UNIVERSITY OF CALGARY

Frailty in older adults (≥50 years) living with Human Immunodeficiency Virus (HIV)

by

Jacqueline M. McMillan

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE

DEGREE OF MASTER OF SCIENCE

GRADUATE PROGRAM IN COMMUNITY HEALTH SCIENCES

CALGARY, ALBERTA

JULY, 2018

Abstract

Antiretroviral therapy (ART) has increased the life expectancy of persons living with HIV/AIDS (PLWHA). Fifty percent of PLWHA are ≥ 50 years of age, and age-related comorbidities are an increasing concern. The prevalence of frailty in HIV is greater than in age-matched controls. We investigated a cohort of older (≥ 50 years) PLWHA at the Southern Alberta Clinic (SAC) in Calgary, Alberta, and screened for frailty. Patients were screened using three frailty measures: a Modified Frailty Phenotype, Clinical Frailty Scale and the Frailty Index. Patients identified as frail were offered a Comprehensive Geriatric Assessment performed by a Geriatrician and the results were shared with the HIV provider and the family physician. Over three hundred patients were screened using the MFP and CFS, and over 700 patients had a FI calculated. Frailty was associated with duration of ART, but not with known duration of HIV infection, CD4 cell count, viral load, or age.

Preface

This thesis is original, unpublished, independent work by the author, McMillan, J.M. The research reported in Chapters 2-4 was covered by Ethics Certificate REB16-1009, issued by the University of Calgary Conjoint Health Ethics Board for the project “Frailty in Older Adults (≥ 50 years) Living with Human Immunodeficiency Virus (HIV)” on October 21, 2016 (renewed on October 16, 2017).

Acknowledgements

The author wishes to acknowledge Dr. David B. Hogan, thesis supervisor, and Drs. M. John Gill and Hartmut Krentz, committee members, for their dedication and support of this research project. Without their time, expertise and mentoring this project would not have been possible.

Table of Contents

LIST OF TABLES

LIST OF FIGURES

APPENDICES: DEFINITIONS OF FRAILTY

List of Symbols, Abbreviations and Nomenclature

SYMBOL	DEFINITION
AIDS	Acquired Immunodeficiency Syndrome
ART	Anti-Retroviral Therapy
CFS	Clinical Frailty Scale
CGA	Comprehensive Geriatric Assessment
FI	Frailty Index
FP	Frailty Phenotype
HAART	Highly-Active Anti-Retroviral Therapy
HIV	Human Immunodeficiency Virus
IQR	Inter-Quartile Range
IVDU	Intra-Venous Drug Use
MFP	Modified Frailty Phenotype
MSM	Men who have Sex with Men
PLWHA	Persons Living With HIV/AIDS
PWID	Person Who Injects Drugs
SAC	Southern Alberta Clinic
SD	Standard Deviation
SE	Standard Error

CHAPTER ONE: INTRODUCTION

1.1.1 Aging with HIV

With the widespread use of antiretroviral therapy (ART), the longevity of persons living with HIV/AIDS (PLWHA) has increased significantly (1-4). In the United States, the Center for Disease Control (CDC) estimated that by 2013 forty-two percent of PLWHA were ≥ 50 years of age and that by 2020 over half of all PLWHA will be ≥50 years old (5). In the Netherlands it is predicted that the proportion of HIV+ patients in their center who are ≥ 50 years, will increase from 28% in 2010 to 73% by 2030 (6). At the end of 2017 at the Southern Alberta Clinic (SAC) in Calgary 40% (760/1920) of patients receiving HIV care were over ≥50 years of age (Figures 1-3). Twenty years ago, the proportion this age had been only 10% (n=25). As well, relatively more people than in the past are becoming infected at older ages. Currently over ten percent of new HIV diagnoses locally are in people ≥ 50 years of age (7) while an estimated 17% of new diagnoses of HIV in the United States are in persons ≥ 50 years of age (5).

Research suggests that PLWHA are at greater risk for age-related conditions such as hypertension (8), diabetes mellitus and insulin resistance (9, 10), cardiovascular disease (10, 11), pulmonary hypertension (12), cancer (13), osteopenia, osteoporosis, fractures (10, 14), liver disease (15), kidney disease (10, 16), peripheral neuropathy (8), frailty (8, 17), cognitive decline (8), and dementia (4, 18)). At this time, it is unclear whether this increased risk is due to ART-related toxicities, chronic HIV infection, or both**.** Dealing with the HIV infection, treatment toxicities and non-HIV related co-morbidities have increased the complexity of managing this patient population.

1.1.2 Frailty in persons aging with HIV

An emerging concern for older PLWHA is frailty. Frailty is manifested by increased vulnerability to stressors due to impairments in multiple, inter-related systems that lead to decline in homeostatic reserve and resiliency (19). Frailty is commonly used to appreciate the heterogeneity of older populations and the diverse ways in which individuals experience the challenges of aging. A

variety of approaches and instruments have been proposed for its detection, yet no single one has been conclusively shown to be superior. Irrespective of how frailty is operationalized, in general populations frail older adults are at increased risk of delirium, falls, hospitalization, progressive functional decline, institutionalization, and mortality (20-23).

In studies to date, frailty has been found to be more prevalent at younger ages in PLWHA compared to non-infected individuals. In a 2016 systematic review using versions of the Cardiovascular Health Study Frailty Phenotype approach (22), the prevalence of frailty in HIV infected individuals ranged from 5-28.6% (24). In the majority of the included studies, the mean age of PLWHA was in the 40's to 50's (24). The study with the highest frailty prevalence (28.6%) assessed frailty on more than one occasion in a given individual and calculated prevalence using two methods (25). When total number of individuals was used as the denominator in the prevalence calculation, the estimated frailty prevalence was 28.6%, however, when total number of person-visits was used as the denominator, the estimated frailty prevalence was lower at 12% (25). These differences make it more challenging to compare results across studies.

In comparison, in a Swiss non-HIV population the prevalence of frailty among those 50-64 years was 2.7% (26). The Canadian Community Health Survey reported that frailty was present in 16% of those 65-74 years of age, a similar prevalence to those found in HIV studies among cohorts 1-2 decades younger (27).

Frailty in HIV is predictive of adverse clinical outcomes. A study of predominantly male veterans with a high proportion of African Americans enrolled in the Veterans Aging Cohort Study (mean age 50 years) found that the presence of frailty increased the 5-year risk of hospitalization by 22% (Hazard Ratio [HR] 1.22 95% Confidence Interval 1.13, 1.33) and mortality by 75% (HR 1.75; 95% CI 1.28, 2.40) (28). Some authors have concluded that frailty should be included as a measure in established HIV longitudinal studies, as it represents a source of valuable information on resilience (24).

In a cohort of aging HIV + individuals who inject drugs, frailty and HIV status were independently associated with increased mortality ([HR 2.77; 95% CI 1.32-5.81] and [HR 3.05; 95% CI 1.89-4.93], respectively) (29). The combined effect of frailty and HIV + status was greater than the sum of the individual effects (HR 7.06; 95% CI 3.49-14.3) (29).

Identified risk factors for frailty include longer known duration (8-12 years) of HIV-infection (OR 14.68; 95% Confidence Interval 7.60, 28.35); AIDS diagnosis (OR 9.89; 95% CI 4.7, 20.8); viral load >50, 000 copies/ mL (OR 2.91; 95% CI 1.08, 7.85); and, CD4 cell count < 300 cells/mL (OR 2.75; 95% CI 1.43, 5.28) (28, 30). In other studies, factors associated with frailty include Hepatitis C co-infection (30), depression (25, 29, 31), both low (31, 32) and high BMI (33), multiple falls (34), cognitive impairment (31, 35), lower education (25, 29, 31), current unemployment (31), yearly income less than $10,000 (USD) (31), greater than or equal to 3 comorbidities (OR 2.06; 95% CI 1.39-3.05), and being single (OR 2.05; 95% CI 1.16-3.60) (29).

In general populations of older adults, there are a number of methods utilized to detect frailty. Three frequently used measures are the Frailty Phenotype, Clinical Frailty Scale and Frailty Index. In the HIV literature, the Frailty Phenotype (or a modified version thereof) and the Frailty Index are two commonly used measures.

The Frailty index has been found to be inversely related to successful cognitive aging in a cohort of older adults living with HIV in Modena, Italy (36). The index is calculated using thirty to forty potential health deficits (which can be symptoms, signs, diseases, functional limitations or laboratory abnormalities). In a given patient, the index is the ratio of the number of health deficits present divided by the number considered. For each 0.1-point increase in the frailty index, the odds of successful cognitive aging were reduced by 36% (OR 0.64, p=0.04) (36). In two recent cross-sectional studies, neurocognitive impairment was associated with a 2-3-fold increase risk of frailty as an outcome (OR 3.08; 95% CI 1.95 to 4.87) (37) and (OR 2.04; 95% CI 1.37 to 3.03) (38). Association does not imply causality; therefore, conclusion may not be drawn regarding whether frailty predicts neurocognitive impairment, or vice versa.

Frailty is not synonymous with disability or functional impairment but is predictive of functional decline. In a study of primarily male HIV + individuals on ART with suppressed viral load between 45-65 years of age, functional status was evaluated (39). The authors compared the Frailty Phenotype, the Short Physical Performance Battery and a 400-meter walk test to determine the prevalence of functional impairment, the agreement of the three measures, and the predictive variables for low function (39). Eight percent were "low function" (frail) according to the FP, 7% by the SPPB and 3% according to the 400-m walk test (39). Correlation of the three measures was fair (K=0.34 to 0.41). Across all 3 measures, lower physical activity, current unemployment, arthritis, neurological disease, debilitating pain, psychiatric disease, 4+ comorbidities and 5+ non-ART medications were all associated with low function (39). Variables related to HIV, on the other hand, were not associated with low or high function (39). Physical impairment or disability may overlap with frailty in some contexts, however, strictly speaking, they are not synonymous.

The Veterans Aging Cohort Study (VACS) Index has been shown to predict hospitalization and mortality in older adults living with HIV (40-42). This index is predictive of adverse outcomes, however does not specifically identify frailty. In the strictest sense, frailty is independent of biological age; in contrast, calculation of a VACS index includes age in years. Higher VACS index scores have been associated with all-cause mortality (41, 42), hospitalization (28), fragility fractures (43), and HIV-associated neurocognitive impairment (44, 45). VACS index scores have been shown to be better predictors of mortality than CD4 cell counts, HIV RNA and age, especially in patients over 50 years and with undetectable viral loads (41, 42). In the era of greater access to ART, HIV-related measures of vulnerability are less relevant, and frailty may have a role to play in identifying vulnerable patients whose HIV parameters are within normal limits.

1.1.3 Proposed pathophysiology of frailty and accelerated aging in HIV

It remains unknown how much the long-term exposure to a pro-inflammatory state triggered by HIV, long-term ART, lifestyle choices (e.g. smoking, increased alcohol intake, substance abuse), or aging itself contribute to the expression of frailty in PLWHA (24, 46). It is uncertain whether HIV represents "accelerated aging" or "accentuated aging" (46). In the former model, diseases

occur at younger ages in PLWHA than in HIV- persons. In the latter model, diseases do not necessarily occur at younger ages, but with greater frequency (46). To clarify the distinction between "accelerated" and "accentuated", "accelerated" may be likened to younger or earlier, whereas "accentuated" may be likened to more frequent. Inflammation and activation of the coagulation cascade are correlated with non-AIDS-defining comorbidity and all-cause mortality, evidenced by elevated Interleukin-6 (IL-6) and D-dimer levels (47). In non-HIV infected persons, IL-6 levels have been associated with frailty (48), and in HIV-infected men, frailty has been associated with elevated IL-6 and C-reactive protein (CRP) levels, and lower free testosterone, and dehydroepiandrosterone (DHEAS) levels (49).

A small study (n=21 patients; n=10 matched controls) evaluating the association between physical function and inflammatory markers in older adults (54-69 years) with HIV found no association, despite elevated CRP and IL-6 levels in HIV+, compared to non-infected controls (50). A second study, however found an association between frailty and elevated IL-6 levels, when compared to non-frail controls (51). In this study, frailty was also associated with a greater number of comorbidities (p=0.006) and higher VACS Index Score (p=0.005) (51).

The association of an inflammatory index, [interleukin-6 (IL-6) and soluble tumour necrosis factor-alpha receptor-1 (sTNFR1)] with frailty and mortality, was evaluated in people who inject drugs in the AIDS Linked to the Intravenous Experience (ALIVE) cohort (52). After adjustment for HIV status, number of comorbidities, sociodemographic and depressive status, increase in IL-6, sTNFR1 and inflammatory index score were each significantly associated with frailty and mortality risk (52). The generalizability of these findings may be limited by the inclusion of people who inject drugs, who were primarily African American and of lower socioeconomic status.

In contrast to inflammatory markers, markers of immune senescence (percentage CD4+CD28- and CD8+CD28- cells) and immune activation (percentage of CD4+CD38+ HLD-DR+ and CD8+CD38+HLA-DR+ cells) were found to be associated with HIV serological status, rather than

frailty status in a matched case control study of HIV + frail and non-frail men, compared to HIV negative men enrolled in the Multicenter AIDS cohort study (MACS) (49).

1.1.4 Geriatric syndromes in persons aging with HIV

Beyond frailty, other geriatric syndromes (e.g. delirium, falls, and incontinence) (53) have been identified more frequently, and at rates approaching that of older, HIV-negative populations. In a study of primarily male, well-controlled HIV+ individuals receiving ART (median age 57 years) the prevalence of several geriatric syndromes was investigated (8). Nine percent were frail, 56% were pre-frail, 46% had cognitive impairment, 46% had difficulty in ≥1 instrumental activity of daily living, 40% had depression, 35% had visual impairment, 26% had fallen in the preceding year, 25% had urinary incontinence, 22% had mobility impairment and 14% had hearing impairment (8). Although frailty has been one of the most widely studied geriatric syndromes, it appears other geriatric syndromes also occur more frequently at younger ages than in HIV-negative populations.

1.1.5 Identification of Frailty

Frailty has been increasingly studied in the aging HIV population. A variety of screening measures for frailty have been used, which limits our ability to compare results across studies. The Comprehensive Geriatric Assessment is viewed by some to by the "gold standard" for identification of frailty (54). In the present study we focused on three of the most commonly employed measures: Frailty Phenotype, Clinical Frailty Scale and Frailty Index. We also performed CGA in a subset of patients in order to further investigate the context and consequences of frailty in older adults at SAC. The most commonly used approach to frailty screening in the HIV literature has been the frailty phenotype or a modified version of the phenotype employing 4 of the 5 traditional variables (with the exclusion of grip strength) or frailty index. Frailty measures currently in use have primarily been validated in HIV- populations. However, the use of the frailty phenotype and frailty index in HIV+ populations has become more widespread and is associated with adverse outcomes (29, 36, 55-58). Ideally, the clinical measurement of frailty should be

simple, inexpensive, require minimal time, widely implemented in order to facilitate comparisons, and validated in an HIV+ cohort.

The Frailty Phenotype (FP) was developed using data from the Cardiovascular Health Study (22). The phenotype model consists of measurement of grip strength using a hand-held dynamometer, a timed 6-meter walk, measurement of change in weight, two questions about exhaustion, and a short, validated questionnaire assessing the presence of physical limitation (Appendices A-D). Frailty is defined by the presence of ≥ 3 of the 5 criteria. Those with 1-2 variables present are defined as pre-frail while those with none are non-frail (22).

Two of the measures within the FP have been observed to decline more rapidly in PLWHA than in HIV- persons. Gait speed has been shown to decline more rapidly in HIV+ than HIV- men ≥ 40 years (59). At 50 years of age, HIV+ men had slower baseline gait speed and developed slow gait speed (<1m/sec) at younger ages than HIV- men (59). In addition, the rate of decline in grip strength has been observed to be greater in HIV+ compared to the HIV- men (60). These observations raise the possibility that these components of the FP may have unique properties and trajectories in PLWHA, which may have consequences for the accurate identification of frail HIV+ individuals when using the FP tool.

The Canadian Study of Health and Aging Clinical Frailty Scale (CFS) (21) (Appendix E) is a judgement-based scale anchored by images and descriptions of where the individual fits on a continuum of fitness/frailty. Frailty is defined as a score of four or greater (note: terminally ill individuals are excluded). This instrument has yet to be investigated in an HIV+ population, however has been used widely in HIV- older adults. Given its ease of use, high inter-observer reliability, previous validation and predictive ability in older HIV- adults (21, 61-63) and correlation with other frailty measures (21, 63) this scale may have a role in identification of frailty in PLWHA.

