini, & Valcour, 2014). Even though Alzheimer's disease and HAND are both considered neurodegenerative disorders, the exact patterns of neurodegeneration differ between the two diseases – for example in Alzheimer's disease neurodegeneration tends to occur primarily in the hippocampal region, while in HAND a frontal-subcortical pattern of neurodegeneration is typically seen (Cohen et al., 2015). The exact mechanism by which HIV interacts in the brain to worsen cognitive symptoms is unknown however recent research has demonstrated that both HIV and cART influence neurovasculature (with increased rates of atherosclerosis, diabetes, and cardiovascular disease risk factors demonstrated in

middle-aged HIV populations), thereby potentiating neurodegenerative disease (Cohen et al., 2015; Hellmuth et al., 2014). Systemic and CNS inflammation in people living with HIV may also contribute to the acceleration of aging, with cognitive impairment arising as a result of HIV-associated small vessel cerebrovascular disease (Saylor & Sacktor, 2016). A cross-sectional study examining the rate of silent cerebral small-vessel disease (CSVD) in people with well-controlled HIV compared to age and sex matched seronegative controls found that the risk of CSVD was significantly increased in people living with HIV (aOR = 2.3, 95% CI 1.5-3.6) (Moulignier et al., 2018). Neuroinflammation can also lead to decreased neuroplasticity and cognitive reserve, thereby increasing the risk of poorer cognitive function in those living with HIV (Vance, Fazeli, Grant, Slater, & Raper, 2013).

Functional MRI studies in individuals living with HIV have demonstrated evidence of both premature and accelerated aging in the brain, with individuals with HIV having lower cerebral blood flow as well as a less efficient network (Holt et al., 2012). The implications of this in individuals living with HIV is that they need to utilize greater resources in order to maintain cognition, and in patients aging with HIV, drawing from a lower cognitive reserve adds a further challenge in the maintenance of cognition (Holt et al., 2012). Structural MRI and fMRI studies have demonstrated that HIV patients with HAND have a diminished cognitive reserve and are therefore unable to accommodate for age-related related changes in attention when compared to HIV participants without a diagnosis of HAND (Chang et al., 2013).

The effect of accelerated aging in HIV has been demonstrated on a molecular level using DNA methylation levels through the development of an ‘epigenetic clock’ (based on dinucleotide markers) in order to calculate predicted age (or, DNA methylation age) in brain tissue and blood samples of HIV-infected participants compared with uninfected controls (Horvath & Levine, 2015). The epigenetic clock is strongly correlated with chronological age when compared to other biomarkers such as telomere length, correlates

well in multiple cell types (for example CD4 T cells, monocytes, B cells, glial cells, and neurons), and other measures of physical and mental fitness in older age, and is able to predict all-cause mortality (Horvath & Levine, 2015). Significant age acceleration effects were seen in HIV positive cases when compared to their seronegative controls, however, the magnitude of these effects were dependent upon brain region: age acceleration was seen in both the occipital cortex and the cerebellum but not the frontal lobe. The estimate of this effect was calculated in years with the results suggesting that brain ages of HIV positive cases were on average 7.4 years older than seronegative controls (9.3 years in the occipital cortex, 5 years in the cerebellum, and 0.1 years in the frontal lobe). The blood specimens demonstrated that the DNA methylation age of HIV positive cases was on average 5.2 years greater when compared to seronegative controls (Horvath & Levine, 2015). Subsequent research using the epigenetic clock has demonstrated that individuals living with HAND demonstrate greater accelerated aging when compared to neuropsychologically normal participants with an average age acceleration of 3.5 years (Levine et al., 2016).

The pattern of accelerated aging in HIV is seen in many processes including on a biological level with the acceleration of immune senescence as well as at the clinical level with the increase of multimorbidity, frailty, and polypharmacy seen in those living with HIV (Pathai, Bajillan, Landay, & High, 2013). ART toxicity in and of itself may also contribute to the increased rate of aging and increased rate of age-related illnesses thereby confounding the effects of aging with HIV (Pathai et al., 2013).

2.2 HIV-Associated Neurocognitive Disorder

The definitions and classifications of neurocognitive impairments in people living with HIV/AIDS have changed significantly in the past thirty years. One of the first examples of a classification scheme was the Memorial Sloan Kettering (MSK) scheme, which referred to the ‘AIDS Dementia Complex’ as a distinct neurological disorder encompassing cognitive, motor, and behavioural symptoms (Price & Brew, 1988). The

AIDS dementia complex had six clinical stages, with stage zero indicating normal mental and motor function to stage four (also referred to as 'end stage'), indicative of a nearly vegetative state where intellectual functioning was severely impaired (Price & Brew, 1988). One of the major limitations of the MSK scheme is that it did not distinguish behavioural and cognitive impairments that arise as a result of neurocognitive disorders versus impairments that arise as a result of myelopathy (neurological deficits relating to spinal cord trauma) (Grant & Sacktor, 2012).

In 1991 the American Academy of Neurology published a diagnostic system that divided severe forms of cognitive and motor impairments, defined as 'HIV-Associated Dementia Complex', from milder impairments which were referred to as Minor Cognitive Motor Disorder (MCMD) (Grant & Sacktor, 2012). The American Academy of Neurology schema was further updated in 2006 by the U.S. National Institute of Mental Health into what is now referred to as the Frascati Criteria (Grant & Sacktor, 2012). These criteria highlight that cognitive disturbance is a central feature of HIV-Associated Neurocognitive Disorder (Grant & Sacktor, 2012). HIV-Associated Neurocognitive Disorder (HAND) is a term that encompasses the spectrum of cognitive disorders in those living with HIV. These disorders range in order of severity from HIV-associated asymptomatic neurocognitive impairment (ANI) characterized by mild impairment in at least two cognitive domains but no functional impairments, to HIV-associated mild neurocognitive disorder (MND) characterized by mild to moderate impairment in at least two cognitive domains leading to moderate functional impairment, to HIV-associated dementia (HAD), which is characterized by severe impairment in at least two cognitive domains leading to severe functional impairment (Figure 3).

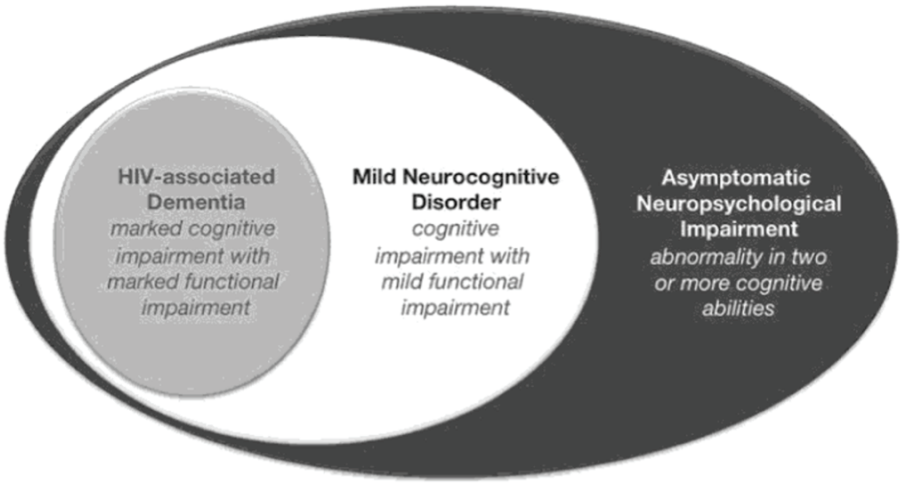


Figure 3. Schematic representation of the Frascati Criteria for HAND.
Reprinted from The Neurology of AIDS (p. 491) by I. Grant & N. Sacktor, 2012, New York: Oxford University Press. Copyright 2012 by the Oxford University Press. Reprinted with permission.

In ANI, impairment in the cognitive domains is defined as at least one standard deviation below the mean of normative scores which have been demographically adjusted according to normative standards (Antinori et al., 2007). At least five different cognitive domains must be examined, including attention-information processing, language, abstraction-executive, complex perceptual motor skills, memory (including learning and recall), and simple motor skills or sensory perceptual abilities (Antinori et al., 2007). In order for these cognitive impairments to be defined as ANI they must not be attributable to any sort of delirium, for example, delirium that can occur as a result of another central nervous system (CNS) disease, vascular trauma such as stroke, the effects of drugs, or any other disorder. Additionally, the cognitive impairment must not be able to be accounted for by some other type of comorbidity (Antinori et al., 2007).

HIV-associated MND is similar to HIV-associated ANI, however a diagnosis requires the addition of impairment in everyday functioning. In order for a diagnosis of HIV-associated MND, an individual must exhibit mild to moderate cognitive impairment in at

least two of the areas listed above, defined as at least one standard deviation below the mean of normative scores that have been demographically adjusted (Antinori et al., 2007). Like ANI, this cognitive impairment must not be explained by other delirium or dementia and must also not be accounted for by another comorbidity (Antinori et al., 2007). However, unlike ANI, this impairment must interfere with activities of daily living. These impairments in daily living can be categorized into either self-reported inefficiencies (such as issues with mental acuity, or trouble with keeping up with the demands of work, homemaking, or social functioning), or inefficiencies reported by those close to the individual, for example witnessing a decline in mental acuity leading to the inefficiencies experienced in work, homemaking, or social functioning (Antinori et al., 2007).

The most severe diagnosis on the HAND spectrum is HAD. In order for an individual to be diagnosed with HAD, they must experience cognitive impairment in at least two domains listed above, defined as a score at least two standard deviations below the normative mean (Antinori et al., 2007). Again, this impairment in cognitive functioning must not be explained by other comorbidities or deliriums resulting from other means. The cognitive impairment must also result in a marked interference in day to day functioning and activities of daily living (Antinori et al., 2007). Individuals who are diagnosed with HAD have cognitive impairments that interfere significantly with their day-to-day lives and as such they are usually unable to work or care for themselves (Grant & Sacktor, 2012). People living with HIV who are experiencing neurocognitive challenges or have been diagnosed with HAND may require increased social support and support from health care professionals including increased access to resources, assistance, counselling (Liboro et al., 2019). Early and effective screening is therefore important for the identification of these disorders which can help clinicians to treat these disorders at an earlier stage and aid in helping service providers identify those in need of support.

The advent of cART has been crucial not only in reducing the rates of HAND (and especially the rates of HAD) but also in slowing the development and progression of HAND. Before the advent of cART, approximately 15%-16% of individuals with AIDS had a diagnosis of HAD (Heaton et al., 2011; Sacktor et al., 2002; Valcour, Shikuma, Watters, & Sacktor, 2004). A cross-sectional study of 1555 HIV-infected adults with a mean age of 43.2 (8.5) years conducted by the CNS HIV Antiretroviral Therapy Effects (CHARTER) study in the United States showed that while the more severe HAD diagnosis is now rare and only accounts for approximately 2.4% of HAND cases, the less severe cases of HAND are still common, with ANI and MND accounting for 32.7% and 11.7% of HAND cases, respectively, with neuropsychologically normal participants accounting for the remaining 53.2% of participants (Heaton et al., 2010). The Multicenter AIDS Cohort Study (MACS), a prospective cohort study of gay and bisexual men, showed a significant ($p < 0.05$) increase in overall frequency of HAND diagnoses over the study period, from 25% in 2007-2008 and 2009-2010 to 31% in 2011-2012 (Sacktor, 2016). Notably, the rate of ANI increased significantly from 12% in 2007-2008 and 8% in 2009-2010 to 19% in 2011-2012 (2007–2008 to 2011–2012, $p= 0.14$; 2009–2010 to 2011– 2012, $p = 0.016$) (Sacktor, 2016).

The types of deficits seen in HAND have also changed between the pre- and post-cART era. A study comparing the rates and manifestations of neurocognitive impairment in the pre-cART versus post-cART eras found that pre-cART neurocognitive impairment was associated with a subcortical pattern of involvement rather than the more cortical pattern seen post-cART neurocognitive impairment (Heaton et al., 2011). The neuropsychological manifestations between the pre-cART and post-cART era also differed, with pre-cART neurocognitive impairments more commonly occurring in the motor speed/dexterity, speed of information processing, and verbal fluency domains and the post-cART neurocognitive impairments most commonly occurring in the memory/ learning and executive function domains (Heaton et al., 2011). Pre-cART neuroimaging studies demonstrate that HIV infection led to a decrease in neuronal function and a

concurrent increase in inflammation in the brain - factors that both improved with the subsequent administration of cART (Clifford & Ances, 2013).

The US CHARTER Cohort demonstrated that individuals with ANI have a shorter time to progression to symptomatic HAND than their neuropsychologically normal counterparts (Grant et al., 2014). Further, ANI is associated with a two fold (when using self-report measures of daily functioning) to six fold (when using objective, performance-based measures of daily functioning) increase in risk for the future development of symptomatic disorders (MND or HAD) when compared to those who were neuropsychologically normal (Grant et al., 2014). The Multicenter AIDS Cohort Study (MACS) replicated these findings, demonstrating that participants with ANI showed a two-fold increase risk of developing symptomatic HAND (Sacktor et al., 2016). These results have also been replicated in the Ontario HIV Treatment Network (OHTN) Cohort Study, where individuals with ANI demonstrated an almost two fold increased risk in progression to symptomatic HAND (Rourke et al., 2015).A study examining geriatric conditions in older adults (≥ 60 years of age) living with HIV who had been diagnosed with MND demonstrated that over half (55%) of participants met the criteria of pre-frailty as determined by the Frailty phenotype and further reported high rates of incontinence (58%), falls (41%), depressive symptoms (39%), and mobility issues (32%), dependence with instrumental activities of daily living (IADL; 55%) or activities of daily living (ADL; 41%) (Hosaka et al., 2019).

2.3 Multimorbidity

Multimorbidity refers to the co-occurrence and accumulation of multiple chronic or acute diseases within an individual (Valderas, et al., 2009). Multimorbidity is a separate but related construct to comorbidity, which is defined as the presence of an additional disease in relation to an index disease in a particular individual (Valderas, et al., 2009). Both constructs measure diseases occurring concurrently in one individual. In the present study HIV is considered the index condition. Multimorbidity is also distinct from frailty. While

multimorbidity attempts to measure the accumulation of chronic diseases (for example, osteoporosis, diabetes), frailty also includes smaller, sub-clinical changes (for example, low bone mineral density and abnormal glucose).

Historically, care for those living with HIV focused on alleviating immunodeficiency related ailments such as opportunistic infections, however, since the introduction of cART there has been a shift in focus to non-AIDS diseases (Hasse et al., 2011). A Swiss cohort study demonstrated a significantly higher incidence of clinical AIDS and mortality, as well as some comorbidities such as stroke, myocardial infarction, diabetes mellitus, and non-AIDS defining malignancies in HIV-patients older than 50 years when compared to younger HIV-patients (Hasse et al., 2011; Guaraldi, Silva, & Stentarelli, 2014). Over half of deaths and clinical events in those patients on cART are classified as non-AIDS defining conditions and are not attributable to AIDS-defining conditions (Justice, 2010). A Canadian population-based retrospective cohort study spanning from 1995 to 2014 demonstrated a significant decline in deaths attributable to HIV/AIDS, with deaths in people living with HIV/AIDS being more often attributable to chronic conditions such as cancer, cardiovascular disease, and other non-communicable diseases (Burchell et al., 2019).

Patients with HIV are more likely to develop non-communicable comorbidities than seronegative matched controls and are also more likely to exhibit polypathology (defined as the presence of two or more non-communicable comorbidities, or, in other words, multimorbidity) at a rate similar to seronegative controls that are 10 years older (Guaraldi et al., 2011). Patients with HIV have a significantly increased likelihood of developing renal failure, diabetes, bone fractures, hypertension, and cardiovascular disease and are also more likely to develop these comorbidities at earlier ages when compared with controls (Figure 4) (Guaraldi et al., 2011). Patients with lower nadir CD4 count and prolonged ART exposure are especially at risk for developing polypathology (Guaraldi et al., 2011).

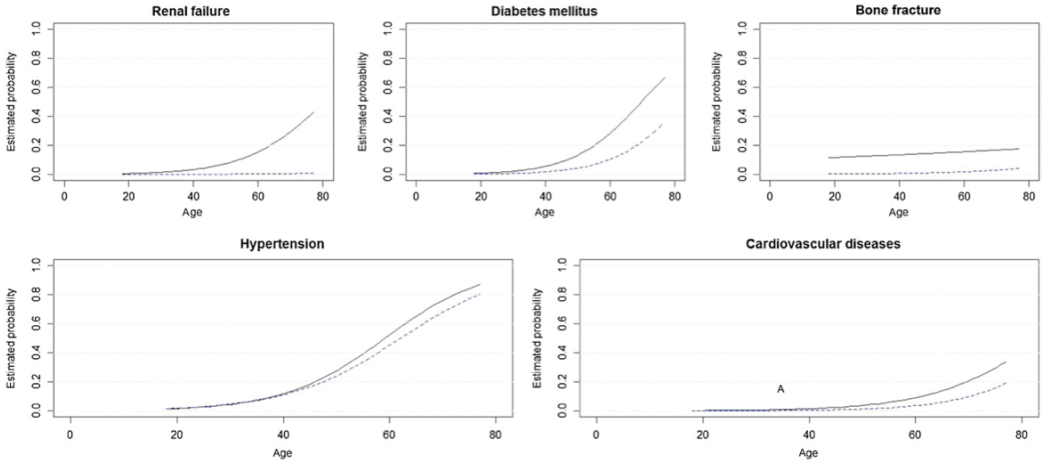


Figure 4. Comparative risk of hypertension, diabetes mellitus, renal failure, cardiovascular disease, and fracture, by age, among patients with HIV versus age-, sex-, and race-matched control subjects.
Note: Comparative risk (defined by odds ratio) was assessed using logistic regression analysis. Solid lines indicate the comparative risk for HIV patients while the dashed lines indicate risk for their matched controls. From "Premature Age-related Comorbidities Among HIV-infected Persons Compared With The General Population" by Guaraldi, G., Orlando, G., Zona, S., Menozzi, M., Carli, F., Garlassi, E., … Palella, F., 2011, Clinical Infectious Diseases, 53(11), p. 1123. Copyright 2011 by the Oxford University Press. Reprinted with permission.

The rates of multimorbidity in those aging with HIV is high, with over 60% of HIV-infected individuals between the ages of 50 to 59 having at least one comorbid diagnosis (Goulet et al., 2007). The prevalence of multimorbidity in people living with HIV has increased, from 8.2% to 22.4% between the years of 2000 to 2009, with hypercholesterolemia and hypertension presenting as the most common conditions (Wong et al., 2017). Increased multimorbidity prevalence is also seen with increasing age (Wong et al., 2017). In a Canadian sample of people living with HIV, 34.4% of participants had at least one comorbidity and 10.8% of participants demonstrated multimorbidity (defined as having two or more chronic conditions), a rate significantly higher than the general

Ontario population (prevalence ratio 1.30, 95% CI 1.18 - 1.44) (Kendall et al., 2014). The prevalence of multimorbidity also increased with increasing age (Kendall et al., 2014).

Multimorbidity is thought to predispose an individual to developing HAND (Hellmuth et al., 2014). The CHARTER study demonstrates a clear association between cognitive diagnoses and comorbidities (Heaton et al., 2010; Valcour, 2013). Comorbidities such as diabetes further exacerbate neuropathology in those aging with HIV and lead to additional brain atrophy, white matter loss, and an increased likelihood of cerebral infarcts (Holt, Kraft-Terry, Chang, 2012). The increased rate of multimorbidity in aging HIV patients therefore highlights an important area for future investigation.

The Veteran Aging Cohort Study Index (VACS Index) is a comprehensive risk index which considers age, CD4 count, HIV RNA, AIDS-defining illnesses, hemoglobin, renal function, liver function, chronic hepatitis B and C, and diagnoses of alcohol and drug dependence in order to determine the overall risk of mortality in those living with HIV (Justice, 2010). Each of these components are summed via a point system in order to generate the risk of mortality, with higher scores indicating a higher risk of mortality (Justice, 2010). As the index accounts for both traditional AIDS markers and common indicators of comorbid injury on various organ systems, it is better able to discriminate survival when compared to an index that only takes AIDS-defining illnesses, CD4 count, and HIV-1 RNA into account (Justice, 2010). A cross-cohort study which used data from over 13 cohorts in order to compare the predictive validity of the VACS index versus a restricted index (an index restricted to CD4 count, HIV-1 RNA, and age) found that the VACS index showed greater discrimination and was better able to make accurate mortality estimates (Justice et al., 2013). Additionally, because the VACS index combines the indicators of comorbid injury across multiple organ systems, it is better able to reflect the multisystem organ injury seen in people living with HIV (Marquine et al., 2014). Higher VACS index scores are associated with an increased risk of global neurocognitive impairment, even after adjusting for psychiatric comorbidities (Marquine et al., 2014).

The components of the VACS index that are most strongly associated with neurocognitive impairment are older age, lower hemoglobin, and lower CD4 counts (Marquine et al., 2014). Higher VACS index scores are also associated with a decline in overall neuropsychological functioning over time, even after adjusting for baseline neuropsychological performance, cognitive symptoms, depression, HIV disease markers, medical comorbidities, and demographic variables (Rourke et al., 2015).

2.4 Frailty

There are multiple ways to define age, the most common of course being chronological age. While chronological age is an important factor when it comes to determining one's probability of survival, it fails to tell us an individual's level of overall health (Mitnitski, Mogilner, & Rockwood, 2001). A more useful measure of aging may be biological age, which is the construct underlying frailty. The term 'frailty' is used to describe the variability in age-related health problems that arises from the age-related deterioration in various physiological systems (Brothers et al., 2014; Rockwood & Mitniski, 2011). Frailty in and of itself contributes to an increase in one's susceptibility and vulnerability to stressors (Brothers et al., 2014; Rockwood & Mitniski, 2011). Increasing levels of frailty also result in a reduced capacity to respond to stressors as a result of the accumulation of these deficits (Rockwood & Mitnitski, 2011). The prevalence of frailty in the general population increases with age and significantly increases the risk of mortality (Song, Mitnitski, & Rockwood, 2010).

Frailty can also be measured in a variety of ways. One method, referred to as the frailty phenotype, measures frailty according to the presence or absence of five specific deficits, including: self reported unintentional weight loss of 10 pounds or more, slow walking speed (as measured by an assessor), weak grip strength (as measured by an assessor), self-reported exhaustion, and low activity and energy expenditure (as measured by the Minnesota Leisure Time Questionnaire) (Fried et al., 2001).

Another method considers frailty as a state, which is quantified in a frailty index. The frailty index counts the number of deficits that an individual presents with at the time of assessment and reports this number as a proportion of the total number of deficits considered (Mitnitski, Mogilner, & Rockwood, 2001). A wide variety of deficits can be included in the frailty index as long as they are related to age and poor health (Brothers et al., 2014). Deficits in health that contribute to frailty can be symptoms, signs, disabilities, and diseases (Searle et al., 2008). Unlike the frailty phenotype, the specific deficits included in the index are not fixed, and can vary from one index to another, based on the information available. The ability of the frailty index to include deficits that are readily clinically available contributes to its versatility and allows for the assessment of frailty in a population of interest from previously collected variables. In order for variables to be included in a frailty index, they must satisfy the following five criteria: (1) variables must be related with health status (for example, while an attribute such as graying hair may be related to increasing age, this attribute is not related to health status and therefore would not be included), (2) the prevalence of the deficit must be known to increase with age, (3) the deficit must not saturate too early (for example, a condition such as presbyopia is almost universal in adults by the age of 55 and therefore such an attribute would not be included), (4) deficits that are considered must collectively cover a range of physiological systems, and (5) if the frailty index is to be used sequentially on the same individual or group of individuals, the deficits that comprise the initial frailty index must be used each time (i.e. no new items may be added or removed as this could alter the comparison), however this is not a concern if different frailty indexes are used between samples (Searle et al., 2008). Approximately thirty to forty deficits should be used to generate the frailty index; its precision increases as the number of deficits within the index increases (Searle et al., 2008). The frailty index is also adaptable as it can be constructed using pre-existing variables that are available within many cohorts or with variables that are readily clinically available.

The frailty index is able to account for the fact that individuals accumulate deficits at different rates as they age or even how they progress through various disease states (Rockwood & Mitnitski, 2011). The high number of deficits included in a frailty index also means that a change in any one deficit (or even, how this deficit is defined) does not produce a change in the frailty classification of an individual. Rather, the frailty index focuses on the accumulation of deficits as a proportion of all factors considered, to derive a frailty score between 0 and 1. Because the frailty index accounts for such a large number and wide variety of deficits it is arguably more robust than other approaches using only a limited number of variables such as the frailty phenotype. The frailty phenotype also excludes those with a history of Parkinson's, stroke, cognitive impairment (defined as Mini-Mental scores <18), and those taking antidepressants as the authors theorize that these conditions could determine frailty by their presence alone (Fried et al., 2001). The frailty phenotype therefore is not as widely applicable as the frailty index which does not impose these limitations. A systematic review by Theou et al. (2015) demonstrated that there is often variability and a lack of standardization in how the frailty phenotype criteria are defined among authors which can lead to low precision and variance in internal consistency.

The frailty index is distinct from the VACS in that the VACS items are all HIV related, whereas the frailty index includes general health variables such as hypertension, mobility impairments, cancer, and diabetes. The frailty index can therefore be viewed as a step beyond the VACS index as a global health measure. The frailty index also does not take into account chronological age like the VACS index does. The measure of chronological age in a population aging with HIV is not as useful as, for example, the number of years since HIV diagnosis due to the high variability seen in those aging with HIV. Frailty indices with and without HIV-related variables have been shown to perform similarly to the VACS index in their ability to discriminate mortality risk (Guaraldi et al. 2015). The accumulation of deficits in the frailty index is thought to be an important predictor of

future morbidity and mortality and may be useful in predicting future HAND development and progression.

An important principle regarding frailty is that while deficits may have a small effect on health when taken into account individually, the effect of these deficits taken together in a cumulative fashion may be large (Brothers et al., 2014). Indeed, the cumulative effect of these deficits is expected to tell us more about the health of an individual than when considered apart (Rockwood & Mitnitski, 2011). The frailty index also encompasses the notion of multimorbidity and provides a composite measure of the health state of an individual. Increased frailty index scores have been associated with an increased risk of mortality across seven population-based and four clinical/institutional surveys (with a total n=36,424), with each unit increase in frailty increasing the hazard rate for mortality by an average of 4% (95% CI 0.02 - 0.06) (Mitnitski et al., 2005).

