LOWER BODY MUSCLE FUNCTION IN FRAIL AND NON-FRAIL PEOPLE LIVING WITH HIV: A PILOT STUDY

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LIST OF DEFINITIONS

Antiretroviral Therapy: a drug that act on different viral targets and decreases the total burden of HIV, maintains function of the immune system, and prevents opportunistic infections

Frailty: a multidimensional complication that lead to loss of independence, disability, decreased mobility and eventual mortality.

Human Immunodeficiency Virus: a retrovirus that infect humans and over time cause acquired immunodeficiency syndrome (AIDS), a condition in which progressive failure of the immune system allows life-threatening opportunistic infections to thrive.

Dual Energy X-Ray Absorptiometry: a device measuring body composition (bone mineral density, lean body mass, fat mass) using spectral imaging with two X-ray beams with different energy levels.

LIST OF ABBREVIATIONS

ART: Antiretroviral Therapy

DEXA: Dual Energy X-Ray Absorptiometry

FFP: Fried Frailty Phenotype

HHD: Hand-Held Dynamometer

HIV: Human Immunodeficiency Virus

LBMF: Lower Body Muscle Function

LLE: Lower Leg Extension

MLTAQ: Minnesota Leisure Time Activity Questionnaire

MMT: Manual Muscle Test

PLWH: People Living with HIV

TLBF: Total Lower Body Function

TUG: Timed Up and Go

30 CST: 30-Second Chair Stand Test

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ABSTRACT

Age-related accelerated physical declines occur in people living with HIV (PLWH) a decade earlier than HIV-uninfected (HIV-) individuals resulting in complications that lead to physical dysfunction and loss of independence. Fried's Frailty Phenotype (FFP) is a common frailty assessment used to assess these multidimensional complications in PLWH, however lacks sufficient lower body muscle function measurements. The purpose of this study was to objectively assess lower body muscle function (LBMF) in FFP groups using the 30-second chair stand test (30CST) and the Manual Muscle Testing (MMT). Forty PLWH ≥50 years on antiretroviral therapy (ART), categorized into frailty groups (non-frail, pre-frail, frail), were assessed for and lower leg extension (LLE) strength. Average age was 60 (interquartile: 57-66), 95% were male, and 67.5% Caucasian. Both TLBF and body fat (BF) discriminated between ($p<0.05$) and among ($p<0.01$) frailty groups. LLE strength showed no differences between groups. Total lean body mass (LBM) and fat free mass (FFM) only discriminated between ($p<0.05$) non-frail and combined frailty groups (pre-frail + frail). BF significantly correlated with pre-frail TLBF and frail LLE strength groups while lean LBM significantly correlated only with pre-frail LLE strength. To our knowledge, this is the first study to assess 30 CST, MMT, and body composition in the presence of frailty in PLWH. Our findings indicate that 30 CST and body composition are measures that can be utilized in identifying declines in lower body muscle function in frail PLWH.

Keywords: Frailty, Lower Body Muscle Function, Strength, Human Immunodeficiency Virus

PART 1

INTRODUCTION

By 2030 the number of people living with HIV (PLWH) 50 years and older will increase from 28% to 73% [1, 2] resulting in age-related accelerated physical declines in HIV-positive (HIV+) associated conditions, occurring at a rate of ≤ 10.3 years sooner than HIV negative people (HIV-)[3, 4]. These age-related declines predispose PLWH to comorbidities such as cardiovascular disease [5, 6], inflammation [7-9], diabetes [10], osteoporosis [2, 11], and loss of muscle mass [12-14] resulting in disability [13], physical dysfunction [12], loss of independence, hospitalization, or mortality [15-18]. Early recognition of comorbidities in PLWH is vital to extending quality of life and preserving independence [19]. Identification of the signs and symptoms of the aforementioned, high-risk HIV+ and age-related chronic mental and physiological decline [20, 21] will allow appropriate preventative and immediate treatment of these vulnerabilities[12, 18, 22, 23]. These vulnerabilities are typically termed frailty.

Frailty, vaguely defined as multidimensional complications that lead to loss of independence, disability, decreased mobility and eventual mortality are due to impairments to physiological stressors [24, 25]. In 2001 Fried and colleagues established 'Fried's Frailty Phenotype' (FFP) for classification of elders using the Cardiovascular Heart Study (CHS) data of men and women ≥65 years. Classification criteria include: 1) shrinking via 'unintentional weight loss' of ≥10 pounds within one year; 2) poor endurance/energy via 'self-reported exhaustion' (associated with maximal oxygen consumption testing (VO_{2max}) [26] and predictive of cardiovascular disease) [65] taken from the Center for Epidemiologic Studies Depression (CES-D) scale; 3) 'low

physical activity' via weighted calculated score of calories per week from the Minnesota Leisure Time Activity Questionnaire (MLTAQ), the original scale [27, 28] was proven valid and reliable relative to submaximal physical work capacity [29, 30], 4) 'slowness' via timed 15-foot walk; and 5) 'weakness' via grip strength. FFP classifications are: 'Robust (non-frail), pre-frail, and, frail,' where 0, 1-2, and 3 or more, respectively when the above criteria are present. The FFP has been proven valid and reliable in elders at risk for morbidity and mortality [24, 25, 31, 32].

FFP has been used primarily in elder research but involves many of the same detrimental declines and comorbidities seen in PLWH. FFP has been useful in research with PLWH. [20,23,30,34-36, 40, 41] However, HIV research often involves modifications to the original FFP classifications making comparisons between and among studies difficult and/or controversial. Understandably, subjective measures such as unintentional weight loss, self-reported exhaustion, and low physical activity allow data collection inconsistencies. Objective measures of slowness and weakness may allow data collection between and among HIV studies to be more consistent and comparable. Modification and changes to subjective classifications include changing weight loss criteria (i.e. weight requirement) [33], different low physical activity measures [34-36], non-sufficient explanation of procedures [7], or referencing FFP without clear classification of procedural uses or changes [20, 37]. Among the five FFP criteria only slowness and weakness via walking time and grip strength, respectively, are objective and provide consistent measures of frailty in PLWH.

Slowness via the timed up and go (TUG) represents functional walking speed and has been validated and is reliable in elder populations [38-41] relative to gait speed

[42-44], physical function measures [45, 46], and falls leading to mortality [38, 47]. Grip strength has been thoroughly studied and proven to be valid and reliable [48-50] in multiple populations, all ages, pathologies [39, 51-53], and in the evaluation of strength and frailty [54, 55]. Frailty is considered transient in HIV-infection compared with the stepwise decline that occurs in elders, indicating that PLWH can transition from frail to non-frail more easily than elders [56]. These two FFP criteria of physical dysfunction lead to additional measures of lower body strength (i.e. strength, mobility, muscle force, etc.) needed to effectively detect physical declines earlier in pre-frail and frail PLWH [35, 57, 58]. To our knowledge FFP has not been validated for use with PLWH.

Therefore, the purpose of this study was to assess total lower body function (TLBF), via the 30-second chair stand test (30 CST), and lower leg extension strength (LLE strength), via MicroFet hand-held dynamometer (HHD), in non-frail, pre-frail and frail PLWH on stable antiretroviral therapy (ART). We further sought to investigate the relationship among body composition, TLBF, and LLE strength in the different frailty groups. The primary aim of this study assessed LTBF via 30 CST and LLE strength via MMT among frailty groups. We proposed hypothesis 1 and 2 would show significant differences in 30 CST and MMT values, respectively among non-frail, pre-frail, and frail. The secondary aim of this study assessed lean body mass (LBM) and body fat (BF) via dual energy x-ray absorptiometry (DEXA) in non-frail, pre-frail, and frail groups. We proposed hypothesis 1 and 2 would show significant differences in LBM and BF values, respectively among frailty groups. The tertiary aim if this study was to assess the correlation between LTBF and LLE strength with body composition (lean body mass [LBM] and body fat [BF]) in non-frail, pre-frail and frail groups. We proposed hypothesis

1 and 2 would show significant correlation between LTBF and LLE strength values, respectively, among frailty groups.

METHODS

Subjects

A sample of 40 PLWH were randomly selected from a pool of over 200 HIV+ positive patients of varied socioeconomic backgrounds recruited from the university's HIV clinic who volunteered to participate in this study. Subjects were ≥40 years of age with viral load ≤100 copies/mL, or 'undetectable', and actively taking ART for at least one year. Medical history data included the study evaluation and previously assessed most-recent medical records of: self-reported race, ethnicity, fall risk, alcohol, smoking, recreational drug usage (total number of years), depression and anxiety (either diagnosed or undiagnosed); CD4 and HIV-1 RNA viral load, number of years on ART, age at diagnosis, and co-morbidities. The study was approved by the University's Committee on Human Studies Institutional Review Board (IRB). IRB approved informed consent form was signed by all subjects prior to study participation.

Study Design

The study design consisted of a 3-group cross-sectional analyses of lower body muscle function and body composition in PLWH. Independent variables included the FFP groups: non-frail, pre-frail, and frail. Dependent variables included TLBF via 30 CST, LLE strength via MicroFet HHD, and body composition via a DEXA scan. Significance was set at $p<0.05$.

Fried Frailty Phenotype Criteria

Group assignment involved determination via the following 5 FFP criteria listed below [25, 59]. Subjects were classified as non-frail (0 FFP criteria), pre-frail (1-2 FFP criteria), and frail (3 or more FFP criteria).

1. 'Unintentional weight loss': measured by loss of ≥ 10 lbs. of total body mass within the past year: obtained from previous medical history and weight during data collection. When weight loss was not due to diet and/or exercise this FFP criteria was accepted.
2. 'Self-reported exhaustion': measured via Likert scale rating (0 = less than 1 day; 1 = 1-2 days; 2 = 3-4 days; 3 = most of the time) from the Center of Epidemiologic Studies Depression Scale (CES-D) *"How often in the last week did you feel this way?"* The following 2 questions were used: 1) 'I felt everything I did was an effort', and 2) 'I could not get going'. When a score of 2 (3-4 days) or 3 (most of the time) was noted this FFP criteria was accepted.
3. 'Low physical activity': measured via a modified Minnesota Leisure Time Activity Questionnaire (MLTAQ) weighted score of calories expended per week (using MET calculation for each type of activity) for the previous four weeks. Moderate to vigorous activity was considered appropriate for weighted scores (i.e. walking, jogging, playing basketball, etc.). When scores of <383 and <270 calories per week for men and women, respectively were noted this FFP criteria was accepted.
4. 'Slowness': measured via the Timed Up and Go (TUG) a timed walking speed test in which participants are asked to walk 15-feet [38, 43]. A modification to the

TUG walking speed was utilized in this study to assess functional mobility modification included: starting the test seated in a standard chair (43 cm) rising from the seated position then walking 7.5 ft around a cone and walking another 7.5-feet back to the starting seated position in the chair. Timing began when the subject's back left the chair during initial rise and stopped when the original start position was obtained.[40]. TUG time was measured via 3 trials with 60-second rest periods between trials. The shortest time of 3 trials was adjusted for height and gender [25]as follows: Men with heights of ≤173 cm or >173 and times >7s or >6s, respectively and women with heights ≤159 cm and > 159 cm and times >7s or >6s, respectively[25]. When these criterion times were met this FFP criteria was accepted.

5. 'Weakness': Right hand grip strength/force measured with the Jamar hand dynamometer was assessed via 3 trials with 60-second rest periods between trials. The dynamometer was gripped in the thumb up position at 90 degrees of elbow flexion at the subject's side. Scores were based on gender and body mass (BMI) norms for non-infected persons [52]. When men with BMIs of <24, 24.1 to 28, or >28 and grip strengths of <29, <30, or <32, respectively and women with BMIs of <23, 23.1-26, 26.1 to 29, or >29 and grip strengths of <17, <17.3, <18, or <21, respectively were noted on their best trial this FFP criteria was accepted.

Objective Lower Body Muscle Function Measures

All subject data (except blood and DEXA) were collected on the same day by the same trained clinical practitioner, in the university's HIV clinic. Data were collected in the following order: 1) Informed consent; 2) Medical History; 3) Weight; 4) Height; 5)

Blood Pressure; 6) Frailty Assessment; 7) Blood draw (30 cc); 8) Lower Body Muscle Function: a. Muscle strength test, b. 30 second chair stand; 9) Body composition via DEXA.

Manual muscle tests (MMT) are the primary technique used to evaluate muscle function and quality (strength) by sports medicine/orthopedic physicians, physical therapist, athletic trainers, and other allied health professionals. MMT testing has been proven valid and reliable when assessed by a trained individual (i.e. Athletic Trainer, Physical Therapist) and is considered standard of practice. The MicroFet handheld dynamometer (HHD) is a digital force gauge used to measure muscle force production in Newton Meters or foot/pounds per square inch. The HHD was used to measure isometric knee extensor strength/force (LLE strength) of all subjects. The clinical practitioner's MMT reliability was .98. Knee extension data were collected via 3 trials with 30 second rest period between trials. The test was administered seated on a "high low" table in order to position the hips at 110^{o} of flexion, and the right knee at 30^{o} of flexion. The HHD was placed on the right anterior lower leg 1 inch above the medial malleolus. Maximal isometric pressure was applied to the HHD (no movement) with resistance by the clinical practitioner.[60]

The 30 CST was used to measure total lower body function (TLBF). The test began seated on a standard (43 cm) padded chair with both arms placed across the chest. Subjects were asked to stand up and sit down completely as many times as possible in 30-seconds. [61, 62]. Time began as soon as the subject stood up then sat back down. The score was calculated by counting the number of complete stands that

were accomplished in 30-seconds. Only one trial was administered and subjects were allowed to rest at any time during the 30-second time period, if necessary. [61]

Body Composition Measures

Dual X-Ray Absorptiometry (DEXA) Lunar software was used to measure body composition. Lean body mass and body fat were recorded (lbs. and percentage [%]). A clinic physician administered 1 total body scan, with the subject positioned supine on the scanning surface with ankles and legs strapped together (below the patella) with Velcro straps. Both hands were placed palms down parallel to the subject's body. The radiation dose was approximately 1/10 that of a standard chest X-ray where the risk is negligible according to the Radiological Society of North America [4, 63].

Statistical Analysis

A significant level of 0.05 was used for testing statistical hypotheses. The same effect size among HIV patients was utilized, with 20 per group (40 total). Standardized effect size (Cohen's-d) was approximately 1.15 between two groups [64]. Assuming a more conservative effect size such as 0.85, more than 80% statistical power will occur with the above sample. Power estimates were performed using G*Power. Data summarized using descriptive statistics were expressed as median and interquartile range (IQ1-IQ3), and categorical data were expressed as frequency and percentage. Wilcoxon Rank Sum and Kruskal-Wallis tests were applied to compare continues clinical and demographics measures among frailty groups, whereas the Chi-squared test was used for comparing categorical measures. Bivariate associations among

continuous outcomes were evaluated using Spearman's rank correlation coefficient, along with 95% confidence intervals. The primary aim was evaluated by comparing TLBF and LLE strength variables among frailty groups. The secondary aim was evaluated by comparing body composition among frailty groups. The tertiary aim was evaluated by correlating body composition and LBMF measures among frailty groups. All data were analyzed using SPSS Statistics version 26.0 (IBM Corp., Somers, NY) software.

RESULTS

Subjects

FFP criteria incidence and specific subject characteristics are presented in table 1. The majority of subjects were Caucasian (67%) and male (92.5%) . Twenty were non-frail, ten were pre-frail, and ten were frail. Median age, body mass, weight, blood pressure, CD4+, HIV RNA, and total years on ART were not significant between groups. BMI for frail groups showed significant differences. Among the frailty groups, frail group had the highest rate of anxiety, depression, instability with turning, fear of falling, and had fallen in the past year compared to non- and pre-frail groups, however chi-square revealed non-significant differences between groups. Subject data are presented via median values and interquartile ranges due to group numbers. FFP criteria prevalence among all subjects, and within and between groups are presented in Table 2.