The Frailty Index (FI) is calculated using thirty to forty potential health deficits (symptoms, signs, diseases, functional limitations or laboratory abnormalities) which are selected based on certain criteria (i.e., associated with health status, likelihood increases with age, does not saturate at an early age, cover a range of symptoms, remain consistent when used longitudinally in a study population) (23). For each patient, the FI is the ratio of the number of health deficits present divided by the number considered. The FI is a continuous value between zero and one with higher numbers associated with increased frailty. Its advantage is in the granularity provided by a continuous scale and it is designed to be used as such. Previous studies and researchers have defined cut-off FI values to define levels of frailty, such as FI ≥0.21 defined as frail, ≥0.30 defined as more-frail and ≥0.45 as most-frail based on a community-based sample from the Canadian Community Health Survey (27). A cut-point of ≥0.7 has been defined as boundary beyond which further deficit accumulation is unlikely, but rather death becomes likely (64).

1.1.6 Proposed interventions for frailty

Smoking (OR 1.37; 95% CI 1.01-1.86), obesity (OR 1.42; 95% CI 1.02-1.98), low physical activity (OR 1.95; 95% CI 1.46-2.61), less than high school education (OR 1.57; 95% CI 1.13-2.17) and ART selection (initial non-nucleoside reverse transcriptase inhibitors), have been associated with increased prevalence of frailty (38). These factors are potentially modifiable and may provide feasible interventions to address or prevent frailty.

In a study of community-dwelling, HIV-negative older adults, frailty status improved (i.e. from frail to pre-frail, or from pre-frail to non-frail) with cognitive training, physical training, nutritional supplementation or a combination of these (65). In a study of older adults with HIV and functional impairment, a prescription for walking and resistance training using resistance bands, lead to improved physical performance, 6-minute walk distance, gait speed, chair rise and knee extensor strength at the end of 12 weeks compared to the control group (66). The treatment group also had improved Beck Depression Inventory Scores and scores on two quality-of-life domains (66).

In addition, a recent systematic review found that adherence to a Mediterranean Diet was associated with reduced incidence of frailty (OR 0.44; 95% CI 0.29 to 0.66) (67). This evidence from an HIV- population is preliminary but may guide future interventional studies.

1.2 SIGNIFICANCE OF PROJECT

The population of persons living with HIV is aging as a result of the success of antiretroviral therapy. With this success comes the challenge of managing the comorbidities of aging, including frailty. Frailty has been shown to be more prevalent, at younger ages in PLWHA than in HIV-negative populations. Frailty increases an individual's risk of adverse outcomes including hospitalization, mortality, cognitive and functional decline. There is no universally agreed upon best measure for identification of frailty. Some may identify Comprehensive Geriatric Assessment (CGA) as the "gold standard" for identifying frailty, yet it is resource intensive, limiting its availability (54). CGA is a multidimensional clinical assessment that incorporates medical, psychosocial and functional capability of the individual in order to create a treatment plan (68). It is unclear which clinical measure is best for identification of frailty in PLWHA.

The aims of this study were several-fold: to determine whether similar prevalence rates of frailty would be observed at Southern Alberta Clinic (SAC) in Calgary as in other HIV cohorts; to evaluate risk factors for frailty at SAC; to compare the use of three measures for the identification of frailty, including one novel tool; and to explore the context, impact and consequences of frailty, based on findings of the Comprehensive Geriatric Assessment.

1.3 OBJECTIVES:

1.3.1 The primary objective of this study was to calculate the period prevalence of frailty using three different approaches in a cohort of HIV+ patients engaged in care at the Southern Alberta Clinic.

Whether similar rates and risk factors found in previous studies will be found in a more heterogeneous HIV population is currently unknown. In older populations frailty is more common in females (21), a population under-represented in previous studies. The SAC population differs from previous studies of frailty in HIV by the inclusion of a heterogeneous patient population. The majority of studies to date have used versions of the Cardiovascular Health Study Frailty Phenotype originally described by Fried et al. (22), which we obtained in modified version. The Frailty Index has recently been investigated in an HIV population in Italy (69), and we calculated a FI using routinely collected variables at SAC, modelled after that used in Modena (23).

A novel element of our study was the use of the Clinical Frailty Scale which has been widely used in care settings but to our knowledge not previously studied in the HIV population (21). Additionally, we explored the context, components, contributors and consequences of frailty through the Comprehensive Geriatric Assessment (CGA) which has not yet been widely used HIV care.

1.3.2 Secondary objectives:

a) Compare the prevalence of frailty at SAC to previously studied HIV populations (Table 1)
b) Compare the prevalence of frailty at SAC to age-matched HIV-negative populations (Table 2)
c) Explore potential risk factors for frailty (identified in previous studies), including age, sex, known duration of infection, ART exposure, current and nadir CD4 cell count (lowest ever measured CD4 count), viral load status, and smoking status
d) Explore the agreement between the frailty measures in identification of frailty
e) Explore the association between the identification of frailty and one-year mortality
f) Determine which scale is a better predictor of adverse outcomes (i.e., mortality)
g) Explore the context, impact and consequences of frailty, based on findings of the Comprehensive Geriatric Assessment

1.4 RESEARCH HYPOTHESES

We hypothesized that the prevalence of frailty at SAC would be higher at earlier ages than in the general Canadian population based on what has been reported in previous studies (20, 21). We propose that the Clinical Frailty Scale, which to our knowledge is used here for the first time in an HIV population, will accurately identify frailty at SAC, with minimal burden on staff.

We anticipated that the knowledge generated would be of value to clinicians and patients and have the potential to inform changes in clinical practice at SAC. For instance, routine frailty screening in older adults may prompt referral of appropriate patients to allied health services (e.g. Home Care, Social Work, Physical Therapy, Pharmacy) and for Geriatric Medicine consultation. The results of this study may be more generalizable than previous studies. In addition to introducing a Canadian context, the population at SAC includes a greater proportion of females and greater ethnic diversity than previous studies.

CHAPTER TWO: METHODS

2.1 Study Design

The study design for the main analysis was a one-year cross-sectional, observational study. Patients 50 years of age and over who attended a clinic visit at Southern Alberta Clinic during the study period were eligible for enrolment. The study period began November 1, 2016 and ended October 31, 2017. Patients who were less than 50 years of age during the study period were excluded (Please see Figure 4 for patient inclusion and exclusion Flow Diagram).

During the one-year study period, a Frailty Index was calculated for patients who were 50 years of age and above and for whom sufficient clinical information was available. In addition, during the study period, when eligible patients attended a clinic visit, if time permitted, trained staff at SAC performed an in-clinic screening assessment for frailty using the Modified Frailty Phenotype and Clinical Frailty Scale. Once a patient was screened in-clinic once during the study period, they were not screened again during the period. The goal was to perform in-clinic frailty

screening for as many patients as possible during the study period, however due to the time required to perform the Modified Frailty Phenotype and Clinical Frailty Scale we anticipated constraints on the number of patients who would be able to be screened with in-clinic assessment by staff at SAC.

In contrast, all patients 50 years of age and above for whom sufficient data were available had a Frailty Index calculated.

The main analysis (period prevalence of frailty) was assessed within this cross-sectional study design. However, in addition, a small convenience sample of patients was also followed-up later in the study period. The small convenience sample included patients who either died within the one-year study period or who were assessed by Comprehensive Geriatric Assessment during the one-year study period.

2.2 Study Population

The Southern Alberta Clinic (SAC) provides centralized HIV care to all infected patients in southern Alberta. It is the sole provider of ART in this area and in contrast to many HIV programs, SAC cares for males and females, young and old, multiple ethnic backgrounds, people who inject drugs, co-infected patients (Hepatitis C or Hepatitis B and HIV), men who have sex with men, and immigrants (Table 3). HIV care provided at the clinic is comprehensive and continuing without transfer of care to outside providers. SAC has seen over the last decade significant aging of its patient population. During the study period, nearly 40% of patients were ≥50 years of age, a proportion that has been increasing over the past two decades (10% twenty years ago and 20% ten years ago).

The SAC database records pertinent patient-level details including known duration of infection, ART exposure, comorbidities, routine blood chemistry measures, and sociodemographic variables which were evaluated to explore the relationships of each variable with the outcome of frailty.

The database also houses information such as incident hospitalizations and mortality which permits evaluation of the predictive ability of frailty for adverse outcomes.

The mean age of the entire SAC cohort was 45.9 years during the study period (range 8 to 90 years). There were differences in risk for acquisition of HIV infection, and in ethnicity between the entire cohort compared to those 50 years of age and above (Table 3). For example, approximately 39% in the entire cohort reported their risk category for acquisition of HIV infection as homosexual (defined as "homosexual" or "homosexual and intravenous drug use") compared to approximately 45% of patients in the group aged 50 years and above. In contrast, nearly 48% of the entire cohort reported heterosexual (defined as "heterosexual" or "heterosexual and endemic region" or "heterosexual and intravenous drug use") as their risk for acquisition of HIV infection compared to 40% in the group 50 years of age and above. With respect to ethnicity, 52% of the entire cohort self-identified as Caucasian, compared to approximately 74% in the group 50 years of age and above. Of the entire cohort, 25% self-reported as African Canadian, compared to 12% in the group aged 50 years and above.

2.3 Frailty Assessment

Beginning on November 1, 2016, SAC introduced, as part of routine care, annual screening for frailty on all patients ≥50 years of age. Patients attend SAC on average every 4 months, and we anticipated that over the course of one year, a large proportion of patients ≥50 years would undergo frailty screening.

Screening of patients 50 years of age and above consisted of three measures, including one measure (the Frailty Index) that is based on routinely collected data that does not require an in-clinic assessment, and two measures (the Modified Frailty Phenotype and Clinical Frailty Scale) which require an in-clinic assessment to screen for frailty. The MFP and CFS were dependent on clinic staff identifying patients attending clinic who were 50 years of age and above, and time-permitting, performing each of the required assessments for the frailty screen. Patients who underwent the in-clinic screening assessment for frailty we termed "screened" patients.

Clinical staff performing the in-clinic frailty assessments (Modified Frailty Phenotype and Clinical Frailty Scale) included registered nurses, occupational therapy and social work students. Clinical staff were trained by JM in performance of each component of the MFP (details below and in appendices) and CFS. Instructions were given to base the CFS score on all clinical information available, which may include timed 6-meter walk, grip strength, weight loss and questionnaire answers, for example. There was no instruction to perform individual components of the assessment in a particular order, therefore staff were able to collect data in any order that they chose.

Throughout the study, clinical staff were observed periodically in their methods for frailty data collection. For instance, clinical staff were observed while they performed grip strength testing and the 6-meter walk test, to evaluate intra-observer consistency. In addition, when feasible, such as on a repeat visit, JM repeated the collection of frailty data for a patient who had already undergone in-clinic frailty screening to assess for inter-observer agreement.

2.4 Definition of Frailty

2.4.1 Modified Frailty Phenotype

Testing for Modified Frailty Phenotype consisted of a timed 6-meter walk (Appendix A), grip strength measurement using a dynamometer (Appendix B), measurement of weight, two questions about exhaustion (Appendix C), and a short, validated questionnaire assessing the presence of physical limitation (Appendix D). Low grip strength was determined from age- and gender-matched Canadian normative data (70). Individuals with a gait speed <1meter/second on a 6-meter walk test have been found to be at greater risk of hospitalization and death (71), therefore the cut-off of <1 metre/second was used to define participants with slow gait speed. In Fried's original definition of frailty, slow gait speed was defined as the lowest 20^{th} percentile based on height (22), however we used the general cut-off of <1m/sec. Weight loss was defined by unintentional loss of greater than 1.5 kilograms/4months based on objective in-clinic weight measurement, rather than self-reported weight loss. This is based on the Fried frailty phenotype definition of weight loss of 10 pounds (4.5 kilograms) in the preceding year (22), and adjusted for the frequency of follow-up

at SAC occurring every 4 months. Individuals were identified as "exhausted" if they answered one, or both questions about exhaustion in the affirmative, in agreement with previous studies. The 12-item validated questionnaire regarding physical function was scored as in the Veterans Aging Cohort Study, whereby, greater scores represent greater functional ability ("yes, I can do this" =2; "yes, I can do this, but only slowly" =1; "no, I cannot do this" =0) (72). The sum of scores was divided by the maximum score (24) and multiplied by 100 to determine a percentage score with percentage values less than 67% indicating functional impairment (72). The presence of frailty was based on the Cardiovascular Heart Study frailty phenotype (22) with individuals classified as frail if they displayed ≥3 of the 5 criteria defined above.

We also calculated the percentage of patients who met criteria for each of the individual components of the MFP, as well as the agreement between the presence of an individual MFP criterion and the outcome of frailty as defined by the MFP.

2.4.2 Clinical Frailty Scale

The evaluating clinician completed the judgement-based Canadian Study of Health and Aging Clinical Frailty Scale (CFS) (21) (see Appendix E) with frailty defined as a score of 4 or greater (note: terminally ill individuals were excluded).

2.4.3 Frailty Index

The third frailty measure was calculation of a frailty index (FI) using standard methodology (23) based on data routinely collected at Southern Alberta Clinic. For each patient, the FI was the ratio of the number of health deficits present divided by the number considered. No additional data was used. The selection of items for the FI aligned with the FI used in Modena, Italy. Items met the criteria previously outlined with no more than 5% of clinic patients having missing data (23). Each deficit was dichotomized with the presence of deficit =1 and absence of the deficit=0 (21). This approach to assessing frailty has been widely utilized on various populations in the literature and has been recently introduced in an HIV population in Italy (69). We used the same deficits as the

Italian study, however this was not necessary to permit comparison across studies (23). Items included in the Frailty Index are present in Appendix F. Advantages of the FI are that it permits the assessment of frailty severity and is more sensitive to change than other frailty measures (23).

2.5 Evaluate the agreement among the three measures in identification of frailty

Cohen's Kappa statistics were calculated to measure the agreement between individual measures in their identification of frailty. Agreement was compared between the MFP and CFS, between the MFP and FI and between the CFS and FI. The outcome of frailty for the MFP and CFS is binary, defined as the presence or absence of frailty. However, the FI is a continuous measure without universally accepted cut-points for creating binary categories of frail and non-frail. For the purpose of comparison we followed cut-points for the FI defined by previous authors (27) whereby FI $\geq$0.21, $\geq$0.30 and $\geq$0.45 were utilized to classify frail, more-frail and most-frail, respectively. These are artificial cut-points, however, created from community-dwelling Canadian data, and the intended use of the FI is on a continuous scale.

2.6 Comprehensive Geriatric Assessment

A convenience sample of individuals identified by the Clinical Frailty Scale as frail (score $\geq$4/9) were offered a Comprehensive Geriatric Assessment (CGA), which has been shown to improve survival rates and functional status in frail older adults and lead to more desirable placement destination following acute care admission (20, 68). CFS was chosen to identify patients to be offered CGA because it could be determined in real-time, by the clinic staff, so that the patient could be approached and offered CGA while they were at the clinic. In this way, clinic staff were able to schedule the next appointment for the patient with the geriatric medicine specialist. In contrast, the MFP and FI both required recoding of variables and calculations to identify potentially frail patients which would have introduced a delay between the patient's clinic visit, determination of the patient's frailty status, and follow-up contact with the patient to offer a CGA with the geriatrician. Patients were invited for CGA with a general explanation, such as this, "we have a new doctor who has joined our team who works with people as they are getting older…If you are interested, she could see you at your next visit to see if there is anything that could be done

to help you improve your quality of health". The conversation would then be based on the questions the patient may ask. The clinic staff tended not to say to the patient that they were frail or that they may be frail. A maximum of twenty-four clinic visits were available during the study period (November 1, 2016-October 31, 2017). This is the equivalent of one half-day clinic per month.

CGA consists of a comprehensive medical history, medication review, physical examination, review of results of investigations, social-demographic variables and function abilities. It was performed by a specialist in Geriatric Medicine (JM) occurred at SAC during a regular follow-up visit and took approximately 2-hours to complete. It included a chart and medication review, semi-structured interview and physical exam, including a systemic review of physical health, functional status, psychological health (including cognition and affect) and socioenvironmental status. Medications were reviewed by the performing physician and in some cases, the SAC pharmacist, for potentially inappropriate medications, requirement for dosage adjustment and medication omissions, which may have been indicated based on the patient's medical diagnoses. Results were provided to the SAC physician responsible for the patient and the patient's family physician. Eligible patients were provided with a letter describing this component of the study and were required to provide written, informed consent to participate.