2.4.1 Frailty and HIV

Several factors have been associated with frailty among those living with HIV, including HIV related measures such as longer disease duration, lower CD4 and nadir CD4 counts, the presence of a detectable viral load, and longer duration of cART; comorbidities such as hepatitis C, low or high BMI, lipodystrophy, diabetes, and kidney disease; hepatitis C co-infection, depressive symptoms, markers of chronic inflammation (IL-6, D-dimer, sCD14); as well as social factors such as lower education, current unemployment, or low income (Brothers et al., 2014; Brothers & Rockwood, 2014; Fukui, Piggot, & Erlandson, 2018). Increased and earlier rates of frailty in individuals with HIV have been attributed to the HIV infection itself, low rates of control of the HIV virus early in infection, the presence of comorbidities, as well as lifestyle habits such as smoking and substance use (Thurn & Gustafson, 2017). A study examining brain volumetric changes using T1 weighted MRI in older adults living with HIV($\geq$ 40, Mean = 50.6, SD = 6.8) found that frailty (as assessed by the frailty phenotype) is associated with a decreased volume of

cerebellar white matter and subcortical grey matter, regions associated with both motor control and cognition (Kallianpur et al., 2016).

Both the frailty phenotype and the frailty index have been previously used to describe frailty, the prevalence of frailty, hospitalization, morbidity, and mortality in HIV populations. A comparison of the two measures in an HIV cohort demonstrated that the frailty index and frailty phenotype were modestly positively correlated, sharing similar right-skewed distributions and an increase of frailty score with age (Guaraldi et al., 2017). Both frailty measures were associated with multimorbidity, with the frailty index also being associated with Instrumental Activities of Daily Living impairment and falls history (Guaraldi et al., 2017). Overall, the frailty index demonstrated a stronger association with age, nadir CD4 count, comorbidities, falls, and disability (Guaraldi et al., 2017). Higher VACS index scores have been demonstrated to be independently associated with prefrailty and frailty in an older HIV cohort (mean age = 48 years) as assessed by the frailty phenotype (OR 1.025, $p = 0.019$), with prefrail and frail participants demonstrating significantly higher median VACS index scores when compared to non-frail participants (Escota et al., 2015). VACS index scores were however unable to predict transitions between non-frail and prefrail/frail states over a one-year follow-up, suggesting that the ability of the VACS index to monitor frailty transitions in the HIV population is limited (Escota et al., 2015).

The prevalence of frailty (as determined by the Frailty Phenotype) in HIV populations has been described in both male and female cohorts. In the Multicenter AIDS Cohort Study the prevalence of frailty among HIV+ men was significantly ($p = 0.002$) higher than HIV- men with prevalence rates of 12% and 9%, respectively (with a mean of 10%) (Althoff et al., 2013). Among the HIV+ men, those who presented as frail at any visit had lower median CD4 counts, were less likely to have a suppressed viral load, were twice as likely to have a history of AIDS, and had been on HAART for one year longer than those who had never presented as frail (Althoff et al., 2013). The proportion of men defined as

frail also increased with age and was significantly greater in HIV+ men aged 50-64 years when compared to HIV- men (Althoff et al., 2013). In the Women's Interagency HIV Study (WIHS) the prevalence of frailty was significantly greater for HIV+ women compared at risk HIV- women (17% versus 10% respectively, $p<0.0001$) (Gustafson et al., 2016; Thurn & Gustafson, 2017). Low CD4 count, age greater than 40 years, current and previous smoking, low income, moderate (versus low) fibrosis-4 levels, and moderate (versus high) estimated glomerular filtrations rates were positively associated with frailty in this cohort (Gustafson et al., 2016; Thurn & Gustafson, 2017). A systematic review estimating the prevalence and predictors of frailty using the frailty phenotype demonstrated that frailty prevalence varied from 5.0% to 28.6% among various HIV studies (Levett, Cresswell, Malik, Fisher, & Wrighte, 2016). Individuals with HIV were more likely to be frail, and the predictors of frailty included older age, comorbidities, AIDs diagnosis, and low current and nadir CD4 counts (Levett et al., 2016).

Frailty has also been assessed as part of a constellation of other geriatric syndromes including falls, urinary incontinence, functional impairment sensory impairment, depression, and cognitive impairment in a cross-sectional study of HIV+ individuals aged 50 and older on cART with an undetectable viral load (Green et al., 2015). The prevalence of pre-frailty in this cohort was 56.1%, while the prevalence of frailty was 9.0% (with pre-frailty classified as the presence of 1 or 2 frailty phenotype deficits, and frailty classified as the presence of 3 or more frailty phenotype deficits) (Green et al., 2015). Other frequent geriatric conditions in the cohort included difficulty with one or more instrumental actives of daily living (such as medication and housework) with a prevalence of 46.5%, and cognitive impairment (defined as a score <26 in the Montreal Cognitive Assessment tool) with a prevalence of 46.5% (Green et al., 2015). Non-caucasian race, increasing number of comorbidities, and lower nadir CD4 count were associated with an increased risk of one or more geriatric syndromes (Green et al., 2015). A study on both HIV+ and HIV- VACS cohort participants used an adaptive survey-based

frailty phenotype measure assessing physical shrinking, exhaustion, slowness, and decreased physical activity to measure frailty and predictors of hospitalization and mortality (defining pre-frailty as the presence of 1-2 deficits, and frailty as the presence of 3 or more deficits) demonstrated that both pre-frailty and frailty were associated with hospitalization (HR =1.44, 95% CI 1.33 - 1.54 and HR 1.78, 95% CI 1.28 - 2.13, respectively) and mortality (HR = 1.44 95% CI 1.25-1.66 and HR = 1.75, 95% CI 1.28 - 2.40 respectively) (Akgün et al., 2014).

A study using a modified Frailty Phenotype measure to examine the rates of frailty among people living with HIV to seronegative controls matched on sex, education level, and 5-year age categories found that HIV+ participants had significantly higher levels of frailty (6.1% vs. 0.6%, $p<0.01$) and pre-fraily (28.1% vs. 11.9%, $p<0.01$) when compared to the matched seronegative controls (Ding et al., 2017). In both HIV+ participants and seronegative controls, those classified as frail or pre-frail had higher rates of depressive symptoms, were more likely to have a low body mass index (<18.5), and also had higher rates of insomnia symptoms (Ding et al., 2017). The association between HIV infection and pre-frailty and frailty remained significant after adjusting for age, sex, education level, BMI, waist circumference, and comorbidity (OR = 3.79; 95% CI 2.50–5.73; $P <$ .001) (Ding et al., 2018).

The utility of a frailty index in an HIV cohort has been validated in previous studies. A 37-item frailty index was able to predict survival and incident multimorbidity in a longitudinal HIV cohort (Guaraldi et al., 2015). These authors found that frailty indices containing HIV-related variables (including CD4 count, nadir CD4 count, HIV viral load, and duration of HIV infection among others) performed similarly to frailty indices without HIV variables in their ability to discriminate mortality risk (Guaraldi et al., 2015). Increased levels of frailty in HIV are associated with future frailty severity and mortality (Brothers et al., 2017). A longitudinal study examining the four-year predictors of frailty severity (as assessed by a 31-item frailty index) and mortality in an HIV-cohort

demonstrated that baseline frailty index scores, female sex, nadir CD4 count, duration of HIV infection, duration of ARV exposure, and smoking pack-years all independently predicted frailty index scores at follow up (with risk ratios of RR 1.06, 95% CI 1.05–1.07; RR 0.93, 95% CI 0.87–0.98; RR 0.96, 95% CI 0.93–0.99; RR 1.06, 95% CI 1.01–1.12; (RR 1.08, 95% CI 1.02–1.14; and 1.03, 1.01–1.05, respectively) (Brothers et al., 2017). The independent predictors of mortality at the four-year follow up included baseline frailty index scores (OR 1.19, 95% CI 1.02–1.38), current CD4 count (OR 0.34, 95% CI 0.20–0.60), and injection drug use (2.89, 95% CI 1.30–6.42) (Brothers et al., 2017).

2.4.2 Frailty, HIV, and Cognition

Low levels of frailty are associated with improved cognitive outcomes in people living with HIV (Wallace et al. 2017). In an HIV cohort of participants aged 50 and older, lower levels of frailty (as assessed by a 37-item frailty index) were associated with successful cognitive aging (SCA), defined as the absence of depressive symptoms, cognitive impairment, and functional impairment (Wallace et al., 2017). Further, participants in the successful cognitive aging group (comprising 38.8% of the total sample) had significantly fewer HIV-Associated Non-AIDS (HANA) conditions out of the eight examined, including cardiovascular disease, end-stage kidney disease, cancer, osteoporosis, hypertension, type 2 diabetes mellitus, liver cirrhosis, and chronic obstructive pulmonary disease (0.9±1.0 in the SCA group versus 1.3±1.0 in the non-SCA group, $p<0.05$). Frailty, hypertension, and multimorbidity were all significantly associated with lower odds of successful cognitive aging (OR = 0.40, $p= 0.40$, OR = 0.35, $p=0.05$, OR = 0.64, $p=0.04$, respectively) (Wallace et al., 2017).

Higher frailty index scores (as assessed by a 26-item frailty index including HIV variables) have been associated with decreased neurocognitive function and performance in people living with HIV in the following cognitive domains: verbal fluency, executive functioning, processing speed, and motor skills (Oppenheim et al., 2018).The association

between frailty (as defined by the frailty phenotype) and the development of HAND has previously been assessed in a cross-sectional study of adults living with HIV aged 50 and above (Zamudio-Rodríguez et al., 2017). Both pre-frailty (defined as exhibiting one or two frailty phenotype deficits) and frailty (defined as exhibiting three or more deficits) were shown to be associated with MND in unadjusted analyses. Individuals in the pre-frail category demonstrated a significant association with MND after adjusting for age, education, HIV duration, viral load, CD4 count, nadir Cd4, and comorbidities (RR = 5.70, 95% CI = 1.09–29.82) (Zamudio-Rodríguez et al., 2017). HIV+ individuals identified as pre-frail or frail (according to a modified Frailty Phenotype) have been found to be older, have higher rates of cognitive impairment, and have higher numbers of comorbidities when compared those who were classified as non-frail (Ding et al., 2018).

Frailty and neurocognitive impairment is associated with a more than double increase in risk of a poor health outcome such as recurrent falls, disability, and death in HIV+ participants when compared to HIV+ participants without frailty or neurocognitive impairment (prevalence ratio (PR) 2.65; 95% CI 1.98 - 3.54, $p<0.001$) (Erlandson et al., 2019). Frail participants without neurocognitive impairment also had a more than double risk of a poor health outcome when compared to those participants without frailty or neurocognitive impairment (PR 2.26; 95%CI 1.71 - 2.99, $p<0.001$) (Erlandson et al., 2019). Further, participants with neurocognitive impairment alone (no frailty) had a significantly increased risk of a poor health outcome when compared to participants without frailty or neurocognitive impairment (PR 1.73; 95% CI 1.36, 2.20, $p<0.001$) (Erlandson et al., 2019). These findings demonstrate that frailty and neurocognitive impairment independently put individual living with HIV at risk of poor health outcomes, a risk which further is increased when participants exhibit both frailty and neurocognitive impairment. Further, frailty alone is able to strongly predict those at risk of poor health outcomes.

Patients with higher nadir CD4 counts (>200 cells/ml) demonstrate significantly better performance in attention, working memory, and executive function (Muñoz-Mereno et al., 2008). In a cross-sectional study of adults over the age of 50 living with HIV, aerobic fitness (as determined by peak VO_2 during a graded, progressive treadmill test) was related to cognitive performance, with lower levels of fitness associated with an increased risk of cognitive impairment (Mapstone et al., 2013). Further, participants with higher levels of aerobic fitness were significantly less likely to have the more severe HAND diagnoses such as MND (OR=0.65, p=0.01) and HAD (OR=0.64, p<0.01) (Mapstone et al., 2013).

Methamphetamine use disorders in patients living with HIV is associated with higher frailty (as assessed by a 27-item frailty index) when compared to HIV patients without a methamphetamine use disorder (b = -0.13, p < .001) and seronegative controls without a use disorder (b = -0.06, p = .007) (Paolillo et al., 2019). Among participants with methamphetamine use disorders, higher frailty was negatively associated with decreased global neurocognition (b = -17.6, p = .018)
as well as increased dependence in instrumental activities of daily living (OR = 1.56, p = .021). Increased frailty was also negatively associated with neurocognitive functioning (executive function r = -0.34, p =.03; working memory r = -0.33, p = .03) (Paolillo et al., 2019).

The present study aims to further increase our understanding of the relationship between frailty and HIV by determining if frailty is able to predict the development of HAND, as well as to determine whether increasing frailty is associated with an increased risk of progression through the various HAND states. This study also aims to explore whether different levels of frailty affects the mobility between HAND states. To date, neither the association between frailty and the development and progression of HAND, nor the mobility between HAND states have been assessed through the use of the frailty index. Further, the examinations between the association of neurocognitive impairment and

frailty in people living with HIV has only been examined cross-sectionally. This is the first study to examine the relationship between frailty and HAND progression longitudinally. As frailty increases the risk of mortality and poor outcomes in people living and aging with HIV, the identification and measurement of frailty serves as a useful tool to identify those at most risk in order to implement appropriate clinical interventions.

CHAPTER THREE: OBJECTIVES

The relationship between frailty and the development and progression of HAND is so far poorly understood, which highlights a major gap in our understanding of this cognitive disorder. The proposed study aims to explore the major contributing factors in the development and progression of HAND.

The overall goal of this study is to examine the association between frailty and the development progression of HAND among people aging with HIV.

Specifically, the main objectives of the study are:

Objective 1: To determine the prevalence of HIV-associated neurocognitive disorder (HAND) in a population-based cohort of individuals living with HIV in Ontario.

Objective 2: To determine the association between frailty and the development of HIV-associated neurocognitive disorder (HAND).

Objective 3: To determine the association between frailty and the progression of HIV-associated neurocognitive disorder (HAND).

It is hypothesized that individuals with increasing frailty will be more likely to develop HAND than those with low or no frailty. Further, it is hypothesized that increasing levels of frailty will be associated with quicker progression to HAND.

CHAPTER FOUR: METHODS

4.1 Data Source and Study Population

This study uses data from the Ontario HIV Treatment Network (OHTN) Cohort Study (OCS), a longitudinal cohort of people living with HIV. The OCS is an observational, open dynamic cohort study (Rourke et al., 2013). The OCS began in 1994 and has since collected extensive data on people living with HIV in Ontario. The present study utilizes results from neuropsychological testing that was conducted on an annual basis from October 2007 to January 2015, during which time 76% of participants had two or more visits at which neuropsychological testing was completed (Table 1). The OCS therefore provides a robust data set from which to study the development and progression of neurocognitive change over time among people living with HIV. One of the mandates of using data from the OCS was to commit to meaningful engagement with the HIV/AIDS community through the establishment of a community advisory committee consisting of members of the HIV community who are engaged in HIV/AIDS activism and advocacy in their respective communities. The community advisory committee helped to guide the focus of this project as well as the interpretation of the findings (Chapter 7).

Table 1. *Number of Participants per Neuropsychological Testing Visit*

Visit Number	Number of Participants	Percent of Total (%)
1	1152	100
2	875	76.0
3	650	56.4
4	434	37.7
5	221	19.2
6	110	9.5
7	54	4.7

Note. These numbers represent the total number of participants after exclusions.

4.2 Inclusion/Exclusion Criteria

Participants are eligible to participate in the OCS if they have received a positive HIV antibody test or if they have other laboratory evidence of HIV infection (Rourke et al., 2013). Individuals under the age of 16 as well as adults who are unable to give informed consent are ineligible from participating in the OCS (Rourke et al., 2013). Participants with a pre-existing cognitive related diagnosis such as Parkinson's, or Alzheimer's disease were excluded from the present study in order to decrease confounding and increase internal validity (Table 2).

Table 2. *List of Exclusions with Corresponding ICD-9 and ICD-10 Codes*

Exclusion	ICD-9-CM Diagnosis Code	ICD-10-CM Diagnosis Code (from ICD-10 Version 2016)
Parkinson's disease	332.0	G20
Dementia in Parkinson's disease	-	F02.3
Alzheimer's disease	331.0	G30
Dementia in Alzheimer's disease	-	F00*
Vascular dementia	290.4	F01
Dementia with Lewy bodies (DLB) (also classified in 'dementia in other diseases classified elsewhere').	331.82	G31.8
Mixed dementia	-	F01.3 (also captured under G30.8 'other Alzheimer disease')
Frontotemporal dementia	331.19	G31.0
Creutzfeldt-Jakob disease (CJD)	46.19	A81.0
Dementia in CJD	-	F02.1*
Normal pressure hydrocephalus	331.5	G91.2
Huntington's disease	333.4	G10
Dementia in Huntington disease	-	F02.2*
Wernicke-Korsakov's Syndrome	291.1	F10.96

Exclusion	ICD-9-CM Diagnosis Code	ICD-10-CM Diagnosis Code (from ICD-10 Version 2016)
Dementia in other diseases classified elsewhere	-	F02.8*
Unspecified dementia	294.2	F03

Of the 1180 participants initially assessed for inclusion 1152 were included in the study (Figure 5). All adults that completed the OCS Neuropsychological testing battery were included in the analysis for Objective 1. For Objectives 2 and 3, only participants that had at least two visits were included in the analysis.

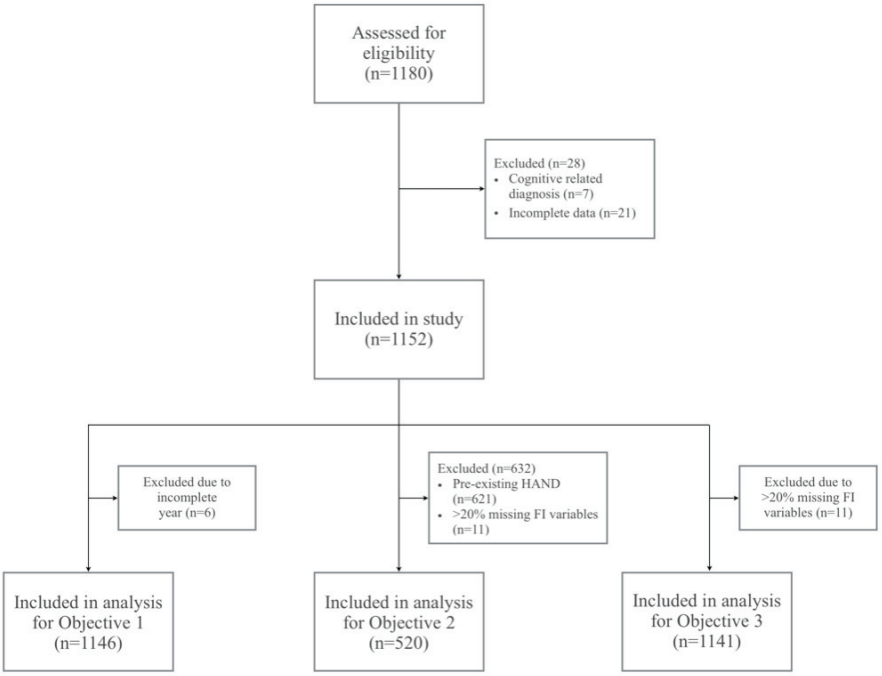


Figure 5. Participant inclusion and exclusion criteria flow chart.
Note: Of the 28 participants initially assessed for eligibility that were excluded, n=7 met criteria for a cognitive related diagnosis (Table 2), and n=21 were excluded due to having incomplete neuropsychological data (of these 21, n=2 were excluded as neuropsychological data from their first visits were not complete and therefore these participants had no 'visit 1' data at all). For objective 1 the years 2007 and 2015 were

dropped due to the fact that they were incomplete (2007 only had information from October through to December, and for the year 2015 there was only information for January), therefore participants with visits only in these years (n=6) were dropped.

4.3 HAND

4.3.1 Neuropsychological Testing

All participants entered into the study completed a full neuropsychological testing battery (Table 3). Appendix A lists these tests, the aspect of cognition that each test aims to measure, as well as a brief description of each test. Neuropsychological testing is conducted every 12 months on average in the OCS.

Table 3. *OCS Neuropsychological Test Battery*

Test Name	Cognitive Measure
Hopkins Verbal Learning Test - Revised [a]	Verbal working memory
Grooved Pegboard [b]	Fine motor dexterity
WAIS-R Digit Symbol Test [c]	Complex psychomotor speed
WMS-III Spatial Span [d]	Spatial working memory

[a] Benedict R, Schretlen, D., Groninger L, & Barndt J. (1998). Hopkins Verbal Learning Test – Revised: Normative Data and Analysis of Inter- Form and Test-Retest Reliability. The Clinical Neuropsychologist. 12(1): 43-55.
[b] Matthews, C., and Klove, H. (1964). Instruction manual for the Adult Neuropsychology Test Battery. University of Wisconsin Medical School, Madison, WI. [c] Wechsler, D. (1981). WAIS-R Manual. Wechsler Adult Intelligence Scale-Revised. The Psychological Corporation, San Antonio. [d] Wechsler, D. (1997). WMS-III Administration and Scoring Manual. The Psychological Corporation, San Antonio.

4.3.2 Cognitive Symptoms

Cognitive symptoms were assessed with the four-item Medical Outcomes Study Cognitive Functioning Scale (MOS-COG) (Appendix B) (Stewart, Ware, Sherbourne, & Wells, 1992). The MOS-COG assesses whether participants have difficulty with reasoning, forgetfulness, attention, and difficulty concentrating in order to determine whether cognitive impairments interfere with daily functioning. The responses from the four MOS-COG symptoms were recoded into binary variables: Yes (All of the time/Most

of the time/A Good Bit of the Time), or No (Some of the time/A little of the time/none of the time).

4.3.3 HAND Classification

HAND is defined within the OCS according to the following methodology.

The following six measures are collected from the OCS neuropsychological test battery.

1. HVLT-R total recall (correct responses).
2. HVLT-R delayed recall (correct responses).
3. Pegboard dominant hand (time in seconds).
4. Pegboard non-dominant hand (time in seconds).
5. WAIS-R digit symbol test (correct responses).
6. WMS-III spatial span (correct responses).

From the above 6 measures, demographically corrected standard scores, or, *T* scores were calculated using published norms (Heaton, Taylor, & Manly, 2002; Heaton, Miller, Taylor, & Grant, 2004; Norman et al., 2011). These *T* scores are then transformed into deficit scores according to criteria proposed by Carey et al. (2004) (Table 4). Deficit scores are calculated by converting the demographically corrected standard scores, or *T* scores, for each individual to deficit scores which range from 0 (no impairment) to 5 (severe impairment) (Carey et al., 2004).

Table 4. *Conversion Table for the Transformation of T Scores into Deficit Scores*

T Scores	Deficit Score	Impairment Descriptor
≥ 40	0	Normal
39-35	1	Mild
34-30	2	Mild-to-Moderate
29-25	3	Moderate
24-20	4	Moderate-to-Severe
≤ 19	5	Severe

Note. Adapted from "Predictive Validity of Global Deficit Scores in Detecting Neuropsychological Impairment in HIV Infection" by C. L. Carey, S. P. Woods, R. Gonzalez, E. Conover, T.D. Marcotte,

I. Grant. R.K. Heaton, & the HNRC Group, 2004, *Journal of Clinical and Experimental Neuropsychology*, *26*(3), p. 308. Copyright 2004 by Taylor & Francis Ltd.

The deficit scores for each participant are then averaged to produce a Global Deficit Score (Carey et al., 2004). Participants are classified as having neuropsychological impairment using a GDS ≥ 0.5 cut off.

HAND status is then assigned according to the Antinori et al. (2007) criteria, which combines results from the neuropsychological testing and cognitive impairments leading to interferences in daily functioning. Participants are classified into HAND categories (ANI, MND, HAD) using the Global Deficit Score (derived from the above neuropsychological tests *T* scores) (Carey et al., 2004) as well as self-reported cognitive symptoms from the MOS-COG. HAND status is assigned by the OCS according to the criteria shown in Table 5.

Table 5. *HAND Status Assignment Combining Global Deficit Scores and Self-Reported Cognitive Symptoms assessed via the MOS-COG*

	Self-reported Cognitive Deficit (MOS-COG)	
Global Deficit Score (GDS)	None	One or More
<0.5	Normal	Normal
0.5-2	ANI	MND
> 2	HAD	HAD

Note. Participants are classified as having neuropsychological impairment using a GDS ≥ 0.5 cut off. In the OCS participants with GDS > 2.0 are classified as having HAD regardless of symptoms. HAND scores are calculated by the OCS team.

Data variables related to the determination of HAND scores differed from the data variables obtained from the OCS questionnaires, including ethnicity and gender/sex. Ethnicity data had to be recoded in order to match the normative U.S. data used to generate *T* scores. The normative data is available for White, Black, and Hispanic Americans. As a result, “Black” normative data was used for those who reported their

ethnicity as African, Caribbean, or Black in the questionnaire, and these individuals were coded as “Black”. “Hispanic American” normative data was used for participants who reported ethnicity as Aboriginal, Asian, Latin American, and Other, and these individuals were coded as “Other”. “White” normative data was used for participants who reported ethnicity as white, and these participants remained coded as “White”. Currently no Canadian normative data exists, hence the need to use American normative data. The sex variable is different from the questionnaire results (which includes categories for trans, inter-sexed, and ‘other’) and therefore had to be recoded in order to determine HAND scores, as biological sex is used for the demographic correction of *T* scores.

4.4 Construction of the 60-item Frailty Index

The frailty index (FI) was constructed using OCS data. Deficits that were related to cognitive function were excluded from the index. In the construction of a frailty index deficits are added until there are at least 30 to 40 deficits, as the more deficits that are added, the more precise the estimate becomes (Searle et al., 2008). When too few deficits are taken into account, the estimates become unstable (Searle et al., 2008). A separate frailty index was created for each participant visit (up to a total of 7 visits).