Table 1. Subject Median Demographics and Clinical Characteristics: Age, Age Group, Gender, Height, Body Mass, BMI, Race, Comorbid Conditions, Fall Risk, and HIV Clinical Factors in Non-Frail, Pre-Frail, and Frail Groups

	Total (n = 40)	**Non-Frail (n = 20)**	**Pre-Frail (n = 10)**	**Frail (n = 10)**
Age¥	61 (57-66)	61 (57-65)	61.5 (49-69.5)	60 (57-66)
Age Group				
40-49 years old	5.4%	0%	20%	0%
50-59 years old	32.4%	40%	20%	50%
60-69 years old	51.4%	55%	40%	40%
70-79 years old	8.1%	5%	10%	10%
Male	92.5%	95%	90%	90%
Female	7.5%	5%	10%	10%
Height¥	170.5 (165.4-177.8)	170.5 (164.9-179.2)	171.6 (168-175.2)	167.4 (164.5-177.5)
Body mass¥	73.8 (67.2-84.3)	69.5 (65.6-83.7)	75.22 (70.5-83.5)	80.9 (68.4-89.8)
BMI (kg/m^2)¥	25.3 (23.7-28.4)┼	24.3 (14-25.5)	25.7 (24.4-29.2)	27.2 (25.1-30.5)*
<25 kg/m^2	43.2%	55%	40%	20%
25-29.9 kg/m^2	45.9%	45%	50%	50%
> 30 kg/m^2	10.8%	0%	10%	30%
Race				
Native American	2.5%	5%	0%	0%
African American	7.5%	10%	0%	10%
Hawaiian/Pacific	17.5%	25%	10%	10%
Asian	17.5%	15%	20%	20%
Caucasian	67.5%	60%	90%	60%
Other	12.5%	15%	10%	10%
Comorbid Conditions				
Anxiety	37.5%	20%	40%	70%
Depression	50%	40%	50%	70%
Diabetes Mellitus	5%	10%	0%	0%
Hypertension	22.5%	15%	10%	50%
Neuropathy	32.5%	20%	50%	40%
Other	37.5%	35%	30%	50%
Fall Risk				
Fallen in past year	27.5%	15%	20%	60%
Afraid of falling	30%	10%	40%	60%
Instability with turning	25%	5%	20%	70%
Chair instability	12.5%	0%	10%	40%
HIV Clinical Factors				
HIV RNA, <20 cpy/mL	95%	85%	90%	80%
CD4 cells/mm¥	697 (385-940)	533 (409.2-739.5)	504 (390.2-572.7)	767 (425.2-803)
ART years¥	21 (14.5-26)	20.5 (14-25.5)	17.5 (12.5-28)	22.0 (20.3-28.3)

BMI = Body mass index, HIV = Human Immunodeficiency Virus, ART = Antiretroviral Therapy, Body mass = kgs, Height = cm

¥ Continuous data presented as median (IQR), all other data represented as percentages

┼ p<0.05 difference from combined pre-frail + frail using Chi-square Test

* p<0.05, difference from non-frail group using Chi-square Test

Table 2. Prevalence of Grip Strength, TUG, CES-D, Weight Loss, and MLTAQ caloric output between total (Pre-Frail + Frail), Pre-frail, and Frail Groups

Frailty Criteria	**Total (n = 40)** n(%)	**Pre-Frail (n = 10)** n(%)	**Frail (n = 10)** n(%)
Grip Strength	11 (27.5)	7 (70)	4 (40)
TUG	10 (25)	4 (40)	6 (60)
CES-D	7 (17.5)	1 (10)	6 (60)
Weight Loss	5 (12.5)	1 (10)	4 (40)
MLTAQ	13 (32.5)	3 (30)	10 (100)

TUG = Timed Up and Go, CES-D = Center for Epidemiologic Studies Depression Scale, MLTAQ = Minnesota Leisure Time Activity Questionnaire

Lower Body Muscle Function Measures

Grip Strength, TUG, MLTAQ weekly caloric output, TLBF, and right unilateral LLE strength variables are presented in Table 3. Significant differences were found between non-frail, pre-frail, and frail groups for the aforementioned outcomes. Significance remained unchanged after adjusting for Age and BMI using analysis of variance (ANOVA) test. Significant differences were found between TLBF of non-frail and both pre-frail and frail groups. Correlations for pre-frail and frail groups are presented in table 5 and 6. TLBF in the pre-frail group was significantly correlated to grip strength ($p<0.05$) and TUG ($p<0.05$), while the frail group showed non-significant correlations. Non-significant correlations were found among LLE strength and FFP groups. LLE strength of the pre-frail group revealed a significant correlation to grip strength ($p<0.05$), TUG ($p<0.05$), leg LBM ($p<0.05$), and total LBM ($p<0.05$). LLE strength of the frail group showed significant correlations to trunk BF% ($p<0.05$) and total BF% ($p<0.01$).

Table 3. Measures of Grip Strength, TUG, MLTAQ caloric output, TLBF, and LL Strength in Non-Frail, Pre-Frail, and Frail Groups

Measures	**Non-Frail** (n = 20)	**Pre-Frail** (n = 10)	**Frail** (n = 10)
FFP¥			
Grip Strength	36.30(32.8-45)†	29.0 (20.3-34.8)**	31.0 (26-35.5)*
TUG	5.42(5.0-5.8)†	7.0 (6.1-8.8)**	8.3 (7.2-9.9)**
MLTAQ	1185.00 (880-1755)†	602.5 (283.5-1686.2)	247.5 (90-323.7)**
LBMF¥			
TLBF	17.5 (15-20.7)†	13.0 (9.2-14.7)**	10.5 (10-14.5)**
LLE Strength	55.6 (45.4-71.8)	49.8 (30.5-62.5)	46.8 (40.4-57.1)

FFP = Fried Frailty Phenotype, Grip Strength (kgs), TUG = timed up and go (seconds), MLTAQ = Minnesota Leisure Time Activity Questionnaire (caloric output), LBMF = lower body muscle function, TLBF = total lower body function, LLE Strength = lower leg extension strength

¥ Continuous data presented as median (IQR)

† p<0.01, difference from combined frail + pre-frail

* p<0.05, difference from non-frail

** p<0.01 difference from non-frail

Body Composition

Median and interquartile ranges for body fat percentage, lean body mass, and bone mineral content via DEXA are presented in Table 4. Significant differences were found in the pre-frail and frail group in trunk BF%, with pre-frail showing differences in total BF%. LBM was not significant between frailty groups. Correlations for pre-frail and frail groups are presented in table 5 and 6. TLBF in the pre-frail group showed significant correlations with leg, trunk, and Total BF% (all $p<0.05$), while the frail group showed no relationships. LLE strength in the pre-frail group showed significant correlations with leg and total LBM ($p<0.05$). LLE strength in the frail group showed significant correlations with trunk and total BF% ($p<0.05$).

Table 4. DEXA Values for BF%, LBM, Total FFM, Total LBM, Total FFM%, and Total BF% in Non-Frail, Pre-Frail, and Frail Groups

DEXA	Non-Frail (n = 20)	Pre-Frail (n = 10)	Frail (n = 10)
BF%			
Legs	24.3 (20.7-28.9)	26.1 (21.6-31.0)	27.4 (22.2-34.6)
Trunk	31.6 (24.9-34.3)†	39.3 (33.7-48.2)**	39.1 (32.0-49.3)*
Total	27.8 (22.3-30.4)†	34.1 (28.4-38.9)*	32.1 (26.1-43.3)
LBM			
Legs	32.4 (25.6-39.1)	33.6 (32.4-39.0)	35.1 (33.5-38.3)
Trunk	51.4 (45.9-60.1)	50.5 (48.8-59.5)	47.7 (47.4-59.1)
Total	102.8 (87.1-122.3)	105.2 (101.0-123.8)	104.9 (100.1-123.6)
Total FFM	108.5 (96.1-132.6)	111.7 (107.2-116.7)	127.9 (105.6-136.6)
Total LBM	68.7 (66.3-73.4)†	62.3 (58.2-67.8)*	64.5 (54.1-70.0)
Total FFM%	72.1 (69.5-77.5)†	65.8 (61.0-71.5)*	67.8 (56.7-73.8)
Total BF%	27.8 (22.3-30.4)†	34.1 (28.4-38.9)*	32.1 (26.1-43.3)

DEXA = dual energy x-ray absorptiometry, BF% = body fat percent, LBM = lean body mass, FFM = fat free mass; Total LBM and FFM recorded in lbs.
† $p<0.05$, difference from combined pre-frail + frail
* $p<0.05$, difference from non-frail
** $p<0.01$ difference from non-frail

Table 5. Correlations between TLBF, LLE Strength, TUG, Leg BF%, Trunk BF%, Total BF%, Leg LBM, Trunk LBM, and Total LBM in Pre-Frail Group

	TLBF	LLE Strength	Grip Strength	TUG	Leg BF%	Trunk BF%	Total BF%	Leg LBM	Trunk LBM
TLBF	-								
LLE Strength	0.808*	-							
Grip Strength	0.753*	0.753*	-						
TUG	-0.726*	-0.841*	-0.659*	-					
Leg BF%	-0.664*	-0.624	-0.569	0.471	-				
Trunk BF%	-0.718*	-0.522	-0.268	0.366	0.761*	-			
Total BF%	-0.724*	-0.586	-0.376	0.401	-0.891*	0.971**	-		
Leg LBM	0.348	0.685*	0.580	-0.341	-0.285	-0.119	-0.207	-	
Trunk LBM	0.515	0.600	0.666*	0.198	-0.613	-0.423	-0.532	0.815**	-
Total LBM	0.497	0.665*	0.658*	-0.267	-0.267	-0.351	-0.452	0.928**	0.968**

TLBF = total lower body function, LLE strength = lower leg extension strength, TUG = timed up and go, BF% = body fat percent, LBM = lean body mass measured in lbs.
*Pearson correlation is significant at $p<0.05$
** Pearson correlation is significant at $p<0.01$

Table 6. Correlations between TLBF, LLE Strength, TUG, Leg BF%, Trunk BF%, Total BF%, Leg LBM, Trunk LBM, and Total LBM in Frail Group

	TLBF	LLE Strength	Grip Strength	TUG	Leg BF%	Trunk BF%	Total BF%	Leg LBM	Trunk LBM
TLBF	-								
LLE Strength	0.134	-							
Grip Strength	-0.329	0.508	-						
TUG	-0.078	0.163	0.642*	-					
Leg BF%	-0.121	-0.540	-0.016	0.471	-				
Trunk BF%	-0.151	-0.782*	-0.344	0.366	0.655*	-			
Total BF%	-0.172	-0.768**	-0.270	0.401	0.842**	0.956**	-		
Leg LBM	-0.521	0.002	0.047	-0.341	-0.157	-0.158	-0.177	-	
Trunk LBM	-0.397	0.025	0.566	-0.198	0.117	-0.133	-0.069	0.673*	-
Total LBM	-0.438	0.081	0.477	-0.267	-0.021	-0.192	-0.165	0.792**	0.966**

TLBF = total lower body function, LLE strength = lower leg extension strength, TUG = timed up and go (seconds), BF% = body fat percent, LBM = lean body mass measured (lbs.)
*Pearson correlation is significant at $p<0.05$
** Pearson correlation is significant at $p<0.01$

DISCUSSION

Muscle strength and physical function play a crucial role in identifying frailty in ageing PLWH. To our knowledge, this is the first clinical study conducted to assess TLBF (30 CST), LLE strength (MMT), and body composition (LBM and BF) in PLWH who were grouped according to FFP. The most significant finding of this study was that the 30 CST and body composition differentiated between FFP groups, showing agreement between the objective measures of FFP.

Only 2 HIV studies have used the 30 second chair stand to quantify physical condition of PLWH, with their 30 CST results for non-frail, pre-frail and frail groups were 13-14, 13, and 10.5 stands similar to our results of 17, 13, and 10.5 stands for the same groups [87, 88]. While our non-frail group produced more stands in 30 second than their non-frail group our results appear to clinically support the use of the 30 CST to differentiate FFP groups similarities in PLWH. Thereby indicating that the 30 CST may be used as an alternative objective measure to identify PLWH and those at-risk for physical dysfunction. [57, 65-67],

Clinically meaningful significant differences for the 30 CST reported that a deficit of 2.0-2.6 chair stands from normal reference ranges [68]. Revealing that our sample of PLWH had clinically significant less (worse) chair stands in pre-frail and frail groups compared to the non-frail. There are currently no normative data on PLWH and the 30 CST. Compared to the most comprehensive study of normative values of 30 CST in adults and elders, PLWH in our study in the pre-frail group in the 6th decade averaged 13 chair stands which aligns more with normative chair stand values for the 7th (12.9-13 chair stands) decade of life. Our frail group in the 6th decade averaged 10.5 chair stands which aligned more with normative chair stand values of individuals in the 8th (10-12 chair stands) and 9th (9.4 chair stands) decades of life.[67] Physical function may be declining at a faster rate in PLWH than compared to HIV-uninfected population.

Our LLE strength results were different between groups, however pre-frail LLE strength was strongly associated with LLBM and total LBM, showing a relationship between physical function measures of strength and force production. Since frail adults and elders have less physical capacity and reduced power in lower extremities[66] justification for the use of a hand-held dynamometer seemed plausible frail PLWH. Our subjects produced less LLE force/strength in non-frail, pre-frail and frail groups (11.39, 10.20, 9.59 kg/m^2) than HIV-positive (15.72 kg/m^2) and HIV-negative healthy controls (17.08 kg/m^2). These inconsistencies in LLE force/strength could have been due to the wide age range of study participants (30% were 15-39 years, 70% were 40-69 years). However, our correlations of Lower Body functional strength and mobility (TLBF) against LL extension strength were similar, or superior, to previously reported results in normal individuals[50]. Other studies show LLE strength is not an indicator of chair

rise[69, 70] or is the strongest explanation of chair rise in healthy adults 50-85 years[65, 70, 71], even though 50% of lower-limb function is due to lower limb strength, activation of muscles for initiating the chair stand progresses from the lower leg to upper leg[72], showing the possibility that hip extension strength may be a better indicator of strength in the chair rise. True comparisons of 30 CST and HHD in frail PLWH cannot be made due to lack of research in this area.

A confounding factor to the use of HHD was tester strength and gender. The HHD results yielded no differences between frailty groups, however high correlations and significance in LLE strength (HHD) and 30 CST were revealed. Although differences were not significant, knee extensor strength via manual muscle testing with or without HHD may only be an effective and objective when the MMT administered is physically stronger than the patient or subject. Physical limitations in gender such as inconsistent examiner force production via a female examiner testing the lower extremity of a male subject has been proven to be a validity and reliability factor. In our study all groups consisted of males and one female while our data collector was female and smaller in stature than most of the male subjects who's LLE strength is (quadriceps) typically second only in force production than the hip extensors (psoas major) providing spurious LLE data which was not valid or reliable when testing male frailty groups.[60, 73, 74]

BF% was able to distinguish among all three groups, while LBM could only distinguish between non-frail and pre-frail. Strong associations of both pre-frail TLBF and frail LLE were observed in trunk BF% and total BF%, In this study, strong relationships between the 30 CST and leg, trunk, and total BF% aligned with the

concept that central obesity and fat distribution are predictors of frailty[75]. In subjects with similar demographics in HIV the presence of body fat was higher in our sample than previously reported however elevated fat mass and trunk fat were demonstrated in all studies against HIV-negative comparisons[12, 35, 75]. This is consistent with the finding that immune restoration via elevated $CD4^+$ and suppressed viral load predispose frail PLWH to being overweight or obese as opposed to wasting [58, 76, 77]. Higher incidences of obesity in HIV, similar to the non-infected population, may encourage greater awareness of the need to incorporate exercise interventions to decrease the incidence of higher adiposity to prevent frailty.

Another interesting finding was that the entire frail group did not utilize significant calories per week in terms of exercise and physical activity according to the MLTAQ. Additionally, the majority of subjects in the frail group were afraid of falling, had fallen in the past year, reported depression and anxiety as the most common comorbidities. Among the various FFP studies, none of them provided data in calories expended per week for each frailty group. The importance of proper exercise habits that target strength, balance, agility, and fall-risk education routinely (daily and/or weekly) may be the key to decrease the fear of falls, actual falls, and prepare PLWH for normal daily activities (i.e. climbing stairs, standing, sitting, pivoting quickly, etc.) [10, 64].