The CGA provides context and meaning to the frailty concept. For instance, the CGA often reveals further details about a "case" which are not disclosed elsewhere in the screening process for frailty, such as frequent falls, low mood or anxiety, social isolation, domestic violence or a history of substance misuse.

2.7 Data Analysis

Patients were grouped by sex and age intervals (50-64 years and ≥ 65 years years) in order to determine the sex- and age-related period prevalence of frailty within the clinic population. Descriptive statistics were used to calculate and compare the Modified Frailty Phenotype, Frailty

Index and Clinical Frailty Scales scores. Calculations of these values and visualization of data distributions was performed using Stata version 14.2 (College Station, Texas, USA).

For binary outcomes, such as frailty, defined by the MFP or CFS, we compared between-group means and proportions, respectively, using two-sample t-tests and Chi-Square tests. The significance level, alpha was set at $\alpha=0.05$ for a two-tailed test. Specifically, to compare the mean age, duration of known HIV infection, duration of ART, nadir and current CD4 cell count between patients identified as frail and non-frail we used two-sample t-tests. These tests were calculated separately for the MFP and CFS. To compare binary variables between frail and non-frail groups we used Chi-Square tests. Specifically, for smoking status, sex, viral load status (detectable versus undetectable) and binary age category (50-64 years and ≥65 years) we compared between group proportions with Chi-Square test statistic.

We compared the mean FI of frail and non-frail patients as defined by the MFP or CFS using two-sample t-tests. We compared the mean age between patients identified as frail and non-frail using MFP and CFS using two-sample t-tests. We did not correct for multiple comparisons.

For predictor and outcome variables when both were continuous (for example, age as a continuous variable and frailty index as a continuous outcome) we used multivariate logistic regression to test for association. Predictive variables were selected based on previous research findings (28, 30) and included age, known duration of HIV infection, duration of ART exposure, nadir (lowest ever measured CD4 count) and current CD4 count and viral load. Linear regression was used to test the relationship between individual variables and frailty.

The period prevalence of frailty in the study population was compared to published data on similarly aged populations of PLWHA, as well as non-HIV populations (Tables 1 and 2).

Cohen's Kappa coefficients were calculated to assess inter-test agreement. The magnitude of agreement was defined as 0-0.20 slight agreement; 0.21-0.40 fair agreement; 0.41-0.60 moderate agreement; 0.61-0.80 substantial agreement; and 0.81 to 1.0 nearly perfect agreement.

Mortality and cause of death was obtained from the SAC database. We categorized frail causes of death as those due to medical diagnoses, comorbidities, and complications and consequences of chronic medical diagnoses. We categorized non-frail causes of death as those due to violence, intoxication or that were accidental in nature.

Findings of the CGA were analyzed in duplicate by JM and D.B.H. both Geriatric Medicine specialists. The CGA was performed by JM and documentation was recorded in a dictated clinic letter addressed to the primary SAC provider and the patient's family physician. A copy of the dictated clinic letter was analyzed by JM and D.B.H. and the clinical data within the letter was used to complete a standardized data collection worksheet. The worksheet was completed independently by each assessor. Data collected on the worksheet included: sex, age, duration of known HIV infection, comorbidities (both number of comorbidities and specific diagnoses), number of non-ART medications (both prescribed and over-the-counter), social determinants (smoking status, alcohol and drug use and misuse, marital status, housing status), functional status (degree of dependence with both basic and instrumental activities of daily living), and primary medical concerns of the patient (e.g. cognitive and emotive concerns, physical limitations, concerns around continence, mobility, falls, sleep and pertinent findings of medical comorbidities, such as poorly controlled diabetes, angina or chronic obstructive pulmonary disease, for example). The data collection was designed to provide further context, detail and consequences of frailty.

Data was anonymously recorded in our research files, physically located at SAC, on the password-protected SAC administrative database and accessible only to individuals directly involved with the study. Patients were identified by a study number with no personal identifying information. Results were reported in aggregate, and where individual data cells contained fewer than 10 participants, cells were combined to minimize the possibility of patient identification. The clinical chart was kept at SAC in a secure filing system.

2.8 Ethics

Ethics approval was granted by the University of Calgary Research Ethics Board (October 21, 2016; and renewed October 16, 2017). All individuals who participated in the Comprehensive Geriatric Assessment provided written, informed consent.

CHAPTER THREE: RESULTS

3.1 Patient Demographics

Seven hundred and ten patients at SAC were ≥ 50 years of age between November 1, 2016 and October 31, 2017. Details of population demographics are presented in Table 4. The mean age of patients ≥ 50 years was 58.2 years (standard deviation +/- 6.5 years; range 50-90 years). The median age was slightly younger at 56 years (interquartile range 53-62 years) due to the right-skewed distribution of the age data. The majority of patients were male (85%) between the ages of 50-64 years (85.5%), while 14.5% were greater than 65 years of age. Patients had been living with HIV for a mean known duration of 16.3 years (SD +/- 8.3 years; range 0-35 years); the median was 16 years (IQR 10-23 years). The mean duration of ART was slightly lower than the known duration of infection, with a mean of 13.7 years (SD +/- 7.5 years; range 0-31 years); the median duration of ART was 13 years (IQR 7-20 years). Overall, patients had normal CD4 cell counts, with a mean of 609.5 cells/µL (+/-324.2 cells/µL). Additionally, the majority of patients (>90%) had CD4 cell counts >200 cells/ µL with >60% of patients with CD4 cell counts >500 cells/µL. Greater than 90% of patients had undetectable viral loads (<40 copies/mL). During the one-year study period, patients attended SAC on average 2.6 times (+/-1.1), with a range of zero visits during the year (n=61; 8.6%) to eight visits during the year (n=3; 0.4%) (Figure 4).

3.2 Characteristics of patients screened for frailty

Frailty index was calculated for 710 patients in the sample population using routinely-collected, observational administrative data. Three hundred and thirty-four patients (of the 710) additionally underwent in-clinic frailty screening performed by trained SAC staff. These 334 were assessed for

frailty using the Clinical Frailty Scale. Three-hundred and thirty-eight patients underwent in-clinic frailty assessment utilizing the Modified Frailty Phenotype (the same 334 who were screened using the CFS, plus 4 additional patients) (Figure 5). It is not clear why four patients who underwent in-clinic screening with the MFP did not have a CFS performed.

The inclusion of patients within the in-clinic frailty screen utilizing the MFP and CFS was based on a convenience sampling of patients. Due to time constraints and competing responsibilities of the clinic staff who performed the in-clinic frailty assessments it was not feasible for the entire cohort of 710 patients 50 years of age and above to undergo in-clinic screening. The time to complete the MFP and CFS adds approximately 10-20 minutes to each clinic visit. On busy clinic days, if insufficient numbers of staff were available, if trained staff were unavailable, or if other clinical priorities were of greater importance, then in-clinic assessments were not performed. When time and staffing constraints were not present, then patients 50 years of age and above were approached during their routine SAC visit for in-clinic screening. We did not record the number of patients who declined screening, however, the clinic staff reported that this was not a concern, and that most patients were agreeable to the in-clinic frailty screen. Patients who did not undergo in-clinic assessment were excluded based on clinic factors (time and resources) rather than patient factors (patient declining assessment).

Characteristics of screened and unscreened patients, and frailty values are presented in Table 5. Patients who were screened in the clinic were on average older (mean age 59.1 years) compared to those not screened (mean age 57.7 years; p=0.0006) and had longer known duration of HIV infection (mean known duration 16.8 years versus 15.9 years; p=0.0788). There was no difference between patients who were screened and those who were not screened in current CD4 cell count or duration of ART.

3.3 Primary Objective: Period prevalence of frailty using three different measures

3.3.1 Frailty Index

Frailty index was calculated for 710 patients ≥ 50 years using routinely-collected observational health data. Thirty-two variables were considered for calculation of the frailty index. The variables were chosen based on previous calculation of frailty indices in patients with HIV in Modena, Italy (57) (Appendix F). The mean frailty index was 0.349 (SD +/- 0.105; range 0.0938- 0.6562) and the median was 0.344 (IQR 0.281-0.406) (Figure 4). The mean frailty index was higher in males (0.353; SD+/- 0.105) than in females (0.330; SD+/- 0.107; p= 0.0219) and in the group aged ≥65 years (0.362; SD +/- 0.123) compared to those 50-64 years (0.347; SD+/-0.102), but the latter difference was not statistically significant (p=0.1029) (Table 6). Patients who underwent in-clinic screening for frailty using the CFS and MFP had higher mean frailty indices than those who did not (0.367 +/- 0.093 versus 0.334+/- 0.112; p< 0.0001).

In multivariate regression analysis, age (continuous, years) and known duration of HIV (continuous, years) were not statistically associated with the FI, but duration of ART and both current and nadir (lowest ever measured) CD4 cell count were (Table 7). For each 10-year increase in duration of ART exposure, the FI increased by 0.029 (p<0.001). For CD4 cell counts, each 100 cell/µL decrease in nadir CD4 cell count was associated with an increase of 0.0096 in the FI (p=0.001) and each 100 cell/µL decrease in current CD4 cell count was associated with an increase of 0.0032 in the FI (p=0.014).

Over ninety-percent of patients from the entire cohort (n=710) had frailty indices ≥ 0.21 (n=641; 90.3%), over 70% had FI values ≥ 0.30 (n=509; 71.5%) and 16% had FI ≥ 0.45 (n=114; 16.01%). The frailty index appeared normally distributed (Figure 4). The 95th, 90th and 75th percentile FI values were 0.531, 0.469 and 0.406, respectively.

3.3.2 Clinical Frailty Scale

Three-hundred and thirty-four patients were screened during a routine clinic visit using the Clinical Frailty Scale. With frailty defined as a score ≥ 4, 45 patients (13.5%) were identified as frail and 289 (86.5%) were not frail (Figure 5). The mean age of patients identified as frail was 63.5 years (+/-8.9 years) and of the non-frail was 58.4 years (+/-6.0; p<0.0001) (Table 8). The mean known duration of infection of the frail and non-frail patients based on the CFS did not differ (16.2 years +/- 8.0 years versus 16.9 years +/- 8.5 years; p=0.3064). The mean duration of ART did not differ between those classified as frail versus non-frail (14.6 years +/- 7.4 years versus 14.0 +/- 7.6 years; p=0.3057). Current CD4 cell count did not statistically differ by frailty status but approached statistical significance (535 versus 611 cells/µL for frail versus non-frail, respectively; p= 0.0515). No patients were assigned scores on the CFS greater than 5 (Figure 5).

3.3.3 Modified Frailty Phenotype

Three-hundred and thirty-eight patients were screened in-clinic using the Modified Frailty Phenotype. By this method, 48 patients (14.2%) were identified as frail, defined as the presence of ≥ 3 out of 5 variables (Table 9). The mean age of frail patients was slightly older than those who were classified as non-frail (60.3 +/- 6.8 years versus 59.0 +/- 6.7 years; p=0.0977) but the difference was not statistically significant. There was no difference in known duration of infection (16.6 versus 16.9 years; p= 0.3907), time on ART (14.5 versus 14.1 years; 0.3778) or current CD4 cell count (621 versus 600 cells/µL; p= 0.3237) between patients identified as frail compared to those identified as non-frail, respectively (Table 9).

Individual components of the Modified Frailty Phenotype

A majority of patients (61%) had weak grip strength, and one-quarter of patients reported exhaustion and had unintentional weight loss (27% and 25%, respectively) (Table 10). Slow walking speed and functional impairment were observed less frequently (13% and 8% of patients, respectively). The components which correlated best with the identification of frailty were functional impairment (K=0.6178), self-reported exhaustion (K=0.5197) and slow walking speed

(κ=0.5107). Unintentional weight loss (κ=0.3134) and weak grip strength (κ=0.1381) correlated poorly (Table 11).

3.4 Secondary Objectives

3.4.1 Compare the prevalence of frailty at SAC to previously studied HIV + populations

Previous studies of frailty in HIV have employed the FP (or a modified version) and FI. The present study is the first, to the authors' knowledge, to employ the CFS to identify frailty in PLWHA.

The systematic review performed by Levett et al in 2016 included only studies which employed the FP. Reported frailty prevalence in PLWHA ranged from 5 to 28.6% (24) (Table 1). The authors did not provide a pooled estimate because of the heterogeneity of included studies (24). As noted above, the highest estimate (28.6%) was reported in a study in which prevalence was calculated using total number of individuals as the denominator (25). When total number of person-visits was used as the denominator in the calculation the estimated prevalence decreased to 12% (25).

In the present study, 338 patients were evaluated using the MFP and 14.2% were identified as frail (mean age 58 years). Previous studies of similarly-aged individuals have estimated frailty prevalence from 8% to 12% with mean or median ages ranging from 50.8 to 57 years (8, 25, 39). The study by Greene et al. enrolled 156 PLWHA with a median age of 57 years (the closest average age of participants to the present study) and found frailty prevalence to be 9% (8). This estimate is not significantly different than the estimate of 14.2% in the present study of 338 individuals ($Z=1.6212$; $p=0.0525$).

In the present study, the mean FI was 0.349 (SD +/- 0.105). In a previous study of PLWHA the mean FI was 0.31 (SD +/- 0.1) with a mean age of 46 years (+/- 8) (69). The between group

difference in means was statistically significant (t=9.1632; p<0.0005), however, the mean age in the comparator group was 46 years, compared to the mean age in the present study of 58 years.

3.4.2 Compare the prevalence of frailty at SAC to HIV- populations

In the present study, greater than 90% of PLWHA had a FI over 0.21. Using FI ≥0.21 to identify frailty in previous studies resulted in 16% of 65-74-year-olds, 29% of 75-84-year-olds and 52% of 85-years and above being identified as frail (27). In the present study, the mean FI was 0.349 (+/- 0.105). In the Canadian community-based HIV- study referenced above, the mean FI was 0.16 with a mean age of 75 years (27). In the Canadian Longitudinal Study on Aging the mean FI for men aged 55-64 years was 0.116 (73). Comparison of proportions and means could not be performed due to inadequate data from the comparator study population with respect to sample size and standard deviation values.

In the present study, 14% of individuals were identified as frail based on the MFP. In contrast, a Swiss study calculated a frailty prevalence of 2.7% in 50-65-year-olds using a MFP (26). The difference in proportions between these two studies was significantly different (z=9.7354; p< 0.0005).

3.4.3 Explore potential risk factors for frailty

Frailty Index was associated with both current and nadir CD4 cell counts, and duration of ART exposure, but was not associated with age (continuous or binary: 50-64 years or ≥65 years), known duration of infection or smoking status (Tables 6 and 7).

Frailty determined by both the CFS and MFP was associated with age (continuous value, years), but was not associated with known duration of HIV infection, duration of ART exposure, or nadir or current CD4 cell count (Tables 8 and 9, respectively).

3.4.4 Calculate the agreement between the frailty measures in identifying frailty

Forty-five patients (13.5%) were identified as frail by the CFS and forty-eight patients (14.4%) were identified as frail by the MFP. We calculated agreement between patients who had undergone all three measures, therefore we only used data from the 334 patients who had undergone all three of: CFS, MFP and FI. Using the FI cut-points of ≥0.21, ≥ 0.30 and ≥ 0.45, ninety-five percent of patients were frail (318/334), 79% were more-frail (263/334) and 19% were most-frail (63/334).

We calculated a Cohen's Kappa test statistic for each two-way comparison (Table 12). The CFS and MFP had the greatest agreement with a kappa of κ=0.3880 (SE 0.0547) indicating fair agreement. There was slight agreement for the other comparisons with kappa values between κ=0.0083 and κ=0.1870. There was a trend of increasing agreement when comparing the CFS and MFP to higher FI values. For example, the kappa value increased from κ=0.0083 to κ=0.1870 when comparing the CFS to FI ≥ 0.21, compared to the CFS compared to FI ≥ 0.45. The CFS tended to have greater agreement with the FI than did the MFP.