Questions regarding symptom distress are assessed within the OCS extended questionnaire. Participants are asked about specific symptoms and whether or not they have experienced these symptoms in the four weeks prior to their testing date. Each question is coded by the test administrator as: Yes, No, Don’t Know, or Refused. Mobility, self-care, usual activities, pain/discomfort, and anxiety/depression are assessed using the EQ-5D.

Ideally each variable in the frailty index should not have more than 5% missing. With clinical populations and clinical exams this target can be difficult to achieve and so the criterion for missing was expanded to include all variables that include at least 80% of participants. All variables that had more than 20% missing values were deleted from the

frailty index. The HIV-related variables most recent CD4 count, most recent viral load, and 'ever diagnosed with AIDS' did not reach the cutoff and were deleted from the index. For a variable to be included within the frailty index, at least 1% of the population must exhibit the deficit. Variables that did not meet this criterion (such as stroke and peripheral vascular disease) were deleted from the index.

Participants that had more than 20% missing out of the total variables were excluded. Therefore, participants with >12 missing values (for the 60-item frailty index) and >8 missing values (for the 39-item frailty index described in Section 4.4.1) were deleted (Table 6).

Table 6. *Number of Participants Excluded Due to >20% Missing Frailty Index Variables for Each Visit*

	60-Item Frailty Index			39-Item Frailty Index		
Visit	n before exclusion	n excluded	Final n	n before exclusion	n excluded	Final n
1	1152	11	1141	1141	9	1132
2	875	5	870	870	3	867
3	650	2	648	648	2	646
4	434	1	433	433	0	433
5	221	0	221	221	0	221
6	110	0	110	110	0	110
7	54	0	54	54	0	54

Participants who did not have complete neuropsychological testing data were excluded. Questionnaire testing dates and neuropsychological testing dates were matched so that the information for each came from the same date of testing (some participants had questionnaire dates prior to neuropsychological testing dates - in this instance these dates were dropped and the appropriate matching date to the neuropsychological interview,

from which the HAND score is calculated, was used). Values coded as ‘don’t know’ or ‘refused’ from the questionnaire were recoded as missing. For the EQ5D responses coded as 1, 2, and 3 were recoded to 0, 0.5, and 1 respectively.

For clinical laboratory tests cutoff reference values for normal and abnormal values were obtained from the Medical Council of Canada (Clinical Laboratory Tests Normal Values, 2017). All values were provided in SI units. All values apply to adults. For LDL values the low-risk cutoff values were used (<3.37 mmol/L). For the following tests, ‘fasting’ and ‘unspecified’ categories were collapsed in order to reach the percentage threshold for inclusion: cholesterol total, HDL, LDL, and triglycerides. The cutoff values for fasting and unspecified tests for cholesterol total, HDL, LDL, and triglycerides are the same, therefore collapsing these variables did not introduce any issues. For bilirubin, ‘total bilirubin’ values were used as there was not a sufficient number of observations for ‘direct’ and ‘indirect’ bilirubin values. For glucose there was a sufficient number of observations for ‘glucose fasting’, and so these values were used and ‘glucose random’ and ‘glucose unspecified’ values were dropped. Total lymphocyte count was used as lymphocyte percentage did not yield enough observations.

For each of the lab tests, lab test dates that preceded the baseline interview were selected. If the date preceded the interview test date by more than 2 years, they were recoded as missing. Lab test dates were expanded to include those occurring within 2 years in order to reach the threshold for inclusion. Lab tests older than 2 years were not included as they were no longer considered to be relevant. In cases where lab test dates followed the questionnaire and neuropsychological testing date, the first observation closest to the interview date was chosen.

The following comorbidity variables were collapsed: all cancers (non-AIDS related), diabetes (type 1, type 2, and unspecified), hepatitis (all types and unspecified), kidney disease (acute kidney injury, chronic kidney disease, and unspecified), kidney failure

(regular and acute), liver disease (chronic liver disease/cirrhosis, end stage liver disease, and non-alcoholic fatty liver disease).

Cancers that are considered AIDS-Defining Illnesses (ADI) were kept separate from the collapsed cancer variable. For example, Kaposi's Sarcoma and Non-Hodgkins Lymphoma were considered separately and were not included in the collapsed cancer variable. Any other cancers that were reported as ADI (such as cervical cancer or lymphoma) but had less than the required amount of observations were excluded from the frailty index.

Comorbidities were only included if they occurred on or before the interview dates for neuropsychological testing. Comorbidity diagnoses preceding the neuropsychological testing dates by more than five years were eliminated. The larger window for inclusion of comorbidity diagnoses was justified because many of the comorbidities included are considered chronic, and as such many of these diagnoses would be recurrent. Stroke and peripheral vascular disease were eliminated from the frailty index as less than 1% of the population had these particular diagnoses within the past five years.

The HIV-related comorbidities include cytomegalovirus, Kaposi's sarcoma, pneumocystis pneumonia (PCP), pneumonia (recurrent), tuberculosis (AIDS-defining), wasting syndrome due to HIV, lymphoma (non-Hodgkins, AIDS-defining), Nadir-CD4, duration of HIV, and ART status. Nadir CD4 had one observation per participant. If the nadir CD4 value occurred before the interview date then it was included in the index. If the nadir CD4 lab test date occurred after the interview date of interest then it was recoded as missing for the current frailty index visit.

Duration of HIV was calculated by subtracting the minimum HIV diagnosis date (either from chart abstraction, lab tests, patient report, or questionnaire) from the date of testing. In the OCS if the full diagnosis date is unknown (i.e. day or month or both), the day was

imputed with 1, and the month with January. Dates with less imputation (only day) are chosen over the dates with more imputation (both day and month).

All binary variables were recoded, with 0 indicating the absence of a deficit, and 1 indicating the presence of a deficit. The frailty index is able to accommodate both ordinal and continuous variables by recoding the continuum or rank into a 0 to 1 scale (Searle et al., 2008). The frailty index score for each participant was calculated by summing their total score and dividing it by the total number of non-missing items. For example if a participant had 15 out of potentially 60 deficits (and no missing items), their frailty index would be 15/60 = 0.25. If a participant was missing one of the 60 total items in the index, their sum would be divided by 59, if they were missing two items their total score would be divided by 58, and so on. The upper limit of the frailty index, or the 99% limit to deficit accumulation is seen at a maximum of 0.7 (Searle et al., 2008). Frailty was categorized into the following four levels: 0.00 - 0.09, 0.10 - 0.19, 0.20-0.29, and 0.30+ (non-frail, low frailty, moderate frailty, and high frailty, respectively) (Table 7).

Table 7. *Frailty Categorization and Corresponding Label*

Frailty Score	Frailty Category Label
0.00 - 0.09	Non-frail
0.10 - 0.19	Low frailty
0.20 - 0.29	Moderate frailty
0.30+	High frailty

The final frailty index included 60 items, including 11 non-HIV related comorbidities and 10 HIV-related comorbidities (Table 8).

Table 8. *Variables Included in the 60-Item Frailty Index and Corresponding Deficit Coding*

No.	Variable	Deficit Coding	Timeframe for Inclusion
60-item frailty index			
Chemistry		Anything outside of normal ranges below coded as deficit. Deficit = 1	
1	Albumin	35-50 g/L	Lab test dates that preceded the baseline interview were selected. If the date preceded the interview test dates > 2 years, they were recoded as missing (Section 4.6.1.).
2	ALT	17-63 U/L	
3	AST	18-40 U/L	
4	Bilirubin (total)	<26 µmol/L	
5	Cholesterol (fasting and unspecified)	<5.2 mmol/L	
6	HDL (fasting and unspecified)	>0.9 mmol/L	
7	LDL (fasting and unspecified)	<3.37 mmol/L	
8	Triglycerides (fasting and unspecified)	<1.7 mmol/L	
9	Creatinine	Female: 50-90 µmol/L, Male: 70-120 µmol/L	
10	Glucose (fasting)	3.3 - 5.8 mmol/L	
11	Hemoglobin	Female: 123-157 g/L, Male: 130-170 g/L	
12	Urea	2.5-8.0 mmol/L	
Hematology		Anything outside of normal ranges below coded as deficit.	
13	Total Lymphocyte Count	1.0-4.0 x 10^9 L	Lab test dates that preceded the baseline interview were selected. If the date preceded the interview test dates > 2 years, they were recoded as missing (Section 4.6.1).
14	Platelets	130-400 x 10^9 L	
Comorbidities			
15	Cancer (non-AIDS)	Yes = 1, No = 0	Comorbidities were only included if they occurred on or before the interview dates for neuropsych. testing. Comorbidity diagnoses preceding the neuropsych dates by > than five years were eliminated (Section 4.6.1).
16	Coronary Artery Disease	Yes = 1, No = 0	
17	Diabetes (I, II, Unspecified)	Yes = 1, No = 0	
18	Dyslipidemia	Yes = 1, No = 0	
19	Hepatitis (All types & Unspecified)	Yes = 1, No = 0	
20	Herpes Simplex Virus (HSV)	Yes = 1, No = 0	

No.	Variable	Deficit Coding	Timeframe for Inclusion
21	Hypertension	Yes = 1, No = 0	
22	Kidney Disease (Acute, Chronic, Unspecified)	Yes = 1, No = 0	
23	Kidney Failure (Regular & Acute)	Yes = 1, No = 0	
24	Liver Disease (NAFLD, Chronic/Cirrhosis, ESLD)	Yes = 1, No = 0	
25	Myocardial Infarction (Acute)	Yes = 1, No = 0	
Symptom Distress			
26	Fatigue/loss of energy	Yes = 1, No = 0	Questionnaire testing dates and neuropsychological testing dates were matched so that the information for each came from the same date of testing (for exceptions see Section 4.6.1).
27	Fevers, chills, or sweats	Yes = 1, No = 0	
28	Feeling dizzy or lightheaded	Yes = 1, No = 0	
29	Pain/numb./tingle hands or feet	Yes = 1, No = 0	
30	Trouble remembering	Yes = 1, No = 0	
31	Nausea/Vomiting	Yes = 1, No = 0	
32	Diarrhea/loose bowel movements	Yes = 1, No = 0	
33	Feeling sad/down/depressed	Yes = 1, No = 0	
34	Feeling nervous/anxious	Yes = 1, No = 0	
35	Difficulty falling/staying asleep	Yes = 1, No = 0	
36	Skin problems (rash/dry/itch)	Yes = 1, No = 0	
37	Cough/trouble catching breath	Yes = 1, No = 0	
38	Headache	Yes = 1, No = 0	
39	Loss appetite/change in taste food	Yes = 1, No = 0	
40	Bloating/pain/gas in stomach	Yes = 1, No = 0	
41	Muscle aches or joint pain	Yes = 1, No = 0	
42	Problems with having sex	Yes = 1, No = 0	
43	Body changes (fat deposits/ weight gain)	Yes = 1, No = 0	
44	Problems with weight loss or wasting	Yes = 1, No = 0	
45	Hair loss or change in way hair looks	Yes = 1, No = 0	
EQ5D			
46	Mobility	Score of 3 = 1, Score of 2 = 0.5, Score of 1 = 0	Questionnaire testing dates and neuropsychological testing

No.	Variable	Deficit Coding	Timeframe for Inclusion
47	Self Care	Score of 3 = 1, Score of 2 = 0.5, Score of 1 = 0	dates were matched so that the information for each came from the same date of testing (Section 4.6.1).
48	Usual Activities	Score of 3 = 1, Score of 2 = 0.5, Score of 1 = 0	
49	Pain/Discomfort	Score of 3 = 1, Score of 2 = 0.5, Score of 1 = 0	
50	Anxiety/Depression	Score of 3 = 1, Score of 2 = 0.5, Score of 1 = 0	
HIV-Related			
51	Nadir CD4	< 200 cells/mm^3 = 1, ≥ 200 cells/mm^3 = 0	Nadir CD4 has one observation per participant. If the nadir CD4 lab date < the interview date then it was included in the index, otherwise it was excluded (Section 4.6.1).
52	Duration of HIV	≥ 10 years = 1, < 10 years = 0	*No limitations on timeframe for inclusion.*
53	ART	No = 1, Yes = 0	*No limitations on timeframe for inclusion.*
54	Cytomegalovirus	Yes = 1, No = 0	Comorbidities (items 54-60) were only included if they occurred on or before the interview dates for neuropsych. testing. Comorbidity diagnoses preceding the neuropsych dates by > than five years were eliminated (Section 4.6.1).
55	Kaposi's Sarcoma	Yes = 1, No = 0	
56	Pneumocystis Pneumonia (PCP)	Yes = 1, No = 0	
57	Pneumonia, Recurrent	Yes = 1, No = 0	
58	TB (AIDS-Defininig, Unspecified)	Yes = 1, No = 0	
59	Wasting Syndrome Due to HIV	Yes = 1, No = 0	
60	Lymphoma, NH (AIDS-Defining)	Yes = 1, No = 0	

Note. All normal ranges for laboratory values from Clinical Laboratory Tests Normal Values *(2017).* In *The Medical Council of Canada.* Copyright 2017 by The Medical Council of Canada.

For visit 2 lab test dates that preceded the visit 2 interview date were selected. If the date preceded the interview test dates by more than 2 years, they were recoded as missing. In cases where lab test dates followed the questionnaire and neuropsychological testing date, the first observation closest to the interview date was chosen. For the 60-item frailty index for visits 3 through 7, lab test values, comorbidity values, and nadir CD4 dates were selected as above.

4.4.1 Construction of the 39-item Frailty Index

The 60-item frailty index was modified to a 39-item frailty index by removing the comorbidities and HIV-related variables in order to conduct further analyses (variables 15-25 and variables 51-60 in Table 8, respectively). The 39-item frailty index was constructed as a sensitivity analysis for the main 60-item frailty index in order to confirm that frailty index scores were not solely being driven by HIV variables and comorbidities and to allow us to understand what the frailty index contributes over and above these variables. The 39-item index was constructed for the same individuals as the 60-item frailty index with the additional exclusions for participants with >20% missing (8 or more variables) who were eliminated from the analysis (Table 6).

4.5 Covariates for the 60-item Frailty Index

The following covariates were examined to determine whether or not they were significant independent predictors of the development and progression of HAND for the 60-item frailty index: age (continuous), sex (male or female), education (years), cigarette history, cannabis history, recreational drug use, harmful alcohol use, and depression.

4.5.1 Demographic Characteristics

Demographic characteristics such as age, gender, race, and years of education were sourced from the OCS Core questionnaire as well as the OCS extended questionnaire. Participant status (i.e. lost to follow-up, deceased, etc) is collected on an ongoing basis in the OCS. The gender variable from the questionnaire which includes categories for trans, inter-sexed, and ‘other’ was recoded into a binary “male” or “female” biological sex variable in order to determine HAND scores for n=9 participants.

4.5.2 Cigarette History, Cannabis History, and Recreational Drug Use

Cigarette history was categorized into three categories (current smoker = within the last 30 days; former smoker = smoking in the past but no smoking within the last 30 days;

and never smoker). Cannabis history (e.g. marijuana, pot, hash) was categorized into three categories (current cannabis user = within the last year; former cannabis user = use of cannabis in the past but not within the past year; never a cannabis user = never a cannabis user, or used it only once or twice). Non-medicinal drug/substance use is defined in the OCS questionnaire as recreational or non-medicinal use of any drug (prescribed, over the counter, or street drugs). These substances are considered non-medicinal when they are not used as prescribed or according to the instructions. The various classes of drugs may include: steroids, stimulants (e.g. amphetamines, cocaine), club drugs (e.g. ecstasy), opiates (e.g. morphine, heroin) or tranquilizers (e.g. valium). Recreational drug use was categorized into a binary category depending on use within the previous 6 months.

4.5.3 Alcohol Use

Alcohol use is assessed using the Alcohol Use Disorders Identification Test (AUDIT) (Babor, Higgins-Biddle, Saunders, & Monteiro, 1992). The AUDIT is a 10-item test developed by the World Health Organization (WHO) to assess alcohol use and to determine if an individual is at risk for alcohol abuse. The OCS uses the clinician-administered/interview version within the OCS questionnaire. The AUDIT interview encourages interviewers to define standard sizes of alcoholic beverages. One drink is defined as follows: a small (8 oz; ½ pint) glass of beer, a single shot or measure of liquor or spirits, or a single glass of wine. Participants are asked to answer questions regarding on alcohol consumption including how often they drink, how many drinks they typically have per day, how often they have more than 6 drinks on one occasion, and how often they have found that they are unable to stop drinking once they have started. Additionally, participants are asked if alcohol has interfered negatively with their life (i.e. failing to do what is expected, needing a drink first thing in the morning, feelings of guilt or remorse after drinking, and the inability to remember the events of a night due to drinking). Finally, participants are asked if they or someone they know has been injured as a result of their drinking and if a relative, friend, doctor, or another health care worker has

expressed concern about their drinking habits and suggested that they cut down. A score of 8 or more indicates harmful or hazardous alcohol use. Harmful alcohol use was categorized into a binary variable with 1 indicating harmful or hazardous alcohol use (AUDIT 10 score ≥ 8).

4.5.4 Depression

Depression is assessed via The Centre for Epidemiologic Studies Depression Scale (CES-D) (Appendix A). The CES-D is a short self-report scale designed to measure depressive symptoms in the general population (Radloff, 1997). Participants are asked to rate the frequency of 20 separate items that they might have felt or behaved during the past week ranging from 'rarely or none of the time' (less than 1 day) to 'most or all of the time' (5-7 days). The 20 items in the CES-D measure symptoms of depression in various categories such as sadness (dysphoria), loss of interest (anhedonia), thinking/concentration, fatigue, and suicidal ideation. Individuals with a score of less than 16 are not considered to be at risk for depression or a major depressive episode. CES-D was categorized into a binary variable with 1 corresponding to a score between 16 and 60 (indicating high depressive symptoms), and 0 corresponding to a score between of 15 to 0.

4.5.5 Covariates for the 39-Item Frailty Index

For the 39-item frailty index the following 10 HIV-related variables (removed from the 60-item frailty index) were also assessed as covariates: cytomegalovirus, Kaposi's sarcoma, pneumocystis pneumonia (PCP), pneumonia (recurrent), tuberculosis (AIDS-defininig), wasting syndrome due to HIV, lymphoma (non-Hodgkins, AIDS-defining), Nadir-CD4, duration of HIV, and ART status.

4.6 Analytic Plan

Statistical analysis were conducted using STATA IC 13.1 and R 3.1.2.

4.6.1 Descriptive Statistics

Descriptive statistics by HAND status (neuropsychologically normal, ANI, MND, and HAD) were used to summarize the data according to sample characteristics.

For normally distributed continuous variables, the measure of central tendency is given by the mean. For skewed continuous variables, the measure of central tendency is given by the median. Tests for skewness/kurtosis were performed for each continuous variable. Categorical and binary variable groups were compared using Pearson's chi-squared test. Continuous variables (such as age) were compared using ANOVA. Skewed continuous variables (such as education, and years since HIV diagnosis) were compared using Kruskal-Wallis (>2 groups) or Wilcoxon rank-sum (2 groups).

Comorbidities were only included if they occurred on or before the interview dates for neuropsychological testing. Comorbidity diagnosis dates greater than five years before the neuropsychological testing date were eliminated. This is the same protocol that was followed for the creation of the frailty index (section 4.6).

4.6.2 Analysis for Objective 1: To determine the prevalence of HIV-associated neurocognitive disorder (HAND).

The period prevalence rate of individuals diagnosed with HAND was examined by determining the number of individuals living with HIV who were diagnosed with HAND over a one year period and dividing it by the total number of participants examined. The prevalence for each disorder on the HAND spectrum was calculated (ANI, MND, and HAD) on an annual basis from the years 2008 to 2014. The years 2007 and 2015 were dropped due to the fact that they were incomplete (2007 only had information from October through to December, and for the year 2015 there was only information for January).

4.6.3 Analysis for Objective 2: To determine the association between frailty and the development of HIV-associated neurocognitive disorder (HAND).

Participants with pre-existing HAND were excluded from this analysis.

A graphical method was used to check for violations of the proportional hazards assumption by plotting the Kaplan-Meier observed survival curves and comparing them with the Cox predicted curves. Since the predictors satisfied the proportional hazard assumption, Cox Proportional Hazards modeling (with covariates) was used to determine the association between baseline frailty and the development of HAND with the 60-item frailty index including all variables and with the 39-item frailty index which excluded HIV-related variables and comorbidities. Cox proportional hazards regression takes into account multiple factors and is able to incorporate both censoring and time dependent variables.

A backward elimination of the multivariate logistic regression model, with all explanatory variables, was used to establish the final model. The likelihood ratio test was used to compare the model before and after the elimination of the variable with the highest p-value in order to determine if significant ($p<0.10$) differences between the models existed. Multivariate models were run for frailty as a categorical measure as well as frailty as a continuous measure for the entire study population and then again when separated by sex.

4.6.4 Analysis for Objective 3: To determine the association between frailty and the progression of HIV-associated neurocognitive disorder (HAND).

Markov modeling was used to determine the association between frailty and the progression of HAND. Participants with pre-existing HAND were included in this analysis.

A transition matrix was constructed for each of the four levels of frailty (non-frail, low frailty, moderate frailty, and high frailty). Transition matrices allow for the estimation of the probability of moving across the four discrete HAND states (normal, ANI, MND, HAD) according to a participant's level of frailty (Craig & Sendi, 2002). Each level of HAND is a distinct state that a participant can be in at any time and each participant can only be assigned to one state at any given time. Because each HAND state is pre-determined and does not depend on a distribution, the resulting transition matrix is referred to as a size transition matrix (Formby, Smith, & Zheng, 2003). Participants can move from different states or remain in the same state. The interval between each time point is referred to as the cycle length, which is 12 months on average within the OCS cohort.

Markov chains combine probabilities and matrix operations in order to model any process that proceeds through distinct states (Craig & Sendi, 2002; Porta, 2014). In health research Markov chains are commonly used to model the process of moving through a chronic disease with defined severity states over a specific time interval (Porta, 2014). Markov chains have previously been used in HIV populations to determine those most at risk of developing Mycobacterium avian complex (MAC) infection by estimating the probability of moving between distinct CD4-cell count ranges (Craig & Sendi, 2002). Markov chains can therefore be used to describe how participants progress though the four HAND states based on their level of frailty. Movements between each HAND state are defined by probabilities (Figure 6). The probability of being in any HAND state according to varying levels of frailty can be defined. Markov chains are defined by the Markov property, that is, the present state of an individual only depends upon the most recent past state - not on any states prior (Craig & Sendi, 2002). In other words, the probability of being in a future state is not determined by the history of any past states within the system (Porta, 2014). When applied to the present study this means that a participant's present HAND state only depends on their HAND state prior to the current HAND state, not on any other prior HAND states. In this way, Markov models are often

thought of as 'memoryless' models (Craig & Sendi, 2002; Porta, 2014). As the probabilities of developing HAND vary across time and across participants, the Markov chain was non-homogenous (as opposed to homogenous Markov chains where the probability of transitioning from one state to another remains constant) (Craig & Sendi, 2002). While the transition matrices tell us the probability of moving between states over time, it does not give the probability of starting in a certain state (Porta, 2014). The probability of transitioning of states from one visit to the next is found by multiplying the probabilities of transitioning through the states. Markov chains can therefore be useful for predicting future HAND states, given a participant's current frailty level.

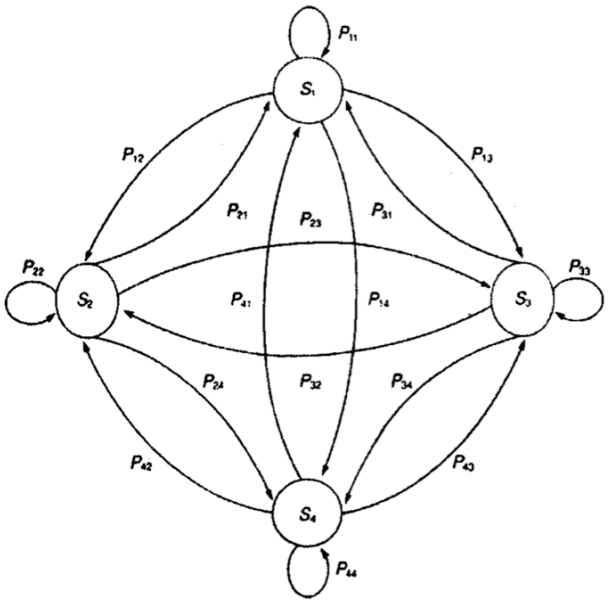


Figure 6. Simplified Markov process with four states.
From "Markov System for Image Vector Quantization Coding" by Tai, S.C., Wu, Y.G., & Huang L.S., 2000, Optical Engineering, 39(5), p. 1339. Copyright 2000 by Society of Photo-Optical Instrumentation Engineers. Reprinted with permission.

The aforementioned transition matrices allowed us to calculate the Determinant Index, using previously established methods (Geweke, Marshall, & Zarkin, 1986; Trede, 1999).

The Determinant Index is a matrix-based mobility measure which allowed us to calculate how many times a participant transitioned between HAND states based on their frailty category. In other words, this mobility measure determines the average probability that a participant will move into a different HAND state in the following period (in this case, in the following visit) (Formby et al., 2003). The Determinant Index ranges from 0 (indicating no mobility) to 1 (indicating high mobility). The Determinant Index was calculated for each category of frailty. A test statistic was used to determine if mobility between HAND states (indicated by the Determinant Index) was significantly different for each category of frailty.

CHAPTER FIVE: RESULTS

5.1 60-Item Frailty Index

Frailty index scores at baseline visit ranged from 0.00 to 0.54 with a mean frailty score of 0.22 (SD = 0.10), corresponding to 13.2 deficits out of a possible total of 60 deficits. There were no significant differences in mean frailty index score between visits (Table 9). A test for normality demonstrated that the baseline frailty index scores were positively skewed (0.36, $p<0.01$) (Figure 7).

Baseline frailty scores did not differ significantly between sex: females had a mean frailty index score of 0.21 (SD 0.10) and males had a mean frailty index score of 0.22 (SD 0.10), $p=0.19$. The baseline rate of deficit accumulation on a log scale was 0.0029 (95% CI 0.0016-0.0042, $p<0.001$). In other words, baseline frailty index scores increased 0.29% with each year of age ($p<0.001$). Participants aged 55-59 had the highest mean baseline FI score (M = 0.25, SD = 0.102), followed by participants aged 50-54 (M = 0.24, SD = 0.108) (Table 10).