FFP is currently the most widely used measurement in PLWH currently. The majority of studies focus on using FFP in relation with inflammation and immunity[7, 8, 36, 76], prevalence of frailty in PLWH [34, 78], body composition [21, 35], and comorbidities [20, 21]. Only a few focused on physical dysfunction[21, 75, 79]. Inconsistencies include FFP protocol complete, partial or modified use [21, 34-36, 75]

and self-reported data [56, 76, 78, 80]. Other studies have utilized metabolic testing[58] and subjective indexes[10, 81, 82] to determine frailty. Traditional frailty measures used in the elders have not been validated in HIV-associated frailty and may only partially reflect the full extent of physical dysfunction. Age-related declines have been well established in both elders and PLWH. Currently, no highly scrutinized standard frailty measures or physical normative values exist for PLWH thereby limiting comparisons between studies.

LIMITATIONS OF STUDY

The study sample of PLWH consisted almost exclusively of white males and was limited to one female per frailty group. Studies have revealed differences in study results when socioeconomic background, ethnicity, race, educational level are variants. [1, 19, 83, 84]. This study may not be generalized to the entire population of HIV-infected people. Second, female examiner force production limitations probably negatively affected lower body strength resistance and resulted in inconsistent HHD data which then affected correlations calculated between measurements and body composition[60]. Third, we did not include an HIV- control group. A control group would have allowed comparison of LBMF and frailty measurements to the non-infected population in order to obtain strong comparisons. Finally, FFP has not been validated in HIV and may not be an accurate measure of physiologic decline in PLWH.

CONCLUSIONS

The 30-second chair stand test is an objective easily administered tool that may be used in conjunction with FFP criteria to help identify physical declines in pre-frail, and frail PLWH. While assessments of muscle strength via hand-held dynamometry is considered “standard practice” it requires more skill may produce spurious data when the clinical practitioner must evaluate an individual who is stronger than the practitioner particularly when a lower body muscle or muscle group is tested. Unfortunately, lower body function is critical in ambulation and individual independence. Body fat, but not lean body mass, and its associations with lower body muscle function tests are identifiable body composition measures that are indicators of frailty.

RECOMMENDATIONS

A thorough review of frailty and physical function in PLWH will give insight into all the current measurements and factors that attribute to frailty or frailty-like physical dysfunction. Normative data for the 30 CST and other objective measures of frailty in PLWH is currently insufficient. More research should be focused on objective measures of frailty. The 30 CST should be considered an additional objective measure of function and independence and administered to different age groups, particularly since osteoarthritis naturally increases with age as with other comorbid conditions. Due to the nature of HIV-infection, ART, and other non-age-related dysfunction in PLWH, validation of FFP is recommended in this population.

PART II

The high rate of hospitalizations, morbidity, and deaths in elders have been attributed to falls, fall risk, fractures, osteoporosis, diabetes, cardiovascular disease, hypertension, and muscle weakness. The degree of comorbidities experienced in elders[34, 85-87] is comparable to the comorbidities also experienced in human immunodeficiency virus (HIV)[5-9]. Due to the nature of physical decline, it has been proposed that frailty, or vulnerabilities to stressors causing physiologic decline, in elders similarly happens in PLWH[18, 33, 34, 86, 88]. Fried Frailty Phenotype (FFP), a popular and validated tool in elders[24, 25, 89], has worked its way into the HIV community and research on frailty[7, 8, 33, 34, 36, 78, 90]. Fried's Frailty Phenotype only proposes the use of two objective physical function tests, grip strength and walking speed. In order to identify PLWH at-risk for functional decline, other measures of lower body function and strength need to be tested. Hand-Held Dynamometry (HHD) and the 30 CST are proposed to be good indicators of physical dysfunction in elders. Since physical dysfunction in PLWH is similar to HIV-uninfected elders, these tests may be appropriate to discriminate between different frailty and decline in physical function groups.

Physical Declines between Elders and HIV

Age-Related Declines in Strength in Adults/Elders

Gross et al. (1998) examined the differences between muscle strength and speed in young and older women during a chair rise. Muscle activity and joint kinematics during the chair rise at normal and fast speeds were measured in 26 elderly (70.1 ± 5.8 years) and 12 young (24.2 ± 2.4 years) women. Muscle strength was

assessed with a one-repetition maximum (1RM) test for hip abduction, hip adduction, hip flexion, hip extension, knee flexion, knee extension, and leg press with subjects (after warm-up period) lifting weight until reaching 1RM. Chair rise was measured using an 18 cm height chair, beginning from a seated position with hands on hips, and rising at normal speed and as fast as possible. After one practice trial three normal speed followed by three fast speed trials were performed with reflective markers placed over various lower body bony landmarks. Significance was present between generation of force and age in all muscle strength tests, with average strength twice as great in young subjects than elders. Hip flexor and extensor strength were strongly correlated in young subjects and strength in one muscle group moderately predicted strength in other muscle groups. Activation of muscle groups were as follows: tibialis anterior, gastrocnemius, soleus, hamstrings, rectus femoris, vastus group, and gluteus maximus. The authors concluded elder subjects showed weaker muscle strength than younger counterparts. Hip muscle strength was the most important strength factor in the chair-rise. Age contributed to strength and stability differences of both groups.[69]

Metter et al. (1999) explored muscle quality in relation to age in both upper and lower body isometric strength in men and women. An upper body apparatus positioned the shoulder perpendicular to the floor (against the midline of body) with the forearm parallel and hand-grip strain-gauge transducer able to measure in four directions (up, down, forward, backward). Knee extensor (quadriceps) strength was measured using a Kin-Com Model 125E dynamometer with isometric measurements at 120 degrees of knee extension. Muscle mass was estimated cross sectional muscle area (CSA) using mid-arm circumference, correcting for skinfold thickness, and 24-hour creatine excretion

(CREAT). Total body mass was estimated using CREAT and fat free mass using DEXA. One-way ANOVA showed significant ($p<0.001$) differences between age-group (i.e. 20-29 years, 30-39 years, 40-49 years, 50-59 years, 60-69 years, 70-79 years, 80+). [91]

Lynch et al. (1999) investigated the age and gender-associated differences in muscle quality (MQ) in both arms and legs throughout the adult lifespan. 502 (224 men, 278 women, 19-93 years old) participants completed a weekly minutes of weight training questionnaire, a dual-energy X-ray absorptiometry (DEXA) total body scan, and an isokinetic dynamometer to assess peak torque. Arm and leg muscle quality (MQ) was measured by dividing concentric peak torque and eccentric peak torque by muscle mass (MM). On-way ANOVA showed significant main effects for age-associated change compared with young adults (20-39 years) between different age ranges (i.e. 60-69-year, 70-79 year, >80 year) and arm/leg MM, concentric and eccentric peak torque ($p<0.05$). Throughout lifespan, men had lower body fat percentage, greater MM than women ($p<0.01$), and body mass significantly lower ($p<0.05$) in >80-year decade than young adult men. Beginning at 60-69-decade men presented with significantly ($p<0.01$) lower arm and leg MM, while women presented with lower leg MM beginning in 40-49-decade ($p<0.05$). Overall age-associated declines are present in arm and leg MQ, with greater decline present in leg MQ than arm MQ, and PT declining more with advancing age in both men and women.[92]

Newman et al. (2003) investigated strength, muscle mass, and muscle quality relationship to age, race, and body composition in older adults. The Health, Ageing and Body Composition Study (Health ABC) includes 3,075 older adults (48.4% men and 51.6% women) age 70-79, and 41.6% African American. Isokinetic dynamometry (Kim-

Con dynamometer) measured knee extension strength and an isometric dynamometer (Jamar) for grip strength. Maximal isokinetic torque (Nm) assessed angular velocity at 60º/s, with start and stop angles at 90º and 30º, and three to six maximal torque production trials occurred. Isometric grip strength was assessed bilaterally, with maximal force of two trials taken. DEXA assessed lean mass, bone mineral content, and fat mass of upper and lower extremities. The ratio of strength to muscle mass of upper and lower extremities defined muscle quality. Assessments in 1,286 men (73.7±2.9 years) showed mean BMI 27.0±3.9 kg/m^2, total fat percent 25.3±5.2, leg torque (Nm) 132.15±33.12, and lean leg mass (kg) 9.24±1.40. Assessments in 1,337 women (73.4±2.8 years) showed BMI 27.6±5.4 kg/m^2, total fat percent 37.3±6.0, lean torque (Nm) 81.85±21.57, and lean leg mass 6.72±1.28. Significant differences of gender were noted in age, height, weight, BMI, total fat percentage, lean torque, and lean muscle mass ($p<0.01$). Significant differences of race were noted in men in age, total fat percent, lean torque, and lean leg mass ($p<0.05$). Significant differences of race were noted in women men in weight, BMI, total fat percent, lean torque, and lean muscle mass. Older white men had significant decreases in both leg torque and leg lean mass ($p<0.0001$) while black men did not. Older white and black women had significant decreases in leg torque ($p<0.0001$) and leg lean mass ($p=0.0021$ and $p=0.0004$). 9-10% leg lean mass was reported to be lower with every yearly increase in age from 70-79. Leg strength was 2.5 N-m and 1.8 N-m lower per year in men and women from 70-79, respectively. Gender differences in grip strength between women (24.48±6.25) and men (39.80±8.95) were significant ($p<0.001$). Gender differences in arm lean mass (kg) between women (2.20±0.44) and men (3.66±0.61) were significant ($p<0.05$). Race

differences between white and black women in grip strength (23.26±5.32 vs. 26.02±6.95) and arm lean mass (2.00±0.33 vs. 2.45 ±0.44) were significant ($p<0.05$). Race differences between white and black men in grip strength (38.76±8.05 vs. 41.68±10.14) and arm lean mass (3.51±0.53 vs. 3.91±0.66) were significant ($p<0.05$). The authors concluded that strength and muscle quality are lower for older than younger adults and body fatness shows independent contribution on age-related decline in strength and muscle quality. Preservation of lean mass and prevention of fat gain may help in preserving strength and muscle quality in older adults. [93]

Cawthon et al. (2009) investigated associated risk of hospitalization in non-disabled elders with muscle strength, lean muscle mass, physical performance, specific force, thigh muscle area, and thigh muscle density using data from the Health ABC study. Maximal isokinetic (Kin-Com dynamometer) knee extension was measured at 60º/s with six attempts for three acceptable trials and average of maximal knee extension taken. Physical functioning was measured using 6-meter walking test (i.e. walking at usual pace 2 times) and sit-to-stand test (i.e. 5 repetition chair rises for time). DEXA assessed lean mass and total body fat percentages. CT scans measured mid-thigh CSA and muscle density. Specific force and torque were calculated taking the ratio of strength to mass for upper and lower extremities. A total of 3,075 participants consisted of 60.8% men and 51.5% women hospitalized during follow-up ($p<0.001$). Greater grip strength was associated with higher muscle density ($p=0.022$), Specific force in walking speed, and chair stands per second were all associated with muscle density showing increased performance with higher muscle density ($p<0.001$). 51% higher risk of hospitalization was noted in participants with lowest muscle density during

follow-up (p<.001). A 70% increased risk of hospitalization with slowest walking speed during follow-up (MIRR: 1.70, 95% CI: 1.45, 1.98) and a 65% increased risk of hospitalization was noted in the lowest extremity specific force (MIRR 1.65, 95% CI: 1.39, 1.96). Muscle size, arm lean mass, or leg lean mass showed no associated risks of hospitalizations. 2.45-fold higher odds (adjusted for age, race, and sex) and 1.88-fold higher odds (adjusted for medical conditions, weight, percent fat) of hospitalization were present with poor performance of all four strength and function measures. Decreases in physical function, muscle weakness, muscle density and specific muscle force are associated with increased risk of hospitalization over a 5-year period. Strongest risks of hospitalizations were shown with poor walking speed and knee extension strength. The authors concluded poor physical performance, decreased muscle strength, and low muscle density increase the hospitalization risk in adults 70-79 years of age. [94]

Age-Related Physical Decline in People Living with HIV

Triant et al. (2008) investigated the fracture prevalence of osteoporosis and osteopenia among HIV-infected for increased risk of fracture using a large health care system. The Research Patient Data Registry (RPDR) received recorded data from two hospitals. HIV-infection was classified using the International Classification of Diseases (ICD), prevalence of fractures was determined using ICD-9 codes, and data was received from 1996 – 2008. A total of 8,525 HIV-infected and 2,208,792 non-HIV infected were recorded. Female (34.9%) ages in HIV-infected and non-HIV infected ranged from 30-39 (25.4% vs. 18.1%), 40-49 (33.6% vs. 17.2%), 50-59 (20.1% vs. 14.5%), 60-69 (4.8% vs. 10.7%), and 70-79 (2.6% and 7.2%). Male (65.2%) ages in

HIV-infected and non-HIV infected ranged from 20-29 (3.9% vs. 10.6%), 30-39 (17.3% vs. 14.8%), 40-49 (38.3% vs. 15.6%), 50-59 (28.2% vs. 13.9%), and 60-69 (8.1% vs. 11.5%). Prevalence per 100 persons of fractures for total HIV-infected for total fracture, vertebral fracture, hip fracture, and wrist fracture presented with 245 (CI 95% 2.52-2.32) 86 (95% CI 0.80–1.22), 61 (95% CI 0.54–0.89), and 118 (95% CI 1.14-1.63) fractures. Prevalence of fractures in HIV-infected between age ranges in males ($p<0.0001$) and females ($p=0.002$) was significant. HIV-infected and non-infected showed significant differences in African Americans (females $p<0.03$) and Caucasians (females $p<0.001$; males $p<0.0001$) with no significance between Hispanic. Comparisons of HIV-infected and non-infected of fracture prevalence in age ranges (i.e. 20-29, 20-30, 40-49, etc.) showed significant differences between female ($p=0.002$) and male ($p<0.0001$) groups. HIV-infected patients showed higher incidence of vertebral, wrist, hip, and combined fractures from data over an 11-year period. Age-related increases in fractures were present in HIV-infected men and women. The authors concluded that strong evidence presented a higher prevalence of fractures across genders and fracture sites for HIV-infected individuals.[95]

Grund et al. (2009) investigated the effect of ART on the bone mineral density in HIV-infected individuals. Participants were placed into two separate groups, a viral suppression (VS) and drug conservation (DC). The DC group were given intermittent doses of the ART drugs to maintain the CD4 count between 250cells/ul and 350cells/ul. The VS group maintained their regular regiment of drug dosage through the study. A total of 214 participants (98 in VS group and 116 in DC group) consisted of 19% female and a mean age of 44 years old. A baseline and annual dual-energy radiographic

absorptiometry (DXA), annual scans done over duration of follow-up with subjects. DXA was taken from two sites, total hip and lumber spine (L1-L4). A quantitative computed tomography (qCT) taken of lumber spine (L2-L4) to evaluate volumetric density of trabecular bone. National Osteoporosis Foundation and WHO referenced for osteoporosis values in patient [DXA T (total hip and lumbar spine)-score: <-2.5 and low BMD (osteoporosis/osteopenia) via T-scores <-1] respectively. Baseline median Z-scores of each test are DXA total hip (-0.2), DXA lumbar spine (-0.6), and qCT lumber spine (-0.1). 8 of the 214 had osteoporosis, not mentioned if known before study or as a result of study (none were receiving treatment). Patients from either group followed through over 2.4 years (range .9-4.1 years). VS group showed a decline in BMD at an average rate of .8% [P<0.001 (total hip)], .4% [P<.04 (spine)], and 2.4% [P<0.001 (qCT lumbar spine)] per year. DC group showed stable or increased measures after 1 year. Following the first year DC subjects showed similar decline to the VS group. Those on ART showed larger differences in the follow-ups of the study (DXA: P<.02, between ART status and treatment group; qCT of P=.05), no other variations of, race, sex, age, or other baseline factors had any affect. Based on the results of the study, the use of ART drug regiments, regardless of dose usage has a negative correlation with BMD.