3.4.5 Explore the association between frailty and mortality

Eighteen patients (2.5%) died during the one-year study period. The mean Frailty Index of the 18 patients who died was statistically higher than those who survived (0.403 +/- 0.116 versus 0.348 +/- 0.105; p=0.0144) (Table 13). Patients who died were older than those who survived (mean age 63.2 +/- 9.9 years versus 58.1 +/- 6.4 years; p=0.0005). Patients who died had significantly lower current CD4 cell counts than those who survived (378 cells/µL versus 616 cells/µL; p= 0.001); however, there was no difference between those who died, compared to those who survived in either the known duration of infection or duration of ART. Only 4 patients who died had undergone in-clinic screening with the CFS and MFP. Three of the four patients who died were identified by the CFS and MFP as frail, one was not.

Individual causes of death were classified as those felt to be associated with frailty and those not. Six were cancer-related deaths, 3 were attributed to ischemic heart disease and one each was due

to stroke and chronic obstructive pulmonary disease. Analysis of these 11 “frail” deaths revealed a mean frailty index was 0.41 (0.33 to 0.50). In contrast, seven deaths were less clearly associated with frailty, including 5 “unknown” causes of death, and one each attributed to accident/other violent death and acute intoxication. The mean frailty index of the “non-frail” deaths was 0.33 (0.27 to 0.40).

3.4.6 Determine which frailty measure best predicts mortality

Eighteen patients died (2.5%) during the one-year study period. For each of the eighteen patients who died data were available for calculation of a FI. As noted above, the mean FI of the 18 patients who died was statistically higher than those who survived (0.403 +/- 0.116 versus 0.348 +/- 0.105; p=0.0144). Four patients who died had undergone in-clinic screening for frailty prior to death. Three of the four were identified as frail by the MFP and CFS. The small number of patients both who died, and who received in-clinic screening with the MFP and CFS prior to death, limited our ability to evaluate which tool best predicted mortality.

3.4.7 Comprehensive Geriatric Assessment

Twenty-two patients identified by the CFS as frail were referred and underwent CGA. Seven pf the twenty-two patients consented to have the details of the assessment included here in aggregate format in order to maintain the privacy and confidentiality of each individual. The seven patients were primarily male (two females) with a mean age of 62 years (range 54-68 years) and a mean known duration of HIV infection of 21 years (range 13-31 years). Each patient had a number of non-HIV comorbidities (range 7-17 comorbidities), polypharmacy (range 4-12 non-ART medications), relative social isolation, functional and cognitive issues. The majority were seen alone, impeding the ability to confirm functional and cognitive status with a collateral historian, such as a family member or friend. The majority also declined cognitive testing, but concerns were present either from the chart or the assessing physician.

CHAPTER FOUR: DISCUSSION

4.1 Summary of Research Findings

In this one-year study in Southern Alberta, 710 patients receiving HIV care were ≥ 50 years of age, representing nearly 40% of SAC patients. Similar to other HIV+ cohorts, the majority of patients were male (85%) between the ages of 50-64 years, with 15% ≥ 65 years. Patients at SAC had been living with HIV infection for many years (mean 16 years) and had been receiving ART for nearly as long (13.7 years) with excellent immune recovery (mean CD4 cell count 610 cells/μL). These demographics are consistent with other HIV cohorts in North America and abroad and reflect increasing longevity of PLWHA.

We employed three measures of frailty screening assessment, two which have been examined in previous HIV cohorts (the Frailty Index and Frailty Phenotype), and one scale that is novel in an HIV cohort, the Clinical Frailty Scale.

Patients who were screened for frailty during a routine clinic visit were older than those who were not screened, but there was no difference between screened and unscreened patients in known duration of HIV infection or duration of ART. Sixty-one patients (8.6%) did not attend a SAC appointment during the study period and therefore were ineligible for in-clinic frailty screening. Patients who attended SAC more than once were eligible for screening only once during the one-year study. Clinic staff identified patients attending SAC for routine follow-up who were ≥ 50 years of age and offered screening. The clinic staff are faced with competing interests when deciding how to use their time during these short follow-up visits. The staff shared that they were more likely to dedicate this time to patients who were older, and whom they intuitively identified as being more vulnerable. This resulted in not all patients being offered screening during the one-year study period, with a bias towards older patients. Individual patients who were approached to be screened for frailty for the most part, were agreeable with very few declining screening, although we did not collect this data.

4.1.1 Frailty Index

The mean frailty index for patients ≥50 years at SAC was 0.35 and was significantly higher in males than in females (0.35 versus 0.33). These findings are intriguing given that in general populations, frailty is more common in females than in males. This requires further study. Patients ≥65 years had slightly higher frailty index values compared to those aged 50-64 years (0.35 versus 0.36) but this was not significant. In regression modelling, duration of ART was associated with frailty, as was CD4 cell count, but age (continuous, years) and known duration of HIV infection were not. Studies investigating the role of ART (specifically, nucleotide reverse transcriptase inhibitors, NRTIs) and the effect on immunological (CD4 count) recovery and telomere length in HIV have had mixed findings, with some suggesting poorer CD4 count recovery and shorter telomere length in patients receiving NRTIs, but other studies not (74-77). This highlights an important area for future study, specifically to determine whether ART, may, to a greater extent impact aging and frailty, than known duration of HIV infection.

With regard to age, these results reflect what is seen in other clinic-based cohorts (such as is seen in heart failure and cancer patients) where FI is higher than the general population at all ages, but is not associated with increasing age, as it is in community-based populations. Our estimate is higher than has been observed in other clinic-based samples, however is similar to the HIV cohort in Italy (mean FI 0.31) (57). In chronic kidney disease patients in Australia (mean age 65 years) the mean FI was 0.25 (78). In coronary artery disease patients in the same community as ours (Calgary, Alberta), the mean FI values ranged from 0.154 to 0.170 depending on the treatment received for CAD (79). These findings suggest that similar to other clinic populations, frailty in HIV is not associated with age as it is in community samples, but rather is higher at all ages. Interestingly, Frailty Index was higher in this cohort than has been observed in other clinic-based samples. If this finding is replicated it deserves further longitudinal investigation to evaluate for potential causative factors (e.g. the role of HIV and ART duration).

The question remains how to incorporate FI into clinical practice. In community-based samples FI cut-offs of ≥ 0.21, ≥ 0.30 and ≥ 0.45 have previously been categorized as frail, more-frail and

most-frail (27). This would result in 90%, 70% and 16% of the SAC cohort ≥ 50 years of age being categorized as frail, more-frail and most-frail, respectively. The more pragmatic approach may be to employ a cut-off which is known to be meaningful in an HIV population. In our study, the 75th percentile of FI values was 0.406, and the mean FI of patients who died was 0.403 (compared to 0.348 for those who survived; p=0.0144). We propose using a range of 0.40 to 0.50 in PLWHA in order to identify the most vulnerable patients, and those most likely to derive benefit. Patients with a FI greater than 0.5, are arguably in a terminal phase of their disease trajectory and may derive less value from CGA, and greater benefit from a palliative approach. A FI greater than 0.40 would identify 178 patients as frail, and a FI of 0.50 would identify 66 patients as frail (and arguably so severely frail that a palliative approach may be more appropriate). Between 0.40 and 0.50, patients may derive benefit from further assessment, such as by means of a Comprehensive Geriatric Assessment. These proposals are exploratory and require further study with prospective evaluation of long-term implications of this approach.

Based on our proposal above, in our region, 112 patients in this cohort would potentially benefit from CGA, at the discretion of the primary SAC provider. Resources would likely not permit this number of patients to be referred for CGA, however, other interventions may include pharmacy review for drug-drug and drug-disease interactions and adjustments for medication omissions and inappropriate prescribing. Additionally, social work, physiotherapy and occupational therapy, and home care may provide resources and benefit to these patients, such as by facilitating access to community resources, adaptations for mobility and for the home, and assistance with daily functioning to permit patients to dwell in their homes for longer. These are areas of future study which are under development and were not addressed within this thesis project.

4.1.2 Clinical Frailty Scale and Modified Frailty Phenotype

The Clinical Frailty Scale and Modified Frailty Phenotype identified 13.5% and 14.2% of patients, respectively, as frail. The Cohen's Kappa test of agreement between the CFS and MFP was κ= 0.3880 (SE 0.0547) which indicates fair agreement. This is within the range observed in

a previous systematic review of frailty prevalence in HIV (24). The observed prevalence approaches that observed in HIV- patients who are 1-2 decades older and is much higher than a similarly-aged HIV- population in Switzerland (prevalence 2.7%) (26). These results were expected, and are in keeping with previous studies, however, the labour intensity of performing these assessments in a busy HIV clinic remain relevant, as does the finding that more than 60% of patients had weak grip strength.

Grip strength has been shown to decline more rapidly in men aging with HIV, and therefore this measure may be suboptimal for use in this population because there may be a fundamental difference in the expression of weakness in PLWHA (60). Variability existed in prior studies with regards to the equipment used, and in the protocol followed to measure handgrip strength. Most studies use the Jamar hand-held dynamometer which has good-to-excellent test-retest ($r>0.80$) (80) and excellent inter-rater ($r=0.98$) (81) reliability, and is accepted as the gold standard (82). Few studies of frailty in PLWHA have provided detail on the protocol used, potentially making comparison of results inaccurate. Variation in protocol, such as seated versus standing and elbow flexed versus extended can affect measurement values. We followed the protocol of the American Society of Hand Therapists (ASHT) (83), which has the greatest clarity and is the most frequently used, in part or in whole, by previous studies.

We observed that clinic staff preferentially screened older patients for frailty, which introduces potential bias. This bias may be minimized by using FI as a screening tool because it would be calculated on every patient without additional clinical time or staff adjudication. We propose that FI be calculated on a yearly basis in PLWHA ≥ 50 years of age. FI does not interfere with clinic flow or add equipment or expense. It can be employed across diverse clinical settings with access to routinely collected health records and would allow for easier comparison between HIV cohorts. The Frailty Phenotype has also been criticized for its lack of inclusion of social and cognitive variables which may contribute to frail status, and recognition that measurement of grip strength has inherent challenges. The FI addresses these weaknesses because these aspects of frailty can be incorporated into the index.

There were 18 deaths in our cohort, and as would be expected death was more common in older patients and in those with lower CD4 cell counts. The frailty index was significantly higher in patients who died (0.40 versus 0.35) raising the potential value of this measure in identifying vulnerable patients who would benefit from increased clinical contact, or a Comprehensive Geriatric Assessment.

4.1.3 Comprehensive Geriatric Assessment

Comprehensive Geriatric Assessment in a small convenience sample of patients who were identified as frail through in-clinic screening with CFS highlighted pertinent and unique characteristics of PLWHA. Each patient had a significant amount of comorbidity, was exposed to non-ART polypharmacy, was relatively socially isolated, and experiencing physical and/or neurocognitive decline (whether subjectively or based on the observations of clinic staff). We propose that these patients would benefit from brief cognitive testing, depression screening, functional screening (e.g. Timed Up and Go test), medication review (looking for drug-drug interactions, and possible referral for pharmacist consultation), and review of the management of the non-HIV-related comorbidities. The analysis of the CGA in PLWHA is exploratory in nature. In previous studies of CGA in older PLWHA it has been shown that older adults aging with HIV experience aging-related concerns that are identified by CGA including falls, urinary incontinence, functional and cognitive impairment, frailty and depression (8).

4.2 Strengths and Limitations

This research has a number of strengths. SAC provides centralized HIV care to all PLWHA in Southern Alberta including males and females, multiple ethnic backgrounds, people who inject drugs, co-infected patients (Hepatitis C or Hepatitis B and HIV), men who have sex with men, and immigrants. First Nations patients cared for at SAC provide an opportunity to determine whether these patients experience aging and frailty at similar rates. In Alberta, HIV incidence rates are 4-8-times higher in First Nations men and women, than non-First Nations people,

respectively (84). We did not study the association between frailty in First Nations people living with HIV compared to non-First Nations people, but this may be an area of future study. Previous frailty prevalence studies have been undertaken in more homogeneous populations, many of which were predominantly male, men-who-have-sex-with men and/or IVD-users without the broad heterogeneity within our cohort.

This research study was the first time, to our knowledge, that the Clinical Frailty Scale (CFS) has been evaluated in a population of individuals with HIV. The advantages of the CFS are the ease of use, correlation with the Frailty Index, predictive ability for health outcomes (21), and minimal added time to complete during routine clinic visits. The Comprehensive Geriatric Assessment has recently been explored in older PLWHA and has the advantage of being considered the "gold standard" (54) for assessment of frailty in older adults. The CGA not only identifies frailty, but additionally provides recommendations for interventions, which are more relevant and patient-centered than simply identifying, without treating frailty. CGA has been shown to improve survival rates and functional status in frail older adults and to lead to more desirable placement destination following acute care admission (68).

Limitations of this study include those inherent to the study design, as well as limitations related to the methods and measurements. Cross-sectional assessment of frailty and potential risk factors leads to inability to draw causal conclusions because of the lack of temporality (all data are collected at the same time; therefore, one cannot, with certainty, attribute exposure as a cause of disease). Cross- sectional design may also be a poor method of evaluating rare outcomes, however, it is assumed, based on previous literature, that frailty is not a rare outcome in this population.

A convenience sample of patients were assessed on more than one occasion and included patients who either died or underwent CGA. This sample formed a small prospective cohort within the larger study. Biases inherent to prospective cohort studies include selection bias (who was screened versus not screened in-clinic for frailty and who was invited for and consented to

CGA), attrition (patients may have moved away or been lost-to-follow-up), missing data (patients may have moved away and/or died), and immortality bias (patients who died may not have survived long enough into the study period to have undergone an in-clinic frailty screen).

Other limitations include those related to the measurement tools: the MFP, FI and CFS, each of which is susceptible to measurement error. We followed rigorous procedures for measurement of each variable, and minimized as much as possible, inter-observer variation in measurement. SAC staff were instructed in the correct method for measuring grip strength, 6-meter walk test, and CFS. Staff adherence to protocol was reviewed throughout the study by JM. In addition, JM repeated the measurement of grip strength, the 6-meter walk and the CFS in patients who participated in the CGA in order to evaluate inter-observer reliability. Intra-observer reliability was assessed by having the same observer measure grip strength, the 6-meter walk, and the CFS in duplicate, on the same study participant. We found no differences on repeat assessment, by either the same observer or a new observer, however statistical analysis of these observations was not performed. Observers signed data collection sheets in order to review results and ensure consistency across study staff.

The findings of the MFP may have influenced the score assigned to the CFS given by the assessing clinician, however this should not be viewed as diagnostic suspicion bias. The information provided by the MFP should not be viewed as introducing prejudice, but rather as providing a more comprehensive clinical assessment of the individual patient. The CFS is designed to be scored based on the assessor having a complete set of clinical information on which to base his or her judgement. The order of data collection should be viewed in the same way, it is the final sum of variables present and absent, rather than the influence of one variable on the next, that defines the outcome of frailty. The agreement between the CFS and MFP was fair (Cohen's Kappa $\kappa = 0.3880$) suggesting that the two measures identified different individuals as frail. Based on this observation, any bias introduced by the order of collection of data did not lead to misclassification bias because the tools classified different people as frail.

4.3 Research Significance, Impact and Knowledge Translation

This research is knowledge-generating. It has given SAC a perspective of the current and future medical conditions and challenges of older PLWHA. These results may improve both personal care as well as prospective program planning.

Potential long-term implications of this research range from better care of aging PLWHA to improved planning for future clinic and societal resources that will be needed to care for HIV+ patients. End-of-project knowledge translation, at the patient and clinic-level may include referral of frail patients for Comprehensive Geriatric Assessment. CGA provides an opportunity to tailor patient-level treatment decisions, such as initiating treatment for osteoporosis, dementia, urinary incontinence or falls.

At the clinic level, this knowledge sharing may lead to developing treatment protocols such as routine screening for frailty and guidelines around when to refer frail patients for CGA in an effort to provide more comprehensive and patient-centered care. Further, knowledge sharing with clinic staff will enable them to identify patients who are potentially frail, as well as gain knowledge about the predictors and consequences of frailty in this population. On a societal level, dissemination of findings to administrators and decision-makers may inform planning for future health care and residential care needs for this population.

In the future, we anticipate using this information to prospectively follow patients to determine the effect of frailty on clinical outcomes such as mortality and hospitalization, in an effort to validate the use of the FI and CFS in PLWHA. Other potential studies include interventional studies exploring the impact of interventions in frail PLWHA, such as more diligently addressing smoking, low physical activity, obesity and social isolation.