Of the 1141 participants assessed at baseline, n=113 were non-frail, n=384 had low frailty, n=368 had moderate frailty, and n=276 had high frailty (9.90%, 33.65%, 32.25%, and 24.19%, respectively). There were significant ($p<0.001$) differences in age when assessing baseline frailty categorically, with increasing levels of frailty demonstrating a higher mean age (M =41.3, SD=10.4; M = 43.4, SD = 11.2; M = 45.3, SD=10.9; and M = 45.5, SD=9.2 for non-frail, low frailty, moderate frailty, and high frailty participants respectively). There were no significant differences in sex distribution for each of the four frailty categories ($p=0.59$).

Table 9. *Summary Statistics for 60-Item Frailty Index Visits 1 to 7*

Visit	*N*	Mean	SD	Minimum	Maximum
1	1141	0.22	0.10	0	0.54
2	870	0.22	0.10	0	0.53
3	648	0.22	0.10	0	0.51
4	433	0.22	0.10	0	0.53
5	221	0.22	0.10	0	0.57
6	110	0.22	0.10	0.02	0.53
7	54	0.24	0.11	0.08	0.51

Note. The participants in each visit carry forward to the next visit, i.e. 870 participants out of the initial 1141 participants had a 2nd visit.

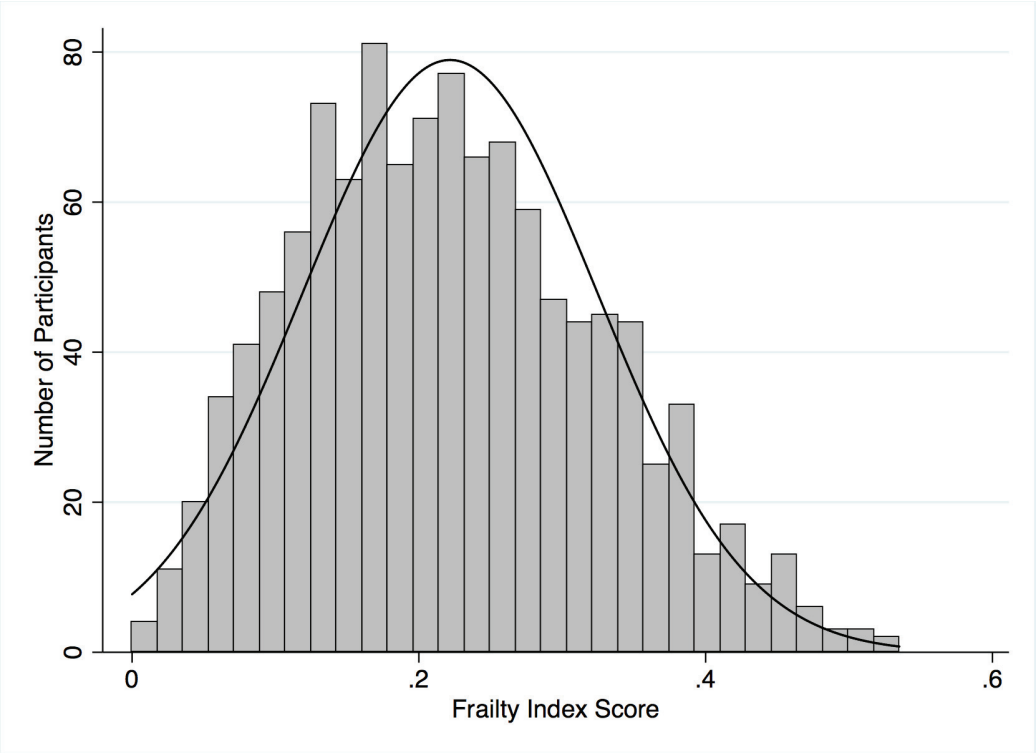


Figure 7. Baseline frailty index distribution with overlaid density curve for n = 1141 participants.

Table 10. *Mean Baseline Frailty Index Score by Age Category*

Age	Mean	SD
<25	0.18	0.072
25-29	0.18	0.087
30-34	0.20	0.099
35-39	0.22	0.111
40-44	0.23	0.109
45-49	0.22	0.095
50-54	0.24	0.108
55-59	0.25	0.102
60-64	0.20	0.087

Age	Mean	SD
64-69	0.22	0.093
70-74	0.17	0.070
75-79	0.22	0.088

Note. Statistics for ages ≥80 have been removed due to small numbers.

The most common chemistry/hematology related deficit was triglyceride levels (n=465, 40.8%), and subsequently, the most common comorbidity among participants was dyslipidemia (n=375, 32.9%) (Table 11). The next most common comorbidities were herpes simplex virus (HSV), hepatitis, and hypertension (13.1%, 8.3%, and 7.2%, respectively). In terms of symptom distress, the most common was fatigue/loss of energy, with 62.4% of participants reporting being bothered by this symptom. Over half of participants reported feeling sad/down/depressed (59.2%), difficulty falling/staying asleep (53.5%), and feeling nervous/anxious (52.4%). The two most common EQ5D symptoms included anxiety/depression (45%) and pain/discomfort (43.5%). In terms of HIV-related variables, the most common deficits among participants included nadir CD4 level <200 cells/mm^3 (51.7%) and HIV duration ≥ 10 years (45.2%).

Table 11. *Baseline 60-Item Frailty Index Deficit Totals*

No.	Variable	Participants with Deficit at Baseline n (% of total)	
Chemistry			
1	Albumin	133	11.7%
2	ALT	279	24.5%
3	AST	274	24.0%
4	Bilirubin (total)	142	12.4%
5	Cholesterol (fasting and unspecified)	295	25.9%
6	HDL (fasting and unspecified)	308	27.0%
7	LDL (fasting and unspecified)	204	17.9%
8	Triglycerides (fasting and unspecified)	465	40.8%
9	Creatinine	258	22.6%

No.	Variable	Participants with Deficit at Baseline n (% of total)	
10	Glucose (fasting)	190	16.7%
11	Hemoglobin	208	18.2%
12	Urea	81	7.1%
Hematology			
13	Total Lymphocyte Count	79	6.9%
14	Platelets	82	7.2%
Comorbidities			
15	Cancer (non-AIDS)	59	5.2%
16	Coronary Artery Disease	23	2.0%
17	Diabetes (I, II, Unspecified)	27	2.4%
18	Dyslipidemia	375	32.9%
19	Hepatitis (All types & Unspecified)	95	8.3%
20	Herpes Simplex Virus (HSV)	149	13.1%
21	Hypertension	82	7.2%
22	Kidney Disease (Acute, Chronic, Unspecified)	15	1.3%
23	Kidney Failure (Regular & Acute)	12	1.1%
24	Liver Disease (NAFLD, Chronic/ Cirrhosis, ESLD)	79	6.9%
25	Myocardial Infarction (Acute)	12	1.1%
Symptom Distress			
26	Fatigue/loss of energy	712	62.4%
27	Fevers, chills, or sweats	346	30.3%
28	Feeling dizzy or lightheaded	399	35.0%
29	Pain/numb./tingle hands or feet	469	41.1%
30	Trouble remembering	556	48.7%
31	Nausea/Vomiting	236	20.7%
32	Diarrhea/loose bowel movements	439	38.5%
33	Feeling sad/down/depressed	676	59.2%
34	Feeling nervous/anxious	598	52.4%
35	Difficulty falling/staying asleep	611	53.5%
36	Skin problems (rash/dry/itch)	425	37.2%
37	Cough/trouble catching breath	304	26.6%
38	Headache	383	33.6%
39	Loss appetite/change in taste food	311	27.3%

No.	Variable	Participants with Deficit at Baseline n (% of total)	
40	Bloating/pain/gas in stomach	471	41.3%
41	Muscle aches or joint pain	549	48.1%
42	Problems with having sex	451	39.5%
43	Body changes (fat deposits/weight gain)	399	35.0%
44	Problems with weight loss or wasting	235	20.6%
45	Hair loss or change in way hair looks	173	15.2%
EQ5D			
46	Mobility	204	17.9%
47	Self Care	45	3.9%
48	Usual Activities	246	21.6%
49	Pain/Discomfort	496	43.5%
50	Anxiety/Depression	514	45.0%
HIV-Related			
51	Nadir CD4	590	51.7%
52	Duration of HIV	516	45.2%
53	ART	77	6.7%
54	Cytomegalovirus	15	1.3%
55	Kaposi's Sarcoma	23	2.0%
56	Pneumocystis Pneumonia (PCP)	54	4.7%
57	Pneumonia, Recurrent	110	9.6%
58	TB (AIDS-Defining, Unspecified)	17	1.5%
59	Wasting Syndrome Due to HIV	54	4.7%
60	Lymphoma, NH (AIDS-Defining)	13	1.1%

Note. For EQ5D scores, scores of 0.5 and 0.1 are considered as a deficit, the cell total for this category reflects the sum of both. Percentage is calculated by dividing the number of participants with the deficits by 1141 (the total number of participants considered).

5.2 Descriptive Statistics at Baseline

Demographic and clinical characteristics by baseline HAND status of the 1152 participants are presented in Table 12. At baseline 45.8% of participants were classified as neuropsychologically normal, 35.1% of participants had ANI, 14.8% of participants had MND, and 4.3% of participants were classified as having HAD. The mean age of

participants was 44.3 years (SD 10.6). Participants with ANI and HAD were older than the mean age of the total sample (with mean ages of 45.2 (11.1) and 45.1 (11.3), respectively). The majority of participants were male (77.3%) and white (58.3%). Median years of education was 14 (IQR 12-16). The gross household income category with the highest proportion of participants was <$20,000 (29.4%), followed by $20,000-$40,000 (19.3%).

There were significant differences among HIV-related variables for the study sample. The median duration of HIV, measured in years since clinical diagnosis, for the entire sample was 8.7 years (IQR 3.4 - 16.1). Participants in the neuropsychologically normal group had the lowest median duration (7.6, IQR 2.7-15.7) and participants with a HAD diagnosis had the longest HIV duration (median 12.4 years, IQR 7.3 - 17.1). The majority of participants were on antiretroviral therapy (93.3%), with the lowest rate in the neuropsychologically normal group (91.1%) and the highest rate in the HAD group (100%). On average, those on cART had a mean HIV duration of 10.5 years, while those not on cART had a mean HIV duration of 4.02 years. Nadir CD4 count decreased as HAND status progressed (with the exception of MND), participants with MND had a median nadir CD4 count of 120.0 (IQR, 24-224) and participants with HAD had a median nadir CD4 count of 125.5 (IQR 45-198). Participants with HAD had the highest rate of PCP (12.2%). There were no significant differences in rates of cytomegalovirus, Kaposi's sarcoma, recurrent pneumonia, TB, wasting syndrome, or lymphoma by HAND status.

Both cigarette history and cannabis history were significantly different between HAND groups (p=0.001 and p=0.004, respectively). MND and HAD participants had a higher rate of smoking (43.9% and 34.7% respectively) when compared to neuropsychologically normal and ANI groups. Participants with HAD also had the highest rate of non-smoking (53.1%). Over a third of participants (34.1%) identified as current cannabis users with the highest rates of cannabis smokers in the neuropsychologically normal group (38%),

followed by the MND group (36.5%). Those with HAD had the highest rate of non-use among participants (63.3%). 17.4% of participants identified as recreational drug users, and there were no significant differences in recreational drug use between HAND groups. There were significant differences in both alcohol use (p<0.001) and depression (p<0.001). The highest rates of harmful alcohol use were seen in the neuropsychologically normal (22.9%) and MND groups (21.1%). MND participants had a high rate of depression (69.0%) when compared to the other groups, with the second highest rate seen in HAD participants (34.7%). There were no significant differences among comorbidity rates between groups, with the exception of dyslipidemia (p=0.02).

Overall, participants with MND or HAD at baseline, compared to those who were neuropsychologically normal at baseline were more likely to be female, of "other" ethnicity, have a lower gross household income, a longer duration of HIV, more likely to be on cART, have a lower Nadir CD4 count, and increased rate of PCP. Additionally, participants with MND and HAD were more likely to be current cigarette smokers, less likely to be cannabis users, less likely to engage in recreational drug use, less likely to be harmful alcohol users, more likely to have depression, and more likely to have dyslipidemia when compared to those who were neuropsychologically normal.

Table 12. *Sample Characteristics by HAND Status at Baseline*

		HAND Status at Baseline				
	Total (n=1152)	Normal (n = 528)	ANI (n= 404)	MND (n=171)	HAD (n=49)	p-value
Age (Years)	44.3 (10.6)	43.9 (10.3)	45.2 (11.1)	43.2 (10.2)	45.1 (11.3)	0.13
Gender						
Female	262 (22.7%)	98 (18.6%)	98 (24.3%)	54 (31.6%)	12 (24.5%)	**0.004**
Male	890 (77.3%)	430 (81.4%)	306 (75.7%)	117 (68.4%)	37 (75.5%)	
Race						
Black	307 (26.7%)	145 (27.5%)	95 (23.5%)	55 (32.2%)	12 (24.5%)	**<0.001**
Other	173 (15.0%)	54 (10.2%)	84 (20.8%)	28 (16.4%)	7 (14.3%)	
White	672 (58.3%)	329 (62.3%)	225 (55.7%)	88 (51.5%)	30 (61.2%)	

	HAND Status at Baseline					
	Total (n=1152)	Normal (n = 528)	ANI (n= 404)	MND (n=171)	HAD (n=49)	p-value
Education (median, IQR)	14 (12-16)	14 (12-15)	14 (12-16)	13 (12-15)	14 (12-15)	**0.002**
Gross Household Income[a]						
<$20,000	339 (29.4%)	130 (27.7%)	112 (28.9%)	73 (52.9%)	24 (53.3%)	**<0.001**
$20 000 - $40 000	222 (19.3%)	102 (21.7%)	81 (20.9%)	33 (23.9%)	6 (13.3%)	
$40 000 - $60 000	137 (11.9%)	65 (13.8%)	60 (15.5%)	9 (6.5%)	-	
$60 000 - $80 000	110 (9.6%)	51 (10.9%)	46 (11.9%)	6 (4.3%)	7 (15.6%)	
$80 000 - $100 000	84 (7.3%)	50 (10.6%)	30 (7.8%)	-	-	
>$100 000	148 (12.9%)	72 (15.3%)	58 (15.0%)	14 (10.1%)	-	
Years since HIV diagnosis (median, IQR)	8.65 (3.36-16.1)	7.63 (2.67-15.7)	9.85 (4.01-16.0)	8.27 (3.32-16.3)	12.4 (7.32-17.1)	**0.003**
On antiretroviral therapy (%)						
Yes	1075 (93.3%)	481 (91.1%)	386 (95.5%)	159 (93.0%)	49 (100.0%)	**0.012**
No	77 (6.7%)	47 (8.9%)	18 (4.5%)	12 (7.0%)	0 (0.0%)	
Nadir CD4 (median, IQR)	156 (50-250)	173.5 (62-278)	157 (50-240)	120 (24-224)	125.5 (45-198)	**0.001**
Nadir CD4[a]						
<200 cells/mm^3	593 (51.5%)	241 (45.6%)	224 (55.4%)	96 (56.1%)	32 (65.3%)	**0.003**
≥200 cells/mm^3	367 (31.9%)	189 (35.8%)	127 (31.4%)	41 (24.0%)	10 (20.4%)	
Cytomegalovirus						
Yes	15 (1.30%)	7 (1.3%)	7 (1.7%)	-	-	0.59
No	1137 (98.7%)	521 (98.7%)	397 (98.3%)	170 (99.4%)	49 (100.0%)	
Kaposi's Sarcoma						
Yes	23 (2.0%)	12 (2.3%)	8 (2.0%)	-	-	0.74
No	1129 (98%)	516 (97.7%)	396 (98.0%)	168 (98.2%)	49 (100.0%)	
PCP						
Yes	54 (4.7%)	27 (5.1%)	11 (2.7%)	10 (5.8%)	6 (12.2%)	**0.015**

	HAND Status at Baseline					
	Total (n=1152)	Normal (n = 528)	ANI (n= 404)	MND (n=171)	HAD (n=49)	p-value
No	1098 (95.3%)	501 (94.9%)	393 (97.3%)	161 (94.2%)	43 (87.8%)	
Pneumonia (Recurrent)						
Yes	110 (9.60%)	43 (8.1%)	38 (9.4%)	24 (14.0%)	5 (10.2%)	0.16
No	1042 (90.4%)	485 (91.9%)	366 (90.6%)	147 (86.0%)	44 (89.8%)	
TB (AIDS-Defining)						
Yes	17 (1.50%)	8 (1.5%)	5 (1.2%)	-	-	0.62
No	1135 (98.5%)	520 (98.5%)	399 (98.8%)	167 (97.7%)	49 (100.0%)	
Wasting Syndrome						
Yes	54 (4.70%)	24 (4.5%)	20 (5.0%)	8 (4.7%)	-	0.99
No	1098 (95.3%)	504 (95.5%)	384 (95.0%)	163 (95.3%)	47 (95.9%)	
Lymphoma (AIDS-Defining)						
Yes	13 (1.10%)	9 (1.7%)	-	-	-	0.37
No	1139 (98.9%)	519 (98.3%)	401 (99.3%)	170 (99.4%)	49 (100.0%)	
Cigarette History[a]						
Current Smoker	384 (33.3%)	162 (30.7%)	130 (32.2%)	75 (43.9%)	17 (34.7%)	**0.001**
Former Smoker	237 (20.6%)	134 (25.4%)	72 (17.8%)	25 (14.6%)	6 (12.2%)	
Never Smoker	530 (46.0%)	231 (43.8%)	202 (50.0%)	71 (41.5%)	26 (53.1%)	
Cannabis History[a]						
Current User	393 (34.1%)	200 (38.0%)	120 (29.7%)	62 (36.5%)	11 (22.4%)	**0.004**
Former User	187 (16.2%)	98 (18.6%)	59 (14.6%)	23 (13.5%)	7 (14.3%)	
Never a User	570 (48.5%)	229 (43.5%)	225 (55.7%)	85 (50.0%)	31 (63.3%)	
Recreational Drug Use (%)[a]						
Yes	200 (17.4%)	103 (19.5%)	59 (14.6%)	32 (18.7%)	6 (12.2%)	0.17
No	951 (82.6%)	424 (80.3%)	345 (85.4%)	139 (81.3%)	43 (87.8%)	
Harmful Alcohol Use (AUDIT10≥8)						

	HAND Status at Baseline					
	Total (n=1152)	Normal (n = 528)	ANI (n= 404)	MND (n=171)	HAD (n=49)	p-value
Yes	204 (17.7%)	121 (22.9%)	41 (10.1%)	36 (21.1%)	6 (12.2%)	**<0.001**
No	948 (82.3%)	407 (77.1%)	363 (89.9%)	135 (78.9%)	43 (87.8%)	
Depression (CESD-20 ≥ 16)[a]						
Yes	411 (35.7%)	177 (33.5%)	99 (24.5%)	118 (69.0%)	17 (34.7%)	**<0.001**
No	712 (61.8%)	339 (64.2%)	297 (73.5%)	48 (28.1%)	28 (57.1%)	
Cancer (non-AIDS)						
Yes	59 (5.10%)	25 (4.7%)	26 (6.4%)	8 (4.7%)	-	0.23
No	1093 (94.9%)	503 (95.3%)	378 (93.6%)	163 (95.3%)	49 (100.0%)	
Coronary Artery Disease						
Yes	23 (2.0%)	10 (1.9%)	6 (1.5%)	6 (3.5%)	-	0.46
No	1129 (98.0%)	518 (98.1%)	398 (98.5%)	165 (96.5%)	48 (98.0%)	
Diabetes						
Yes	27 (2.30%)	7 (1.3%)	13 (3.2%)	5 (2.9%)	-	0.20
No	1125 (97.7%)	521 (98.7%)	391 (96.8%)	166 (97.1%)	47 (95.9%)	
Dyslipidemia						
Yes	375 (32.6%)	153 (29.0%)	155 (38.4%)	51 (29.8%)	16 (32.7%)	**0.02**
No	777 (67.4%)	375 (71.0%)	249 (61.6%)	120 (70.2%)	33 (67.3%)	
Hepatitis						
Yes	97 (8.42%)	37 (7.0%)	40 (9.9%)	16 (9.4%)	-	0.44
No	1055 (91.6%)	491 (93.0%)	364 (90.1%)	155 (90.6%)	45 (91.8%)	
Herpes Simplex Virus						
Yes	149 (12.9%)	65 (12.3%)	48 (11.9%)	28 (16.4%)	8 (16.3%)	0.41
No	1003 (87.1%)	463 (87.7%)	356 (88.1%)	143 (83.6%)	41 (83.7%)	
Hypertension						
Yes	83 (7.20%)	39 (7.4%)	26 (6.4%)	13 (7.6%)	5 (10.2%)	0.78
No	1069 (92.8%)	489 (92.6%)	378 (93.6%)	158 (92.4%)	44 (89.8%)	
Kidney Disease						
Yes	15 (1.30%)	-	7 (1.7%)	-	-	0.22

	HAND Status at Baseline					
	Total (n=1152)	Normal (n = 528)	ANI (n= 404)	MND (n=171)	HAD (n=49)	p-value
No	1137 (98.7%)	525 (99.4%)	397 (98.3%)	167 (97.7%)	48 (98.0%)	
Kidney Failure						
Yes	12 (1.0%)	6 (1.1%)	-	-	-	0.83
No	1140 (99.0%)	522 (98.9%)	401 (99.3%)	169 (98.8%)	48 (98.0%)	
Liver Disease						
Yes	80 (7.0%)	35 (6.6%)	28 (6.9%)	10 (5.8%)	7 (14.3%)	0.21
No	1072 (93.0%)	493 (93.4%)	376 (93.1%)	161 (94.2%)	42 (85.7%)	
Myocardial Infarction						
Yes	12 (1.0%)	-	-	-	-	0.63
No	1140 (99.0%)	524 (99.2%)	400 (99.0%)	168 (98.2%)	48 (98.0%)	

Note. Data variables related to the determination of HAND scores differed from the data variables obtained from questionnaires, including ethnicity and gender/sex. Ethnicity data had to be recoded in order to match the normative U.S. data used to generate *T* scores. The normative data is available for White, Black, and Hispanic Americans. As a result, "Black" normative data was used for those who reported their ethnicity as African, Caribbean, or Black in the questionnaire, and these individuals were coded as "Black". "Hispanic American" normative data was used for participants who reported ethnicity as Aboriginal, Asian, Latin American, and Other, and these individuals were coded as "Other". "White" normative data was used for participants who reported ethnicity as white, and these participants remained coded as "White". Currently no Canadian normative data exists, hence the need to use American normative data. The sex variable is different from the questionnaire results (which includes categories for trans, inter-sexed, and 'other') had to be recoded for n= 9 participants in order to determine HAND scores, as biological sex is used for demographic correction of *T* scores. - denotes cell sizes that have been suppressed due to small numbers.
[a]Columns do not add up to 100% due to missing values.

5.3 The prevalence of HIV-associated neurocognitive disorder (HAND).

The baseline prevalence for each category of HAND from the years 2008 to 2014 was calculated for n=1146 participants (Figure 8). The prevalence of 'normal' diagnoses at baseline increased from 44.3% in 2008 to 62.30% in 2014, while the prevalence of ANI, MND, and HAD diagnoses at baseline decreased over the same period (34.3% to 27.9%, 15.1% to 9.84%, and 6.18% to 0 %, respectively).

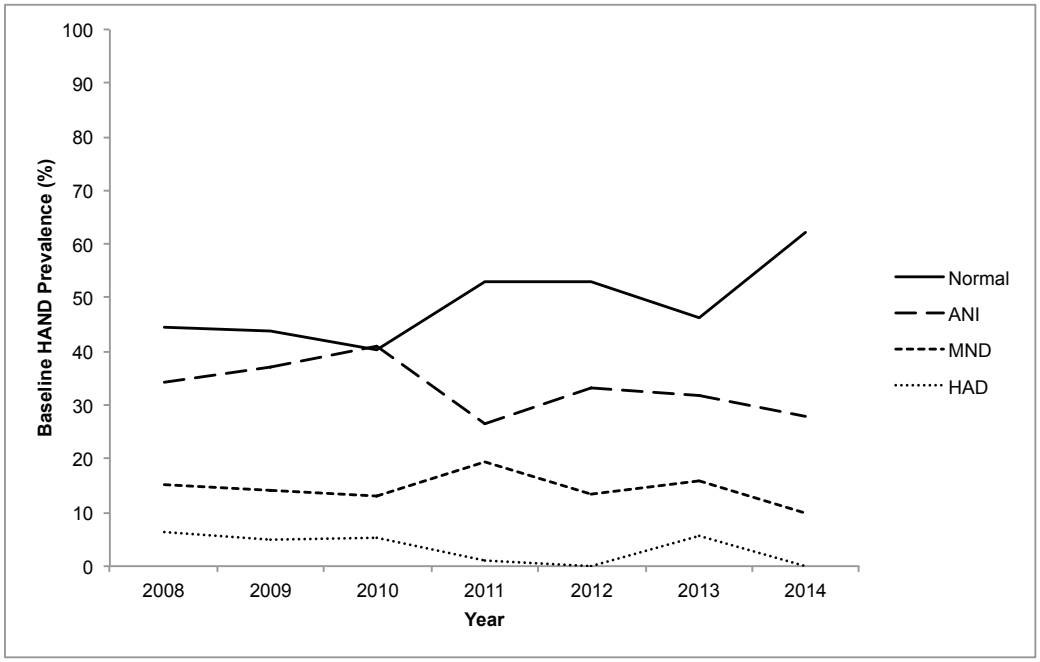


Figure 8. Baseline HAND prevalence (%) for n=1146 participants from the years 2008 to 2014.

The total prevalence (for all visits) for each category of HAND from the years 2008 to 2014 was calculated for n=1146 participants, totalling 3445 observations (Figure 9). As the prevalence of 'normal' diagnoses at baseline increased over time, the prevalence of ANI, MND, and HAD diagnoses at baseline decreased over the same period (34.2% to 29.5%, 15.1% to 13.5%, and 6.09% to 2.32%, respectively).