Oursler et al. (2011) studied the relationship between self-reported physical function with age-associated ICD-9 codes in HIV-infected patients enrolled in the Veterans Aging Cohort Study-8 Site (VACS-8). VACS function scale was used to quantify physical function using a 12-item survey asking questions about daily living (i.e. feeding, bathing, etc.), instrumental daily activities (i.e. light – moderate – heavy work), mobility (i.e. light walking activities), and vigorous activity (i.e. running, sports). Out of

6,254 individuals, 3,147 HIV- (92.1% male, 62% African American, 39.2% BMI 18.6-24.9 kg/m^2, 22.8% diabetes, 53.0% hypertension, 14.8% depression, 3.7% peripheral neuropathy) and 3,107 HIV+ (97.5% male, 66.6% African American, 37.3% BMI 18.6-24.9 kg/m^2, 12.8% diabetes, 30.0% hypertension, 13.5% depression, 1.9% peripheral neuropathy) consisted of age ranges of ≤44 (25% and 27.3%), 45-49 years (21.3% and 23.4%), 50-54 years (22.3% and 22.4%) and ≥55 years (31.5% and 26.8%) showing significant differences ($p<0.001$). Weekly exercise for HIV- and HIV+ for never, < 1 time, 1-2 times, 3-4 times, ≥5 times showed 10.5% vs. 12.8%, 18.2% vs. 17.1%, 26.5% vs. 24.7%, 24.9% vs. 26.7%, 19.9% vs. 18.7%, respectively ($p\leq0.05$). Significant differences between groups included age, gender, BMI, diabetes, hypertension (all $p<0.001$), and peripheral vascular disease ($p=0.003$). Physical function scale presented with higher scores for weekly exercise of ≥5 times (86.0±0.8), 3–4 times (85.0±0.7), 1–2 times (81.8±0.8), and < 1 time (77.0±0.8) compared to never exercisers (68.0±0.9; all $p<0.001$). Decline in physical function was 3-times greater for HIV+ than HIV-. Age and HIV-status presented better function in ≤44 years and worse in >55 years ($p<0.01$). The authors concluded that advanced HIV disease is associated with worse physical function scores. Age-related comorbidity risk factor should be considered as risk factor for poor physical function.

Guaraldo et al. (2011) investigated the premature ageing and the prevalence of risk factors for age-related non-infectious comorbidities in HIV-infected persons. Polypathology (Pp) was defined as presence of ≥ 2 non-infectious comorbidities (NICMs). Age was stratified into 40s, 50s, and 60 years. A total of 2854 participants were HIV-infected with 8562 uninfected controls, with 63% men. Comorbidity

prevalence in CVD in HIV-infected versus controls was significant in ≤40 years (0.91% vs. 0.24%; p=0.049), 41–50 years (2.26% vs. 0.64%; p=.001), and 51–60 years (5.97% vs. 2.65%; p=0.002). Comorbidity prevalence in hypertension in HIV-infected versus controls was significant in 51–60 years (19.72% vs. 17.17%; p=0 .018) and ≥60 years (38.94% vs. 31.93%; p=0.007). Comorbidity prevalence in bone fractures in HIV-infected versus controls was significant in ≤40 years (10.77% vs. 0.73%), 41–50 years (15.20% vs. 0.93%), 51–60 years (14.82% vs. 1.33%), and ≥60 years (12.50% vs 2.45%), with all categories p<0.001. Comorbidity prevalence in diabetes mellitus in HIV-infected versus controls was significant in ≤40 years (3.28% vs. 1.40%; p=0.009), 41–50 years (9.16% vs. 2.92%; p=0.001), 51–60 years (19.69% vs. 6.78%; p<0.001) and ≥60 years (38.97% vs. 15.93%; p<0.001). HIV-infected Pp prevalence in ≤40 years, 41-50 years, 51-60 years, and ≥60 years presented 3.9%, 9.0%, 20% and 46.9%, respectively. Control Pp prevalence in ≤40 years, 41-50 years, 51-60 years, and ≥60 years presented 0.5%, 1.9%, 6.6%, and 18.7%. The authors concluded that age-related NICMs, especially presence of ≥ 2, were significantly more common in HIV-infected population compared to controls, and at least a decade in advance.

Zamudio-Rodriguez et al. (2013) et al investigated the comorbidity burden with older age and health-related quality of life negative effects in HIV-infected persons. A total of 206 participants were classified into age groups as younger (≤ 40 years old) and older (≥ 50 years old) with four groups: younger HIV- (n = 56; 29.1 ± 5.8 years, 69.6% male), older HIV-negative (n = 65, 56 ± 4.9 years, 70.8% male), younger HIV+ (n = 50, 30.9 ± 4.8 years, 82% male), older HIV+ (n = 91, 56.7 ± 5.3 years, 81.3% male). Charlson Co-morbidity index (CCI) was used to quantify level of comorbidity burden.

The RAND 36-item Short Form Health Survey (SF-36) evaluated health-related quality of life. The overall regression model predicting the CCI was significant [$F(7,248) = 8.82$, Adjusted R^2 $p < 0.001$]. Interactions were reported between age and HIV (Estimate = 0.46, $p = 0.005$). Higher CCI was observed in older HIV+ group compared to all groups ($p<0.001$). Significant regression models were observed for both the physical ($p < 0.001$) and mental ($p<0.001$) health related quality of life(HRQoL) subscales. Omnibus group difference showed diabetes, syndromic neuropsychological impairment and malignancy (i.e. leukemia/ lymphoma) were significantly different ($p<0.001$). Significantly higher co-morbidity index in HIV+ older were reported with medium effect sizes relative to older HIV- ($g=0.62$), younger HIV + ($g=0.64$), and younger HIV- ($g=0.72$) cohorts. HIV+ older group had at least one comorbid medical condition that was noted to be 22%, 18%, and 13% higher in HIV- younger, HIV- older, and HIV+ younger groups, respectively. The authors concluded that higher medical co-morbidities are associated with poorer physical HRQoL and are more prevalent in older HIV+ adults, highlighting the need for early detection and treatment to reduce comorbid conditions. [96]

Smit et al. (2015) investigated and constructed an individual-based model to represent ageing, drug-drug interactions, polypharmacy, and onset of non-communicable diseases (NCDs) in HIV-infected patients in the Netherlands using data from the Dutch ATHENA cohort. The Dutch ATHENA cohort is a national observational cohort with clinical, biological, and immunological data collected since 1996. The constructed model follows HIV-infected patients from start of treatment until termination of simulation in 2030 or death. A total of 10,278 patients included 84% (n=8586) male

and 16% (n=1692) females. NCDs in men and women presented with 6% diabetes, 23% hypertension, 2% myocardial infarction, 8% osteoporosis, and 2% stroke. The model predicts that from 2010 to 2030 patients older than 50 years, 60 years, and 70 years will increase from 28% to 73%, 8% to 39%, and 8% to 12%, respectively. Projected increases from 2010 to 2030 in 1 or more NCD and 3 or more NCDs will increase from 29% to 84% and 0.3% to 28%, respectively. 16% or HIV-infected patients in 2030 will not have any NCDs. Predictions in 2030 of prevalence of cardiovascular disease (78%) and diabetes (17%) will increase NCDs. The authors constructed a model showing increased burden of age-related NCDs and proportion of HIV-infected individuals on ART resulting in potential complications with HIV-treatment. [1]

Farinatti et al. (2017) investigated the validity of a model to estimate appendicular skeletal muscle mass (ASM) and differentiate between sarcopenic and non-sarcopenic in HIV-infected patients. Validation and cross-validation were administered through 2 different laboratory visits. The first visit consisting of anthropometric data, body mass, arm and thigh circumference, and DXA scan measurements. The second visit consisting of isokinetic knee extensor and flexor strength measurements via Biodex isokinetic dynamometer. From a total of 56 subjects 17 women (47.2+6.9 years) and 9 women (48.1+6.6 years) for cross validation. A 5-minute warm-up on a cycle ergometer and a familiarization of machine with 15 repetition angular velocity fixed at 120º/s occurred. The protocol involved 0-90º knee motion at a fixed speed of 60º/s and 3 sets of 10 repetitions of maximal effort with 120-second rest interval between sets. Validity was tested through correlations and differences between DXA and estimated ASM through Pearson coefficients and paired t-tests. Cross-validation was tested with

predicted residual sum of squares (PRESS). Significant correlations with ASM were significant in sex ($p<0.0001$), BMI ($p=0.004$) arm and thigh circumference ($p<0.0001$). In the validation sample (n = 56), actual and estimated ASM were significant in peak torque extension, peak torque flexion, total work extension, total work flexion ($p<0.0001$). In the cross-validation sample (n = 17), actual and estimated ASM were significant in peak torque extension ($p<0.0001$, $p<0.0001$), peak torque flexion ($p<0.05$, $p<0.0001$), total work extension ($p<0.05$, $p<0.05$), and total work flexion ($p<0.05$, $p<0.05$). The overall predictive model is valid in identifying risk of disability due to sarcopenia in HIV. HIV-infected participants exhibited lower strength scores in relation to less muscle mass and were more likely to be classified as high risk for disability and sarcopenia. The authors concluded decreases in strength and muscle function in PLWH may occur faster than in healthy individuals.[12]

Echeverra et al. (2018) assessed the prevalence and progression of sarcopenia in HIV-1 infected subjects. Sarcopenia was determined according to appendicular skeletal muscle mass (ASM) as the ratio between skeletal muscle mass index (SMI) by DXA and height2 (kg/m2), stratified by gender and age (<40, 41-50, and >50 years), with a sarcopenia positive score when SMI was 5.5 kg/m2 in women and 7.26 kg/m2 in men. A total of 1,720 DXA scans from 860 HIV- infected participants were included. Prevalence of sarcopenia was 25.7% (95% CI: 22.8-28.7), was more present in age 41-50 years (40%) and >50 years (59%), and when stratified for sex women and men ($p=0.001$) older than 50 years had 43% and 8.8%, respectively. Sarcopenic patients presented with 35% osteopenia and 10.5 % osteoporosis. Sarcopenia follow up DXA scans between 7-10 years (n = 109) increased from 37.6% to 49.4% ($p=0.001$) and

greater than 10 years (n = 209) increased from 22 to 25.4% (p=0.046). When gender was considered, prevalence of sarcopenia increased from 56% to 66% (p=0.016) in women and from 26.7% to 29.7% in men (p = 0.057). When age was considered, prevalence of sarcopenia in >50 years increased from 43% to 52% (p=0.001) in women and 8.8% to 9% (p=0.0422) in men. The authors concluded that there was a high prevalence of sarcopenia, especially in women, with HIV-1 infection. A longer HIV-infection duration was associated with greater risk of sarcopenia.[13]

Gowda et al. (2016) investigated risk factors and low muscle mass in HIV/viral hepatitis coinfection patients. A total of 3,518 participant data from multicenter AIDS cohort study (MACS) and Women's Interagency HIV Study (WIHS) between 2000 and 2013 were included. Viral hepatitis included positive hepatitis B virus (HBV) surface antigen (HBsAg) or detectable hepatitis C virus (HCV) RNA. Low muscle mass was determined by mid-upper arm muscle circumference (MUAC) and validated through correlations (rho = 0.71; p<0.001) of fat-free mass determined by single frequency bioelectrical impedance analysis (SF-BIA). Prevalence of low muscle mass was higher in coinfected (n = 45/164 [27%]), compared to viral hepatitis alone (n=23/223 [10%]), and HIV alone (n=132/1,070 [12%]). Among coinfected patients, absence of HIV suppression was the only risk factor for low muscle mass while Nadir CD4 count, active alcohol consumption, and active injection drug use were not associated with low muscle mass. The authors concluded that HIV/viral hepatitis coinfection presents with lower muscle mass than HIV-monoinfected individuals, with HIV suppression absence being a vital risk factor. [14]

Frailty

Frailty in Elders

Fried et al. (2001) investigated the prevalence and incidence of predicting adverse outcomes and validity related to frailty in older adults. Data was used from the Cardiovascular Health Study consisting of men and women 65 years or older from 1989-1993. Interviews, health habits, weight loss information, self-assessments of health, and other disease-related data were collected via Minnesota Leisure time Activity Questionnaire, Instrumental Activities of Daily living (IADL), Activities of Daily Living (ADLs), Center for Epidemiological Studies-Depression scale (CES-D). An operational definition of frailty phenotype was identified by the presence of 3 or more of the following: shrinking (unintentional weight loss of ≥10 pounds in 5% of body weight within past year), weakness (lowest 20% grip strength at baseline, adjusted for gender and body mass index), poor endurance/energy (CES-D Scale identification with 2 questions), slowness (20% slowest walking speed of 15-feet adjusting for gender and height), low physical activity (weighted score of kilocalories expended per week). A total of 5,317 subjects included 2,496 non-frail (76% age 65-74, 22.6% age 75-84, 1.3% age 85+), 2,480 pre-frail (62.9% age 65-74, 32.7% age 75-84, 4.5% age 85+), and 368 frail (38.0% age 65-74, 48.9% age 75-84, 13% 85+). Total population consisted of 84.5% Caucasian, 14.5% African American, 37.1% self-assessed ‘good’ health, 25.2% assessed ‘very good’ health, and 14.3% assessed ‘excellent’ health. The non-frail group presented with 57.9% female, 42.1% male, 12.1% diabetes, 38.8% hypertension, 58.9% 1-2 comorbid diseases, 22.7% 3 to ≥5 comorbid diseases, and 2.6% with a CES-D of ≥10. The intermediate group presented with 57.7%

female, 42.3% male, 18.2% diabetes, 45.9% hypertension, 58.0% 1-2 comorbid diseases, 26.7% 3 to ≥5 comorbid diseases, and 14.0% with a CES-D of ≥10. The frail group presented with 68.5% female, 31.5% male, 25.0% diabetes, 50.8% hypertension, 51.6% 1-2 comorbid diseases, 41.1% 3 to ≥5 comorbid diseases, and 31.0% with a CES-D of ≥10. Significance was reported between all three groups in gender, race, self-assessed health, prevalence of diseases at baseline, number of chronic conditions, self-reported disability, cognitive function, and depressive symptoms (all $p<0.001$). The prevalence of frailty components from highest to lowest was low activity (22%) > slow walking (20%) and grip strength (20%) > exhaustion (17%) > weight loss (6%). From baseline to 3 year follow up between non-frail, pre-frail, and frail incidences of death (3% vs. 7% vs. 18%), first hospitalization (33% vs. 43% vs. 59%), first fall (15% vs. 19% vs. 28%), worsening ADL disability (8% vs. 20% vs. 39%) and worsening mobility disability (23% vs. 40% vs. 51%) were all significant ($p<0.0001$). From baseline to 7 year follow up between non-frail, pre-frail, and frail incidences of death (12% vs. 23% vs. 43%), first hospitalization (79% vs. 83% vs. 96%), first fall (27% vs. 33% vs. 41%), worsening ADL disability (23% vs. 41% vs. 63%), and worsening mobility disability (41% vs. 58% vs. 71%) were significant ($p<0.0001$). Frail individuals were more likely to be female, older, African American, poor health with higher rates of comorbidities and disabilities than non-frail or pre-frail groups (all $p<0.05$). The authors concluded there is a physiologic cycle of frailty that shows a phenotype. A standardized phenotype for frailty in older adults has predictive validity for adverse outcomes such as falls, hospitalizations, death, and disability. [25]

Malmstrom et al (2014) assessed the comparisons of frailty between the International Academy of Nutrition and Aging (FRAIL) scale, Study of Osteoporotic Fractures (SOF) scale, Cardiovascular Health Study (CHS) phenotype scale, and Frailty Index. FRAIL scale consisted of scores from 0-5 measuring fatigue (fatigue in previous four weeks), resistance (difficulty walking 10 steps alone), ambulation (difficulty walking several hundred yards), illness (≥ 5 or more illnesses), and weight loss (5% decline within 12 months). CHS frailty-phenotype consists of unintentional weight loss (5% decline within 12 months), exhaustion (feeling tired within 4 weeks), low activity (Yale Physical Activity Scale), weakness (grip strength stratified by gender and BMI), and slowness (difficulty/unable to walk 0.25 of a mile) with categorizations of frail (3-5 domains), prefrail (1-2 domains), and robust (o domains). SOF consisted of points for weight loss (5% decline within 12 months), chair stands (completion of 5 chair stands), and energy level (reported energy past four weeks) and categorized as frail (2-3 points), prefrail (1 point), and robust (0 points). FI consisted of 25 items (scored -25, one point per item) including self-rated health, difficulty walking 1 mile and several hundred yards, climbing 1 flight of stairs,

participating in vigorous or moderate activities, emotional and sleep problems, and cardiovascular or pulmonary issues. Scores were based on Falls Efficacy Scale worst quintile with classifications of frail (>0.25), pre-frail (0.25-0.20) and robust (<20). A total of 998 subjects included age tertials of 51.4±1.1 (n = 263), 56.0±1.5 (n = 254), and 61.5±2.0 (n = 262) with 26%, 46%, and 95% 60 years or older at baseline, 3-year, and 9-year follow up, respectively. Baseline of FRAIL, SOF, CHS, FI scales were 42.0%, 32.0%, 51.6%, and 9.4% for prefrail and 6.4%, 9.2%, 6.3%, and 22.6% for frail,

respectively. The FI was a better predictor for ≥1 new IADLs at 3 years than the FRAIL, CHS, and SOF scales. The FRAIL scale outperformed the CHS and SOF scales. ≥1 new IADL 9 years, the FI was better compared to the FRAIL, CHS, and SOF scales, with no differences between FRAIL, CHS, and SOF scales. FI and FRAIL scale predicted mortality in frail but not pre-frail. The authors concluded that the FI and FRAIL scale are predictors of mortality, while all four scales predict disability. The Fi and FRAIL showed strong predictive validity for disability and mortality in older adults.[32]