REFERENCES

1. Mocroft A. Changing patterns of mortality across Europe in patients Infected with HIV-1. Lancet. 1998;352:1725-30.
2. Palella F. Declining morbidity and mortality among patients with advanced Human Immunodeficiency Virus Infection. N Engl J Med. 1998;338(13):853-60.
3. Lewden C. HIV-Infected Adults With a CD4 Cell Count Greater Than 500 Cells/mm3 on Long-Term Combination Antiretroviral Therapy Reach Same Mortality Rates as the General Population. J Acquir Immune Defic Synd. 2007;46(1):72-7.
4. Mocroft A. Changes in the cause of death among HIV positive subjects across Europe: results from the EuroSIDA study. AIDS. 2002;16:1663-71.
5. CDC. HIV Among People Aged 50 and Over. 2017.
6. Smit M, Brinkman K, Geerlings S, Smit C, Thyagarajan K, Sighem Av, et al. Future challenges for clinical care of an ageing population infected with HIV: a modelling study. The Lancet Infectious Diseases. 2015;15(7):810-8.
7. Krentz HB, Gill MJ. Increased costs of HIV care associated with aging in an HIV-infected population. HIV Med. 2015;16(1):38-47.
8. Greene M. Geriatric Syndromes in Older HIV-Infected Adults. J Acquir Immune Defic Synd. 2015;69(2):161-7.
9. Brown TT. Antiretroviral Therapy and the Prevalence and Incidence of Diabetes Mellitus in the Multicenter AIDS Cohort Study. Arch Intern Med. 2005;165:1179-84.
10. Guaraldi G. Premature Age-Related Comorbidities Among HIV-Infected Persons Compared with the General Population. Clin Infect Dis. 2011;53(11):1120-6.
11. Triant VA, Lee H, Hadigan C, Grinspoon SK. Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease. J Clin Endocrinol Metab. 2007;92(7):2506-12.
12. Hsue P. Role of HIV and Human Herpes Virus-8 Infection in Pulmonary Arterial Hypertension. AIDS. 2008;22:825-33.
13. Kirk GD, Merlo C, P OD, Mehta SH, Galai N, Vlahov D, et al. HIV infection is associated with an increased risk for lung cancer, independent of smoking. Clin Infect Dis. 2007;45(1):103-10.
14. Arnsten J. Decreased Bone Mineral Density and Increased Fracture Risk in Aging Men with or at Risk for HIV Infection. AIDS. 2007;21:617-23.
15. Weber R. Liver-Related Deaths in Persons Infected with the Human Immunodeficiency Virus. The D:A:D Study. Arch Intern Med. 2006;166:1632-41.
16. Choi AI, Rodriguez RA, Bacchetti P, Bertenthal D, Volberding PA, O'Hare AM. Racial differences in end-stage renal disease rates in HIV infection versus diabetes. J Am Soc Nephrol. 2007;18(11):2968-74.
17. Desquilbet L. HIV-1 Infection is Associated with an Earlier Occurrence of a Phenotype Related to Frailty. J Gerontol A Biol Sci Med Sci. 2007;62A(11):1279-86.
18. Deeks SG, Phillips AN. HIV infection, antiretroviral treatment, ageing, and non-AIDS related morbidity. BMJ. 2009;338:a3172.
19. Bergman H. Frailty: An Emerging Research and Clinical Paradigm-Issues and Controversies. J Gerontol A Biol Sci Med Sci. 2007;62A(7):731-7.
20. Rockwood K. Prevalence, attributes and outcomes of fitness and frailty in community-dwelling older adults: report from the Canadian Study of Health and Aging. J Gerontol A Biol Sci Med Sci. 2004;59(12):1310-17.
21. Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ. 2005;173(5):489-95.

22. Fried L. Frailty in Older Adults: Evidence for a Phenotype. J Gerontol A Biol Sci Med Sci. 2001;56A(3):M146-M56.
23. Searle SD, Mitnitski A, Gahbauer EA, Gill TM, Rockwood K. A standard procedure for creating a frailty index. BMC Geriatr. 2008;8:24.
24. Levett TJ, Cresswell FV, Malik MA, Fisher M, Wright J. Systematic Review of Prevalence and Predictors of Frailty in Individuals with Human Immunodeficiency Virus. J Am Geriatr Soc. 2016;64(5):1006-14.
25. Althoff KN, Jacobson LP, Cranston RD, Detels R, Phair JP, Li X, et al. Age, comorbidities, and AIDS predict a frailty phenotype in men who have sex with men. J Gerontol A Biol Sci Med Sci. 2014;69(2):189-98.
26. Guesseous I LJ, Bowling CB, Theler JM, Paccaud F, Gaspoz JM, McClellan W. Prevalence of frailty indicators and association with socioeconomic status in middle-aged and older adults in a Swiss region with universal health insurance coverage: a population-based cross-sectional study. J Aging Res. 2014.
27. Hoover M RM, Sanmartin C, Bernier J. Validation of an index to estimate the prevalence of frailty among community-dwelling seniors. Statistics Canada Health Reports. 2015;24(9).
28. Akgun K. An Adapted Frailty-Related Phenotype and the VACS Index as Predictors of Hospitalization and Mortality in HIV-Infected and Uninfected Individuals. J Acquir Immune Defic Synd. 2014;67(4):397-404.
29. Piggott DA, Muzaale AD, Mehta SH, Brown TT, Patel KV, Leng SX, et al. Frailty, HIV infection, and mortality in an aging cohort of injection drug users. PLoS One. 2013;8(1):e54910.
30. Ianas V, Berg E, Mohler MJ, Wendel C, Klotz SA. Antiretroviral therapy protects against frailty in HIV-1 infection. J Int Assoc Provid AIDS Care. 2013;12(1):62-6.
31. Onen NF, Agbebi A, Shacham E, Stamm KE, Onen AR, Overton ET. Frailty among HIV-infected persons in an urban outpatient care setting. J Infect. 2009;59(5):346-52.
32. Pathai S. Frailty in HIV-Infected Adults in South Africa. J Acquir Immune Defic Synd. 2013;62(1):43-51.
33. Shah K, Hilton TN, Myers L, Pinto JF, Luque AE, Hall WJ. A new frailty syndrome: central obesity and frailty in older adults with the human immunodeficiency virus. J Am Geriatr Soc. 2012;60(3):545-9.
34. Erlandson K. Risk Factors for Falls in HIV-Infected Persons. J Acquir Immune Defic Synd. 2012;61(4):484-9.
35. Marquine MJ. The Veterans Aging Cohort Study Index is Associated with Concurrent Risk for Neurocognitive Impairment. J Acquir Immune Defic Synd. 2014;65:190-7.
36. Wallace LM, Ferrara M, Brothers TD, Garlassi S, Kirkland SA, Theou O, et al. Lower Frailty Is Associated with Successful Cognitive Aging Among Older Adults with HIV. AIDS Res Hum Retroviruses. 2017;33(2):157-63.
37. Ding Y, Lin H, Shen W, Wu Q, Gao M, He N. Interaction Effects between HIV and Aging on Selective Neurocognitive Impairment. Journal of neuroimmune pharmacology : the official journal of the Society on NeuroImmune Pharmacology. 2017.
38. Erlandson KM, Wu K, Koletar SL, Kalayjian RC, Ellis RJ, Taiwo B, et al. Association Between Frailty and Components of the Frailty Phenotype With Modifiable Risk Factors and Antiretroviral Therapy. The Journal of infectious diseases. 2017;215(6):933-7.
39. Erlandson KM, Allshouse AA, Jankowski CM, Duong S, Mawhinney S, Kohrt WM, et al. Comparison of functional status instruments in HIV-infected adults on effective antiretroviral therapy. HIV Clin Trials. 2012;13(6):324-34.
40. Justice AC, Freiberg MS, Tracy R, Kuller L, Tate JP, Goetz MB, et al. 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 : an official publication of the Infectious Diseases Society of America. 2012;54(7):984-94.

41. Justice AC, Modur SP, Tate JP, Althoff KN, Jacobson LP, Gebo KA, et al. Predictive accuracy of the Veterans Aging Cohort Study index for mortality with HIV infection: a North American cross cohort analysis. Journal of acquired immune deficiency syndromes (1999). 2013;62(2):149-63.
42. Tate JP JA, Hughes MD et al. An internationally generalizable risk index for mortality after one year of antiretroviral therapy. AIDS. 2013;27(4):563-72.
43. Womack JA GJ, Gibert C, Brandt CA. Physiologic Frailty and Fragility Fracture in HIV-Infected Male Veterans. CID. 2013;56(10):1498-504.
44. Marquine MJ, Umlauf A, Rooney AS, Fazeli PL, Gouaux BD, Paul Woods S, et al. The veterans aging cohort study index is associated with concurrent risk for neurocognitive impairment. Journal of acquired immune deficiency syndromes (1999). 2014;65(2):190-7.
45. Marquine MJ, Montoya JL, Umlauf A, Fazeli PL, Gouaux B, Heaton RK, et al. The Veterans Aging Cohort Study (VACS) Index and Neurocognitive Change: A Longitudinal Study. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2016;63(5):694-702.
46. Pathai S, Bajillan H, Landay AL, High KP. Is HIV a model of accelerated or accentuated aging? J Gerontol A Biol Sci Med Sci. 2014;69(7):833-42.
47. Kuller LH, Tracy R, Belloso W, De Wit S, Drummond F, Lane HC, et al. Inflammatory and coagulation biomarkers and mortality in patients with HIV infection. PLoS Med. 2008;5(10):e203.
48. Leng SX CA, Andersen RE, Blackman MR, et al. Serum levels of insulin-like growth factor-I (IGF-I) and dehydroepiandrosterone sulfate (DHEA-S), and their relationships with serum interleukin-6, in the geriatric syndrome of frailty. Aging clinical and experimental research. 2004;16:153-7.
49. Erlandson KM, Ng DK, Jacobson LP, Margolick JB, Dobs AS, Palella FJ, Jr., et al. Inflammation, Immune Activation, Immunosenescence, and Hormonal Biomarkers in the Frailty-Related Phenotype of Men With or at Risk for HIV Infection. The Journal of infectious diseases. 2017;215(2):228-37.
50. Wallet MA, Buford TW, Joseph AM, Sankuratri M, Leeuwenburgh C, Pahor M, et al. Increased inflammation but similar physical composition and function in older-aged, HIV-1 infected subjects. BMC Immunol. 2015;16:43.
51. Erlandson KM, Allshouse AA, Jankowski CM, Lee EJ, Rufner KM, Palmer BE, et al. Association of functional impairment with inflammation and immune activation in HIV type 1-infected adults receiving effective antiretroviral therapy. J Infect Dis. 2013;208(2):249-59.
52. Piggott DA, Varadhan R, Mehta SH, Brown TT, Li H, Walston JD, et al. Frailty, Inflammation, and Mortality Among Persons Aging With HIV Infection and Injection Drug Use. The journals of gerontology Series A, Biological sciences and medical sciences. 2015;70(12):1542-7.
53. Inouye SK SS, Tinetti ME, Kuchel GA. Geriatric Syndromes: clinical, research, and policy implications of a core geriatric concept. J Am Geriatr Soc. 2007;55(5):780-91.
54. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. The Lancet. 2013;381(9868):752-62.
55. Piggott DA, Muzaale AD, Varadhan R, Mehta SH, Westergaard RP, Brown TT, et al. Frailty and Cause-Specific Hospitalization Among Persons Aging With HIV Infection and Injection Drug Use. The journals of gerontology Series A, Biological sciences and medical sciences. 2017;72(3):389-94.
56. Guaraldi G, Malagoli, A, Theou, O, et al. Correlates of frailty phenotype and frailty index and their associations with clinical outcomes. HIV Medicine. 2017;18:764-71.
57. Guaraldi G, Brothers, T.D., Zona, S, et al. A frailty index predicts survival and incident multimorbidity independent of markers of HIV disease severity. AIDS. 2015;29:1633-41.
58. Brothers TD, Kirkland, S, Theou, O, et al. Predictors of transitions in frailty severity and mortality among people aging with HIV. PLoS One. 2017;12(10):e0185352.
59. Schrack JA AK, Jacobson LP. Accelerated Longitudinal Gait Speed Decline in HIV-Infected Older Men. J Acquir Immune Defic Syndr. 2015;7(4):370-6.

60. Schrack JA, Jacobson LP, Althoff KN, Erlandson KM, Jamieson BD, Koletar SL, et al. Effect of HIV-infection and cumulative viral load on age-related decline in grip strength. AIDS. 2016;30(17):2645-52.
61. Juma S, Taabazuing MM, Montero-Odasso M. Clinical Frailty Scale in an Acute Medicine Unit: a Simple Tool That Predicts Length of Stay. Can Geriatr J. 2016;19(2):34-9.
62. Basic D, Shanley C. Frailty in an older inpatient population: using the clinical frailty scale to predict patient outcomes. J Aging Health. 2015;27(4):670-85.
63. Ritt M, Bollheimer LC, Sieber CC, Gassmann KG. Prediction of one-year mortality by five different frailty instruments: A comparative study in hospitalized geriatric patients. Arch Gerontol Geriatr. 2016;66:66-72.
64. Rockwood K MA. Limits to Deficit Accumulation in Elderly People. Mechanisms of ageing and development. 2006;127(5):494-6.
65. Abara WE, Adekeye OA, Xu J, Heiman HJ, Rust G. Correlates of Combination Antiretroviral Adherence Among Recently Diagnosed Older HIV-Infected Adults Between 50 and 64 years. AIDS and behavior. 2016;20(11):2674-81.
66. Shah KN, Majeed Z, Yoruk YB, Yang H, Hilton TN, McMahon JM, et al. Enhancing physical function in HIV-infected older adults: A randomized controlled clinical trial. Health psychology : official journal of the Division of Health Psychology, American Psychological Association. 2016;35(6):563-73.
67. Kojima G, Avgerinou, C, Iliffe, S, Walters, K. Adherence to Mediterranean Diet Reduces Incident Frailty Risk: Systematic Review and Meta-Analysis. Journal of the American Geriatrics Society. 2018;66(4):783-8.
68. Ellis G, Whitehead MA, Robinson D, O'Neill D, Langhorne P. Comprehensive geriatric assessment for older adults admitted to hospital: meta-analysis of randomised controlled trials. BMJ. 2011;343:d6553.
69. Guaraldi G, Brothers TD, Zona S, Stentarelli C, Carli F, Malagoli A, et al. A frailty index predicts survival and incident multimorbidity independent of markers of HIV disease severity. AIDS. 2015;29(13):1633-41.
70. Wong S. Grip Strength Reference Values for Canadians Aged 6 to 79: Canadian Health Measures Survey, 2007 to 2013. Statistics Canada Health Reports. 2016;27(10):3-10.
71. Cesari M, Kritchevsky SB, Penninx BW, Nicklas BJ, Simonsick EM, Newman AB, et al. Prognostic value of usual gait speed in well-functioning older people--results from the Health, Aging and Body Composition Study. J Am Geriatr Soc. 2005;53(10):1675-80.
72. Oursler KK, Goulet JL, Crystal S, Justice AC, Crothers K, Butt AA, et al. Association of age and comorbidity with physical function in HIV-infected and uninfected patients: results from the Veterans Aging Cohort Study. AIDS Patient Care STDS. 2011;25(1):13-20.
73. Hogan DB. Frailty Index in Canadian Longitudinal Study of Aging (CLSA) patients. In: McMillan JM, editor. Canada2018.
74. Pathai S LS, Gilbert CE, McGuinness D, McGlynn L, Weiss HA, Port J, Christ T, Barclay K, Wood R, Bekker LG, Shiels PG. Accelerated biological ageing in HIV-infected individuals in South Africa: a case-control study. AIDS. 2013;27:2375-84.
75. Blanco JR JI, Martinez A, Siles E, Larrayoz IM, Canuelo A, Gutierrez F, Gonzalez-Garcia J, Vidal F, Moreno S. Shorter telomere length predicts poorer immunological recovery in virologically suppressed HIV-1-infected patients treated with combined antiretroviral therapy. JAIDS. 2015;68(1):21-9.
76. Solomon A TS, Leeansyah E, Arribas J, Hill A, Van Delft Y, Moecklinghoff C, Lewin SR. No difference in the rate of change in telomere length or telomerase activity in HIV-infected patients after three years of darunavir/ritonavir with and without nucleoside analogues in the MONET trial. Plos ONE. 2014;9(11):e109718.