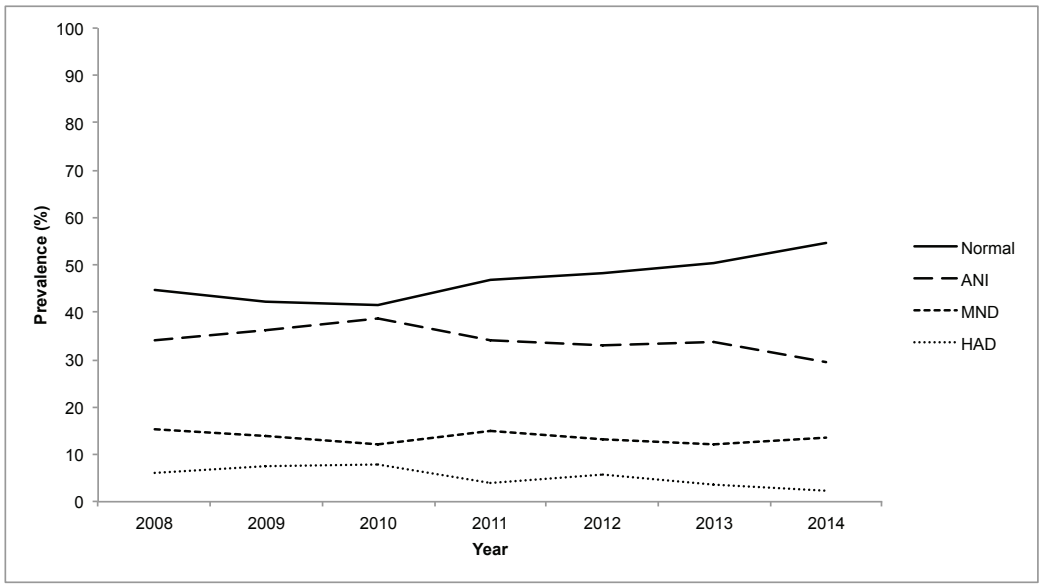


Figure 9. Total HAND prevalence (%) by year for n=1146 participants from the years 2008 to 2014 over multiple visits, totalling 3445 observations (all observations).

5.4 The association between frailty and the development of HIV-associated neurocognitive disorder (HAND) using a 60-item frailty index.

A failure was declared as the development of HAND (i.e. a HAND score of 2, 3, or 4). Individuals who had already developed ANI, MND, or HAD at baseline were excluded from this analysis. Out of the total 1141 participants, n= 520 participants (n =95 females and n=425 males providing 3640 total observations) were classified as neuropsychologically normal at baseline and are therefore included in this analysis. Three participants had missing data for either cigarette history, cannabis history, or recreational drug use and were therefore eliminated from unadjusted analyses for these specific covariates and for all further multivariate analyses.

In order to conduct a survival analysis with data with multiple failure time points (i.e. Visit 2 through 7) the Andersen and Gill (1982) approach was used. This approach makes two main assumptions. First, that the data are ordered and that events occur in sequence (i.e. HAND status at Visit 2 occurs before HAND status at visit 3, and so on) (Andersen & Gill, 1982). Second, that all failure types are equal to one another (i.e. a HAND

diagnosis of 2 (ANI) at visit 2 is equal to a HAND diagnosis of 2 (ANI) at visit 7) (Andersen & Gill, 1982).

A graphical method was used to check for violations of the proportional hazards assumption by plotting the Kaplan-Meier observed survival curves and comparing them with the Cox predicted curves. Since the predicted and observed curves were similar, the proportional-hazards assumption was not violated.

Participants with high frailty (0.3+) at baseline had shorter time of progression to HAND than those in the lower frailty categories (Figure 10). Notably, participants with low and moderate frailty at baseline show very similar progression to HAND development over the 7 visit period, though still progress quicker than non-frail participants. The log-rank test for equality of survivor functions shows that the differences between the survivor functions (Figure 10) are statistically significant (p =0.002).

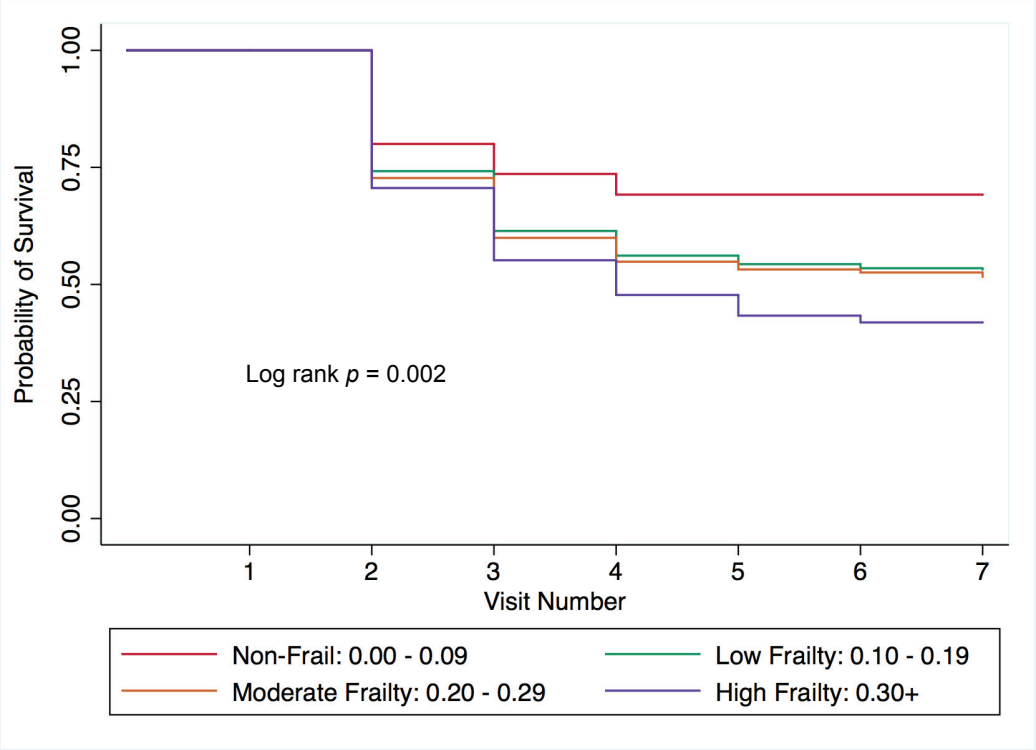


Figure 10. Kaplan-Meier survival estimates by frailty category - 60-item Frailty Index.

Cox proportional hazards modelling with covariates was used to assess whether baseline frailty was associated with the development of HAND at subsequent visits.

Unadjusted analyses for the 60-item frailty index demonstrated that frailty was associated with the development of HAND when frailty was assessed categorically (low frailty hazard ratio 1.68, 95% CI 1.00-2.80, $p<0.05$; moderate frailty HR 1.75, 95% CI 1.04-2.92, $p=0.03$; and high frailty HR 2.27, 95% CI 1.36-3.81, $p=0.002$) (Table 13). Age was also significantly associated with the development of HAND (HR 1.01, 95% CI 1.00-1.02, $p = 0.02$) (Table 13). Males had a reduced likelihood of developing HAND when compared to females (HR 0.62, 95% CI 0.48-0.80, $p<0.001$).

The final model when assessing frailty categorically indicates that high frailty, increasing age, and female sex were significantly associated with an increased risk of HAND (Table 13). Low and moderate levels of frailty were not associated with an increased risk of HAND.

Unadjusted analyses assessing frailty as a continuous score again demonstrated that frailty was associated with the development of HAND (HR 1.18, 95% CI 1.05 - 1.31, $p=0.004$). The multivariate analysis assessing frailty continuously demonstrated that frailty, increasing age, and female sex were again significantly associated with an increased risk of HAND (HR 1.16, 95% CI 1.04 - 1.30, $p=0.010$; HR 1.01, 95% CI 1.00 - 1.02, $p=0.018$; HR 0.60, 95% CI 0.47 - 0.78, $p<0.001$, respectively).

Table 13. *Unadjusted and Multivariate Cox Proportional Hazard Ratios for the Development of HAND According to Baseline Frailty Category - 60 Item Frailty Index*

	Unadjusted			Multivariate - Categorical Frailty		
	Hazard Ratio	95% CI	p-value	Hazard Ratio	95% CI	P-value
FI Category (referent: 0.00 to 0.09)						
0.10 - 0.19	1.68	[1.00-2.80]	**0.048**	1.50	[0.89 - 2.50]	0.125
0.20 - 0.29	1.75	[1.04 - 2.92]	**0.034**	1.56	[0.93 - 2.62]	0.093
0.30+	2.27	[1.36 - 3.81]	**0.002**	2.05	[1.22 - 3.45]	**0.007**
Age	1.01	[1.00 - 1.02]	**0.022**	1.01	[1.00 - 1.02]	**0.022**
Sex (referent: female)	0.62	[0.48 - 0.80]	**<0.001**	0.61	[0.47 - 0.78]	**<0.001**
Education	1.02	[0.98 - 1.06]	0.423	-	-	-
Cigarette History (referent: Never User)						
Former User	1.06	[0.81 - 1.39]	0.664	-	-	-
Current User	0.97	[0.75 - 1.26]	0.822	-	-	-
Cannabis History (referent: Never User)						
Former User	0.76	[0.55 - 1.05]	0.096	-	-	-
Current User	0.90	[0.71 - 1.15]	0.394	-	-	-
Recreational Drug Use	0.76	[0.56 - 1.03]	0.079	-	-	-
Harmful Alcohol Use	0.81	[0.61 - 1.07]	0.133	-	-	-

Note. All hazard ratios contain data for n=520 participants except for 'Cigarette History', 'Cannabis History', and 'Recreational Drug Use' which have n=519 participants due to missing data on these variables. n = 3 participants had missing data for either cigarette history, cannabis history, or recreational drug use. The multivariate analysis therefore includes n=517 participants.

When stratified by sex, unadjusted analysis revealed that moderate and high levels of frailty were associated with increased risk of HAND development in males, however this

association was not seen in females (Table 14). With each unit increase in the frailty index there is was significant increased risk of HAND development in males. Increasing age was associated with an increased risk of developing HAND in males, however, this effect was not seen in females. Education, cigarette history, cannabis history, and recreational drug use were not significant predictors of HAND development for males or females. Harmful alcohol use was not a significant predictor of HAND development in males, however it was significantly associated with decreased HAND development in females.

Multivariate analysis according to frailty category revealed that high frailty and increasing age was associated with an increased risk of HAND development in males (Table 14). For the female multivariate analysis removing harmful alcohol from the model resulted in a significant change to the model which was observed in the likelihood ratio test ($p = 0.037$).

Unadjusted analyses assessing frailty as a continuous score again demonstrated that frailty was associated with the development of HAND in males (HR 1.30, 95% CI 1.15 - 1.48, $p<0.001$), but not in females (HR 0.79, 95% CI 0.62 - 1.04, $p = 0.092$). Multivariate analysis using a continuous frailty index score also demonstrated that increasing frailty and age was associated with an increased risk of developing HAND in males (HR 1.29, 95% CI 1.13 - 1.46, $p<0.001$ and HR 1.02, 95% CI 1.01 - 1.03, $p=0.002$, respectively).

The final multivariate model for females demonstrates that frailty was not significantly associated with HAND development when frailty was assessed categorically or continuously. However, considering that females comprise only 18.4 percent of the total study population for this analysis (95 participants of a total of 517 considered in the multivariate analysis) there is low confidence as to whether these are meaningful results from which any conclusions can be drawn.

Table 14. *Unadjusted and Multivariate Cox Proportional Hazard Ratios for the Development of HAND According to Baseline Frailty Category by Sex - 60 Item Frailty Index*

	Males (n=425)						Females (n=95)					
	Unadjusted			Multivariate			Unadjusted			Multivariate		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
FI Category (referent: 0.00 to 0.09)												
0.10 - 0.19	1.54	[0.85 - 2.79]	0.158	1.44	[0.79 - 2.62]	0.234	1.05	[0.38 - 2.92]	0.927	1.09	[0.39- 3.05]	0.862
0.20 - 0.29	2.05	[1.14 - 3.69]	**0.017**	1.90	[1.05 - 3.42]	**0.033**	0.66	[0.23 - 1.91]	0.440	0.72	[0.25 - 2.11]	0.550
0.30+	2.70	[1.50 - 4.86]	**0.001**	2.49	[1.38 - 4.48]	**0.002**	0.83	[0.27 - 2.51]	0.746	0.99	[0.33 - 3.01]	0.990
Age	1.02	[1.01 - 1.03]	**0.001**	1.02	[1.01 - 1.03]	**0.002**	1.02	[0.97 - 1.02]	0.610	-	-	-
Education	1.02	[0.97 - 1.07]	0.393	-	-	-	1.03	[0.96 - 1.12]	0.397	-	-	-
Cigarette History (referent: Never User)												
Former User	1.15	[0.84 - 1.57]	0.387	-	-	-	1.11	[0.62 - 1.99]	0.717	-	-	-
Current User	1.02	[0.75 - 1.39]	0.891	-	-	-	1.08	[0.64 - 1.82]	0.774	-	-	-
Cannabis History (referent: Never User)												
Former User	0.92	[0.64 - 1.32]	0.660	-	-	-	0.55	[0.20 - 1.52]	0.251	-	-	-
Current User	1.04	[0.78 - 1.39]	0.797	-	-	-	1.03	[0.58 - 1.84]	0.910	-	-	-
Recreational Drug Use	0.83	[0.60 - 1.16]	0.270	-	-	-	0.70	[0.28 - 1.72]	0.434	-	-	-
Harmful Alcohol Use	0.95	[0.71 - 1.28]	0.757	-	-	-	0.40	[0.16 - 1.00]	**0.050**	0.42	[0.17 - 1.06]	0.065

Note. n = 3 male participants had missing data for either cigarette history, cannabis history, or recreational drug use. The unadjusted analysis for these categories for male participants therefore includes n=424 participants and the multivariate analysis for male participants therefore includes n=422 participants.

5.4.1 The association between frailty and the development of HIV-associated neurocognitive disorder (HAND) using a 39-item frailty index.

The 60-item frailty index was modified to a 39-item frailty index by removing comorbidities and HIV-related variables and used as a sensitivity analysis in order to confirm that frailty index scores were more than HIV variables and comorbidities alone (Table 8). All analyses are as above (Section 5.4).

Baseline frailty index scores for the 39-item frailty index ranged from 0.00 to 0.76 with a mean frailty score of 0.29 (SD = 0.15) (Table 15).

Table 15. *Summary Statistics for 60-Item and 39-Item Frailty Index Visits 1 to 7*

	60-Item Frailty Index					39-Item Frailty Index					
Visit	*N*	Mean	SD	Min	Max	*N*	Mean	SD	Min	Max	p-value
1	1141	0.22	0.10	0	0.54	1132	0.29	0.15	0	0.76	**<.001**
2	870	0.22	0.10	0	0.53	867	0.28	0.14	0	0.76	**<.001**
3	648	0.22	0.10	0	0.51	646	0.27	0.14	0	0.68	**<.001**
4	433	0.22	0.10	0	0.53	433	0.27	0.14	0	0.68	**<.001**
5	221	0.22	0.10	0	0.57	221	0.26	0.13	0	0.62	**<.001**
6	110	0.22	0.10	0.02	0.53	110	0.27	0.13	0	0.63	**<.001**
7	54	0.24	0.11	0.08	0.51	54	0.28	0.15	0.08	0.68	**<.001**

Note. The participants in each visit carry forward to the next visit, i.e. 870 participants out of the initial 1141 participants had a 2nd visit.

The multivariate analysis for the 39-item frailty index had n=513 participants (n = 418 males, the same as the 60-item frailty index).

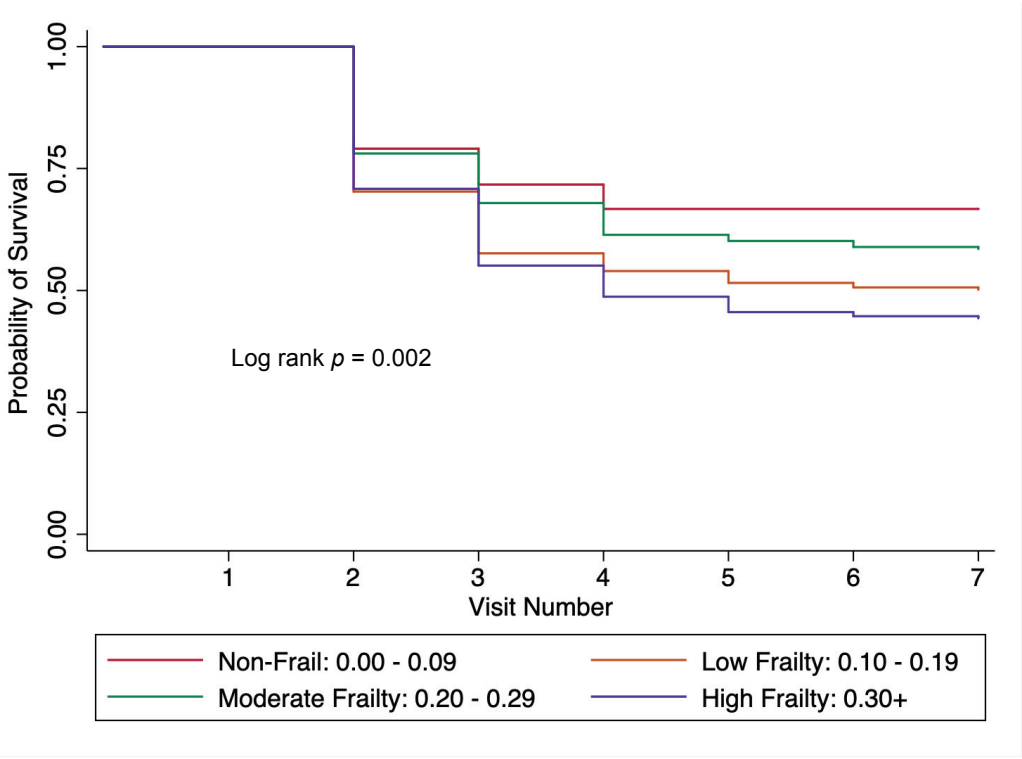


Figure 11. Kaplan-Meier survival estimates by frailty category - 39-item Frailty Index.

Participants with high frailty (0.3+) at baseline have shorter time of progression to HAND than those in the lower frailty categories (Figure 11). Participants with low and moderate frailty show very similar progression to HAND development over the 7 year period, though still progress more quickly than non-frail participants. Notably, participants with low frailty progress more quickly than participants with moderate frailty. The log-rank test for equality of survivor functions shows that the differences between the survivor functions (Figure 11) are statistically significant (p =0.002).

A backward elimination of the multivariate logistic regression model, with all explanatory variables, was used to establish the final model. The likelihood ratio test was used to compare the model before and after the elimination of the variable with the highest p-value in order to determine if significant ($p<0.10$) differences between the

models existed. Multivariate models were run for frailty as a categorical measure as well as frailty as a continuous measure.

Unadjusted analyses for the 39-item frailty index demonstrated that significant predictors for the development of HAND were high frailty, age, and female sex when frailty was assessed categorically (Table 17). Low and moderate levels of frailty were not associated with an increased risk of HAND.

Multivariate analysis of the 39-item frailty index by frailty category demonstrated that high frailty was significantly associated with an increased risk of HAND, while low and moderate levels of frailty were not (Table 16).

Unadjusted analyses assessing frailty as a continuous score again demonstrated that frailty was associated with the development of HAND (HR 1.10, 95% CI 1.02 - 1.19, p=0.011). Multivariate analysis of the 39-item frailty index by continuous frailty score also demonstrated a significant association with HAND development (HR 1.09, 95% CI 1.01 - 1.18, p=0.023).

Age was not significantly associated with HAND development when frailty was assessed categorically or continuously in the multivariate models. Males show a decreased risk in the development of HAND. As seen in the unadjusted analysis, increased duration of HIV leads to an increased risk of the development of HAND, while wasting syndrome and not being on ART are associated with a decreased risk of the development of HAND. No other HIV covariates reached significance.

Table 16. *Unadjusted and Multivariate Cox Proportional Hazard Ratios for the Development of HAND According to Baseline Frailty Category - 39 Item Frailty Index*

	Unadjusted			Multivariate		
	Hazard Ratio	95% CI	p-value	Hazard Ratio	95% CI	p-value
FI Category (referent: 0.00 to 0.09)						
0.10 - 0.19	1.65	[0.96 - 2.84]	0.073	1.31	[0.76 - 2.27]	0.334
0.20 - 0.29	1.33	[0.77 - 2.28]	0.308	1.05	[0.61 - 1.82]	0.854
0.30+	1.94	[1.16 - 3.25]	**0.012**	1.54	[0.92 - 2.60]	**0.104**
Age	1.01	[1.00 - 1.02]	**0.027**	-	-	-
Sex (referent: female)	0.62	[0.48 - 0.80]	**<0.001**	0.63	[0.49 - 0.81]	**<0.001**
Education	1.02	[0.98 - 1.06]	0.444	-	-	-
Cigarette History (referent: Never User)						
Former User	1.05	[0.80 - 1.38]	0.711	-	-	-
Current User	0.98	[0.75 - 1.27]	0.869	-	-	-
Cannabis History (referent: Never User)						
Former User	0.76	[0.55 - 1.05]	0.099	-	-	-
Current User	0.91	[0.71 - 1.15]	0.442	-	-	-
Recreational Drug Use	0.76	[0.56 - 1.04]	0.086	-	-	-
Harmful Alcohol Use	0.81	[0.61 - 1.07]	0.147	-	-	-
Nadir CD4	1.25	[0.97 - 1.60]	0.087	-	-	-
Duration of HIV	1.37	[1.10 - 1.71	**0.005**	1.29	[1.03 - 1.61]	**0.028**
ART Status (referent: on ART)	0.39	[0.21 - 0.72]	**0.002**	0.45	[0.24 - 0.83]	**0.010**

	Unadjusted			Multivariate		
	Hazard Ratio	95% CI	p-value	Hazard Ratio	95% CI	p-value
Cytomegalovirus	0.47	[0.12 - 1.88]	0.286	-	-	-
Kaposi's Sarcoma	0.55	[0.20 - 1.46]	0.228	-	-	-
Pneumocystis Pneumonia (PCP)	0.72	[0.41 - 1.29]	0.274	-	-	-
Pneumonia, Recurrent	1.21	[0.84 - 1.76]	0.307	-	-	-
TB (AIDS-Defining, Unspecified)	1.24	[0.56 - 2.79]	0.595	-	-	-
Wasting Syndrome Due to HIV	0.27	[0.10 - 0.71]	**0.009**	0.28	[0.10 - 0.75]	**0.012**
Lymphoma, NH (AIDS-Defining)	1.67	[0.86 - 3.25]	0.128	-	-	-

Note. Nadir CD4 n = 419 participants.

When stratified by sex, unadjusted analysis for the 39-item frailty index revealed that high levels of frailty were associated with increased risk of HAND development in males, however this association is not seen in females (Table 17).

For males, unadjusted analysis demonstrates that high frailty, age, decreased nadir CD4, and increased duration of HIV were significantly associated with an increased risk of HAND (Table 17). For females, unadjusted analysis revealed that harmful alcohol use was associated with an decreased risk of HAND (Table 17). Not being on ART and wasting syndrome were associated with a decreased risk of HAND development in both males and females.

Multivariate analysis by sex demonstrated an increased risk of HAND development with high frailty and increasing age, and a decreased risk with the presence of wasting syndrome in males (Table 17). When separating the multivariate analysis by sex, duration was no longer significant for males. Similar to the unadjusted analysis for females,

harmful alcohol use and ART use were associated with a decreased risk of HAND development (Table 17).

Table 17. *Unadjusted and Multivariate Cox Proportional Hazard Ratios for the Development of HAND According to Baseline Frailty Category by Sex - 39 Item Frailty Index*

	Males (n=425)						Females (n=95)					
	Unadjusted			Multivariate			Unadjusted			Multivariate		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
FI Category (referent: 0.00 to 0.09)												
0.10 - 0.19	1.90	[0.96 - 3.76]	0.066	1.65	[0.82 - 3.30]	0.157	0.76	[0.31 - 1.86]	0.551	-	-	-
0.20 - 0.29	1.64	[0.83 - 3.23]	0.151	1.41	[0.71 - 2.80]	0.328	0.47	[0.19 - 1.17]	0.106	-	-	-
0.30+	2.68	[1.41 - 5.11]	**0.003**	2.43	[1.26 - 4.66]	**0.008**	0.53	[0.22 - 1.26]	0.148	-	-	-
Age	1.02	[1.01 - 1.03]	**0.001**	1.02	[1.01 - 1.03]	**0.004**	0.99	[0.97 - 1.02]	0.610	-	-	-
Education	1.02	[0.97 - 1.07]	0.420	-	-	-	1.03	[0.96 - 1.11]	0.397	-	-	-
Cigarette History (referent: Never User)												
Former User	1.14	[0.82 - 1.56]	0.431	-	-	-	1.11	[0.62 - 1.99]	0.717	-	-	-
Current User	1.03	[0.76 - 1.41]	0.848	-	-	-	1.08	[0.64 - 1.82]	0.774	-	-	-
Cannabis History (referent: Never User)												
Former User	0.92	[0.64 - 1.33]	0.662	-	-	-	0.55	[0.20 - 1.52]	0.251	-	-	-
Current User	1.05	[0.79 - 1.40]	0.739	-	-	-	1.03	[0.58 - 1.84]	0.910	-	-	-
Recreational Drug Use	0.84	[0.60 - 1.16]	0.289	-	-	-	0.67	[0.28 - 1.72]	0.434	-	-	-
Harmful Alcohol Use	0.96	[0.71 - 1.30]	0.810	-	-	-	0.40	[0.16 - 1.00]	**0.050**	0.40	[0.16 - 0.98]	**0.046**
Nadir CD4	1.40	[1.04 - 1.89]	**0.028**	-	-	-	0.98	[0.61 - 1.57]	0.936	-	-	-
Duration of HIV	1.47	[1.14 - 1.91]	**0.003**	-	-	-	1.30	[0.83 - 2.02]	0.251	-	-	-
ART Status (referent: on ART)	0.45	[0.23 - 0.88]	**0.019**	0.56	[0.28 - 0.10]	0.092	0.24	[0.06 - 0.96]	**0.044**	0.23	[0.06 - 0.94]	**0.041**

	Males (n=425)						Females (n=95)					
	Unadjusted			Multivariate			Unadjusted			Multivariate		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Cytomegalovirus	0.52	[0.13 - 2.10]	0.359	-	-	-	-	-	-	-	-	-
Kaposi's Sarcoma	0.61	[0.23 - 1.63]	0.321	-	-	-	-	-	-	-	-	-
Pneumocystis Pneumonia (PCP)	0.84	[0.47 - 1.50]	0.557	-	-	-	-	-	-	-	-	-
Pneumonia, Recurrent	1.39	[0.93 - 2.07]	0.110	-	-	-	0.75	[0.28 - 2.05]	0.576	-	-	-
TB (AIDS-Defining, Unspecified)	0.46	[0.64 - 3.26]	0.435	-	-	-	1.46	[0.59 - 3.60]	0.413	-	-	-
Wasting Syndrome Due to HIV	0.34	[0.13 - 0.91]	**0.032**	0.33	[0.12 - 0.89]	**0.028**	-	-	-	-	-	-
Lymphoma, NH (AIDS-Defining)	1.87	[0.96 - 3.65]	0.65	-	-	-	-	-	-	-	-	-

Note. n = 3 male participants had missing data for either cigarette history, cannabis history, or recreational drug use. The bivariate analysis for these categories for male participants therefore includes n=422 participants. For males, n= 77 participants had missing data for Nadir CD4, therefore the bivariate analysis for these participants includes n=344 participants. For females, n= 20 participants had missing data for Nadir CD4, therefore the bivariate analysis for these participants includes n=75 participants. Multivariate analysis for males includes n =422 participants. For females, cytomegalovirus, Kaposi's sarcoma, PCP, Wasting Syndrome and Lymphoma were eliminated due to few to no deficits for these variables.