Lee et al. (2017) explored the accuracy of Fried's Frailty Phenotype measures in primary care settings. Participants ≥ 75 years were assessed by trained nurses in frailty, based on Fried and colleagues' criteria[25], assessed gait speed (4-m walk at usual pace), grip strength (hand dynamometer), self-reported exhaustion (CES-D scale; 2-items), weight loss (previous year), and low physical activity (self-report of level). Out of 383 participants, ranging from 75 to 94 years of age, 46.5% were male and 53.5% were female. In the incidence of single-trait frailty indicators between women and men low exercise (22.9% and 15.5%), grip strength (16.1% and 14.6%), and gait speed (11.7% and 9.0%) were among the highest noted. Gait speed sensitivity, specificity, and accuracy showed 87.5%, 94.6% and 94.2%, respectively. Grip strength sensitivity, specificity, and accuracy showed 100%, 90.5%, and 91.1%, respectively. Low exercise sensitivity, specificity, and accuracy showed 100%, 90.5%, and 91.1%, respectively. Combined markers of gait speed and grip strength sensitivity, specificity, and accuracy showed 87.5%, 99.2%, and 98.4%, respectively. The authors concluded that gait speed and grip strength was sensitive, specific, and accurate as a proxy for frailty phenotype in older adults. [31]

Frailty in HIV

Desquilbet et al. (2007) examined the prevalence of frailty-related phenotype in people with HIV-infection from the Multicenter AIDS Cohort Study (MACS) before the use of highly active antiretroviral therapy (HAART). This study used four of the five Fried Frailty Phenotype (FFP) Fried components[25] to assess frailty in MACS with slowness estimated using questions about difficulty walking various distances. There was no measure of weakness in data. The presence of three components (physical shrinking, exhaustion, slowness, low physical activity) defined participants as frail. Based on Fried's FP, content validity was assessed using qualitative questions on a "yes, limited a lot; yes, limited a little; no, not limited" type of scale for all four components. Construct validity was assessed on the prevalence of increases in frailty with age. Logistic regression models were used with MACS questionnaire items to define frailty phenotype. HIV-infected men manifested physical shrinking (odds ratio [OR] = 12.80), exhaustion (OR = 3.02), slowness (OR = 3.94), low physical activity level (OR = 3.40), and the aggregate FRP (OR = 10.97) compared to uninfected men. The authors concluded that pre-HAART HIV-infected and AIDS patients presented with frailty-like manifestations, with duration of HIV-infection associated with likelihood that the manifestations exist. Low CD4 count and high viral load are two biomarkers that show a common underlying biology in frail HIV-infected individuals. The authors concluded studies of frailty may identify age-related declines in PLWH. [78]

Desquilbet et al. (2009) investigated the causal relationship between physiological dysfunction in frail HIV-infected individuals with CD4 T-cell count and viral

load adverse effects predicting the occurrence of frailty. The Multicenter AIDS Cohort Study participants from the years 1993-2005 were used. Assessments included frailty and CD4 T-cell and viral load via blood and plasma samples. Frailty-related phenotype[25] was identified by answering “Yes” to any of the four questions: “Since your last visit, have you had unintentional weight loss of at least 10 pounds” (shrinking), “Does your health now limit you in walking several blocks?” (slowness), “Does your health now limit you in vigorous activities, such as running, lifting heavy objects, participating in strenuous sports?” (low physical activity), “During the past 4 weeks, as a result of your physical health, have you had difficulty performing your work or other activities” (exhaustion) with a frailty result answering yes to 3 of the 4 questions. After adjusting for variables (CD4+, AIDS status, education, ethnicity) frailty-related phenotype was higher in the pre-HAART era (1994-1995) than in HAART introduction era (1996-1999) ($p<0.01$) and HAART established eras (2000-2005) ($p<0.01$). CD4 T-cell was independently significant predictor of the frailty-related phenotype in HIV-infected men. 50% declines were present in frailty phenotype from pre-HAART to HAART era showing improvement of immune function reduces frailty-like occurrence. The authors concluded that frailty is associated with compromised immunity and predictive of mortality in PLWH. [76]

Rees et al. (2013) explored the rate of frailty in HIV outpatients. Out of 100 HIV-positive patients, 19 presented with frailty phenotype based on Fried and colleagues Fried[25]. Frail and non-frail parameters consisted of 74% and 74% men, 26% and 26% women, 63% and 57% <50 years, 37% and 43% ≥50 years, 42% and 19% neuropathy, and 16% and 7% diabetes. respectively. Frail participants showed a higher rate of

neuropathy and hepatitis C ($p<0.05$). 9-fold increased odds of frailty represented patients with CD4 counts <200 cells/mm3 compared to patients with a CD4 count >350 cells/mm3 (OR = 9.0). Of the 19 frail, 7 were measured 6 months later with only 1 person remaining frail. Longer antiretroviral therapy exposure showed a less incident of frailty ($p<0.05$). The authors concluded that frailty in HIV outpatients is associated with a low CD4 count and antiretroviral use. Frailty in HIV patients is transient especially in younger compared to elderly frail presenting with stepwise decline in function.[56]

Onen et al (2009) evaluated frailty in HIV-infected individuals among racially and socially diverse men and women in outpatient care and establish predictors of frailty. Frailty was defined according to Fried and colleagues[25]. A total of 445 HIV-infected individuals included 39 (9%) were frail and demographically were 45.3 ± 1.6 years, 64.1% male, 71.8% African American, 69.2% < $10,000 income in last year, had between 1-2 (71.8%) comorbid conditions per person, 53.8% had moderate depression, and 59.0% with cognitive impairments. 406 (91%) were non-frail and demographically were 41.3 ± 0.6 years, 71.4% male, 62.3% African American, 45.1% < $10,000 income in last year, had between 0-2 (33.5%) comorbid conditions per person, 17.0% had moderate depression, and 33.7% had cognitive impairments. Statistical differences were reported in age ($p=0.03$), < $10,000 income in last year ($p=0.01$), comorbidity ($p<0.001$), moderate depression ($p<0.001$), and cognitive impairment ($p<0.001$). Frail vs. non-frail HIV-infected presented significant differences in years of diagnosis (10.4 ± 0.9 vs. 8.2 ± 0.3; $p=0.01$), CD4+ <200 cells/mm2 (35.9% vs. 16.4%; $p=0.01$), CD4+ ≥ cells/mm2 (41.0% vs. 63.5%; $p=0.01$), hospitalizations ≤ 1 year (28.2% vs. 11.8%; $p=0.004$), number of admissions per person (0.7 ± 0.2 vs. 0.2 ± 0.02; $p<0.001$), and

days of inpatient stay (4.9 ± 1.9 vs. 0.9 ± 0.1; p<0.001). The authors concluded that there was premature frailty among middle-aged men and women with socioeconomical and racially diverse backgrounds. Frailty was associated with higher comorbidity, immunodeficiency, and hospital in-bed days.[36]

Erlandson et al. (2012) examined the comparison of Fried's Frailty Phenotype (FFP)[25], the Short Physical Performance Battery test (SPPB), and 400-meter walk in HIV-infected adults on ART. FFP was assessed according to Fried and colleagues[25], consisting of unintentional weight loss (i.e. ≥10 lbs. loss in past year), self-reported exhaustion (i.e. 3-4 times per week of 'everything I do is an effort' and 'I just cannot get going'), low physical activity (i.e. Short Form 36), weakness (i.e. hand grip dynamometer), and slowness (i.e. 4.5-m gait speed test). The SBBP consisted of tandem standing (i.e. standing heel to toe for 10-seconds), walking speed (i.e. 4-m walk at usual pace), and sit-to stand test (i.e. 5 repetitions for time). The 400-m walk consisted of walking as quickly as possible for time (i.e. high function = <5.5 minutes, moderate function = ≥5.5 minutes). Groups were categorized into high-, moderate-, and low-function based on scores for each measure. Veterans Aging Cohort Study (VACS) index was calculated to indicate mortality risk. A total of 359 participants (85% male, median age 50.8, 74% Caucasian) completed the assessment. FFP revealed 46%, 46% and 8% were high-, moderate-, and low-functioning, respectively. SPPB revealed 62%, 31%, and 7% were high-, moderate-, and low-functioning, respectively. 400-m walk revealed 46%, 51%, and 3% were high-, moderate, and low-functioning. 61-64% agreement was found for comparison of all three assessments. All three instruments' association with lower function showed lower physical activity (p<0.005), arthritis

(p<0.02), four or more comorbidities (p<0.005). FFP, SPPB, and 400-m walk low-function compared to high-function group showed 1.8 vs. 1.9 vs. 2.5 more comorbid conditions, 2.7 vs. 2.5 vs. 3.1 more medications. SPPB sit-to-stand score <4 had high sensitivity and specificity for predicting low function on FFP (86% and 91%) and 400-m walk (86% and 86%). VACS index score was significant between high and low function between FFP (p=0.03), SPPB (p=0.001), and trending toward significance in 400-m walk (p=0.08). 50% of participants were unable to walk faster than 3.4 miles/hr (Social Security Administration disability), 3% were unable to walk 400-m at any pace, and 7% met criteria for frailty. Only modest agreement across instruments for impairment were shown. FFP is a global assessment including subjective depression overlap, SPPB is lower-extremity function, and 400-m is endurance. The authors concluded that middle-aged HIV-infected individuals have functional impairments similar in 20-30 years older non-infected individuals. Strongest associations were noted in low physical activity, high comorbid disease, medical burden, arthritis, and debilitating pain.[75]

Erlandson et al. (2016) investigated the relationship between inflammation, immune activation, immunosenescence and hormonal biomarkers for frailty phenotype in men with HIV using the MACS. Frailty Fried was modified using 4 self-reported subjective measures of unintentional weight loss, exhaustion, low activity level, and slowness. 155 frail and 141 non-frail HIV-infected men were matched to 150 non-frail HIV-uninfected men. Non-frail and frail HIV-infected me presented with 51% and 40% (p=0.003) for African American race, 23.9 kg/m2 and 25.7 kg/m2 (p=0.02) for BMI, 41% and 22% (p<0.001) for diabetes, 65% and 40% (p<0.001) for hypertension, and 49% and 23% (p<0.003) CD4+ <350 cells/μL, respectively. Inflammation biomarkers in frail

vs non-frail HIV-infected men were IL-6 (52% higher), hsCRP (69% higher), sTNFR1, and sTNFR2 (all p<0.001). T-cell activation (CD38+ HLA- DR+ expression) and T-cell senescence (CD28− expression) were not significant for CD8+ cells and CD4+ cells in frail and non-frail HIV-infected persons. Hormonal regulation DHEA-S (18% lower; P=0.04) and IGF-1 (p<0.001) were significant while free testosterone (17% lower; P=0.02) was significant in non-frail vs. frail HIV infected persons. IL-6, hsCRP, DHEA-S and testosterone levels were associated with frailty among HIV-infected men. Inflammatory markers remain elevated despite the use of ART. Multivariate models adjusted for comorbid conditions showing true results of inflammation and hormonal dysregulation without the influence of comorbidity.[80]

Rees et al. (2016) investigated frail HIV-infected individuals and determine which Fried frailty components were most important in predicting frailty. Frailty was defined based on the five domains presented by Fried and colleagues Fried. Chi-square analysis were administered for comparisons of categorical data while t-tests were used for group differences. Logistic regression analyzed prediction of the model. A total of 122 participants included 23 considered frail and 99 considered non-frail with occurrence in Center for Epidemiological Depression (CES-D) Scale at 100% (n = 23) and 38% (n = 38; p<0.001), low physical activity level at 83% (n = 19) and 16% (n=16; p<0.05), losing >10lbs unintentionally at 65% (n=15) and 13% (n=13; p<0.001), decreased grip strength at 43% (n=10) and 3% (n=3; p<0.02), and gait speed at 39% (n=9) and 13% (n=13; p<0.001), respectively. 30% (n=7) of frail patients presented with mild to moderate depression and 70% (n=16) were classified with having major depressive disorder. The rank of frailty indicators among frail HIV-positive individuals

were exhaustion > low physical activity > shrinking > weakness > slowness. The authors concluded that frail young patients with HIV have a different phenotype than frail elder patients. Sarcopenic measures (slowness, weakness, shrinking) compared to depression and inactivity were not the most common phenotype markers in this sample. [21]

Piggott et al. (2017) investigated the cause-specific hospitalization among frail HIV-infected injection drug users. Assessments included frailty via Fried frailty phenotype (slow gait, weakness, exhaustion, low physical activity, shrinking) and hospitalization events of chronic conditions via medical records from 2005 to 2013. A total of 1,303 participants included 349 robust (age 46.8±8.1; 69.6% male; 13.5% depressive symptoms; 56.5% ≥1 comorbidity), 796 prefrail (age 47.5±7.4; 66.7% male; 23.2% depressive symptoms; 57.7% ≥1 comorbidity) and 158 frail (age 49.7±8.5; 57% male; 41.1% depressive symptoms; 71.9% ≥1 comorbidity). A 4.5 year follow up period presented a median hospitalization time from baseline frailty of 17 months (IQR 7.4, 34.3) with reports of 42% hospitalized one time, 23% with 1 chronic disease hospitalization, 17% with 1 infectious disease hospitalization, and 22% with 1 non-chronic, noninfectious hospitalization. Frailty was associated with all-cause (HR 1.41; 95% CI, 1.06, 1.87), chronic (HR 2.13; 95% CI, 1.46, 3.11), and infectious disease (HR 2.51; 95% CI, 1.60, 3.91) hospitalizations. Strong relationships were present between frailty phenotype in chronic and infectious disease hospitalizations. The authors concluded that identifying and creating interventions for high risk frail HIV-infected individuals may decrease chronic and infectious disease mortality and hospitalizations. [20]

Hawkins et al. (2018) explored the relationship between abdominal obesity, sarcopenia, osteoporosis associated with frailty in HIV-infected individuals using the Bone Strength Sub study (BOSS) within MACS. BOSS includes participants 50-69 years with data on ageing, chronic HIV-infection, and ART on non-skeletal risk factors for fractures. Assessments of frailty phenotype, quantitative computed tomography (CT) and DXA within 12-month time-period were collected. Frailty was defined according to Fried and colleagues[25]. A total of 399 men included 199 (age median age 60.1) HIV-infected and 200 (median age 60.0) HIV-uninfected. Among HIV-infected and HIV-uninfected 35% and 43% were non-frail, 49% and 49% were pre-frail, and 16% and 8% were frail, respectively. Sarcopenia prevalence in HIV-infected men was 41% (76/185) and in HIV-uninfected men was 36% (67/186). Visceral Adipose Tissue (VAT) prevalence in HIV-infected and HIV-uninfected men was 56% (104/185) and 41% (76/186) ($p=0.004$) and osteopenia/osteoporosis was 16% (30/185) and 9% (17/186) ($p=0.003$), respectively. HIV infection and frailty had 2.43-fold increased odds. SAT was not associated with frail or pre-frail HIV-infected participants. Waist circumference (WC) and VAT in HIV-infected were significantly correlated ($r=0.56$, $p<0.0001$). In HIV-infected lumbar spine BMD was not associated with frailty. The authors concluded that sarcopenia and central adiposity (VAT; WC) were strongly associate with frailty in HIV-infected individuals. Assessments of WC in HIV-infected in frailty and metabolic risk has shown rational for use in identifying these factors.[35]