77. Montejano R S-AN, Monge S, Bernardino JI, Perez-Valero I, Montes ML, Valencia E, Martin-Carbonero L, Moreno V, Gonzalez-Garci J, Arnalich F. Impact of Antiretroviral Treatment Containing Tenofovir Difumarate on the Telomere Length of Aviremic HIV-Infected Patients. JAIDS. 2017;76:102-9.
78. Hubbard RE PN, Smith M, Dawson B, Lambat Z, Bak M, Best J and Johnson DW. Feasibility and construct validity of a frailty index for patients with chronic kidney disease. Australasian Journal on Ageing. 2015;34:E9-E12.
79. Freiheit EA HD, Patten SB, Wunsch H, Anderson T, Ghali WA, Knudtson M and Maxwell CJ. Frailty trajectories after treatment for coronary artery disease in older patients. Circ Cardiovasc Qual Outcomes. 2016;9:230-8.
80. Mathiowetz V. Reliability and validity of grip and pinch strength evaluations. J Hand Surg. 1984;9:222-6.
81. Peolsson A. Intra- and inter-tester reliability and reference values for hand strength. J Rehabil Med. 2001;33:36-41.
82. Roberts HC, Denison HJ, Martin HJ, Patel HP, Syddall H, Cooper C, et al. A review of the measurement of grip strength in clinical and epidemiological studies: towards a standardised approach. Age Ageing. 2011;40(4):423-9.
83. Fess E. Grip Strength, 2nd Edition. American Society of Hand Therapists. 1992.
84. Alberta Health HS, Quality and Performance Division, Analytics and Performance Reporting Branch. HIV incidence among first nations people in Alberta: age-standardized incidence rates of HIV by First Nations status, Alberta, 2012-2016. In: Alberta Health HS, Quality and Performance Division, editor. Alberta, Canada: Government of Alberta; 2018.

Table 1. Prevalence of frailty in previously studied HIV populations.

Author Year	Population	Age (years)	% Male	Population N	Frailty Prevalence (%)	Frailty Criteria
Althoff 2013	MACS, MSM	53.8 frail, 50.5 nonfrail (median)	100	1,946	28.6 (12) *	Modified FP (≥3/5 criteria
Desquilbet 2007	MACS	39 (median)	100	245	13.9 (7.2) *	FRP (≥3/4 criteria
Desquilbet 2009	MACS	45 (median)	100	106	5.4	FRP (≥3/4 criteria
Desquilbet 2011	MACS	43 (median)	100	596	13.9	FRP (≥3/4 criteria
Erlandson 2012	University clinic	50.8 (median)	85	359	7.5	Modified FP (≥3/5 criteria)
Greene 2014	Community study	57 (median)	94	142	8.5	FP (≥3/5 criteria)
Ianas 2012	Convenience sample	21-78 (range)	74	100	19	Modified FP (≥3/5 criteria)
Onen 2009	Convenience sample	41.7 (mean)	71	445	9	Modified FP (≥3/5 criteria)
Pathai 2013	Community study	41.1 (mean)	27	504	19.4	Modified FP (≥3/5 criteria)
Piggott 2013	AIDS Linked to IntraVenous Experience; PWID	48.7 (median)	63	1,230	14.6	Modified FP (≥3/5 criteria)
Sandkovsky 2013	University clinic Pilot study	20-70 (range)	71	41	17.1	Modified FP (≥3/5 criteria)
Terzian 2009	Women's Interagency HIV study	41 (median)	0	1,781	9	Modified FP (≥3/5 criteria)

Legend. MACS Multicenter Aids Cohort Study; MSM Men who have Sex with Men; FP Frailty Phenotype; FRP Frailty Related Phenotype; PWID People Who Inject Drugs

*the first prevalence estimate was calculated using total number of individuals in the denominator. The prevalence estimate in brackets () was calculated using the total number of person-visits in the denominator.

Adapted from: Levett TJ, Cresswell FV, Malik MA, Fisher M and Wright J. Systematic Review of Prevalence and Predictors of Frailty in Individuals with Human Immunodeficiency Virus. J Am Geriatr Soc 64: 1006-1012; 2016.

Table 2. **Frailty prevalence in general non-HIV population studies.**

Author Year	Country	Prevalence of Frailty	Frailty Measure	Population
Hoover 2015	Canada	16% 65-74 years 28.6% 75-84 years 52.1% 85+ years	Frailty Index >0.21	Canadian Community Health Survey 59% female
Guessous 2014	Switzerland	2.7% 50-65 years 7.8% entire cohort	FRP (≥4/5 criteria)	Swiss community-based study 51% female
Fried 2001	USA	7%	FP	Cardiovascular Health Study 65-101 years 58% female

Legend. FP Frailty Phenotype; FRP Frailty Related Phenotype

Table 3. Southern Alberta Clinic patient characteristics. Comparison of the entire SAC cohort to the cohort aged 50 years and above. Including sex, risk for acquisition of HIV infection and ethnicity.

	Entire SAC cohort	Cohort ≥ 50 years
Sex		
Male %	74%	85%
Female %	26%	15%
Risk Description		
Homosexual	37.67%	43.24%
Heterosexual	22.20%	21.27%
Heterosexual and endemic area	18.81%	10.28%
Heterosexual and IVDU	6.83%	8.59%
Bisexual	6.22%	10.42%
Unknown	3.9%	1.41%
Homosexual and IVDU	1.28%	1.41%
Bisexual and intravenous drug use (IVDU)	1.13%	1.69%
Blood transfusion	0.92%	1.55%
Maternal-fetal transmission	0.87%	0
Hemophilia	0.15%	0.14%
Ethnic Description		
Caucasian	52.21%	74.37%
African-Canadian	25.49%	11.69%
Aboriginal	6.78%	4.37%
Indo-Asian	4.78%	3.52%
Hispanic	3.03%	1.13%
Unknown	2.72%	0.85%
East Asian	2.47%	1.55%
Other	1.49%	0.85%
Metis	0.98%	1.69%
Inuit	0.05%	0

Table 4. Study Population Characteristics

Total number of patients	712
Age, mean years (+/- SD)	58.2 (6.5)
Age, range years	50-90
Age, median years (IQR)	56 (53-62)
Number of patients between 50-64 years (%)	609 (85.5)
Number of patients >65 years (%)	103 (14.5)
Number of male patients (%)	602 (85)
Known duration of HIV infection, mean years (+/-SD)	16.3 (8.3)
Known duration of HIV infection, median (IQR)	16 (10-23)
Known duration of HIV infection, range years	0-35
Duration of ART, mean years (+/- SD)	13.7 (7.5)
Duration of ART, median years (IQR)	13 (7-20)
Current CD4 cell count, mean cells/uL (+/-SD)	609.5 (324.2)
Current CD4 cell count, median cells/uL (IQR)	579 (559-603)
Number of patients with CD4 cell count ≤200 (%)	50 (7)
Number of patients with CD4 cell count >200 (%)	662 (93)
Number of patients with CD4 cell count 0-75 (%)	12 (1.7)
Number of patients with CD4 cell count 76-200 (%)	38 (5.4)
Number of patients with CD4 cell count 201-500 (%)	206 (29.4)
Number of patients with CD4 cell count >500 (%)	445 (63.5)
Nadir CD4 cell count, mean (+/-SD)	183.6 (155.3)
Nadir CD4 cell count, median (IQR)	158.5 (140-176)
Nadir CD4 cell count, range	1 to 1094
Number of patients with nadir CD4 cell count <200 (%)	422 (59.3)
Number of patients with nadir CD4 cell count ≥ 200 (%)	290 (40.7)
Number of patients with undetectable viral load (%)	654 (92.1)
Number of patients with detectable viral load (%)	56 (7.9)
Smoking, number (%)	243 (38.3)
Deaths, number (%)	18 (2.5)
Deaths, mean age years (+/-SD)	63.2 (9.9)
Survivors, mean age years (+/- SD)	58.1 (0.2)

Table 5. Characteristics of screened and unscreened patients

	Screened	**Not screened**	***p-value***
Screened with Clinical Frailty Scale, number (%)	334 (47)	378 (53)	
Screened with Modified Frailty Phenotype, number (%)	338 (47)	374 (53)	
Age, mean years (+/-SD)	59.1 (6.6)	57.5 (6.4)	0.0005
Known duration of infection, mean years (+/-SD)	16.8 (8.4)	15.9 (8.1)	0.0788
Duration of ART, mean years (+/-SD)	14.1 (7.6)	13.4 (7.4)	0.134
Current CD4 cell count, mean (+/-SD)	600.2 (289.9)	617.9 (352.5)	0.2354
Nadir CD4 cell count, mean (+/-SD)	173 (147.4)	193 (161.6)	0.0436

Table 6. Frailty Index Values

Frailty Index, mean (+/- SD)	0.349 (0.105)	
Frailty Index, range	0.09375-0.65625	
Frailty Index, median (IQR)	0.344 (0.281-0.406)	
Frailty Index, males mean (+/- SD)	0.353 (0.105)	p=0.0219
Frailty Index, females mean (+/- SD)	0.330 (0.107)	
Frailty Index, over 65 years of age, mean (+/- SD)	0.362 (0.123)	p=0.1029
Frailty Index, aged 50-64 years, mean (+/- SD)	0.347 (0.102)	
Frailty Index of patients screened with CFS and MFP, mean (+/-SD)	0.367 (0.093)	p<0.0001
Frailty Index of patients not screened with CFS or MFP, mean (+/-SD)	0.334 (0.112)	
Frailty Index, mean (+/-SD) for current CD4 cell count ≤ 200 cells/µL	0.409 (0.121)	p<0.0001
Frailty Index, mean (+/-SD) for current CD4 cell count >200 cells/µL	0.345 (0.102)	
Number of patients with frailty index >0.21 (%)	641 (90.3)	
Number of patients with frailty index >0.35 (%)	340 (47.8)	
Frailty Index, 95th percentile	0.531	
Frailty Index, 90th percentile	0.469	
Frailty Index, 80th percentile	0.438	
Frailty Index, 75th percentile	0.406	

Table 7. Linear regression. Association among risk factors (continuous variables) and Frailty Index value (continuous outcome).

	Beta coefficient (Standard Error)	*p-value*
Age (years, continuous)	0.0008987 (0.0005856)	0.125
Duration of known HIV infection (years, continuous)	0.0010005 (0.0008993)	0.266
Duration of ART (years, continuous)	0.0027838 (0.0005165)	<0.0001
Nadir CD4 cell count (cell/µL)	-0.0000936 (0.0000289)	0.001
Current CD4 cell count (cells/µL)	-0.0000311 (0.000013)	0.017

Table 8. Characteristics of patients screened for frailty using the Clinical Frailty Scale

	Frail	Non-frail	*p-value*
Number of patients (%)	45 (13.5)	289 (86.5)	
Age, mean years (+/-SD)	63.5 (8.9)	58.4 (6.0)	p<0.0001
Known duration of infection, mean years (+/-SD)	16.2 (8.0)	16.9 (8.5)	p=0.3064
Duration of ART, mean years (+/-SD)	14.6 (7.4)	14.0 (7.6)	p=0.3057
Current CD4 cell count, mean (+/-SD)	534.7 (348.0)	610.5 (279.1)	p=0.0515
Nadir CD4 cell count, mean (+/-SD)	133.7 (130.4)	179.1 (149.1)	p=0.0273

Table 9. Characteristics of patients screened for frailty using the Modified Frailty Phenotype

	Frail	Non-frail	*p-value*
Number of patients (%)	48 (14.2)	290 (85.8)	
Age, mean years (+/-SD)	60.3 (6.8)	59.0 (6.7)	p=0.0977
Known duration of infection, mean years (+/-SD)	16.6 (8.3)	16.9 (8.5)	p=0.3907
Duration of ART, mean years (+/-SD)	14.5 (7.1)	14.1 (7.7)	p=0.3778
Current CD4 cell count, mean (+/-SD)	620.8 (398.4)	599.5 (277.6)	p=0.3237
Nadir CD4 cell count, mean (+/-SD)	166 (146.6)	175 (147.3)	p=0.3475

Table 10. Percentage of patients displaying individual components of the Modified Frailty Phenotype.

	Yes	No
Frail?	14%	86%
Weak grip strength?	61%	39%
Self-reported exhaustion?	26.6%	73.4%
Unintentional weight loss?	24.6%	75.4%
Slow walking speed? (<1 meter/second)	13%	87%
Functional impairment?	8.3%	91.7%

Table 11. Cohen's Kappa values of the association between individual components of the Modified Frailty Phenotype and the identification of frailty defined as 3 or more individual Modified Frailty Phenotype components.

	Cohen's Kappa Coefficient
Functional impairment	0.6178
Self-reported exhaustion	0.5197
Slow walking speed	0.5107
Unintentional weight loss	0.3134
Weak grip strength	0.1381

Table 12. Agreement between the frailty measures in identification of frailty. Cohen's Kappa values and standard error (SE).

	Clinical Frailty Scale	**Modified Frailty Phenotype**
Clinical Frailty Scale	-	-
Modified Frailty Phenotype	0.3880 (SE 0.0547)	-
Frail (FI ≥ 0.21)	0.0083 (SE 0.0096)	0.0095 (SE 0.0100)
More-Frail (FI ≥ 0.30)	0.0469 (SE 0.0215)	0.0442 (SE 0.0223)
Most-Frail (FI ≥ 0.45)	0.1870 (SE 0.0536)	0.1280 (SE 0.0540)

Table 13. Characteristics of patients who died during the one-year study

	Deceased	**Survived**	***p-value***
Number of patients (%)	18 (2.5)	694 (97.5)	
Age, mean years (+/-SD)	63.2 (9.9)	58.1 (6.4)	p=0.0005
Known duration of infection, mean years (+/-SD)	18.8 (7.2)	16.3 (8.3)	p=0.0965
Duration of ART, mean years (+/-SD)	16.3 (6.2)	16.3 (6.2)	p=0.0686
Frailty Index, mean (+/-SD)	0.403 (0.116)	0.348 (0.105)	p=0.0144
Current CD4 cell count, mean (+/-SD)	377.8 (269.8)	615.6 (323.4)	p=0.001