5.5 The association between frailty and the progression of HIV-associated neurocognitive disorder (HAND).

Over the entire study period there were 2,335 transitions between HAND states among n=1141 participants over the 7 visits included in the study period (Table 18). Transitions could occur in either direction (i.e. worsening HAND or improving HAND) for the two middle categories (ANI and MND) but could only go in one direction for Normal (worsening) and HAD (improving). The majority of neuropsychologically normal participants remained stable (73.2%) over the entire study period. Notably, many participants showed improvement over the entire study period. For participants with ANI, 26.1% of participants showed improvement. For participants with MND, 29.5% and 25.7% of participants moved to the ANI and neuropsychologically normal categories,

respectively. While the majority of participants with HAD remained stable (44.2%), 14.0%, 32.6%, and 9.30% moved to the MND, ANI, and normal categories respectively.

Table 18. *Number of Transitions Between HAND States for Entire Study Period*

Present HAND State	Future HAND State				Total Transitions
	Normal	ANI	MND	HAD	
Normal	778 (73.2%)	199 (18.7%)	77 (7.24%)	9 (0.85%)	1063 (100%)
ANI	215 (26.1%)	470 (57.0%)	89 (10.8%)	50 (6.07%)	824 (100%)
MND	82 (25.7%)	94 (29.5%)	120 (37.6%)	23 (7.21%)	319 (100%)
HAD	12 (9.30%)	42 (32.6%)	18 (14.0%)	57 (44.2%)	129 (100%)
Total Transitions	1087	805	304	139	2335

Transition matrices were constructed to demonstrate the probability of moving between HAND states throughout the study period according to frailty category (Table 19).

Table 19. *Transition Matrices for Each Category of Frailty Demonstrating Total Transitions (and Row Percents)*

Frailty Category	HAND Current Visit	HAND Next Visit				Total
		1	2	3	4	
Non-Frail	1	68	19	2	0	89
		(76.4)	(21.35)	(2.25)	(0.00)	(100.00)
	2	25	58	3	9	95
		(26.32)	(61.05)	(3.16)	(9.47)	(100.00)
	3	0	2	2	1	5
		(0.00)	(40.00)	(40.00)	(20.00)	(100.00)
	4	0	3	0	5	8
		(0.00)	(37.50)	(0.00)	(62.50)	(100.00)
	Total	93	82	7	15	197
		(47.21)	(41.62)	(3.55)	(7.61)	(100.00)

Frailty Category	HAND Current Visit	HAND Next Visit				Total
		1	2	3	4	
Low Frailty	1	293	84	17	1	395
		(74.18)	(21.27)	(4.30)	(0.25)	(100.00)
	2	87	201	31	18	337
		(25.82)	(59.64)	(9.20)	(5.34)	(100.00)
	3	13	25	16	2	56
		(23.21)	(44.64)	(28.57)	(3.57)	(100.00)
	4	4	18	3	12	37
		(10.81)	(48.65)	(8.11)	(32.43)	(100.00)
	Total	397	328	67	33	825
		(48.12)	(39.76)	(8.12)	(4.00)	(100.00)
Moderate Frailty	1	262	61	30	6	359
		(72.98)	(16.99)	(8.36)	(1.67)	(100.00)
	2	65	152	35	15	267
		(24.34)	(56.93)	(13.11)	(5.62)	(100.00)
	3	33	34	34	11	112
		(29.46)	(30.36)	(30.36)	(9.82)	(100.00)
	4	5	11	7	14	37
		(13.51)	(29.73)	(18.92)	(37.84)	(100.00)
	Total	365	258	106	46	775
		(47.10)	(33.29)	(13.68)	(5.94)	(100.00)
High Frailty	1	155	35	28	2	220
		(70.45)	(15.91)	(12.73)	(0.91)	(100.00)
	2	38	59	20	8	125
		(30.40)	(47.20)	(16.00)	(6.40)	(100.00)
	3	36	33	68	9	146
		(24.66)	(22.60)	(46.58)	(6.16)	(100.00)

Frailty Category	HAND Current Visit	HAND Next Visit				Total
		1	2	3	4	
	4	3	10	8	26	47
		(6.38)	(21.28)	(17.02)	(55.32)	(100.00)
	Total	232	137	124	45	538
		(43.12)	(25.46)	(23.05)	(8.36)	(100.00)

The transition matrices allowed for the calculation of the transition probability measures and the Determinant Index mobility measure. The Determinant Index matrix-based mobility measure demonstrated that non-frail and high frailty participants had significantly lower mobility between HAND states than those with low and moderate frailty (Table 20). Participants with low frailty had the highest mobility between HAND states (Table 20).

Table 20. *Determinant Index Mobility Measures for Each Category of Frailty*

Frailty Score	Frailty Category	Determinant Measure (A)	95% CI
0.00 - 0.09	Non-Frail	0.91	0.89- 0.93
0.10 - 0.19	Low Frailty	0.98	0.97 - 0.98
0.20 - 0.29	Moderate Frailty	0.97	0.97 - 0.98
0.30+	High Frailty	0.95	0.94 - 0.95

CHAPTER SIX: DISCUSSION

The goal of this study was to examine the association between frailty and the development and progression of HAND. Our findings indicate that frailty, as assessed by a frailty index, is associated with an increased risk of HAND development. Further, those with increasing frailty demonstrated a quicker progression to symptomatic HAND. Both of these findings confirm our initial hypotheses. Last, we found that both non-frail and highly frail participants had significantly lower mobility between HAND states when compared to their low frail and moderately frail counterparts. To date, this is the first study that has examined the association between frailty and the development and progression of HAND as well as the first to document the longitudinal transitions between HAND states in people living with HIV by frailty severity.

6.1 The Frailty Index

The 60 item frailty index constructed from variables in the OCS questionnaires and clinical charts, demonstrated the expected properties for a clinical population. Frailty index scores were normally distributed with the upper limit of deficit accumulation within the expected range and in line with previous literature (Searle et al., 2008). The observation that the upper limit of frailty fell within the expected range suggests that the frailty index did not overestimate the frailty scores of this population (Guaraldi et al., 2015). The distribution of frailty index scores was positively skewed which is typical of a clinical population and replicates findings from previous literature (Guaraldi et al., 2017; Mitnitski et al., 2001; Searle et al., 2008; Theou, Brothers, Peña, Mitnitski & Rockwood, 2014). There were no significant differences among baseline frailty index scores between sexes or between visits. Frailty was highest among participants aged 55-59, followed by participants aged 50-54. At baseline, approximately a third of participants had low and moderate frailty respectively, while almost a quarter of participants had high frailty.

6.1.1 Participant Characteristics at Baseline

At baseline, almost half of participants were classified as neuropsychologically normal, with decreasing proportions of participants classified as having ANI, MND, and HAD, respectively. Only a small proportion of the total participants were diagnosed as having HAD. The distribution of HAND scores are expected for people living with HIV and being treated with cART and replicates previous findings from the CHARTER study (Heaton et al., 2010).

There were significant differences among HIV variables at baseline according to HAND state, including duration of HIV, cART status, nadir CD4, and PCP rates. Participants classified as neuropsychologically normal had the lowest HIV duration, while participants with HAD showed the longest HIV duration suggesting that increasing duration of HIV is associated with an increased risk of HAND development and progression. The increased risk of HAND development with increasing duration of HIV has previously been supported in the literature in the CHARTER study (Grant et al., 2014). Participants classified as neuropsychologically normal showed significantly decreased rates of ART, perhaps suggesting that they might be early in their diagnosis and not yet on an ART regimen. With new guidelines suggesting that ART begins at HIV diagnosis this is expected to change. Nadir CD4 count decreased as HAND progressed with MND and HAD participants having the lowest counts. PCP status was also highest among participants with HAD, suggesting that these patients may be experiencing higher rates of advanced immunosuppression seen in the later stages of HIV disease progression.

The rates of cigarette smoking were significantly higher among participants with MND and HAD, replicating findings in previous literature (Brothers et al., 2017; Gustafson et al., 2016; Thurn & Gustafson, 2017). The rates of depression among participants was high, with MND participants experiencing double the rates of depression when compared

to the other HAND states and when compared to the overall rate of depression among participants. The higher rates of depression in people living with HIV is consistent with previous literature (Althoff et al., 2013; Erlandson et al., 2019; Greene et al., 2015; Heaton et al., 2010; Hosaka et al., 2019) The increased rate of depression seen in individuals with MND is perhaps reflective of previously identified challenges in those living and aging with HIV such as social isolation and lack of social support (Rueda, Law, & Rourke, 2016). Further, in addition to impairment in cognitive functioning, individuals diagnosed with MND have demonstrated impairment in their daily functioning, which possibly contributes to the increased rate of depression in this group.
6.1.2 The prevalence of HIV-associated neurocognitive disorder (HAND).

Both the total and baseline prevalence of neuropsychologically normal diagnoses showed an increase in prevalence over the study period, while HAND diagnoses ANI, MND, and HAD showed a decrease in prevalence over the study period. These findings replicate findings from the CHARTER study which had prevalence estimates of 33%, 12%, and 2% for ANI, MND, and HAD respectively and can be attributed to the increase in use in cART (Heaton et al., 2010; Nightingale et al., 2014). The decline in HAND prevalence can also be attributed to the increase in awareness and earlier diagnosis of HAND, thereby allowing for earlier intervention and treatment. The decline in MND and HAD prevalence will hopefully continue with increased education and awareness, increased screening, earlier diagnosis, and earlier cART therapy.

6.1.2 The association between frailty and the development of HIV-associated neurocognitive disorder (HAND).

The 60-item frailty index was able to predict the development of HAND and the progression through HAND states as well as demonstrate that increasing levels of frailty are associated with increased progression to HAND. Participants with high frailty at baseline showed quicker progression to the development of HAND than those in the lower frailty categories. Participants with low and moderate frailty showed almost

identical HAND progression, perhaps suggesting that these two levels of frailty are not as clearly distinguishable from one another as those in the other categories (i.e. when compared to the non-frail or high frailty categories). Increasing levels of frailty were associated with a significantly increased risk of the development of HAND, with the final model demonstrating that high frailty was associated with a two fold increase in the risk of developing HAND. This expands upon previous findings demonstrating that lower levels of frailty are associated with successful cognitive aging and that higher frailty index scores are associated with decreased neurocognitive functioning in people living with HIV (Ding et al., 2018; Oppenheim et al., 2018; Morgello et al., 2019; Paolillo et al., 2019; Wallace et al., 2017; Zamudio-Rodriguez, 2018). Increasing age was significantly associated with an increased risk of HAND development which replicates findings in both clinical HIV populations and non-clinical elderly populations (Brothers et al., 2017, Guaraldi et al., 2015; Searle et al., 2008). In the present study baseline frailty index scores increased 0.29% with each year of age, a rate similar to previous findings in HIV populations and lower than non-clinical populations which tend to accumulate deficits at a rate of 3% per year (Franconi et al., 2017; Guaraldi et al., 2015; Mitnitski et al., 2005; Rockwood & Mitniski, 2011; Searle et al., 2008). The lower deficit accumulation rate seen in our clinical population suggests that the baseline level of frailty is higher at all ages when compared to a non-clinical population and therefore is not as strongly correlated with age (Mitniski et al. 2005). In terms of sex differences, males were significantly less likely to develop HAND compared to females. This finding replicates previous research demonstrating that females tend to be more frail not only in HIV cohorts but in non-clinical populations as well (Brothers et al., 2017; Guaraldi et al., 2015; Morgello et al., 2019; Mitnitski et al., 2005; Rockwood & Mitnitski, 2008). This finding, should however be interpreted with caution. For one, the proportion of females in the present study comprised only a fifth of the total study sample. This finding is also driven by the fact that the female population within the OCS is significantly different from the male population in that it includes a higher proportion of immigrants from Africa.

The sensitivity analysis using the 39-item frailty index (with comorbidities and HIV-related variables removed) also demonstrated that frailty was significantly associated with the development of HAND. This speaks to the robustness of the frailty index as a measure of frailty and demonstrates that frailty is not solely driven by HIV variables and comorbidities alone. Among the HIV variables in the 39-item frailty index, duration was significantly associated with an increased risk of HAND. Participants who were not on ART had a shorter duration of HIV than those on ART, perhaps due to the fact that those not on ART are likely in the very early stages of the disease and are therefore less likely to demonstrate any cognitive deficits. Additionally, only 6.7% of the study sample was not on ART at baseline.

While both the 39-item frailty index and the 60-item frailty index were predictive of HAND development, the 60-item frailty index with HIV-related variables and comorbidities included is arguably a better predictor of frailty as it provides the most complete, all-encompassing measure of frailty in an individual. A measure that takes into account multiple systems utilizing a wide variety of variables allows for a deeper understanding and assessment of a patient's health. Further, it allows clinicians to accurately assess a patient's overall health and tailor their treatment plans accordingly. HIV-associated variables and comorbidities are important in the assessment of the overall health of a patient and have shown to be strong predictors of cognitive outcomes. Therefore, when using the frailty index clinically in order to guide treatment a frailty index that includes these measures is ultimately more precise than one that does not take these variables into account.

6.1.3 The association between frailty and the progression of HIV-associated neurocognitive disorder (HAND).

The frailty index was found to be predictive of the transition between various HAND states. This suggests that individuals presenting with low and moderate levels of frailty

tend to move between HAND states more readily and that their current categorizations of HAND are not fixed. By the time an individual is classified as having high frailty, their HAND diagnosis is likely to be more fixed and more resistant to change. The reasoning behind this could be that individuals exhibiting high frailty have less room for improvement as with increasing numbers of deficits there are likely multiple systems in play and the chances of meaningfully recovering from a myriad of defects is low. This coincides with the present study finding that participants with higher frailty at baseline have a shorter time to progression to HAND than those in lower frailty categories.

Individuals who are non-frail demonstrate the lowest mobility between HAND states. The reasoning for low mobility in the non-frail group is perhaps due to the low risk of developing HAND in this group in the first place. This suggests that the likelihood of developing HAND will stay low as long as frailty is very low and deficit accumulation is minimized. These findings further demonstrate the need for early and targeted interventions for individuals presenting as frail as well as the need for preventative measures against the development of frailty in people living with HIV.

6.2 Strengths and Limitations

The strengths of the present study include the use of data from the OHTN Cohort Study, a population based study that has rich data over multiple time points, thereby allowing for the study of the development and progression of neurocognitive change over time. The OCS is linked with provincial data sources, which increased the scope of variables included within the index. The OCS recruits from HIV clinics that care for over three quarters of the HIV population in Ontario, and therefore the participants in this study represent a broad population of those receiving care for HIV (Rourke et al., 2013). Neurocognitive status was assessed with the use of validated tools and HAND was defined according to established criteria. To date, this is the first study that has documented the longitudinal transitions between HAND states in people living with HIV, as well as the first to categorize these progressions by different categories of frailty.

There are some important limitations with respect to this study. As is inherent in most studies focusing on aging, survival bias may interfere as the study population selected may over-represent a fitter population, and underrepresent more vulnerable individuals due to increased rates of mortality (Guaraldi, 2014). There is also possible recruitment bias in that those who volunteer for the study may be different from those who do not (Rourke et al., 2013). The OCS continually aims to reduce recruitment bias by aiming to increase participation from underrepresented populations, such as intravenous drug users, individuals from HIV endemic regions, as well as recently diagnosed individuals (Rourke et al., 2013).

The female and male populations within the study were also significantly different in size (with females comprising only one fifth of the total sample) as well as demographics, with a higher proportion of immigrants from Africa within the female group. Some variables had a high percentage of missing values (i.e. clinical values in the questionnaire). These variables were dropped from the frailty index due to not meeting criteria. However, a strength of the frailty index is that it is the number of variables rather than the particular variables chosen that is important, and the specific variables included can vary from dataset to dataset. As long as the criteria for inclusion of variables are met, the particular choice of variable does not matter, which allows for the frailty index to be created in almost any dataset with enough variables. The frailty index is therefore a useful tool and can be constructed in almost any dataset, as long as the appropriate guidelines for selecting variables are in place.

A potential limitation of the present study is the way in which the HAND outcome variable was constructed within the OCS dataset. Within the OCS dataset the HAND variable is defined by combining the GDS score (derived from the results of neuropsychological testing) with self-reported cognitive symptoms (assessed through the MOS-COG). Cognitive functioning is therefore assessed and defined both by

neuropsychological testing and through self-report measures. The Frascati method of combining neuropsychological testing with self-reported cognitive symptoms has been previously established in the literature (Antinori et al., 2007). The first limitation is that the HAND scores within this study are calculated using a shortened-battery defined within the OCS. In a clinical setting, cognitive functioning would be assessed with more extensive testing through the use of longer test batteries with a clinician. However, as is the nature of large-scale epidemiological studies, time and resource intensive clinical testing is not always feasible. Second, the determination of HAND scores relies on self reported cognitive deficits which are arguably not as reliable as more objective measures of cognitive deficits. Previous research has demonstrated that self-report cognitive measures may actually correlate better with measures of mood than with neuropsychological tests and therefore their use might be of limited value (Grant & Sacktor, 2012). The neuropsychological evaluation in patients living with HIV is recommended to contain self-reported assessment in key areas of functioning (such as employment and medication adherence, for example), however it is advised that the self-reported deficits be verified in the medical records as well as via individuals close to the patient who would be aware of their level of functioning (Cattie, Woods, Grant, 2012). This type of verification is unfortunately not possible within this dataset. Third, a further limitation of the HAND variable as defined by the OCS is that ethnicity data had to be recoded in order to match the normative U.S. data used to generate *T* scores. As such, various ethnicity groups had to be collapsed into three main groups (“black”, “white”, and “hispanic American”), thereby causing the loss of information on a variety of ethnicities. Unfortunately, Canadian normative scores are not available at this time and so American normative scores were used, which may not be truly representative for the Canadian population nor the immigrant population within this cohort. Last, for repeated neuropsychological tests, test scores are usually adjusted for the “practice effect”. The practice effect can be defined as the gains in scores that a participant can achieve when taking a test two or more times due to their familiarity with the test. The OCS data is not

corrected for this effect and as a result the *T* scores of the 2nd visit and onwards may be slightly over-estimated.

One method to overcome the limitation imposed by the use of self-reported measures in the HAND variable in the present study would be to assess HAND through the use of the GDS score alone (defining neuropsychological impairment using a GDS $\geq$ 0.5 cut off). The GDS weights data from the neuropsychological testing in a similar method to clinical rating procedures by taking into account the number of deficits as well as the severity of deficits and also by weighting performances that fall within and the above the normal limits to a lesser degree (Carey et al., 2004). When compared to clinical ratings, the GDS shows a strong positive association (ρ = 0:87, p< .0001) (Carey et al., 2004). The GDS also has demonstrated construct validity and is associated with functional impairment (Cattie et al., 2012). Further, the GDS has demonstrated ability to reduce both the number of Type I and Type II errors (Carey et al., 2004). Use of the GDS score is also thought to be a more conservative approach when compared to the Frascati criteria, which has been criticized for having a high false positive rate leading to possible overestimation of HAND (Ciccarelli, 2020; Heaton et al., 2020; Meyer, Boscardin, Kwasa, & Price, 2013). Utilizing the GDS to define cognitive impairment might therefore serve to increase the accuracy and precision of the HAND score especially within a dataset which may already be limited by the shortened neuropsychological testing battery (it is important to note, however, that using only the GDS score within this particular dataset will not overcome the limitation of the shortened neuropsychological testing battery as these measures are used to derive the GDS). The GDS score is unfortunately not without limitations either, and may be limited by its narrow range of values, reported insensitivity to variation in the normal ranges, as well as ceiling effects (Cattie et al., 2012). Future studies should weigh the benefits and risks of including self-report measures and whether the self-report measures are in fact in well correlated with cognition. Further, future studies should aim to select standardized tests in which there is corresponding normative data for their study population as these allow for the adjustment of important demographic factors.

Standardized tests for the neuropsychological battery should be selected for according to time and resource availability and only from standardized accepted methods established in the literature (Antinori et al., 2007).

6.3 Measuring Frailty in HIV

The frailty index has the potential for greater utility than rule-based methods of assessing frailty which impose stricter guidelines and may not have the appropriate information and variables available within a selected dataset. Additionally, rules-based approaches to defining frailty may not be appropriate for all populations and can limit the ability to assess frailty in databases that do not contain the specific variables. Because the frailty index does not have specific pre-determined variables that are fixed the frailty index can be constructed within a wide variety of datasets. This adaptability of the frailty index allowed us to determine an individual's frailty from a multitude of sources as well as to construct these indices retrospectively. Using a cumulative deficit approach such as the frailty index allowed for the construction of the frailty index with over 60-deficits to be built within a pre-existing dataset and allows for the quantification of the variability and often times acceleration of aging seen in those living and aging with HIV.

6.4 Significance and Clinical Implications of Measuring Frailty in Relation to HAND

Given that frailty is associated with the development and progression of HAND, the treatment of frailty is an important element of care for those living with HIV. When we think about treating frailty it is perhaps best to start by thinking about how to prevent frailty in the first place. In the case of HIV this means early diagnosis, access and treatment with cART upon diagnosis, and vigilance in cART adherence monitoring. Identifying frailty in the early stages is crucial in allowing clinicians to treat and prevent future deterioration and deficit accumulation. However, in order to treat frailty there must be methods in place to identify frailty. As demonstrated the frailty index is a proven and robust method used to identify frailty but as with many clinical tools, there are challenges

with implementation into standard practice of care. Clinicians need to be aware of the existence of frailty and how frailty risk assessments can be conducted within their practice. Measuring frailty clinically could allow clinicians to target their interventions and prevent poor outcomes in the future. A key barrier in many clinical settings is the ability to calculate a frailty index with all available data in real time.

Several interventions have been shown to improve frailty outcomes in the general aging population including assessments via specialists such as geriatricians on specialist elderly wards (as compared to admission to the general ward setting) as well as the implementation and adherence to exercise programs (Clegg, 2013). In the HIV population, patients that present as frail (and who are therefore at an increased risk of the development of HAND) should be monitored frequently by HIV and HAND specialists who can assess and recommend appropriate programs for their patients.

The prevention and treatment of HAND should be a priority in the clinical care of people living with HIV/AIDS. The Mind Exchange program, a group comprised of sixty-six HIV specialists from around the world sought to develop evidence-based guidelines for HAND diagnosis and management (Antinori et al., 2013). These guidelines are especially important as they allow for systematic methodology in both the identification and treatment of HAND. Guidelines to help clinicians and health care workers to appropriately screen for and identify HAND as well as those who may be at risk of HAND in an early and effective manner will allow for better treatment outcomes, increased education and knowledge for patients and their families, and increased levels of support from health care providers. The factors that contribute to a patient being high-risk include disease factors such as low CD4 count and longer HIV duration, treatment factors such as low adherence, cART interruption, or short cART duration, comorbidities such as cardiovascular risk factors (hyperlipidemia, hypertension, and diabetes), demographic factors such as older age, low education, and lack of access to care, neurological and psychiatric factors such as neuropsychiatric disorders or drug and alcohol abuse, as well

as complex cART factors and biomarkers (Antinori et al., 2013). It is noted that many of the factors that define a patient as high-risk are included in the frailty index of the present study. Screening for HAND should be conducted in all patients with HIV (not only symptomatic patients) and should begin within six months of initial diagnosis with follow-up assessments occurring annually on average (Antinori et al., 2013). With regards to the diagnosis of HAND, it is recommended that a comprehensive neuropsychological battery covering at least 5 neurocognitive domains be used in the assessment of HAND (Antinori et al., 2013). The treatment of HAND is best accomplished by appropriate cART medications, monitoring cART adherence, as well as the treatment of comorbidities (Antinori et al., 2013).

It is hoped that further decreases in HAND diagnoses will come from advances in neurodiagnosisis as well as advances in cART treatment. Advances in neurodiagnosis techniques will allow for clinicians to make a faster and quicker diagnosis of patients, rather than relying on time-intensive neuropsychological testing. Increased CNS penetration of cART (as quantified by the CNS Penetration Effectiveness (CPE) score) is significantly associated with lower levels of cognitive impairment, with a 17% reduction in the odds of neuropsychological impairment for every 1 point increase in CPE (Carvalhal et al., 2016). Advances in the ability to detect and treat HIV reservoirs in the brain will be an important area for future research in the treatment and prevention of HAND.