Clinical Measures of Physical Function

Hand-Held Dynamometry in HIV-

Deones et al. (1994) investigated reliability of hand-held dynamometry (HHD) and isokinetic dynamometry (IKD). Inter-rater reliability included a total of 10 non-injured unilateral knee extension. Intra-rater reliability between test subjects using HHD was 0.95 ($F[1,9] = 0.81$, $p=0.3915$), and SEM at 0 and 60 degrees was 17.8N and 15.6N respectively. Intra-rater reliability for isokinetic testing was 0.87 ($F[1,20] = 2.76$, $p=0.1410$) at 60 degrees/sec and SEM was 17.6. Reliability between instruments included a total of 21 subjects comparing injured/non-injured knees. ANOVA showed no significant difference between healthy and injured knees when tested via HHD at 0 degrees ($F[1,20] = 2.6$, $p=0.1224$) and 60 degrees ($F[1,20] = 0.05$, $p=0.8267$), but showed significant differences between healthy and injured knees when tested isokinetically at 60 degrees/second ($F[1,20] = 10.47$, $p=0.0041$). Confounding factors included tester strength (female) unable match subjects' strength at 0 and 60 degrees, and confounding factor was that the testers did not stabilize the trunk or extremity of the patient during HHD. Overall, the study found that HHD is not reliable compared to isokinetic testing. The patients' knee injuries were all different and the SD's of their injured knee force outputs were very large (HHD 0°: 74.2N, 60°: 58.3N, IKD 60°/sec: 198.7N). The authors concluded that overall tester strength affected the quadriceps assessment, reporting false values of muscle performance in patient population.[73]

Shaubert et al. (2005) investigated reliability of the hand-held dynamometer on sit-to stand test, timed up and go (TUG), and hand-grip dynamometry in community-dwelling elders. Knee extension strength was assessed using the MicroFET 2 hand-held dynamometer, hand-grip strength was assessed using the Jamar hand dynamometer, functional strength was assessed using sit-to-stand (STS) test, and

functional mobility was assessed using the TUG. A total of 10 subjects (75.5±5.8 years, 80.4±17.5 kg) included 80% women, and 20% men. The TUG ($r=-0.710$, $p<0.05$) and gait speed ($r=0.792$, $p<0.01$) were significantly correlated with knee extension strength and STS test times across all testing sessions. The authors concluded knee extension strength demonstrate significant correlations with measures of functional mobility. Findings support for the use of these 3 measures for monitoring changes in strength and for explaining limitations in function.[50]

Bohannon et al. (2010) assessed the five-repetition sit to stand test (FRSTST) across adolescence to older adults and determined the relationship between knee extension and strength. The FRSTST required participants to stand from a 43 cm armless chair with arms crossed over chest as quickly as possible 5 times. Standing up completely and firm contact with sitting were counted and time began on “go” and ended with fifth sit. 2-repetition practice trials began first, followed by 2 test trials of FRSTST, with the fastest time used. Isometric knee extension force was measured using a MicroFET hand-held dynamometer (HHD) and a Biodex isokinetic dynamometer measured knee extension torque. Stabilization straps with knees at 90 degrees and dynamometer placed proximal to malleoli. 3 trials were taken for each limb for each test for maximal effort. The best of 2 test trials was used. Age of sample ranged from 14 to 85 (46.5 ± 22.7 years) and an average weight of 72.9 ± 16.8 kg. Moderate negative correlations and significance were noted between the FRSTST and strength measures for the entire sample and the older sub-sample. Knee extensor strength measures, along with age, body weight, and stature provided, the strongest explanation FRSTST times. The authors concluded that FRSTST is a functional measure of strength and

knee extension strength via MicroFET HHD especially in 50-85-year old provides a measure of strength.[97]

Stark et al. (2011) investigated the reliability and validity of hand-held dynamometry (HHD) to isokinetic testing such as with a Biodex. The search phrases used were: muscle strength dynamometer, muscle strength dynamometer and/or hand-held dynamometer, and hand-held dynamometer and isokinetic. 17 out of 454 manuscripts met all inclusion criteria and were assessed. The 17 manuscripts contained 19 studies. 8/19 studies indicated that the tester was trained in HHD. 3/19 studies included an ICC, two of which were rated as “good” and one which was “moderate-to-good.” 13/19 studies included a Pearson correlation coefficient, and all 13 were showed positive Pearson values indicating validity between isokinetic and HHD testing. Studies that had poor reliability between HHD and isokinetic testing showed inconsistent positioning or lack of subject stabilization allowing them to utilize other muscle groups during the testing. A meta-analysis was not performed due to the lack of homogeneity of the studies that met inclusion criteria. The authors concluded research indicated HHD was reliable and valid for most isometric muscle strength measurements when compared to isokinetic testing with exceptions only for the largest joint such as knees and hips.[98]

Thorborg et al. (2013) investigated hand- held dynamometry (HHD) intra-tester reliability. Isometric force output for hip abduction, adduction, flexion, extension, and knee flexion was tested using external fixation of the dynamometer via belt. The study included two testers (one male and one female) and 21 test subjects. Each of the test subjects performed two submaximal isometric contractions against the tester’s hand for

practice, followed by four 5-second maximal voluntary contractions (MVC's) against the dynamometer with a 30-second break between contractions. The highest of the 4 MVC's was recorded. Following a 10-minute break, all testing was repeated by the second tester. Inter-rater reliability (ICC 2.1) ranged from 0.76 to 0.95. Standard error of measurement percentage (SEM%) was 5-11%. Minimal detectable change percentage (MDC%) was 14-29%. The article does not state the MDC% or MCID of HHD without external fixation for these motions. Overall, HHD with external fixation seems to be a reliable measure of isometric hip MVC's. The authors concluded that HHD demonstrates poor intra-tester reliability above 200N of force due to the physical limitations of some testers. [74]

30-Second Chair Stand in HIV-

Macfarlane et al. (2006) investigate the 30-second chair stand test (30 CST) validity in a field setting and obtained normative data in 1038 participants for the Hong Kong population, completing one 30 CST followed by a Modified Baecke Questionnaire to determine habitual levels of physical activity. A sub-group of 142 participants completed one 30 CST and performed two maximal isometric strength tests for hip flexion (HF) and knee extension (KE) using the Nicholas Manual Muscle Tester (NMMT). 30 CST was weakly correlated but significant with HF, KE, and combined HF and KE. Reported decrease in 30 CST with increase in participant age was found significant and elderly with consistent physical activity performed more chair stands than non-physically active. Normative values were separated by age category and gender: males 60-64 years, 65-69 years, 70-74 years, 75-79 years, 80-84 years, 85-89 years, and 90+ years demonstrated 14.0 ± 4.3, 12.9 ± 4.6, 11.6 ± 3.3, 11.3 ± 4.4, 11.1 ± 4.2,

8.1 ± 4.0, and 5.8 ± 2.6, respectively. The authors concluded that the construct validity of the 30 CST discriminated between levels of consistent physical activity showing differences in increasing age group. They proposed that isometric HF may not be ideal as a test in a field setting and chair stand tests require strong knee extension to perform the task. [65]

Rikli and Jones (2012) investigated reliable and valid criterion fitness standards for easy-to-use validated functional fitness, via Senior Fitness Test, in older adults. The Senior Fitness Test is comprised of 30-second chair stand test to measure lower body strength (30 CST), a 30-second arm curl to measure upper body strength, a 6-minute walk (6MWT) for aerobic endurance, chair sit-and-reach for lower body flexibility, back scratch for upper body flexibility, and 8-foot up-and-go for agility/dynamic balance. A total of 2,140 subjects were measured, split between make and female for different age ranges of 60-64 (n=144) years, 65-69 (n=369) years, 70-74 (n=538) years, 75-79 (n=515) years, 80-84 (n=306) years, 85-89 (n=180) years, and 90-94 (n=88) years. Caucasians accounted for 89.1% and were relatively well-educated. Fitness standards show average decline of 33.3% and 36.4% over a 30-year period from 60–64 to 90–94 in the 30 CST. The number of chair stands for age ranges 60-64 years, 65-69 years, 70-74 years, 75-79 years, 80-84 years, 85-89 years, and 90-94 years in men and women were 14.8±4.7 vs. 13.8±3.6, 14.0±4.5 vs. 13.7±3.5, 13.0±4.0 vs. 12.8±3.1, 12.9±3.6 vs. 12.5±3.6, 12.4±3.6 vs. 11.9±5.2, 10.1±4.6 vs. 10.7±4.1, and 9.4±3.6 vs. 9.2±4.3. This is the only comprehensive normative data to date with norms for age ranges ≥60 years old. The authors concluded that fitness standards for each test have been established yet confusion still exists in regard to clinical use for older adults. Strong empirical

rational support has been established through this research, which can be used by researchers and clinicians to estimate fitness levels of adults and elders.[67]

Kuo et al. (2013) investigated the effect of chair height on the 30 CST in 55 (70.0 ± 6.3 years) older adults. Participants presented with 32.7% hypertension, 20% diabetes mellitus, 41.8% lower limb arthritis, and 74.5% ≥ 20 minutes of exercise 2 times per week. 40% of participants were men. The 30 CST was performed on an armless height-adjusted chair. Participants began seated with arm crossed over chest, instructed to stand and sit as quickly as possible in 30-seconds, with straightening both knees and making full contact with the chair. One practice trial followed by two test trials were performed on both a 43 cm chair and randomly assigned seat height of 80, 90, 100, 110, and 120% of participants lower leg length. The results of the study showed an increase in 30 CST repetitions with increase in percentage of lower leg length. The authors concluded that chair seat height significantly influences the repetitions in 30 CST in older adults. Lower leg length and chair seat height should be a consideration during this measure.[99]

Millor et al. (2013) investigated velocity parameters of successful and failed 30 CST attempts in 47 frail and non-frail older adults. Of 47 subjects, three groups consisted of frail (n = 13, 85 ± 5 years), pre-frail (n = 16, 78 ± 3 years), and non-frail (n = 18, 54 ± 6 years). Frailty was determined by protocol presented by FFP. The 30 CST was administered with a 40 cm height chair without arm or back rests. Subjects were instructed to being on “1, 2, 3, go”, sit and stand at their own pace, and the trial ended at 30-seconds. An inertial tracker was placed over the L3 region of lumbar spine on each participant to provide 3D accelerator, orientation, and rate of turn data. Non-frail

subjects presented with significantly ($p<0.001$) greater chair stands (22 ± 7) than pre-frail (15 ± 5) and frail (6 ± 1). The frailty group had less physical capacity to perform different phases of 30 CST cycles, showing frail subjects have reduced power in lower extremities. Parameters related to 30 CST are more sensitive to frailty. The authors concluded that differences in frailty level can be found by evaluating the specific way 30 CST cycles are carried out. [66]

Bodilsen et al. (2015) investigated the reliability and feasibility of four physical performance measures in 52 older medical patients in an emergency department: isometric hand grip strength, 4-meter gait speed, 30 CST, and cumulated ambulation score. Grip strength was assessed either seated in a chair or in a hospital bed with the back-rest elevated, with elbow flexed to 90º and instruction to squeeze handle for 5 seconds. One practice trial was allowed, followed by three trials, with the highest value used. Gait speed was assessed over 4-meters, with patients standing behind start line and walking at usual pace on “3-2-1-go” and was stopped after walking 5.5-meters. Two trials were taken, with the fastest trial used. The 30 CST was assessed using a 45cm chair, arms folded across chest, and instructed to stand and sit as many times without stopping in 30-seconds. “3-2-1-start” began the trial, patient stopped after 30-seconds, and after one test trial one official trial score was used. The study included 73.1% female sample with a mean age of 78 ± 8.3. The authors concluded feasibility was good in the grip strength and gait speed measures for basic mobility with inter-rater reliability. Feasibility and inter-rater reliability were moderate for the 30 CST due to 54% of subjects only being able to perform the test. 30 CST in older medical patients (i.e. emergency room) is not the ideal measure.[100]

Lai et al. (2016) investigated six-minute walk test, 30 CST, isometric knee extension, unipedal stance time, and maximal step length in 40 impaired frail end stage liver disease patients (ESLD). Univariable linear regression showed Fried's FP was significant with all tests ($p<0.05$). The non-frail ($n = 30$) group for 30 CST and isometric knee extension presented means of 10 and 122.4 Nm while the frail ($n = 10$) group presented means of 7 repetitions and 86.0 Nm, respectively. The non-frail group for 6 MWT, unipedal stance test, and maximal step presented means of 338 meters, 13.2 seconds, and 27 inches while the frail group presented 231 meters, 4.5 seconds, and 21.6 inches, respectively. The authors concluded that frailty measure of strength and physical performance relies on the number of adverse outcomes that are associated in chronically ill patients (diabetes, hypertension, hepatic encephalopathy, etc.). Objective measures of physical performance captures mortality rates in cirrhotic patients.[101]

Clinical Measures of Physical Function in People Living with HIV

30-Second Chair Stand in HIV+

Khoury et al (2017) investigated physical function using validated physical performance tests in older HIV-infected individuals on ART compared to health controls. Physical performance included 2.4-meter walk (i.e. walk at usual and maximal speed), 30-second chair (30 CST) stand test, grip strength, and 6-minute walk test (6MWT). These measures tested lower extremity strength (30 CST) overall strength (grip strength), aerobic endurance (6MWT), and gait speed (2.4-m walk). Of the 107 HIV-infected adults, 70% were male ($n=75$) with 49%, 46%, and 6% ages ranging from 50-59 years, 60-69 years, and ≥70 years, respectively. Other demographics include 60%

African American, 37% Caucasian, 26 % <25 kg/m^2 BMI, 39% 25-29.9 kg/m^2 BMI, and 35% >30 kg/m^2 BMI. The most common comorbidities included 57% cardiovascular disease, 36% liver disease, 17% renal disease, 17% pulmonary disease, and 16% malignancy. Differences in norms for maximal gait speed (m/s), 30 CST, grip strength (kg), and 6MWT (m) presented differences in norms with 0.21 ± 0.37, -1.11 ± 4.06, 3.68 ± 8.65, and 105.15 ± 100.85, respectively. Males performed significantly better on grip strength and gait speed and older adults performed worse on 6MWT. The authors concluded virologically suppressed HIV-infected persons have significant clinical physical function differences than general population.[68]

Safeek et al. (2018) investigated physical activity in PLWH using accelerometry and its associations among performance-based measures of physical function. Physical performance included 2.4-meter walk (i.e. walk at usual and maximal speed), 30-second chair (30 CST) stand test, grip strength, and 6-minute walk test (6MWT). These measures tested lower extremity strength (30 CST) overall strength (grip strength), aerobic endurance (6MWT), and gait speed (2.4-m walk). PLWH ≥50 years and <50 copies/mL HIV-1 viral loads were included. Of 21 participants, 66.67% were male, 66.05±6.34 years of age, BMI of 29.26±6.05, and a CD4 count 631.52±370.16. Median and interquartile ranges were 3,441.89 (4612.8) steps per day, 254.86 (345.58) daily kilocalories expended, 10.82 (3.27) hours of sedentary activity, 3.69 (2.72) hours of light activity, 5 (9.13) hours of moderate-vigorous activity, 392.6 (1,212.3) 6MWT meters, 14 (6) 30 CST rises, 38 (9.75) kg grip strength in men, 25 (2.25) kg grip strength in women, usual gait speed 1.13 meters per second (m/s), and 1.63 (0.49) m/s maximal gait speed. No significant correlations were shown with 30 CST and calories expended,

steps, vigorous or sedentary activity. Maximal gait speed had moderate correlations for and steps ($r=0.64$, $p<0.01$), kcals expended per day ($r=0.52$, $p<0.01$), sedentary activity ($r=-0.44$, $p<0.05$), light activity ($r=0.53$, $p<0.05$) and vigorous activity ($r=0.50$, $p<0.05$). Older PLWH do not meet the physical activity guidelines of CDC recommended 150 min/week of exercise for persons older than 50. There are no physical activity requirements or standards for PLWH currently. Participants did not meet 10,000 steps-per-day criteria recommended by CDC. The authors concluded that there is a link between physical activity and functional parameters in older PLWH. Promotion of physical activity among older PLWH who are insufficiently active should be a priority for this population.[102]