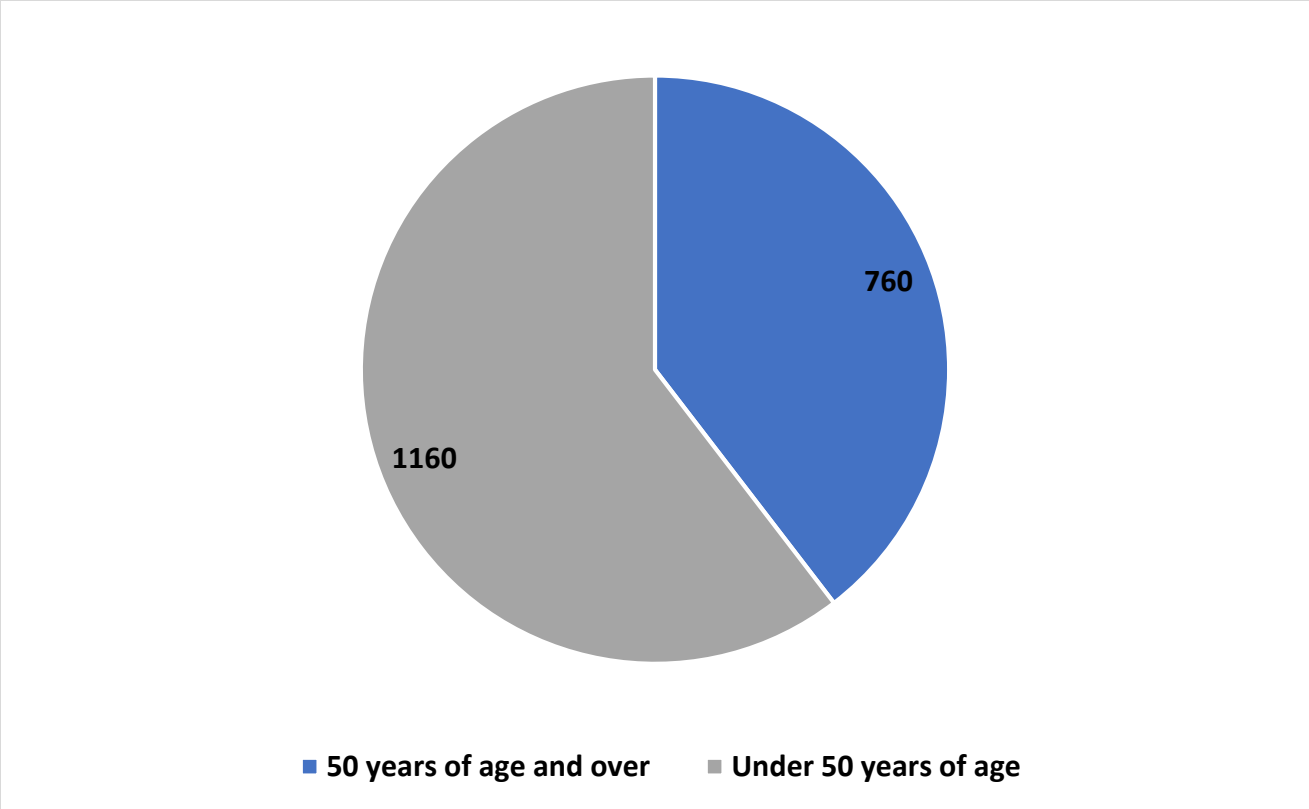
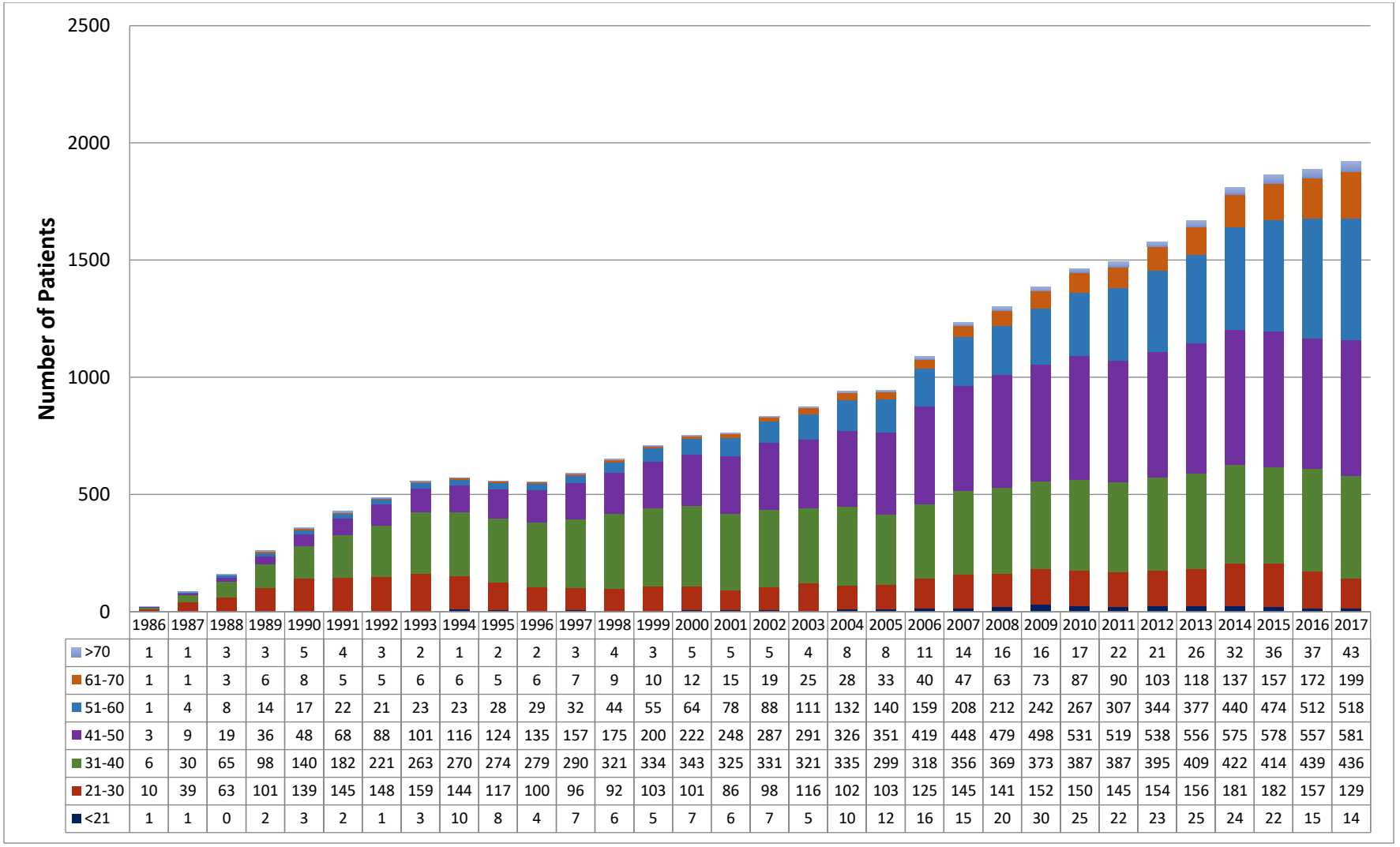
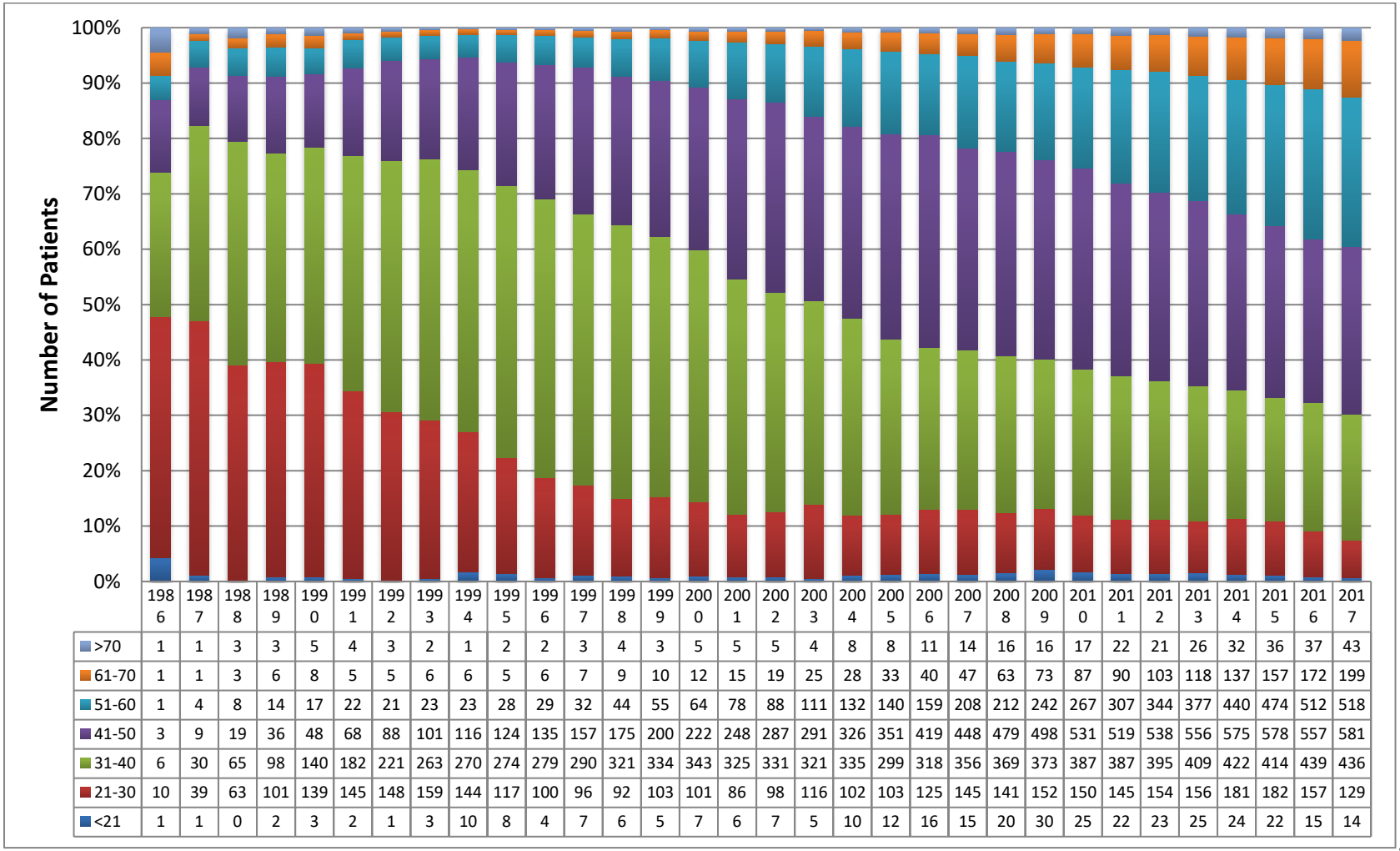


Figure 1. Number of active patients 50 years of age and over compared to under 50 years of age at the Southern Alberta Clinic at the end of 2017.



	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
>70	1	1	3	3	5	4	3	2	1	2	2	3	4	3	5	5	5	4	8	8	11	14	16	16	17	22	21	26	32	36	37	43
61-70	1	1	3	6	8	5	5	6	6	5	6	7	9	10	12	15	19	25	28	33	40	47	63	73	87	90	103	118	137	157	172	199
51-60	1	4	8	14	17	22	21	23	23	28	29	32	44	55	64	78	88	111	132	140	159	208	212	242	267	307	344	377	440	474	512	518
41-50	3	9	19	36	48	68	88	101	116	124	135	157	175	200	222	248	287	291	326	351	419	448	479	498	531	519	538	556	575	578	557	581
31-40	6	30	65	98	140	182	221	263	270	274	279	290	321	334	343	325	331	321	335	299	318	356	369	373	387	387	395	409	422	414	439	436
21-30	10	39	63	101	139	145	148	159	144	117	100	96	92	103	101	86	98	116	102	103	125	145	141	152	150	145	154	156	181	182	157	129
<21	1	1	0	2	3	2	1	3	10	8	4	7	6	5	7	6	7	5	10	12	16	15	20	30	25	22	23	25	24	22	15	14

Figure 2. Age of active Southern Alberta Clinic patients at the end of 2017.



	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
>70	1	1	3	3	5	4	3	2	1	2	2	3	4	3	5	5	5	4	8	8	11	14	16	16	17	22	21	26	32	36	37	43
61-70	1	1	3	6	8	5	5	6	6	5	6	7	9	10	12	15	19	25	28	33	40	47	63	73	87	90	103	118	137	157	172	199
51-60	1	4	8	14	17	22	21	23	23	28	29	32	44	55	64	78	88	111	132	140	159	208	212	242	267	307	344	377	440	474	512	518
41-50	3	9	19	36	48	68	88	101	116	124	135	157	175	200	222	248	287	291	326	351	419	448	479	498	531	519	538	556	575	578	557	581
31-40	6	30	65	98	140	182	221	263	270	274	279	290	321	334	343	325	331	321	335	299	318	356	369	373	387	387	395	409	422	414	439	436
21-30	10	39	63	101	139	145	148	159	144	117	100	96	92	103	101	86	98	116	102	103	125	145	141	152	150	145	154	156	181	182	157	129
<21	1	1	0	2	3	2	1	3	10	8	4	7	6	5	7	6	7	5	10	12	16	15	20	30	25	22	23	25	24	22	15	14

Figure 3. Percentage distribution of active Southern Alberta Clinic patients at the end of 2017

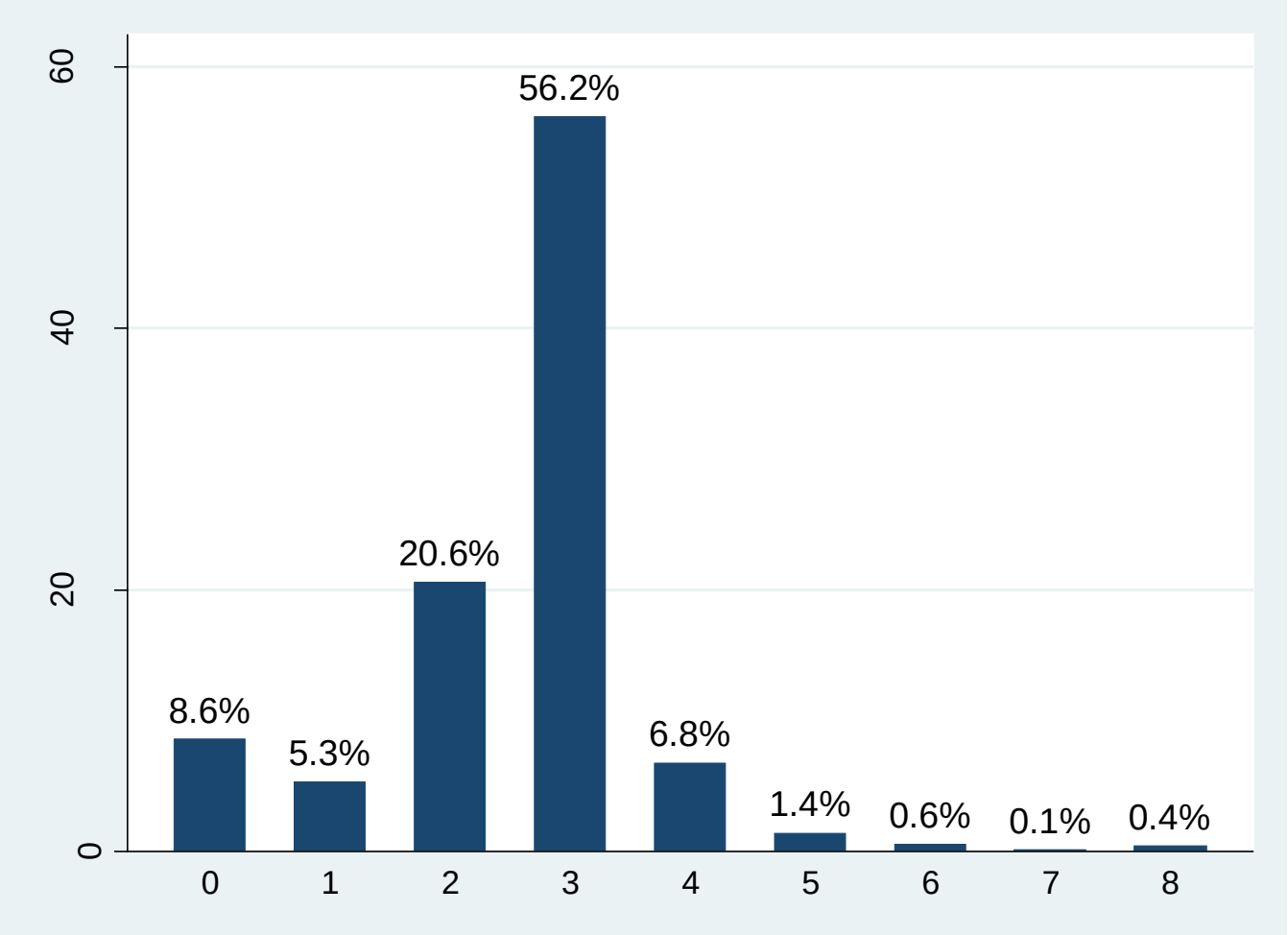


Figure 4. Number of clinics attended by SAC patients ≥ 50 years of age during the one-year study period November 1,2016-October 31, 2017.