There are also important lifestyle changes that can help to prevent and slow the course of HAND. Exercise has been previously suggested as a recommendation for HIV-patients as it has shown benefits in non-HIV infected patients experiencing cognitive difficulties (Valcour, 2013). Exercise also has the benefits of improving depression and increasing social involvement (Valcour, 2013). Poor aerobic fitness is associated with an increased risk of cognitive impairment in HIV positive individuals over the age of fifty (Mapstone et al., 2013). Those with high fitness levels had no cognitive impairments in this cohort,

supporting the hypothesis that aerobic fitness has a neuroprotective effect (Mapstone et al., 2013).

The findings in this study add to a growing body of literature demonstrating the relationship between frailty and reduced cognitive outcomes in those living with HIV. It is hoped that these findings not only demonstrate the utility of measuring frailty in order to predict outcomes and guide clinical practice but also how imperative it is for frailty to be identified early and for deficit accumulation to be minimized. Early detection and treatment of HIV, increased screening of neurocognitive impairments and the identification of those at risk of frailty will serve to further decrease the rates of ANI, MND, and HAD and improve the quality of life among people living with HIV.

6.5 Conclusion

The present study examines the association between frailty and the development of HAND among people aging with HIV through the construction of two separate frailty indices. The main frailty index encompasses both comorbidities and HIV-related variables. In order to understand what frailty contributes over and above multimorbidity and HIV-related variables alone and to demonstrate the incremental effect of these variables within the frailty index, a second frailty index without comorbidity or HIV-related variables was constructed. The main frailty index served as an overall measure to demonstrate the progression of HAND. The addition of multimorbidity and HIV-related variables allows for the best estimate of frailty of an individual as it demonstrates a larger and more precise estimate of deficit accumulation. Additionally, the inclusion of these variables gives us to have a deeper understanding and a more accurate overall measure of frailty in an individual. The investigation of frailty among individuals with HIV allows for the identification of those who are more vulnerable to developing HAND, as well as those more likely to progress through the various HAND states.

We found that frailty was associated with an increased risk of HAND development. Those that presented as frail further showed a quicker progression to symptomatic HAND. Individuals who presented as non-frail had the lowest mobility between HAND states with the possible implication that the likelihood of developing HAND will remain low if frailty, as defined by deficit accumulation, remains low.

Measuring frailty could serve as a useful clinical tool to guide intervention to decrease the risk of development and progression of HAND. The present research demonstrates the need for early identification of frailty in those living with HIV in order to not only treat and prevent further frailty but also to prevent and treat the development and progression of HAND. This research further demonstrates that the accumulation of deficits, rather than the specific deficits themselves can identify those patients most at risk, allowing us to target our care to vulnerable patients. Early intervention and treatment of frailty will ultimately help in the prevention of the development and progression of HAND. This research garners a deeper understanding of the additive effects of the determinants of neurocognitive outcomes and HAND. The relationships among HIV, frailty, and neurocognitive status are important in order to further improve prevention, rehabilitation, and other behavioural and medical interventions in those living and aging with HIV. This research furthers our understanding of these relationships which will ultimately improve the health, treatment, and quality of life for those affected by HIV/AIDS.

CHAPTER SEVEN: COMMUNITY ADVISORY COMMITTEE

7.1 Introduction

Central to the OCS core values is their commitment to the greater involvement of people living with HIV (OHTN, 2020). The OCS is a community driven study and involves stakeholders such as people living with HIV, HIV dedicated health care and service providers, policy makers, scientists, and researchers (Rourke et al., 2013). Proposals submitted to the OCS for review are first reviewed by The Scientific Steering Committee which is responsible for ensuring that projects adhere to the goals and directions of the OCS (Rourke et al., 2013). The OCS Governance Committee, which includes people living with HIV as well as various other stakeholders within the HIV community, further evaluates the proposal to in order to ensure that standards of data security and confidentiality are met and that the proposal is relevant to the greater HIV community (Rourke et al., 2013). One of the mandates of using data from the OCS was to commit to meaningful engagement with the HIV/AIDS community. This was accomplished by establishing a community advisory committee to help guide and interpret the work as well as to ensure that the work is relevant to those living with HIV. Following completion of the study the community advisory committee will continue to advise on knowledge translation and how to best distribute the findings of this project among community groups.

7.2 Methods

The community advisory committee consists of three members of the HIV community who are engaged in HIV/AIDS activism and advocacy in their respective communities. The community advisory committee were invited to be involved in this project when the study was approved by the OCS. Potential community advisory members were recommended by the thesis supervisory committee for this project. Each community advisory member was contacted via email with an outline of the project attached and they were asked if they would be interested in volunteering to be a part of the community

advisory committee for this project. They were encouraged to contact via email, phone, or video call if they had any further questions, for example, regarding the project itself or the level of commitment required. Potential community advisory members were informed that participation in the project would be at the level of commitment of their choosing.

Community advisory committee members were asked for their input on the thesis proposal as well as on findings and limitations of the final thesis draft. Feedback from the community advisory group was given separately during meetings with each individual community member via telephone and video calls. Community advisory committee members have also provided guidance for knowledge translation and dissemination of the findings to the greater community and have put forth their recommendations for future research. Upon study completion the community advisory committee will meet to plan further knowledge translation activities.

7.3 Advisory Committee Members Feedback

The community advisory committee commended the fact that 'people living with HIV/AIDS' and similar terms are used throughout the body of this work instead of the use of acronyms and noted the importance of this to members of the HIV/AIDS community. The use of self-report measures included in this study were emphasized as being valuable tools as they allow for the patients' point of view to be expressed, thereby allowing for patients to have more ownership and control of their condition and health status. It was noted that often times patients are better able to recognize and discriminate small changes in their health which might not be captured by clinicians. Self report tools can thereby empower patients and allow them to better advocate for themselves.

Several limitations of the work were discussed by the community advisory committee. With regards to the study population it was noted that the OCS study population has a higher level of care and social support than those not within the OCS, and further that those within the OCS have a better than average level of medical supervision, both

factors thereby contributing to selection bias. Members of the community advisory committee commented that the data from the OCS may be inherently different than data from patients with less support and lower levels of medical supervision.

A major recommendation put forth by a committee member was that the community advisory committee should be involved sooner in the research process, for example, at the inception of the project rather than once the research proposal has been drafted and approved. This would allow community members to contribute to the design of the project as well as to be more involved in the formation of the research questions. Additional recommendations put forth by the community advisory group include edits to the body of the thesis including highlighting the importance of HAART and how HAART was a major factor in decreasing the prevalence of HAD, exploring the relationship between inflammation and HAND, and highlighting interventions for frailty and HAND as well as interventions that could target frailty and HAND concurrently. With regards to specific interventions the community advisory committee suggested the addition of literature on the benefits of exercise as well as any potential cognitive gaming interventions. Recommendations were also made regarding increasing the clarity of some of the terms and descriptions used throughout the work, for example, clarifying the use of the word mobility as it describes the fluctuation throughout the various HAND states.

The community advisory committee recommended that future research include the design of a frailty index tool that could be used clinically, for example by reducing the number of deficits within the index. Further, it was recommended that the frailty index could be administered as a patient questionnaire as many of the variables included within the index are usually known to the patient. This could aid in alleviating the time constraints on clinicians as it could be sent to patients to complete prior to their exam or within the waiting room. The community advisory committee also recommended that future research should explore the effect of the duration of ART use on the development of frailty and HAND.

The community advisory committee also recommended that a plain language summary be drafted upon the completion of the thesis for knowledge translation activities as well as for the dissemination of the results to the greater community. Current community advisory committee recommendations for knowledge translation include presentations to community groups as well as publication of a community friendly article in CATIE magazine, publication of results in community health forums, and distribution of plain language summaries throughout community organizations such as Realize Canada and the AIDS Committee of Toronto (ACT).

7.4 Conclusion

The input and guidance of the community advisory committee has been integral to this body of work and has enriched the project from the outset. The combined knowledge and lived experienced of members of the community advisory committee has contributed to a deeper understanding, synthesis, and appreciation of the subject material. Having a community advisory committee involving patient groups helps to make sure that the research is aligned with the goals of the community, strengthens the bond between researchers and the community, increases knowledge synthesis and dissemination, and improves the quality of research and patient care.

REFERENCES

Akgün, K. M., Tate, J. P., Crothers, K., Crystal, S., Leaf, D. A., Womack, J., … Oursler, K. K. (2014). An adapted frailty-related phenotype and the VACS index as predictors of hospitalization and mortality in HIV-infected and uninfected individuals. Journal of Acquired Immune Deficiency Syndromes, 67(4), 397–404. https://doi.org/10.1097/QAI.0000000000000341

Alfahad, T. B., & Nath, A. (2013). Update on HIV-associated neurocognitive disorders topical collection on infection. Current Neurology and Neuroscience Reports, 13(10). https://doi.org/10.1007/s11910-013-0387-7

Althoff, K. N., Jacobson, L. P., Cranston, R. D., Detels, R., Phair, J. P., Li, X., & Margolick, J. B. (2014). Age, comorbidities, and AIDS predict a frailty phenotype in men who have sex with men. Journals of Gerontology - Series A Biological Sciences and Medical Sciences, 69 A(2), 189–198. https://doi.org/10.1093/gerona/glt148

Andersen, P. K., & Gill, R. D. (1982). Cox's regression model for counting processes: a large sample study. The Annals of Statistics, 10(4), 1100–1120. https://doi.org/10.1214/aos/1176348654

Antinori, A., Arendt, G., Grant, I., Letendre, S., & Muñoz-Moreno, J. a. (2013). Assessment, diagnosis and treatment of Human Immunodeficiency Virus (HIV)-associated neurocognitive disorders (HAND): A consensus report of the mind exchange program. *Clinical Infectious Diseases*, *56*, 1004–1017. http://doi.org/10.1093/cid/cis975

Antinori, A., Arendt, G., Becker, N., Brew, B.J., Byrd, D.A., Cherner, M., …Wojna, V.E. (2007). Updated research nosology for HIV-associated neurocognitive disorders. *Neurology*, *69*, 1789–99.

Aquaro, S., Caliò, R., Balzarini, J., Bellocchi, M. C., Garaci, E., & Perno, C. F. (2002). Macrophages and HIV infection: Therapeutical approaches toward this strategic virus reservoir. Antiviral Research, 55(2), 209–225. https://doi.org/10.1016/S0166-3542(02)00052-9

Babor TF, Higgins-Biddle JC, Saunders JB, Monteiro MG. (1992). The Alcohol Use Disorders Identification Test (AUDIT): Guidelines for Use in Primary Health Care. Geneva: World Health Organization.

Benedict R, Schretlen, D., Groninger L, & Barndt J. (1998). Hopkins Verbal Learning Test – Revised: Normative Data and Analysis of Inter- Form and Test-Retest Reliability. The Clinical Neuropsychologist. 12(1): 43-55.

Bourgeois AC, Edmunds M, Awan A, Jonah L, Varsaneux O, Siu W. (2017). HIV in Canada - Surveillance Report, 2016. Canadian Communicable Disease Report, 43(12), 248-56. https://doi.org/10.14745/ccdr.v43i12a01

Brandt, 1991. The Hopkins Verbal Learning Test: Development of a new verbal memory test with six equivalent forms. The Clinical Neuropsychologist, 5, 125-142.

Brothers, T. D., Kirkland, S., Guaraldi, G., Falutz, J., Theou, O., Johnston, B. L., & Rockwood, K. (2014). Frailty in people aging with human immunodeficiency virus (HIV) infection. *The Journal of Infectious Diseases*, *210*(8), 1170–9. doi:10.1093/infdis/jiu258

Brothers, T. D., Kirkland, S., Theou, O., Zona, S., Malagoli, A., Wallace, L. M. K., … Rockwood, K. (2017). Predictors of transitions in frailty severity and mortality among people aging with HIV. PLoS ONE, 12(10), 1–13. https://doi.org/10.1371/journal.pone.0185352

Brothers, T. D., & Rockwood, K. (2014). Biologic aging, frailty, and age-related disease in chronic HIV infection. Current Opinion in HIV and AIDS, 9(4), 412–418. https://doi.org/10.1097/COH.0000000000000070

Brown, T. T., & Glesby, M. J. (2012). Management of the metabolic effects of HIV and HIV drugs. Nature Reviews. Endocrinology, 8(1), 11–21. doi:10.1038/nrendo.2011.151

Burchell, A. N., Raboud, J., Donelle, J., Loutfy, M. R., Rourke, S. B., Rogers, T., … Kendall, C. E. (2019). Cause-specific mortality among HIV-infected people in Ontario, 1995–2014: a population-based retrospective cohort study. CMAJ Open, 7(1), E1–E7. https://doi.org/10.9778/cmajo.20180159

Campbell, L. M., Fennema-notestine, C., Saloner, R., Chen, A., Jr, D. F., Umlauf, A., … Heaton, R.K. (2020). Use of neuroimaging to inform optimal neurocognitive criteria for detecting HIV-associated brain abnormalities. *Journal of the International Neuropsychological* Society, *26*(2), 147–162. https://doi.org/10.1017/S1355617719000985

Carey, C. L., Woods, S. P., Gonzalez, R., Conover, E., Marcotte, T. D., Grant, I., & Heaton, R. K. (2004). Predictive validity of global deficit scores in detecting neuropsychological impairment in HIV infection. *Journal of Clinical and Experimental Neuropsychology*, *26*(3), 307–319. http://doi.org/10.1080/13803390490510031

Carvalhal, A., Gill, M. J., Letendre, S. L., Rachlis, A., Bekele, T., Raboud, J., … Rourke, S. B. (2016). Central nervous system penetration effectiveness of antiretroviral drugs and neuropsychological impairment in the Ontario HIV Treatment Network Cohort Study. Journal of NeuroVirology, 22(3), 349–357. https://doi.org/10.1007/s13365-015-0404-5

Cattie, J. E., Woods, S. P, & Grant, I. 2012. Psychological Evaluations. In H.E. Gendelman, I. Grant, I.P. Everall, H.S. Fox, H.A. Gelbard, S.A. Lipton, & S. Swindells (Eds.), *The Neurology of AIDS (*pp. 810 - 824). New York: Oxford University Press

Centers for Disease Control and Prevention. HIV Surveillance Report, 2018 (Updated); vol. 31. http://www.cdc.gov/hiv/library/reports/hiv-surveillance.html. Published May 2020. Accessed June 11th, 2020.

Chambers, L. a., Wilson, M. G., Rueda, S., Gogolishvili, D., Shi, M. Q., Rourke, S. B., & Team, T. P. A. R. (2014). Evidence informing the intersection of HIV, aging and health: A scoping review. *AIDS and Behavior*, *18*, 661–675. http://doi.org/10.1007/s10461-013-0627-5

Chang, L., Holt, J. L., Yakupov, R., Jiang, C. S., & Ernst, T. (2013). Lower cognitive reserve in the aging human immunodeficiency virus-infected brain. Neurobiology of Aging, 34(4), 1240–1253. https://doi.org/10.1016/j.neurobiolaging.2012.10.012

Chelune, G., Heaton, R., & Lehman, R. (1986). Neuropsychological and Personality Correlates of Patients' Complaints of Disability. Advances in Clinical Neuropsychology Volume, 3; *95-126.*

Ciccarelli, N. (2020). Considerations on nosology for HIV-associated neurocognitive disorders: it is time to update? Infection, 48(1), 37–42. https://doi.org/10.1007/s15010-019-01373-8

Clegg, A., Young, J., Iliff, S., Rikkert, M. O., & Rockwood, K. (2013). Frailty in elderly people, *381*. doi:10.1016/S0140-6736(12)62167-9

Clifford, D. B., & Ances, B. M. (2013). HIV-associated neurocognitive disorder. The Lancet Infectious Diseases. Lancet Publishing Group. https://doi.org/10.1016/S1473-3099(13)70269-X

Clinical Laboratory Tests Normal Values (2017). In *The Medical Council of Canada*. Retrieved from https://mcc.ca/objectives/normal-values/

Cohen, R. a, Seider, T. R., & Navia, B. (2015). HIV effects on age-associated neurocognitive dysfunction: premature cognitive aging or neurodegenerative disease? *Alzheimer's Research & Therapy*, *7*(1), 1–10. http://doi.org/10.1186/s13195-015-0123-4

Craig, B. a., & Sendi, P. P. (2002). Estimation of the transition matrix of a discrete-time Markov chain. *Health Economics*, *11*(June 2000), 33–42. http://doi.org/10.1002/hec.654

Crum-Cianflone, N. F., Moore, D. J., Letendre, S., Eberly, L., Weintrob, A., Johnson, E., … Hale, B. R. (2013). Low prevalence of neurocognitive impairment in early diagnosed and managed HIV-infected persons, 371–379. https://doi.org/10.1212/WNL.0b013e31827f0776

Deeks, S. G. (2011). HIV infection, inflammation, immunosenescence, and aging. *Annual Review of Medicine*, *62*, 141–55. doi:10.1146/annurev-med-042909-093756

Desai, S., & Landay, A. (2010). Early immune senescence in HIV disease. *Current HIV/AIDS Reports*, *7*(1), 4–10. doi:10.1007/s11904-009-0038-4

Ding, Y., Lin, H., Liu, X., Wong, F. Y., Sun, Y. V., Marconi, V. C., & He, N. (2017). Higher prevalence of frailty among a sample of HIV-infected middle-aged and Older Chinese adults is associated with neurocognitive impairment and depressive symptoms. Journal of Infectious Diseases, 215(5), 687–692. https://doi.org/10.1093/infdis/jix032

Dupont, M., & Sattentau, Q. J. (2020). Macrophage cell-cell interactions promoting HIV-1 infection. Viruses, 12(5), 1–17. https://doi.org/10.3390/v12050492

Durvasula, R. S., Miller, E. N., Myers, H. F., & Wyatt, G. E. (2001). Predictors of neuropsychological performance in HIV positive women. *Journal of Clinical and Experimental Neuropsychology*, *23*(2), 149–63. http://doi.org/10.1076/jcen.23.2.149.1211

Edelman, E. J., Gordon, K. S., Glover, J., McNicholl, I. R., Fiellin, D. A., & Justice, A. C. (2013). The next therapeutic challenge in HIV: Polypharmacy. Drugs and Aging, 30(8), 613–628. https://doi.org/10.1007/s40266-013-0093-9

Erlandson, K. M., Perez, J., Abdo, M., Robertson, K., Ellis, R. J., Koletar, S. L., … Tassiopoulos, K. (2019). Frailty, neurocognitive impairment, or both in predicting poor health outcomes among adults living with human immunodeficiency virus. Clinical Infectious Diseases, 68(1), 131–138. https://doi.org/10.1093/cid/ciy430

Escota, G. V., Patel, P., Brooks, J. T., Bush, T., Conley, L., Baker, J., … Önen, N. F. (2015). Short Communication: The Veterans Aging Cohort Study Index Is an Effective Tool to Assess Baseline Frailty Status in a Contemporary Cohort of HIV-Infected Persons. AIDS Research and Human Retroviruses, 31(3), 313–317. https://doi.org/10.1089/aid.2014.0225

Formby, J. P., Smith, W. J., & Zheng, B. (2004). Mobility measurement, transition matrices and statistical inference. Journal of Econometrics, 120(1), 181–205. https://doi.org/10.1016/S0304-4076(03)00211-2

Franconi, I., Theou, O., Wallace, L., Malagoli, A., Mussini, C., Rockwood, K., & Guaraldi, G. (2018). Construct validation of a Frailty Index, an HIV Index and a Protective Index from a clinical HIV database. PLoS ONE, 13(10), 1–15. https://doi.org/10.1371/journal.pone.0201394

Fried, L. P., Tangen, C. M., Walston, J., Newman, A. B., Hirsch, C., Gottdiener, J., … McBurnie, M. A. (2001). Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci*, *56*(3), M146–56. http://doi.org/10.1093/gerona/56.3.M146

Fukui, S. M., Piggott, D. A., & Erlandson, K. M. (2018). Inflammation Strikes Again: Frailty and HIV. Current HIV/AIDS Reports, 15(1), 20–29. https://doi.org/10.1007/s11904-018-0372-5

Geweke, J., Marshall, R. C., & Zarkin, G. A. (2006). Mobility Indices in Continuous Time Markov Chains. Econometrica, 54(6), 1407. https://doi.org/10.2307/1914306

Goulet, J. L., Fultz, S. L., Rimland, D., Butt, A., Gibert, C., Rodriguez-Barradas, M., … Justice, A. C. (2007). Do Patterns of Comorbidity Vary by HIV Status, Age, and HIV Severity? *Clinical Infectious Diseases*, *45*(12), 1593–1601. http://doi.org/10.1086/523577

Grant, I., Franklin, D. R., Deutsch, R., Woods, S. P., Vaida, F., Ellis, R. J., … Heaton, R. K. (2014). Asymptomatic HIV-associated neurocognitive impairment increases risk for symptomatic decline. Neurology, 82(23), 2055–2062. https://doi.org/10.1212/WNL.0000000000000492

Grant, I. & Sacktor, N. (2012). HIV-Associated Neurocognitive Disorders. In H.E. Gendelman, I. Grant, I.P. Everall, H.S. Fox, H.A. Gelbard, S.A. Lipton, & S. Swindells (Eds.), *The Neurology of AIDS (*pp. 490 - 503). New York: Oxford University Press

Greene, M., Covinsky, K., Astemborski, J., Piggott, D. A., Brown, T., Leng, S., … Carmel, M. (2014). HHS Public Access. Aids, 28(18), 2711–2719. https://doi.org/10.1097/QAI.0000000000000556.Geriatric

Guaraldi, G., Brothers, T. D., Zona, S., Stentarelli, C., Carli, F., Malagoli, A., … Rockwood, K. (2015). A frailty index predicts survival and incident multimorbidity independent of markers of HIV disease severity. Aids, 29(13), 1633–1641. https://doi.org/10.1097/QAD.0000000000000753

Guaraldi, G., Orlando, G., Zona, S., Menozzi, M., Carli, F., Garlassi, E., … Palella, F. (2011). Premature age-related comorbidities among HIV-infected persons compared with the general population. Clinical Infectious Diseases, 53(11), 1120–1126. https://doi.org/10.1093/cid/cir627

Guaraldi, G., Silva, A. R., & Stentarelli, C. (2014). Multimorbidity and functional status assessment. *Current Opinion in HIV and AIDS*, *9*(4), 386–397. http://doi.org/10.1097/COH.0000000000000079

Guaraldi, G., Malagoli, A., Theou, O., Brothers, T. D., Wallace, L. M. K., Torelli, R., … Rockwood, K. (2017). Correlates of frailty phenotype and frailty index and their associations with clinical outcomes. HIV Medicine, 18(10), 764–771. https://doi.org/10.1111/hiv.12527

Gustafson, D. R., Shi, Q., Thurn, M., Holman, S., Minkoff, H., Cohen, M., … Hoover, D. (2016). Frailty and Constellations of Factors in Aging HIV-infected and Uninfected Women--The Women's Interagency HIV Study. The Journal of Frailty & Aging, 5(1), 43–48. https://doi.org/10.14283/jfa.2016.79

Haddad, N., Li, J., Totten, S., & McGuire, M. (2018). HIV in Canada—Surveillance Report, 2017. Canada Communicable Disease Report, 44(12), 324–332. https://doi.org/10.14745/ccdr.v44i12a03

Haddad, N., Robert, A., Weeks, A., Popovic, N., Siu, W., & Archibald, C. (2019). HIV in Canada—Surveillance Report, 2018. Canada Communicable Disease Report, 45(12), 304–312. https://doi.org/10.14745/ccdr.v45i12a01

Hasse, B., Ledergerber, B., Furrer, H., Battegay, M., Hirschel, B., Cavassini, M., … Weber, R. (2011). Morbidity and aging in HIV-infected persons: The swiss HIV cohort study. *Clinical Infectious Diseases*, *53*(11), 1130–1139. http://doi.org/10.1093/cid/cir62

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*, 2087–2096. 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. https://doi.org/10.1007/s13365-010-0006-1

Heaton R. K., Miller S. W., Taylor M. J., Grant I (2004). Revised Comprehensive Norms for an Expanded Halstead-Reitan Battery: Demographically Adjusted Neuropsychological Norms for African American and Caucasian Adults. Lutz, FL.: Psychological Assessment Resources.

Heaton, R. K., Taylor M. J., Manly J. J. (2002).Demographic effects and use of demographically corrected norms with the WAIS-III and WMS-III. In: Tulsky D, Saklofske D, Heaton RK, et al., eds. Clinical Interpretation of the WAIS-III and WMS-III. San Diego, CA: Academic Press.

Hellmuth, J., Milanini, B., & Valcour, V. (2014). Interactions between ageing and NeuroAIDS. *Current Opinion in HIV and AIDS*, *9*(6), 527–32. doi:10.1097/COH.0000000000000104

Holt, J. L., Kraft-Terry, S. D., & Chang, L. (2012). Neuroimaging studies of the aging HIV-1-infected brain. Journal of NeuroVirology, 18(4), 291–302. https://doi.org/10.1007/s13365-012-0114-1

Horvath, S., & Levine, A. J. (2015). HIV-1 infection accelerates age according to the epigenetic clock. Journal of Infectious Diseases, 212(10), 1563–1573. https://doi.org/10.1093/infdis/jiv277

Hosaka, K. R. J., Greene, M., Premeaux, T. A., Javandel, S., Allen, I. E., Ndhlovu, L. C., & Valcour, V. (2019). Geriatric Syndromes in Older Adults Living with HIV and Cognitive Impairment. Journal of the American Geriatrics Society, 67(9), 1913–1916. https://doi.org/10.1111/jgs.16034

Howlett, S. E. (2015). Assessment of Frailty in Animal Models. Interdisciplinary Topics in Gerontology and Geriatrics, 41, 15–25. https://doi.org/10.1159/000381131

Justice, A. C. (2010). HIV and aging: Time for a new paradigm. *Current HIV/AIDS Reports*, *7*(2), 69–76. http://doi.org/10.1007/s11904-010-0041-9

Justice, A. C., Freiberg, M. S., Tracy, R., Kuller, L., Tate, J. P., Goetz, M. B., … Bryant, K. (2012). Does an index composed of clinical data reflect effects of inflammation, coagulation, and monocyte activation on mortality among those aging with HIV? *Clinical Infectious Diseases*, *54*(7), 984–994. http://doi.org/10.1093/cid/cir989

Justice, A. C., Modur, S. P., Tate, J. P., Althoff, K. N., Jacobson, L. P., Gebo, K. A., … Teams, V. P. (2013). Predictive Accuracy of the Veterans Aging Cohort Study Index for Mortality With HIV Infection : A North American Cross Cohort Analysis, *62*(2), 149–163.