Hand-Held Dynamometry in HIV

Mhariwa et al. (2017) examined the relationship between lower limb strength and self-perceived lower extremity function in PLWH in Zimbabwe. Normative muscle strength values were obtained from HIV-negative individuals. The Lower Extremity Functional scale (LEFS), both reliable and valid in patients with musculoskeletal disorders, is a 20-item questionnaire used by clinicians to measure initial function, progress, and establish goals for patients. A hand-held dynamometer (Nm) measured isometric ‘make contractions’, pushing maximally against dynamometer for 5-seconds, with a second retest 10-15 minutes after. Out of 143, 113 HIV-infected (69.91% ranged 40-69 years, 50.4% male) and 30 HIV-uninfected (20% ranged 40-69 years, 56.6% male) people participated. In age-matched groups of 30 HIV+ and 30 HIV- from sample, mean muscle strength was measured in ankle plantar flexors (12.76 vs. 15.36), ankle

dorsiflexors (9.66 vs. 11.23), hip flexors (11.67 vs. 13.33), hip extensors (15.75 vs. 17.75), hip abductors (11.98 vs. 16.53), hip adductors (11.71 vs. 14.11) were significant ($p \leq 0.0001$). 50% of lower limb function in HIV-infected was due to lower limb strength. Order of contribution of muscle groups to lower limb function (LEFS) from highest to lowest was ankle plantar flexors > knee flexors > hip flexors > hip abductors > hip adductors > hip extensors >ankle dorsi-flexors > knee extensors. The authors concluded that there is a relationship between activation of muscle strength and self-reported physical function in PLWH in Zimbabwe.[72]

Oliveira et al (2017) explored the dynamic and isokinetic parameters of muscle strength in HIV-infected men and women on ART. Muscle strength evaluations were separated by 48-hour intervals (muscle recovery) with 5 of six visits focused on isokinetic or dynamic muscle strength testing. Isokinetic evaluation consisted of three repetitions of 60°/s and five repetitions of 180°/s for knee extension and flexion in concentric-concentric mode on a Biodex® Multi-Joint System. Dynamic strength evaluation included 1-repetition maximum test (1RM) for bench press, leg press, and arm-curls with three trials and an interval of three to five minutes of rest between. HIV-infected men had lower values of dynamic strength for 1RM compared to controls in total (262.5 vs 357.2 kg), bench press (48.6 vs 60.3 kg), leg press (182.7 vs 261 kg) and arm curl (31.2 vs 36.5 kg) exercises. Lower peak torque values were noted in HIV-infected men compared to HIV-uninfected for extension at 60°/s (127.5 vs 185.8 N-m) and 180°/s (80.4 vs 130.6 N-m), and flexion at 60°/s (65 vs 101.2 N-m), and 180°/s (42.9 vs 76.9 N-m). Higher peak torque values were noted in HIV-infected women compared to HIV-uninfected for extension at 60°/s (119.1 vs 99.5 N-m). Statistical

significance was noted between total group HIV-infected compared to non-infected for 1RM leg press and peak torque at 180°/s extension ($p<0.05$). The authors concluded that HIV infection in men is associated with impaired dynamic and isokinetic strength compared to controls. The lower muscle strength observed was not associated with decreased lean body mass. [103]

Other Measures of Importance

Schrack et al. (2016) examined the rate of grip strength decline in middle-age and older adults with HIV-infection compared to HIV-uninfected controls. The MACS data over a 7-year period was used. Using a hand-grip dynamometer (Jamar® hydraulic) participants squeezed machine 3 times “as hard as you can” using dominant hand, with average of three measures taken. Out of 1,552 men, 716 HIV+ (53.4±4.6 years, 25.6±4.2 BMI, 65.5% Caucasian, 19.7% diabetes, 47.6% hypertension, 36.2% peripheral neuropathy) and 836 HIV- (56.0±6.3 years, 27.2±5.0 BMI, 79.3% Caucasian, 18.9% diabetes, 44.0% hypertension, 25.7% peripheral neuropathy) participated. At 50 years, no significant differences were noted in grip strength between HIV+ and HIV- at 37.9kg and 38.2kg ($p=0.70$), respectively. After age 50, HIV+ and HIV- grip strength declined at a rate of 0.42 kg ($p=0.001$) and 0.33 kg ($p<0.001$) for one-year increase in age. Among predictors of grip strength decline lower BMI, non-Caucasian, and peripheral neuropathy were noted, while diabetes and hypertension were not significantly significant. Clinical weakness (grip strength <26 kg) trajectories showed significant declines ($p<0.001$) in 25% of men in HIV+ and HIV- at age 60 and 66, respectively. The hazard of developing clinical weakness was 70% greater in HIV+

compared to HIV- (HR 1.70, p=0.002). The authors concluded that after 50 years of age significant differences are seen in grip strength in HIV+ men compared to HIV-. Clinical weakness may have an increased risk for sarcopenia, mobility limitations, hospitalization, and death. Grip strength is a biomarker of ageing that is clinically easy to measure, learn, and administer, with strength loss a public health concern and focus.

Schrack et al. (2015) investigated the rate of gait speed decline in PLWH compared to HIV-uninfected using the MACS. Gait speed was assessed over a 4-m course with patients asked to walk at “normal, comfortable pace”. Out of 2,025 men, 973 HIV+ (48.7±6.9 years, 25.5±4.1 BMI, 60.2% Caucasian, 12.8% diabetes, 41.6% hypertension, 33.8% peripheral neuropathy) and 1,052 HIV- (52.1±8.3 years, 27.3±5.2 BMI, 75.4% Caucasian, 9.8% diabetes, 40.7% hypertension, 22.2% peripheral neuropathy) contributed to 10.2 and 10.7 study visits over the course of 6 years, respectively. In both HIV+ and HIV- gait speed declined 0.0009 m/s for every year age-increase after 50 years ($p<0.001$). Comparisons of gait speed between groups showed a decline of 0.025 m/s for every year age-increase ($p<0.001$). Predictors of gait speed included height, weight, race, education, hepatitis C status, and peripheral neuropathy. Strong negative correlations between gait speed and age were noted in both HIV+(-0.012 m/s per year, $p<0.001$) and HIV- (-0.011 m/s per year, $p<0.001$) groups. Significant associations were reported in nadir CD4 T-cell count and decline in gait speed (0.002 m/s per year for 50 cell/ul increase, $p=0.029$) without suppressed viral load significance. Trajectory times between HIV+ and HIV- showed 50% of gait decline at age 57 and 66 ($p<0.001$), respectively. The authors concluded that gait speed at 50 years old in HIV+ was on average 0.05 m/s slower and declines were shown faster

Greene et al (2014) investigated the Short Physical Performance Battery (SPPB) assessment on disease markers in HIV-infected compared to HIV-uninfected over 5-year period. The SPPB consists of timed standing balance test (i.e. feet side-by-side, semi-tandem, and tandem for 10-seconds), gait speed (i.e. 4-meter walk at normal pace), and chair rise (i.e. chair rising and sitting 5 times as quickly as possible). Each component was scored from 0-4 for a total of 0-12 points for all activities combined. Out of 12,270 (n=1,627) person-visits, HIV-infected accounted for 30.3% (n=3715, median $CD4^+$ 339.5 cells/μl, median age 51). HIV-infection was independently associated with a 30% increased odd of 10 or less in SPPB (OR = 1.30). Mortality accounted for 10% of deaths (2.75 per 100-person years), with SPPB scores of reduced physical performance, or ≤10 (HR = 2.34), showed greater mortality and death rate than SPPB scored of higher physical performance, or >10 (HR = 6.03). The authors concluded that HIV disease is strongly associated with reduction in physical performance, leading to an increase in mortality. It is noted that difficulties in distinction between physical function in PLWH and other age-associated conditions (i.e. frailty) exist. The SPPB may detect earlier deficits than frailty, and the strongest (most reliable and valid) physical function measures in PLWH have yet to be established.

Shah et al. (2012) investigated the relationship between physical functional, body composition, and physical frailty in community dwelling HIV-infected adults. Mild to moderate frailty was defined as having 2 or more of the following: PPT score of 18-32, VO2peak of 11-18 mL/kg per minute, or report of difficulty with 2 or more instrumental activities of daily living (ADL). The PPT measures physical function in seven domains: 50-walk, putting on and removing coat, picking up a penny, standing up for a chair,

lifting a book, climbing one flight of stairs, and progressive Rhomberg test. Scores ranging from 0 to 4 for all tests with 36 as a perfect score. Climbing four flights of stairs and performing a 360º turn were two additional tasks measured. Physical function measured knee flexor strength (i.e. Biodex isokinetic dynamometer, 120º hip flexion, angular velocity 60º/s), static balance (i.e. single leg stance up to 30-seconds), dynamic balance (i.e. obstacle course consisting of walking quickly, stepping over obstacle, high curb step up, turn and return to start), and fast gait speed (i.e. time to walk 50-ft). Muscle quality was determined by calculating the ratio of isokinetic torque in Nm at knee to appendicular lean mass (kg), determined by DXA. Out of 40 HIV-infected adults, 25 (60%) subjects considered frail presented with 59 ± 7 years of age, 72% male, 598 ± 254 $CD4^+$ cells/ml, 18 ± 5 duration of HIV years, 76% hypertension, 36% diabetes, and 52% hyperlipidemia. 15 (40%) subjects considered non-frail presented with 57 ± 5 years of age, 73% male, 552 ± 235 $CD4^+$ cells/ml, 15 ± 7 duration of HIV years, 53% hypertension, 13% diabetes, and 40% hyperlipidemia. Physical function presented significant differences between frail and non-frail in the PPT (29 ± 2 vs. 33 ± 1; $p<0.0001$), peak anaerobic power (18 ± 6 vs. 23 ± 5; $p<0.01$), obstacle course (10 ± 1 vs. 8 ± 1; $p<0.0001$), single leg stance (16 ± 12 vs. 31 ± 15; $p<0.001$), gait speed (89 ± 10 vs. 102 ± 14; $p<0.001$), and muscle quality (7.2 ± 1 vs. 8.2 ± 1; $p=0.02$). Isokinetic knee strength was not significant between groups. Body composition presented significant differences between frail and non-frail in BMI (31 ± 8 vs. 26 ± 3; $p=0.04$), waist circumference (42 ± 6 vs. 37 ± 5; $p<0.02$), fat mass (26 ± 9 vs. 20 ± 5; $p=0.04$), trunk fat (15 ± 5 vs. 10 ± 3; $p=0.004$), and trends leading to significance in appendicular/trunk fat ratio (0.61 ± 0.2 vs. 0.73 ± 0.2; $p=0.09$) and trunk/total fat ratio

(0.60 ± 0.1 vs. 0.55 ± 0.1; p=0.06). Lean mass was not significant between groups. Correlations between physical performance tests and trunk fat (r = -0.34; p=0.045) and intermuscular fat/total fat ratio (r = -0.60; p=0.02) were significant. The authors concluded that dynamic muscle performance is a major contributor to functional limitations in HIV-infected persons. Important note predictive frailty values using various frailty criteria have not been validated in younger population with HIV. “Future research is needed to validate frailty measures in the HIV population”.

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APPENDIX A: Informed Consent

Hawaii Center for AIDS (HICFA)
Department of Medicine
John A. Burns School of Medicine
University of Hawaii at Manoa
HONOLULU, HAWAII

INFORMED CONSENT TO TAKE PART IN A CLINICAL RESEARCH STUDY

Title of Study:
H049: LOWER BODY MUSCULAR FUNCTION IN FRAIL AND NON-FRAIL PEOPLE LIVING WITH HIV (v.1.0; July 26, 2019)

Principal Investigator:
Iris F. Kimura, PhD, PT
Professor of Medicine
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651 Ilalo St. Suite 231
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Clinical Sub-investigator(s):
Rachel Boyle
Dr. Cecilia Shikuma

INFORMED CONSENT
You are being asked to take part in this research study because you are HIV-infected, over 40 years of age, and have been taking anti-HIV medications for more than 1 year with a viral load that is close or is 'undetectable' (less than 100 copies/mL).

Before you decide whether or not to take part in this study, you must understand the purpose, how it may help, any risks, and what you have to do. This process is called informed consent. The researcher(s) will talk with you about the study and the informed consent form. The consent also gives you information about what health information will be collected as part of the research study and how that information will be used or disclosed. Once you understand the study, and if you agree to take part, you will be asked to sign this consent form. If you sign this form, you are agreeing to take part in this study. You will be given a signed copy to keep. If you do not sign this consent form, you may continue to receive care, but not as part of this study.

Before you learn about the study, it is important that you know the following:

- Taking part in this study is of your own free will.

- You may decide not to take part in the study or stop being in the study at any time without it making any difference to your care now or in the future, or to any benefits that you are allowed.
- If the study changes in any way which could make a difference to your taking part, you will be told about the changes and may be asked to sign a new consent form.

PURPOSE OF THE STUDY

Taking anti-HIV medication for a long time has resulted in negative side effects including sarcopenia (loss of muscle fiber), osteoporosis (low bone density), physical dysfunction, and loss of independence. A higher risk for disability may be due to decreased physical function, muscle strength, and lean body mass (LBM). Recognizing physical dysfunction in the presence of HIV becomes an important factor in extending quality of life and preserving independence.

Physical decline is occurring faster and earlier in people living with HIV (PLWH) compared to people without HIV. Limited mobility, muscular weakness, and balance problems eventually lead to increases in falls, fractures, and frailty. Frailty classifications distinguish individuals at risk for these physical problems and may help identify similar declines in HIV. Frailty, characterized by extreme vulnerability, is a complication that can lead to loss of independence, disability, decreased mobility and eventual mortality. Research suggests that HIV-infection, ageing, and frailty operate similarly in terms of loss of muscle mass, loss of mobility, early disability, and osteoporotic complications.

The main purpose of this study is to assess lower body physical function using 2 different measurements in frail and non-frail PLWH taking anti-HIV medication. The second purpose is to correlate lower-extremity LBM in frail and non-frail PLWH on ART.

LENGTH OF THE STUDY

About 40 participants will take part in this study. This study will consist of screening and testing session, both being administered in one visit. The visit may take 1 - 1 ½ hours.

PROCEDURES

Before this visit, you will be considered eligible for the study if you are considered “frail”, “pre-frail” or “non-fail” according to clinic medical history (you have given your consent to be contacted from a previous study) or are a patient currently seeking medical treatment at the HICFA clinic interested in knowing your frailty status.

If you are eligible, you will be asked to come to the Clint Spencer Clinic for your combined screening and entry visit. You will have the study explained to you and you will have the chance to ask questions. If you decide to take part in this study, you will be asked to sign this consent form. You will be asked questions about how you are feeling, your medical history, the medicines you are taking, any past or present drug or alcohol usage, and go through a physical examination. You will be asked questions to make sure you can safely participate in the frailty and physical function assessment if you choose to participate in this study. Your height, weight, blood pressure, pulse and

temperature will be taken. If you are a woman who can become pregnant, a urine test will be done to make sure you are not pregnant. You will be asked for permission to access your medical records and/or your laboratory data to verify your eligibility for this study.

You will first take a frailty assessment to determine the nature/level of your frailty or non-frailty status. These tests include; history questions about weight loss and physical activity in the past year; hand grip strength (how hard you can squeeze); walking speed (how fast you can walk a certain distance); history questions about fatigue. Once frailty procedures have been completed, you will be assigned to one of the three frailty groups mentioned above.

Next, your physical function and strength will be measured. These tests will include; 30-second chair stand test (how many times you can stand and sit in a chair for 30-seconds); MicroFet hand-held dynamometer (how hard you can kick your leg out against resistance). You will have the amount of lean tissue you have in your lower body measured by a DXA machine. This will involve you lying on a DXA table for about 10 minutes while the machine makes these measurements.

Some blood (30 cc, about 2 tablespoons) will be drawn. The blood will be stored (banked) so that researchers can measure substances in the blood later that may be important in understanding frailty in HIV-infected individuals.

It is important for you to tell the study nurse or researcher whether you take any prescription/over the counter medication, any recent surgeries, or any physical complications as it may affect the study results.

RISKS

Lower-Body Assessment

The assessment may cause my legs to be slightly sore. However, this soreness will not persist/last longer than 2 to 3 days. This soreness may occur, and you can be treated with aerobic (jogging, biking) exercise and ice packs.

DXA scans

DXA scans will be used during this research study to see how you are doing. The cumulative radiation exposure from these tests is considered small and is not likely to adversely affect you or your disease. However, the effects of radiation add up over a lifetime. It is possible that having several of these tests may add to your risk of injury or disease. When deciding to enter this study, think about your past and future contact with radiation. Examples of contact with radiation include x-rays taken for any reason or radiation therapy for cancer treatment.