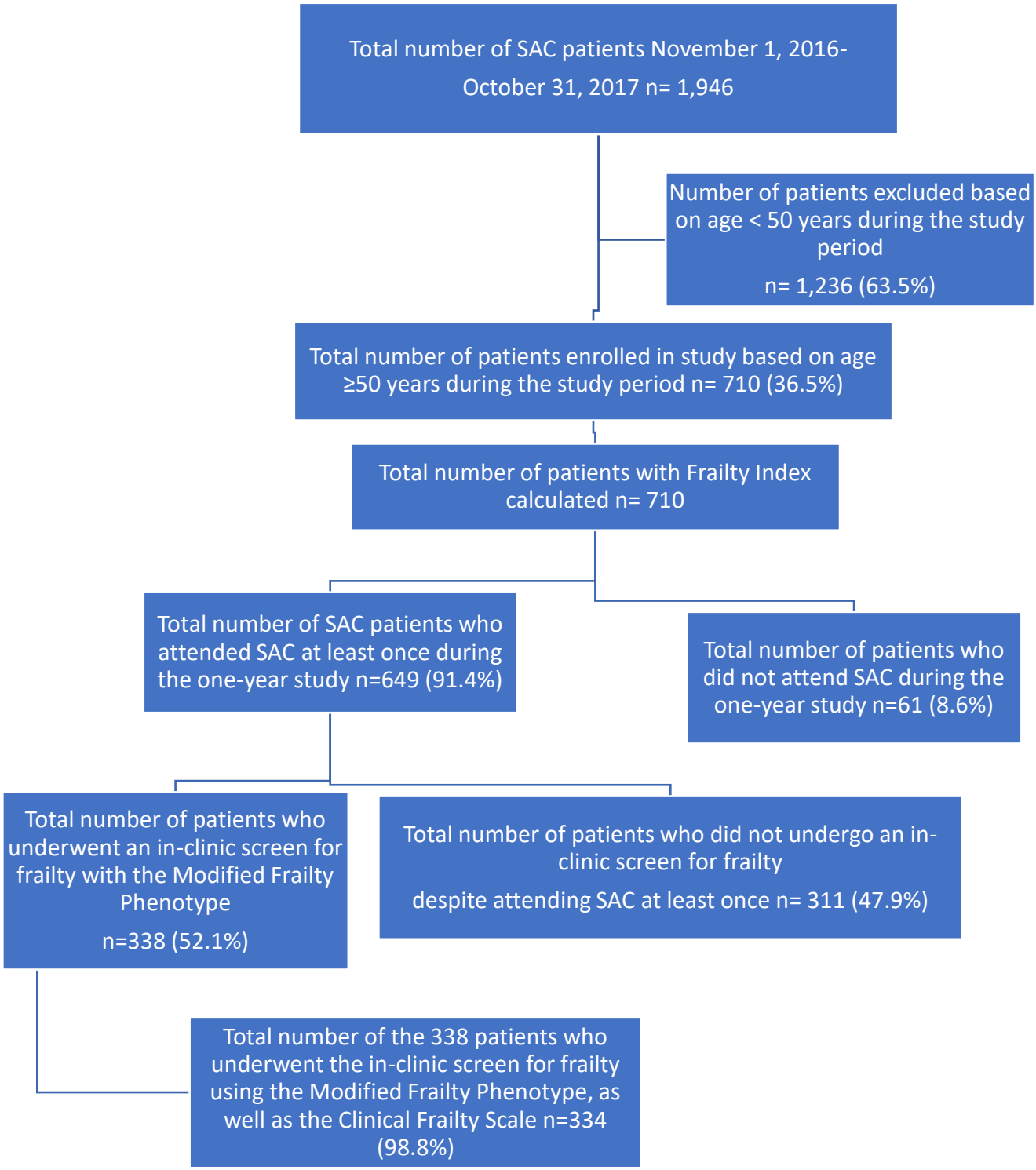


Figure 5. Flow Diagram of patient enrolment at Southern Alberta Clinic for the study period November 1, 2016- October 31, 2017

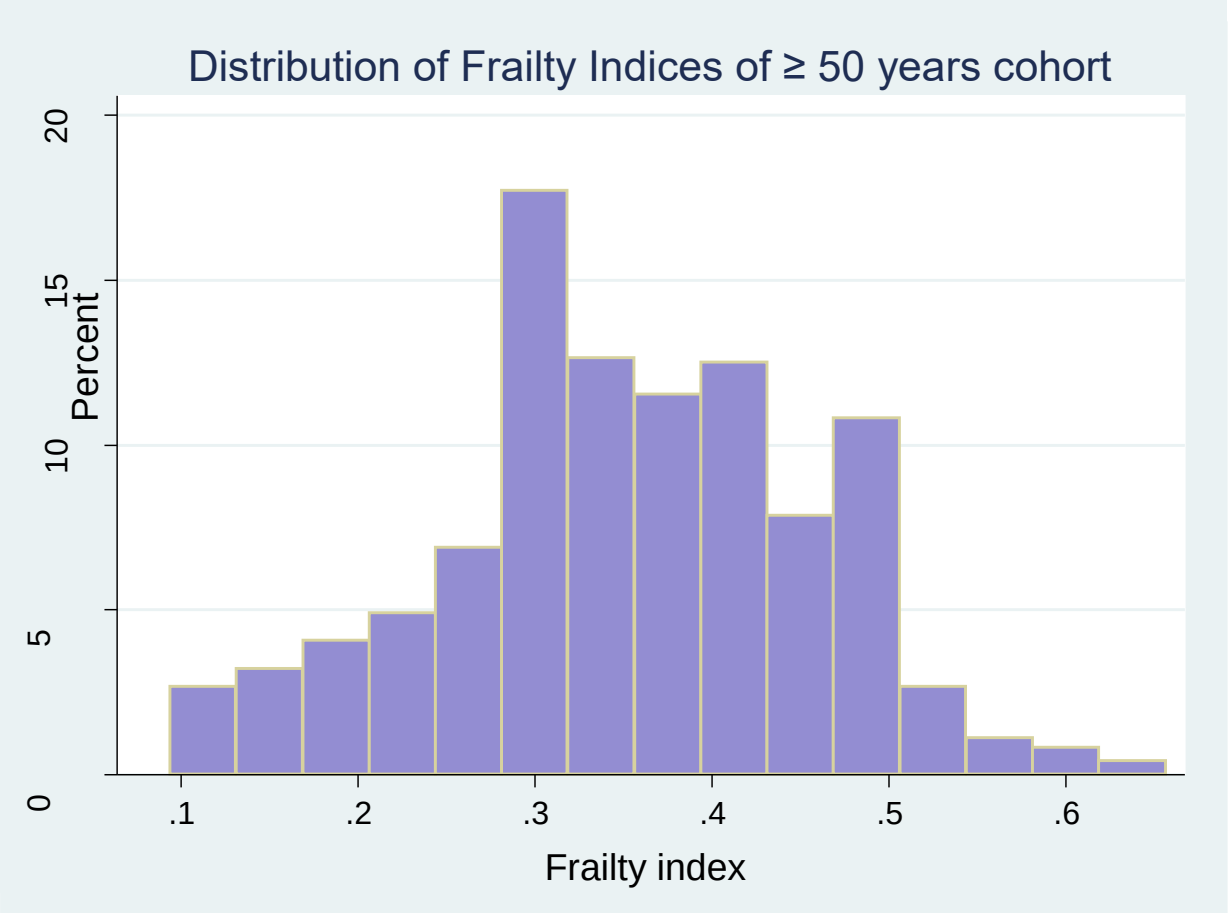


Figure 6. Distribution of frailty indices of individual patients ≥50 years of age at SAC. The mean frailty index was 0.349 (+/- 0.105) and the 0.344 (Interquartile range 0.281 to 0.406). The range of frailty index values was 0.094 to 0.656.

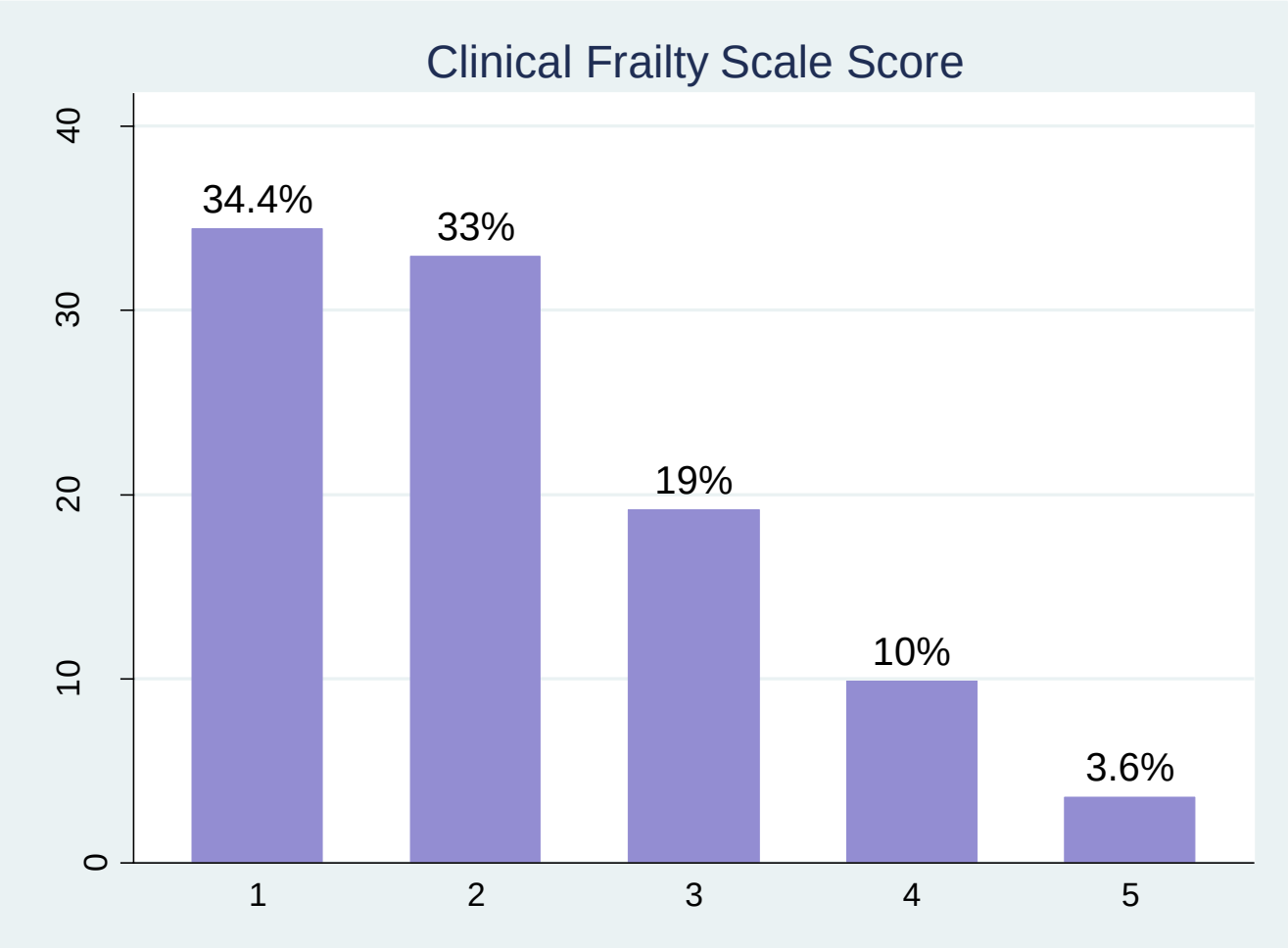


Figure 7. Percentage of patients assigned individual scores on the Clinical Frailty Scale. Three-hundred and thirty-four patients were evaluated using the CFS and no patients were assigned a score greater than 5.

Appendix A. Timed 6-Meter Walk Test: Participants' usual walking speed will be assessed using 6-m walk test. Each participant will complete one trial of the walking test with a standing start. Participants will be instructed to stand with their toes touching the taped start line and walk at their usual pace to a few steps beyond the taped finish line. Trained interviewers walking alongside the participants will record the time to complete the course from the start line to the stop line using a hand-held stopwatch following standardized procedures. Participants are timed from the moment their foot crosses the start line to the moment their foot crosses the stop line. If participants do not follow the instructions, the interviewer will stop the trial to review the instructions and prompt the participant to try again. Walking tests will be conducted at a single location by interviewers trained in administering the walking test and give walking instructions using a standard script. Total course time is converted to meters/second (m/s). Record will be made of participant's use of a walking aid, such as a walker or cane.

Appendix B. Grip Strength: The subject holds the dynamometer in the dominant hand, with the arm at right angles and the elbow by the side of the body. The handle of the dynamometer is adjusted if required - the base should rest on first metacarpal (heel of palm), while the handle should rest on middle of four fingers. When ready the subject squeezes the dynamometer with maximum isometric effort, which is maintained for about 5 seconds. No other body movement is allowed. The subject should be strongly encouraged to give a maximum effort. See videos of the Handgrip Strength Test. Record will be kept of each of three trials, as well as the mean of three trials in kilograms. Participants with conditions of the hand, such as severe osteoarthritis, carpal tunnel syndrome or other painful conditions will be excused from participating.

Appendix C. Exhaustion: Response of "Much or most of the time" to either of the following two statements from the Center for Epidemiologic Studies Depression (CES-D) Scale: "I felt that everything I did was an effort" and "I could not get going."[16]

Appendix D. Subjective patient-reported battery of symptoms questionnaire

These questions are about any physical limitations you might have. For these activities, please indicate which response best describes you.

	Yes, I can do this	**Yes, I can do this but only slowly**	**No, I cannot do this**
Can you do heavy work at home, like scrubbing floors, lifting or moving heavy furniture?			
Can you do moderate work at home like moving a chair or table, or pushing a vacuum cleaner?			
Can you do light work around the house like dusting or washing dishes?			
If you want to, can you participate in active sports such as swimming, tennis, basketball, volleyball or rowing a boat?			
If you want to, can you run a short distance?			
Can you walk uphill or upstairs?			
Can you walk a block or more?			
Can you walk around inside the house?			
Can you walk to a table for meals?			
Can you dress yourself?			
Can you eat without help?			
Can you use the bathroom without help?			

http://medicine.yale.edu/intmed/vacs/instruments/VACS_Patient_Questionnaire_ID_5264_284_639.pdf

provided gratis for unrestricted use from Yale School of Medicine. Veterans Aging Cohort Study.

Appendix E. Clinical Frailty Scale

http://www.davidsolie.com/wp-content/uploads/2015/12/Clinical-Frailty-Scale.pdf

Clinical Frailty Scale*

1 **Very Fit** – People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age.

2 **Well** – People who have **no active disease symptoms** but are less fit than category 1. Often, they exercise or are very **active occasionally**, e.g. seasonally.

3 **Managing Well** – People whose **medical problems are well controlled,** but are **not regularly active** beyond routine walking.

4 **Vulnerable** – While **not dependent** on others for daily help, often **symptoms limit activities.** A common complaint is being "slowed up", and/or being tired during the day.

5 **Mildly Frail** – These people often have **more evident slowing,** and need help in **high order IADLs** (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.

6 **Moderately Frail** – People need help with **all outside activities** and with **keeping house.** Inside, they often have problems with stairs and need **help with bathing** and might need minimal assistance (cuing, standby) with dressing.

7 **Severely Frail** – **Completely dependent for personal care**, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~ 6 months).

8 **Very Severely Frail** – Completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness.

9. **Terminally Ill** - Approaching the end of life. This category applies to people with **a life expectancy <6 months**, who are **not otherwise evidently frail.**

Scoring frailty in people with dementia

The degree of frailty corresponds to the degree of dementia. Common **symptoms in mild dementia** include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal.

In **moderate dementia**, recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting.

In **severe dementia**, they cannot do personal care without help.

* 1. Canadian Study on Health & Aging, Revised 2008.
2. K. Rockwood et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489-495.

DALHOUSIE UNIVERSITY *Inspiring Minds*

Appendix F. Frailty Index

	Proposed/Available at SAC	Guaraldi 32-Item Index (69)
1	Lipodystrophy	Lipo-atrophy and lipo-hypertrophy
2	Non-alcoholic steatohepatitis	Non-alcoholic fatty liver
3	BMI <18 or >25 (calculated)	Same
4	High total cholesterol	>200mg/dl
5	High LDL	>100 mg/dl
6	Low HDL	<40 mg /dl
7	High triglycerides	>150 mg/dl
8	Abnormal WBC count	<4000 cells/ul
9	Anemia	<100 in F, <120 in M
10	Hepatitis C co-infection	Positive
11	Hepatitis B co-infection	Hep B antigen positive
12	Hyponatremia	<125
13	Proteinuria or albuminuria	>5mg/mmol
14	Elevated AST	>31
15	Elevated ALT	>31
16	Abnormal ALP	<38 or >126
17	Elevated GGT	>55
18	Low platelets	<150
18	Abnormal potassium	> 3.5 or >5.3
20	Abnormal phosphorus	<2.5 or >5.1
21	Elevated total bilirubin	>1.1 mg/dl
22	Cardiovascular disease	Clinical diagnosis
23	Hypertension	Measured BP or on treatment
24	Diabetes mellitus II	Fasting BG>125 or on treatment
25	Chronic kidney disease	2 eGFR <60ml/min
26	Cirrhosis	FIB-4 score >3.25
27	Chronic obstructive pulmonary disease	FEV1/FVC ratio <0.7
28	Osteoporosis	DEXA T or Z score <-2.5 or fragility fracture
29	Any cancer	Clinical diagnosis with biopsy confirmation
30	Polypharmacy	>5 drug classes (excluding ART)
31	Abnormal TSH	<0.27 or >4.2
32	Unemployment	Self-report