Kallianpur, K. J., Sakoda, M., Gangcuangco, L. M. A., Ndhlovu, L. C., Umaki, T., Chow, D., … Shikuma, C. M. (2016). Frailty Characteristics in Chronic HIV Patients are Markers of White Matter Atrophy Independently of Age and Depressive Symptoms: A Pilot Study. Open Medicine Journal, 3(1), 138–152. https://doi.org/10.2174/1874220301603010138

Kane, A. E., Hilmer, S. N., Boyer, D., Gavin, K., Nines, D., Howlett, S. E., … Mitchell, S. J. (2016). Impact of Longevity Interventions on a Validated Mouse Clinical Frailty Index. Journals of Gerontology - Series A Biological Sciences and Medical Sciences, 71(3), 333–339. https://doi.org/10.1093/gerona/glu315

Kane, A. E., Hilmer, S. N., Mach, J., Mitchell, S. J., de Cabo, R., & Howlett, S. E. (2016). Animal models of frailty: Current applications in clinical research. Clinical Interventions in Aging, 11, 1519–1529. https://doi.org/10.2147/CIA.S105714

Kaul, M., Garden, G. A., & Lipton, S. A. (2001). Pathways to neuronal injury and apoptosis in HIV-associated dementia. Nature, 410(6831), 988–994. https://doi.org/10.1038/35073667

Kendall, C. E., Wong, J., Taljaard, M., Glazier, R. H., Hogg, W., Younger, J., & Manuel, D. G. (2014). A cross-sectional, population-based study measuring comorbidity among people living with HIV in Ontario. BMC Public Health, 14(1), 1–9. https://doi.org/
10.1186/1471-2458-14-161

Levett, T. J., Cresswell, F. V., Malik, M. A., Fisher, M., & Wright, J. (2016). Systematic Review of Prevalence and Predictors of Frailty in Individuals with Human Immunodeficiency Virus. Journal of the American Geriatrics Society, 64(5), 1006–1014. https://doi.org/10.1111/jgs.14101

Levine, A. J., Quach, A., Moore, D. J., Achim, C. L., Soontornniyomkij, V., Masliah, E., … Horvath, S. (2016). Accelerated epigenetic aging in brain is associated with pre-mortem HIV-associated neurocognitive disorders. Journal of NeuroVirology, 22(3), 366–375. https://doi.org/10.1007/s13365-015-0406-3

Lezak, M. (1995). Neuropsychological Assessment, 3rd Edition. Oxford University Press, London.

Liboro, R. M., Rourke, S. B., Ibañez-Carrasco, F., Eaton, A., Pugh, D., Medina, C., … Ross, L. E. (2019). Strategies Employed by Community-Based Service Providers to Address HIV-Associated Neurocognitive Challenges: A Qualitative Study. Journal of the International Association of Providers of AIDS Care, 18, 1–8. https://doi.org/10.1177/2325958218822336

Mapstone, M., Hilton, T.N., Yang, H., Guido, J.J., Luque, A.E., Hall, W.J., … Shah, K. (2013). Poor Aerobic Fitness May Contribute to Cognitive Decline in HIV-infected Older Adults. Aging and Disease, 4(6), 311–319. https://doi.org/
10.14336/AD.2013.0400311

Marquine, M. J., Umlauf, A., Rooney, A. S., Fazeli, P. L., Gouaux, B. D., Paul Woods, S., … Moore, D. J. (2014). The veterans aging cohort study index is associated with concurrent risk for neurocognitive impairment. *J Acquir Immune Defic Syndr*, *65*(2), 190–197. http://doi.org/10.1097/qai.0000000000000008

Matthews, C., and Klove, H. (1964). Instruction manual for the Adult Neuropsychology Test Battery. University of Wisconsin Medical School, Madison, WI.

Meyer, A. C. L., John Boscardin, W., Kwasa, J. K., & Price, R. W. (2013). Is it time to rethink how neuropsychological tests are used to diagnose mild forms of HIV-associated neurocognitive disorders? Impact of false-positive rates on prevalence and power. Neuroepidemiology, 41(3–4), 208–216. https://doi.org/10.1159/000354629

Mitnitski, a B., Mogilner, a J., & Rockwood, K. (2001). Accumulation of deficits as a proxy measure of aging. *The Scientific World Journal*, *1*, 323–336. http://doi.org/10.1100/tsw.2001.58

Mitnitski, A., Song, X., Skoog, I., Broe, G. A., Cox, J. L., Grunfeld, E., & Rockwood, K. (2005). Relative fitness and frailty of elderly men and women in developed countries and their relationship with mortality. Journal of the American Geriatrics Society, 53(12), 2184–2189. https://doi.org/10.1111/j.1532-5415.2005.00506.x

Morgan, E. E., Woods, S. P., Delano-Wood, L., Bondi, M. W., & Grant, I. (2011). Intraindividual variability in HIV infection: evidence for greater neurocognitive dispersion in older HIV seropositive adults. *Neuropsychology*, *25*(5), 645–54. doi:10.1037/a0023792

Morgello, S., Gensler, G., Sherman, S., Ellis, R. J., Gelman, B. B., Kolson, D. L., … Valdes-Sueiras, M. (2019). Frailty in medically complex individuals with chronic HIV. Aids, 33(10), 1603–1611. https://doi.org/10.1097/QAD.0000000000002250

Moulignier, A., Savatovsky, J., Assoumou, L., Lescure, F. X., Lamirel, C., Godin, O., … Vincensini, J. P. (2018). Silent Cerebral Small-Vessel Disease Is Twice as Prevalent in Middle-Aged Individuals with Well-Controlled, Combination Antiretroviral Therapy-Treated Human Immunodeficiency Virus (HIV) Than in HIV-Uninfected Individuals. Clinical Infectious Diseases, 66(11), 1762–1769. https://doi.org/10.1093/cid/cix1075

Muñoz-Moreno, J. A., Fumaz, C. R., Ferrer, M. J., Prats, A., Negredo, E., Garolera, M., … Clotet, B. (2008). Nadir CD4 Cell Count Predicts Neurocognitive Impairment in HIV-Infected Patients. AIDS Research and Human Retroviruses, 24(10), 1301–1307. https://doi.org/10.1089/aid.2007.0310

Nebuloni, M., Pellegrinelli, A., Ferri, A., Tosoni, A., Bonetto, S., Zerbi, P., … Costanzi, G. (2000). Etiology of microglial nodules in brains of patients with acquired immunodeficiency syndrome. Journal of NeuroVirology, 6(1), 46–50. https://doi.org/10.3109/13550280009006381

Nightingale, S., Winston, A., Letendre, S., Michael, B. D., McArthur, J. C., Khoo, S., & Solomon, T. (2014). Controversies in HIV-associated neurocognitive disorders. *The Lancet. Neurology*, *13*(11), 1139–51. doi:10.1016/S1474-4422(14)70137-1

Norman M.A., Moore D.J., Taylor M., Franklin D., Cysique L., Ake C., et al. (2011). Demographically corrected norms for African Americans and Caucasians on the Hopkins Verbal Learning Test- Revised, Brief Visuospatial Memory Test-Revised, Stroop Color and Word Test, and Wisconsin Card Sorting Test 64-Card Version. Journal of Clinical And Experimental Neuropsychology, 33(7), 793-804.

Oppenheim, H., Paolillo, E. W., Moore, R. C., Ellis, R. J., Letendre, S. L., … Moore, D. J. (2018). Neurocognitive functioning predicts frailty index in HIV. Neurology, 91(2), e162–e170. https://doi.org/10.1212/wnl.0000000000005761

Orlando, G., Meraviglia, P., Cordier, L., Meroni, L., Landonio, S., Giorgi, R., … Cargnel, A. (2006). Antiretroviral treatment and age-related comorbidities in a cohort of older HIV-infected patients. *HIV Medicine*, *7*(8), 549–57. doi:10.1111/j.1468-1293.2006.00420.x

Ontario HIV Treatment Network (OHTN) (2020). *Our values*. Retrieved from the OHTN website: http://www.ohtn.on.ca/our-values/

Ontario HIV Treatment Network (OHTN) (2020). *The greater involvement of people living with HIV (GIPA)*. Retrieved from the OHTN website: http://www.ohtn.on.ca/about/gipa-2/

Paolillo, E. W., Saloner, R., Montoya, J. L., Campbell, L. M., Pasipanodya, E. C., Iudicello, J. E., … Moore, D. J. (2019). Frailty in comorbid HIV and lifetime methamphetamine use disorder: Associations with neurocognitive and everyday functioning. AIDS Research and Human Retroviruses, 35(11–12), 1044–1053. https://doi.org/10.1089/aid.2019.0062

Parks, R. J., Fares, E., MacDonald, J. K., Ernst, M. C., Sinal, C. J., Rockwood, K., & Howlett, S. E. (2012). A procedure for creating a frailty index based on deficit accumulation in aging mice. Journals of Gerontology - Series A Biological Sciences and Medical Sciences, 67 A(3), 217–227. https://doi.org/10.1093/gerona/glr193

Pathai, S., Bajillan, H., Landay, A. L., & High, K. P. (2014). Is HIV a model of accelerated or accentuated aging? Journals of Gerontology - Series A Biological Sciences and Medical Sciences, 69(7), 833–842. https://doi.org/10.1093/gerona/glt168

Paul, R. H., Cooley, S. A., Garcia-Egan, P. M., & Ances, B. M. (2018). Cognitive performance and frailty in older HIV-positive adults. Journal of Acquired Immune Deficiency Syndromes. https://doi.org/10.1097/QAI.0000000000001790

Public Health Agency of Canada. (2018). Summary: Estimates of HIV Incidence, Prevalence and Canada's Progress on Meeting the 90-90-90 HIV Targets, 2016. HIV Surveillance Supplemental Report. Retrieved from https://www.canada.ca/content/dam/phac-aspc/documents/services/publications/diseases-conditions/summary-estimates-hiv-incidence-prevalence-canadas-progress-90-90-90/pub-eng.pdf

Porta, M. (Ed.). (2014). *A Dictionary of Epidemiology* (6th ed.). New York, NY: International Epidemiological Association.

Price, R. W., & Brew, B. J. (1988). The AIDS Dementia Complex. Journal of Infectious Diseases, 158(5), 1079–1083. https://doi.org/10.1093/infdis/158.5.1079

Radloff, L. (1977). The CES-D scale a self-report depression scale for research in the general population. *Applied Psychological Measurement*. http://doi.org/10.1177/014662167700100306

Rueda, S., Law, S., & Rourke, S. B. (2014). Psychosocial, mental health, and behavioral issues of aging with HIV. Current Opinion in HIV and AIDS, 9(4), 325–331. https://doi.org/10.1097/COH.0000000000000071

Rockwood, K., & Mitnitski, A. (2011). Frailty Defined by Deficit Accumulation and Geriatric Medicine Defined by Frailty. Clinics in Geriatric Medicine, 27(1), 17–26. https://doi.org/10.1016/j.cger.2010.08.008

Rourke, S. B., Gardner, S., Burchell, A. N., Raboud, J., Rueda, S., Bayoumi, A. M., … Rachlis, A. (2013). Cohort Profile: The Ontario HIV Treatment Network Cohort Study (OCS). *International Journal of Epidemiology*, *42*(2), 402–11. http://doi.org/10.1093/ije/dyr230

Rourke, S. B., Gill, J., Rachlis, A., Justice, A., Kovacs, C., Arbess, G., …Burchell, A.N. (2015, May). *The Veterans Aging Cohort Study Index predicts change in neurocognitive functions in people with HIV.* Poster presented at the 23rd Annual Canadian Conference on HIV/AIDS Research, Toronto, On.

Rourke, S. B., Gill, J., Rachlis, A., Kovacs, C., Arbess, G., Brunetta, J., … Marcotte, T. (2015). Asymptomatic Neurocognitive Impairment (ANI) is associated with Progression to Symptomatic HIV-associated Neurocognitive Disorders (HAND) in People with HIV : Results from the Ontario HIV Treatment Network (OHTN) Cohort Study. CAHR 2015 Abstract.

Sacktor, N., McDermott, M. P., Marder, K., Schifitto, G., Selnes, O. A., McArthur, J. C., … Epstein, L. (2002). HIV-associated cognitive impairment before and after the advent of combination therapy. Journal of NeuroVirology, 8(2), 136–142. https://doi.org/10.1080/13550280290049615

Sacktor, N., Skolasky, R. L., Seaberg, E., Munro, C., Becker, J. T., Martin, E., … Miller, E. (2016). Prevalence of HIV-associated neurocognitive disorders in the Multicenter AIDS Cohort Study. Neurology, 86(4), 334–340. https://doi.org/10.1212/WNL.0000000000002277

Saylor, D., & Sacktor, N. (2016). Cognitive Impairment Among Older Individuals with HIV Infection. Current Geriatrics Reports, 5(2), 63–70. https://doi.org/10.1007/s13670-016-0165-x

Searle, S. D., Mitnitski, A., Gahbauer, E. a, Gill, T. M., & Rockwood, K. (2008). A standard procedure for creating a frailty index. *BMC Geriatrics*, *8*, 24. http://doi.org/10.1186/1471-2318-8-24

Seider, T. R., Luo, X., Gongvatana, A., Devlin, K. N., De La Monte, S. M., Chasman, J. D., … Cohen, R. A. (2014). Verbal memory declines more rapidly with age in HIV infected versus uninfected adults. *Journal of Clinical and Experimental Neuropsychology*, *36*(4), 356–367. http://doi.org/10.1080/13803395.2014.892061

Song, X., Mitnitski, A., & Rockwood, K. (2010). Prevalence and 10-Year outcomes of frailty in older adults in relation to deficit accumulation. Journal of the American Geriatrics Society, 58(4), 681–687. https://doi.org/10.1111/j.1532-5415.2010.02764.x

Stewart AL, Ware JE, Sherbourne CD, Wells KB. (1992). Psychological distress/well-being and cognitive functioning measures. In: Stewart AL, Ware JE, eds. Measuring Functioning and Well-Being: The Medical Outcomes Study Approach. Durham, NC: Duke University, 1992: 102–142.

Tai, S.C., Wu, Y.G., Huang, L.S. (2000). Markov system for image vector quantization coding. Optical Engineering, 39(5), 1338. https://doi.org/10.1117/1.602501

Theou, O., Brothers, T. D., Peña, F. G., Mitnitski, A., & Rockwood, K. (2014). Identifying common characteristics of frailty across seven scales. Journal of the American Geriatrics Society, 62(5), 901–906. https://doi.org/10.1111/jgs.12773

Theou, O., Cann, L., Blodgett, J., Wallace, L. M. K., Brothers, T. D., & Rockwood, K. (2015). Modifications to the frailty phenotype criteria: Systematic review of the current literature and investigation of 262 frailty phenotypes in the survey of health, ageing, and retirement in Europe. Ageing Research Reviews, 21, 78–94. https://doi.org/10.1016/j.arr.2015.04.001

Thurn, M., & Gustafson, D. R. (2017). Faces of Frailty in Aging with HIV Infection. Current HIV/AIDS Reports, 14(1), 31–37. https://doi.org/10.1007/s11904-017-0348-x

Trede, M. (1999). Statistical Inference for Measures of Income Mobility / Statistische Inferenz zur Messung der Einkommensmobilität. Jahrbücher Für Nationalökonomie Und Statistik, 218(3–4), 473–490. https://doi.org/10.1515/jbnst-1999-3-413

Valcour, V. G. (2013). HIV, aging, and cognition: emerging issues. Topics in Antiviral Medicine, 21(3), 119–123. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/23981600

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(Suppl 1), S79-86. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/15075502

Valderas, J. M., Sibbald, B., & Salisbury, C. (2009). Defi ning Comorbidity: Implications for Understanding Health and Health Services. *Annals Of Family Medicine*, (7), 357–363. http://doi.org/10.1370/afm.983.Martin

Vance, D. E., Fazeli, P. L., Grant, J. S., Slater, L. Z., & Raper, J. L. (2013). The role of neuroplasticity and cognitive reserve in aging with HIV: Recommendations for cognitive protection and rehabilitation. Journal of Neuroscience Nursing, 45(5), 306–316. https://doi.org/10.1097/JNN.0b013e31829d8b29

Wallace, L. M. K., Ferrara, M., Brothers, T. D., Garlassi, S., Kirkland, S. A., Theou, O., … Guaraldi, G. (2017). Lower Frailty Is Associated with Successful Cognitive Aging Among Older Adults with HIV. AIDS Research and Human Retroviruses, 33(2), 157–163. https://doi.org/10.1089/aid.2016.0189

Ware, D., Palella, F. J., Chew, K. W., Friedman, M. R., Souza, G. D., Ho, K., & Plankey, M. (2018). Prevalence and trends of polypharmacy among HIV-positive and -negative men in the Multicenter AIDS Cohort Study from 2004 to 2016, 1–14. https://doi.org/10.1371/journal.pone.0203890

Wechsler, D. (1981). WAIS-R Manual. Wechsler Adult Intelligence Scale-Revised. The Psychological Corporation, San Antonio.

Wechsler, D. (1997). WMS-III Administration and Scoring Manual. The Psychological Corporation, San Antonio.

Wendelken, L. A., & Valcour, V. (2012). Impact of HIV and aging on neuropsychological function. Journal of NeuroVirology, 18(4), 256–263. https://doi.org/10.1007/s13365-012-0094-1

Wing, E. J. (2016). HIV and aging. International Journal of Infectious Diseases, 53, 61–68. https://doi.org/10.1016/j.ijid.2016.10.004

Wong, C., Gange, S. J., Moore, R. D., Justice, A. C., Buchacz, K., Abraham, A. G., … Sterling, T. R. (2018). Multimorbidity among Persons Living with Human Immunodeficiency Virus in the United States. Clinical Infectious Diseases, 66(8), 1230–1238. https://doi.org/10.1093/cid/cix998

Zamudio-Rodríguez, A., Belaunzaran-Zamudio, P. F., Sierra-Madero, J., Cuellar-Rodríguez, J. M., Crabtree-Ramírez, B., Alcalá-Zermeno, J. L., … Avila-Funes, J. A. (2018). Association between Frailty and HIV-Associated Neurodegenerative Disorders among Older Adults Living with HIV. AIDS Research and Human Retroviruses, 34(5), AID. 2017.0100. https://doi.org/10.1089/AID.2017.0100

Appendix A: OCS Brief Neuropsychological Test Battery

Descriptions provided by the OCS team.

WMS-III Spatial Span

Spatial working memory

Brief Neuropsychological Test Battery

The Spatial Span test (Weschler, 1997; Available from The Psychological Corporation) is a measure of working memory for visual-spatial information. In this test, the subject is confronted with a white board on which ten blue blocks are affixed. The examiner taps the blocks in a pre-arranged sequence, and the participant is asked to repeat the sequence by tapping the same blocks in the same order (spatial span forward) or the reverse order (spatial span backwards). The score is the sum of correctly repeated sequences (both forward and backward). The Spatial Span test takes approximately 5-10 minutes.

WAIS-R Digit Symbol

Complex psychomotor speed

The Digit Symbol Test (Weschler, 1981; Available from The Psychological Corporation) is a measure of psychomotor speed. The participant is presented with a key pairing numbers from one to nine with nine different symbols. The participant's task is to write the corresponding symbols below the numbers as quickly as possible. The score is the number of symbols correctly written within the time limit (90 seconds). This test takes 2 minutes to administer.

Hopkins Verbal Learning Test (HVLT)

Verbal working memory

The HVLT (Brandt, 1991; Available from PAR Inc) assesses verbal learning and memory (immediate recall, delayed recall, and delayed recognition). In this test, the examiner

reads a list of 12 words, which consist of three sets of four semantically categorized groups. Each time the examiner reads the list, the participant is asked recall as many of the words as possible, and the examiner records the responses. This reading and recall of the same word list is repeated for a total of three trials. Twenty to 25 minutes after the third learning trial, the examiner asks the participant to recall the word list again, recording the responses. The free recall is followed by a 24-word recognition list containing all twelve target words, plus six semantically related foils and six unrelated ones (Lezak, 1995, p 448). T-scores are calculated for: Total score for three learning trials; Delayed recall total; recognition; and discriminability. Test administration takes approximately 5-10 minutes for the learning trial portion, 20-25 minutes for the delay interval, and 3-5 minutes for the delayed recall and recognition portion.

Grooved Pegboard

Fine motor dexterity

The Grooved Pegboard (Matthews & Klove, 1963; Available from Lafayette Instruments) consists of a small board containing a 5x5 grid of slotted holes, angled in different directions, and a set of identical pegs. Each peg has a ridge along one side, requiring it to be rotated into position for correct insertion. The task, filling all 25 holes, is timed by the examiner. The score is the time to completion in seconds. Both hands are usually tested, beginning with the dominant hand. The test's complexity makes it a sensitive instrument for measuring speed of processing, and for detecting slowing due to medication, disease progression (including HIV-disease progression) and brain injury (Lezak, 1995, pp 683-684.) This test takes approximately 2-6 minutes for a participant to complete both hands.

Center for Epidemiologic Studies – Depression (CES-D) Scale

Depressive symptoms

The CES-D Scale consists of 20 items assessing the frequency of depressive symptoms over the past week. The scale reflects six major dimensions: depressed mood, feelings of guilt and worthlessness, feelings of helplessness and hopelessness, psychomotor retardation, loss of appetite, and sleep disturbance. Although usually self- administered, it can also be administered as a structured interview. Item scores are summed to create an overall score ranging from 0 to 60, with scores of 16 or more regarded as indicative of depression. This test takes approximately 5 minutes.

Appendix B. Medical Outcomes Study Cognitive Functioning Scale (MOS-COG)

How much of the time, during the **past 4 week**…*Read response options.*	All of the time (1)	Most of the time (2)	A good bit of the time (3)	Some of the time (4)	A little of the time (5)	None of the time (6)	Don't know (88)	Refused (99)
a) Did you have difficulty reasoning and solving problems, for example, making plans, making decisions, learning new things?	☐	☐	☐	☐	☐	☐	☐	☐
b) Did you forget things that happened recently, for example, where you put things and when you had appointments?	☐	☐	☐	☐	☐	☐	☐	☐
c) Did you have trouble keeping your attention on any activity for long?	☐	☐	☐	☐	☐	☐	☐	☐
d) Did you have difficulty doing activities involving concentration and thinking?	☐	☐	☐	☐	☐	☐	☐	☐

Note. Adapted from Ontario HIV Treatment Network (OHTN) Cohort Study (OCS) Extended Questionnaire, updated November 8th, 2013.

Appendix C: Assessing Frailty Continuously

The multivariate model when assessing frailty continuously indicates that increasing frailty, increasing age, and female sex are again significantly associated with an increased risk of HAND (Table C1).

Table C1. *Multivariate Cox Proportional Hazard Ratios for the Development of HAND According to Baseline Frailty Score - 60 Item Frailty Index*

	Hazard Ratio	95% CI	p-value
FI Score	1.16	[1.04 - 1.30]	**0.010**
Age	1.01	[1.00 - 1.02]	**0.018**
Sex (referent: female)	0.60	[0.47 - 0.78]	**<0.001**

Note. n = 3 participants had missing data for either cigarette history, cannabis history, or recreational drug use. The multivariate analysis therefore includes n=517 participants.

When stratified by sex, the multivariate analysis when assessing frailty continuously again demonstrated that increasing frailty and age is associated with an increased risk of developing HAND in males (Table C2). A separate multivariate analysis demonstrated that only harmful alcohol use was significantly associated with decreased HAND development in females (Table C2).

Table C2. *Multivariate Cox Proportional Hazard Ratios for the Development of HAND According to Baseline Frailty Score by Sex - 60 Item Frailty Index*

	Males (n=422)			Females (n=95)		
	Hazard Ratio	95% CI	p-value			
FI Score (continuous)	1.29	[1.13 - 1.46]	**<0.001**	-	-	-
Age	1.02	[1.01 - 1.03]	**0.002**	-	-	-
Harmful Alcohol Use	-	-	-	0.40	[0.16 - 1.00]	**0.050**

Note. n = 3 participants had missing data for either cigarette history, cannabis history, or recreational drug use. The multivariate analysis for male participants therefore includes n=422 participants, and the multivariate analysis for females includes n=95 participants.

Multivariate analysis of the 39-item frailty index by continuous frailty score demonstrates that increasing frailty and HIV duration were associated with an increased risk of HAND, while ART status and wasting syndrome were both associated with a decreased risk of HAND development (Table C3).

Table C3. *Multivariate Cox Proportional Hazard Ratios for the Development of HAND According to Baseline Frailty Score - 39 Item Frailty Index*

	39-Item Frailty Index		
	Hazard Ratio	95% CI	p-value
FI Score (Continuous)	1.09	[1.01 - 1.18]	**0.023**
Sex (referent: female)	0.62	[0.48 - 0.80]	**<0.001**
Duration of HIV	1.30	[1.04 - 1.63]	**0.022**
ART Status (referent: on ART)	0.43	[0.24 - 0.80]	**0.007**
Wasting Syndrome Due to HIV	0.28	[0.10 - 0.74]	**0.011**

Multivariate analysis by sex for the 39-item frailty index demonstrates an increased risk of HAND development with increasing frailty and increasing age in males, while a separate multivariate analysis demonstrated that this association is not seen in females (Table C4).

Table C4. *Multivariate Cox Proportional Hazard Ratios for the Development of HAND According to Baseline Frailty Score by Sex - 39 Item Frailty Index*

	Males (n=422)			Females (n=95)		
	Hazard Ratio	95% CI	p-value			
FI Score (continuous)	1.19	[1.09 - 1.30]	**<0.001**	-	-	-
Age	1.02	[1.01 - 1.03]	**0.004**	-	-	-
Harmful Alcohol	-	-	**-**	0.40	[0.16 - 0.98]	**0.046**
ART Status (referent: on ART)	0.52	[0.26 - 1.03]	**0.060**	0.23	[0.06 - 0.94]	**0.041**

	Males (n=422)			Females (n=95)		
	Hazard Ratio	95% CI	p-value			
Wasting Syndrome Due to HIV	0.32	[0.12 - 0.87]	**0.025**	-	-	-