Blood draw

Taking blood during the screening visit may cause some soreness, bleeding and bruising, and (very rarely) infection where the needle enters the body. The risk of bruising will be similar to any other blood draw you have at your doctor's office.

Loss of Confidentiality
While every effort is made to keep your records confidential, it is possible that participating in the study may lead to loss of confidentiality.

BENEFITS
Taking part in this study may not benefit you personally. Knowledge gained from this study may help provide information that may help researchers learn about whether physical function tests might be more sensitive to prevent the development of HIV-related frailty.

OTHER TREATMENT
You may choose to not take part in this study without it making a difference in the care that you get now or in the future.

CONFIDENTIALITY
Federal Privacy Regulations provide safeguards for privacy, security, and authorized access to health information. The confidentiality of all study-related records will be kept according to all applicable laws. Information gained during this study and information known about you will be confidential (private) to the extent permitted by state and federal law. All information collected as part of this study will be coded with a unique number. This number connected to your name, along with all of your research data will be stored in a locked file in a secured building. The results of this research may be presented at meetings or in publications; however, your identity will not be disclosed.

USE AND DISCLOSURE (RELEASE) OF YOUR HEALTH INFORMATION
By signing this form, you are authorizing the collection, use and release of your personal health information in medical records and diagnostic imaging and any health information gathered about you as part of this study. Your information will only be used/disclosed as described in this consent form and as permitted by state and federal laws. Your personal health information is health information about you that could be used to identify you. This information may include information about AIDS or HIV infection, treatment for alcohol and/or drug abuse, or mental health or psychiatric services.

The purposes of releasing your protected health information are to collect the data needed to complete the research, to properly monitor (watch) how the study is done, and to answer research questions related to this study.

There is no expiration date to this authorization.

Who may receive, use or release information:
Your medical records and any health information related to this study may be used or released in connection with this research study to the following:

- Dr. Iris Kimura, co-investigators and her Hawaii Center for AIDS (HICFA) research staff for the purposes of conducting this research study.

- The University of Hawaii Human Studies Program (HSP) for purposes of overseeing the research study and making sure that your ethical rights are being protected.

Who may receive the information by the above groups:
The individuals or groups named above may release your medical records, this consent form and the information about you created by this study to:

- Federal, state and local agencies having oversight over this research, such as The Office for Human Research Protections in the U.S. Department of Health and Human Services,
- Representatives of outside groups hired by the University of Hawaii Human Studies Program (HSP) to make sure studies are done as required.

Right to Withdraw or Stop Taking Part in the Study
You may refuse to sign this authorization. If you refuse to sign the authorization, you will not be able to take part in this study. If you choose not to be in the study, or choose to withdraw from the study, or if you refuse to sign the authorization, it will not make a difference in your usual treatment, or your payment, and it will not change your eligibility for any health plan or health plan benefits that you are allowed.

If you decide to end your taking part in the study or you are removed from the study by the researcher (study doctor), you may revoke (take away) your authorization. In order to take away this authorization, you must send a letter/notice to the researcher in charge of this study. Send the written notice to the researcher to the address listed on the original consent form.

If you take away your authorization, your part in the study will end and the study staff will stop collecting medical information from you and about you. The researchers and sponsor will continue to use information that has already been collected, but no new information about you will be collected unless the information is about an adverse event (a bad side effect) related to the study or to keep the scientific integrity of the study. If an adverse event happens, we may need to review your entire medical record.

Access to Your Information
As is usually the case, you may see the information in your medical record however, the records and information related only to the study that are kept separately will not be available to you until the study is finished. If you wish to review your study records after the completion of the study, you should request this from the study doctor.

COSTS
The costs of the procedures will be paid for by the research study.

You will be given $10 for the screening visit and $10 for the entry study visit.

TREATMENT AND COMPENSATION FOR INJURY
If you have an injury or illness (get sick) as a result of being in this study, immediate emergency medical care and treatment which may be needed will be available at the

usual charge. The sponsor of the study and the study doctor do not have any funding (money) to pay for treating the injury or illness. Your insurance company may not pay for some (or all) of the treatment of the injury or illness as a result of being in this study. If your medical insurance does not pay for these medical costs, you alone will be responsible for payment. There is no way of knowing what the costs will be. You should talk about the kind of insurance coverage you have with your doctor and insurance company before you decide to take part in this study. You can have financial counseling to go over your insurance coverage.

The Hawaii Center for AIDS and the study researchers have not set aside any other kind of compensation (payment) for lost wages or other damages or losses resulting from any injury that you may get from taking part in this study.

REMOVAL FROM THE STUDY

You take part in this study of your own free will. You can stop at any time for any reason and this will not make a difference in the care you receive.

You may be taken off the study without your consent if the researchers or your physicians feel that it is not in the best interest of your health for you to take part in the study.

NEW FINDINGS

You will be told of any important new information learned during the study that may change your willingness to continue in this study.

BLOOD SPECIMEN STORAGE FOR FUTURE RESEARCH

Blood specimens from this study will be banked to be used by Hawaii Center for AIDS (HICFA) investigators or their collaborators for the study of frailty in HIV. Such research is anticipated to be done as funding becomes available to support such assay costs. Your specimen will not be sold or used for commercial economic gain. Storing the blood specimens for these purposes is part in this research study. If you do not want your blood specimens to be used in this manner, you will not be able to participate in this study.

WHO TO CONTACT

If you feel that you have been injured as a result of taking part in this study, you may call Dr. Iris F. Kimura or Dr. Cecilia Shikuma at their offices (ph number 808 692-1310) or after hours via Physician's Exchange (808 524-2575 or 808 566-5039.)

If you have any questions about your treatment, your rights as a volunteer or any other matter relating to this study, you may call Dr. Iris F. Kimura or Dr. Cecilia Shikuma at 808 692-1310 and talk about any questions that you might have.

You may contact the UH Human Studies Program at (808) 956-5007 or uhirb@hawaii.edu. to discuss problems, concerns and questions; obtain information; or offer input with an informed individual who is unaffiliated with the specific research

protocol. Please visit http://go.hawaii.edu/jRd for more information on your rights as a research participant.

****

CONSENT TO BE A RESEARCH SUBJECT

H049: Lower Body Muscular Function in Frail and Non-Frail People Living with HIV (v. 1.0, July 26th, 2019)

XVII. Signatories

I certify that I have read and that I understand the foregoing, that I have been given satisfactory answers to my inquiries concerning project procedures and other matters and that I have been advised that I am free to withdraw my consent and to discontinue participation in the project or activity at any time without prejudice.

I herewith give my consent to participate in this project with the understanding that such consent does not waive any of my legal rights, nor does it release the principal investigator or the institution or any employee or agent thereof from liability for negligence.

_____ _____ _____

Patient/Subject's Name (Print) Signature Date

_____ _____ _____

Name of Person Conducting the Consent Discussion Signature Date

****

CONSENT FOR FUTURE RESEARCH USES OF YOUR BIOLOGICAL SPECIMENS

H049: Lower Body Muscular Function in Frail and Non-Frail People Living with HIV (v. 1.0, July 26th, 2019)

The following questions ask whether biological specimens, specifically blood, collected from you during this research project may be stored and used to support future research.

☐ My specimens may only be stored and used for future HIV research being investigated under this study.
Initial one: Yes _____ No _____

☐ My specimens may be stored and used to support any future HIV research.

Initial one: Yes _____ No _____

□ I will consider providing consent to use my specimens to support any future research. Prior to any future research use, please provide me with a consent form that describes the protocol.
Initial one: Yes _____ No _____

_____ _____ _____

Patient/Subject's Name (Print) Signature Date

_____ _____ _____

Name of Person Conducting the Consent Discussion Signature Date

****

APPENDIX B: Inclusion and Exclusion Criteria Sheet

Inclusion/Exclusion Criteria

Inclusion Criteria – All answers must be "Yes"

Y☐ N☐ Age: ≥ 40 or older

Y☐ N☐ HIV+ patient of the Clint Spencer Clinic or Affiliated

Y☐ N☐ ≤ Viral load 100 copies/mL _____ copies/mL

Y☐ N☐ ≥ 12 months on Antiretroviral Therapy

Exclusion Criteria - All answers must be "No"

Y☐ N☐ Any injury or surgery within the past 12 months that would prohibit patient from being able to participate fully/normally in screening and testing measures

Y☐ N☐ Inability to perform or understand any of the study required procedures

Y☐ N☐ Pregnant / Breast Feeding

APPENDIX C: Medical History Evaluation Sheet

Medical History

Referred by _____

Have you been in a study with us before? Y☐ N☐ _____ Are you a CSC patient? Y☐ N☐

Previous Medical History

Date of Birth:	Age:	Previous Weight/Date:
Sex at birth: ☐ male ☐ female	Gender: ☐ male ☐ female	HIV Diagnosis (Yr.):
Age at diagnosis:	ARV Start (age):	Years on ARV:
CD4/Date:	HIV RNA/Date:	Nadir CD4/Date:

Current Medical History

Height:	Weight:	BP: P:
Race: ☐ Native American/Alaskan Native ☐ Asian ☐ African American ☐ White ☐ Native Hawaiian/Pacific Islander ☐ Other:		**Ethnicity:** ☐ Hispanic ☐ Non-Hispanic
Comorbid Conditions: ☐ COPD ☐ Hepatitis C ☐ Coronary Artery Disease ☐ Hypertension ☐ Diabetes Mellitus ☐ Neuropathy ☐ Dyslipidemia ☐ Other:		**Social Factors:** 1. Do you have depression? Y☐ N☐ 2. Do you have anxiety? Y☐ N☐ 3. Are you homeless? Y☐ N☐ 4. Are you unemployed? Y☐ N☐

Risk Factors

Fall Risk

1. Have you fallen in the past 12 months? Y☐ N☐
2. Are you afraid of falling? Y☐ N☐
3. Have you sought medical attention as a result of your fall? Y☐ N☐
4. Do you feel unstable when you turn a corner or turn around? Y☐ N☐
5. Do you have trouble rising from a chair or sitting down into a chair? Y☐ N☐
6. How many times have you fallen over a lifetime? _____

Drugs and Alcohol:

	Tobacco	Alcohol	Recreational drugs	Past 30 days?
Total # of years				
How often did/do you?				

Researcher's Initials _____

APPENDIX D: Frailty Assessment

Screening: Frailty Assessment

Weight Loss:

≥ Unintentional 10lbs/1-year Past _____lbs. Present _____lbs.

In the last year, have you lost more than 10 pounds unintentionally (not d/t dieting or exercise)?

**May be able to view this information in medical history.* Y☐ N☐

CES-D Scale or Depression Diagnosis:

"How often in the last week did you feel this way?" CES-D Scale answered 2 or 3 for either question: Y☐ N☐

(a) _____ I felt that everything I did was an effort (b)_____I could not get going

0	1	2	3
Less than 1 day	1-2 days	3-4 days	Most of the time

Minnesota Leisure Time Activity Questionnaire:

See Separate MLTAQ Sheet:

Men: Kcal of <383 are frail Total calories calculated: _____ MLTAQ Passed? Y☐ N☐

Women: Kcal of <270 are frail Total calories calculated: _____ MLTAQ Passed? Y☐ N☐

Grip Strength:

Taken 3 times with 30-90 seconds of rest; standing with 90 degrees of elbow flexion.

Men BMI	Men GS kg	Subject Grip Strength
≤ 24	≤ 29	BMI: _____
24.1-28	≤ 30	T1: _____kg
≥ 28	≤ 32	T2: _____kg
Women BMI	Women GS kg	T3: _____kg
≤ 23	≤ 17	Best: _____kg
23.1-26	≤ 17.3	
26.1-29	≤ 18	
≥ 29	≤ 21	

Grip Strength Passed? Y☐ N☐

Timed Up and Go:

Taken 3 times, 30-90s rest; sit, stand, walk 15ft around cone, sit; as fast as subject can.

Men Height	Men TUG	Subject TUG
≤ 173cm	≥ 7 seconds	Height: _____cm
> 173 cm	≥ 6 seconds	T1: _____s
Women Height	Women TUG	T2: _____s
≤ 159 cm	≥ 7 seconds	T3: _____s
> 159 cm	≥ 6 seconds	Best: _____s

TUG passed? Y☐ N☐

Number of frailty domains subject presents: 1 2 3 4 5

FRAIL: Y☐ N☐ (≥3) PRE-FRAIL: Y☐ N☐ (1-2) NON-FRAIL: Y☐ N☐ (none)

Comments:

Researcher's Initials: _____

APPENDIX E: Minnesota Leisure Time Activity Questionnaire

Activity	Did you perform this?		Number of times per week	Number of times per week	Number of times per week	Number of times per week	Time per occasion	
							Hrs.	Mins.
	No	Yes	Week 1	Week 2	Week 3	Week 4		
010 Walking for pleasure								
015 Walking to/from work								
030 Using stairs over elevator								
050 Back Packing								
060 Mountain Climbing								
115 Biking to work/pleasure								
125 Dancing-Ballroom, Square, etc.								
150 Home exercise								
180 Jogging and walking								
200 Running								
210 Weightlifting								
260 Canoeing/rowing competitive								
280 Swimming (Pool/beach)								
310 Scuba diving								
320 Snorkeling								
390 Bowling								
400 Volleyball								
410 Table tennis								
420 Tennis, singles								
430 Tennis, doubles								
480 Basketball								
540 Soccer								
070 Golf: riding cart								
080 Golf: walking/carrying clubs								
Other Activity								

APPENDIX E: Minnesota Leisure Time Activity Questionnaire, continued

Activity	Intensity Code	Duration/week (min)	Total Calories Expended
010 Walking for pleasure	3.5		
015 Walking to/from work	4.0		
030 Using stairs over elevator	8.0		
050 Back Packing	7.0		
060 Mountain Climbing	8.0		
115 Biking to work/pleasure	4.0		
125 Dancing-Ballroom, Square, etc.	5.5		
150 Home exercise	4.5		
180 Jogging and walking	6.0		
200 Running	8.0		
210 Weightlifting	3.0		
260 Canoeing/rowing	3.5-12.0		
280 Swimming (Pool/beach)	6.0		
310 Scuba diving	7.0		
320 Snorkeling	5.0		
390 Bowling	3.0		
400 Volleyball	4.0		
410 Table tennis	4.0		
420 Tennis, singles	8.0		
430 Tennis, doubles	6.0		
480 Basketball	6.0-8.0		
540 Soccer	7.0		
070 Golf: riding cart	3.5		
080 Golf: walking/carrying clubs	5.0-5.5		
Other activity	3.0-12.0		
Men: kcal ≤383	MLTAQ Passed	Y☐ N☐	Total kcal: _____
Women: kcal ≤270	MLTAQ Passed	Y☐ N☐	

APPENDIX F: Lower Body Muscle Function Assessment

Entry: Lower Body Muscle Function Assessment

MicroFet Manual Muscle Test:
Participants will sit with hip flexed to 110-120° and knee flexed to 30° on adjustable table. Researcher will apply equal force to the participant's isometric maximal knee extension. This is not a make or break test. Researcher will allow 30-90 seconds of rest in between each set. Measures will be taken 3 times and recorded below.

Trial 1: _____ Trial 2: _____ Trial 3: _____ Best: _____

30-second Chair Stand Test (30 CST):
Participants will begin seated, arms crossed over chest, in a standard 4-legged chair with no arm rests. The researcher will time the participant for 30-seconds and count the number of repetitions each participant can successfully accomplish. Back of thighs and gluteus must touch the chair and full hip and knee extension must occur for repetition to qualify.

Number of repetitions: _____

Dual Energy X-Ray Absorptiometry (DEXA) Scan:

Region	Tissue (%Fat)	Region (%Fat)	Tissue (g.)	Fat (g.)	Lean (g.)	BMC (g.)	Total Mass (g.)
Left Arm							
Left Leg							
Left Trunk							
Left Total							
Right Arm							
Right Leg							
Right Trunk							
Right Total							
Arms							
Legs							
Trunk							
Android							
Gynoid							
Total							

Fat Mass Ratios		
Trunk/Total	Legs/Total	(Arm/Legs)/Trunk

_____

Researcher's name Researcher Signature Date