Published in final edited form as:

J Acquir Immune Defic Syndr. 2020 November 01; 85(3): 372–378. doi:10.1097/

QAI.0000000000002455.

Physical Function and Frailty Tools in Mortality Prediction of Middle-Aged Adults with HIV

Regan Pelloquin¹, Mona Abdo², Samantha MaWhinney², Catherine M. Jankowski³, Kristine M Erlandson⁴

¹University of Colorado School of Medicine; Aurora, CO

²Colorado School of Public Health; Aurora, CO

³University of Colorado College of Nursing; Aurora, CO

⁴University of Colorado Department of Medicine; Aurora, CO

Abstract

Background: Frailty and physical function impairments occur at an earlier than expected age in people with HIV (PWH). The goal of this study was to determine which tools or combination of tools assessing frailty/physical function were most predictive of mortality in a middle-aged population of PWH.

Methods: Using electronic health records, we determined survival, death, or loss-to-follow-up for 395 PWH, aged 45-65 originally enrolled in a 2009-2010 cross-sectional cohort study. The predictive accuracy of various physical function measures (frailty score, VACS Index, 400-m walk, SPPB, grip strength, and falls) were compared using integrated time-dependent ROC (ROC-AUC) curves in single variable models. Two-variable models were compared to the best single-variable model to determine if AUC improved with additional physical function variables.

Results: At eight-year follow-up, frailty, 400-m walk pace, SPPB, chair rise pace, VACS score, and falls were associated with increased hazard of mortality; grip strength was only predictive in sex-adjusted models. The VACS index and 400-m walk pace were the best individual predictors of mortality with time-dependent ROC-AUC scores of 0.82, followed by SPPB (0.73), chair-rise pace (0.68), falls (0.65), frailty (0.63) and grip strength (0.55). Addition of the 400-m walk to VACS index yielded the only significant improvement in the prediction of survival compared to the VACS index alone (p-value=0.04).

Conclusion: Our study highlights several clinically applicable physical function measures predictive of mortality in middle-aged PWH that can be tailored to specific patient sub-populations and clinical or research encounters.

Keywords

HIV; frailty; mortality; physical function; weakness

Introduction

The clinical relevance and mechanisms underlying impairments in physical function and the development of “frailty” have risen to forefront of gerontology over the past two decades. This is most likely due to the increasing age and medical complexity of the global population. The term frailty has evolved from a general descriptor of a weak, older individual with declining health status into more specific etiologies and phenotypes [1], as evidenced by one description of frailty as a “biologic syndrome of decreased reserve and resistance to stressors, resulting from cumulative declines across multiple physiologic systems, and causing vulnerability to adverse outcomes” [2]. Frailty, when adjusted for variables such as health, disease, and social characteristics, is highly predictive of mortality [2]. Today, hundreds of variations of frailty measurements have been proposed and are currently in use [1], some including objective measures of strength or gait speed and others assessing the burden of comorbid illness. In addition to frailty, objective tools assessing higher-level or lower-level physical functioning, such as time to walk 4-m or time to walk 400-m can also capture current functioning and inform prognosis [3, 4]. Regardless of the tool or definition, studies continue to show that various measures of physical function and frailty are significant risk factors for hospitalization, institutionalization, disability, and death among older adults [3–8].

Indeed, in clinical practice, measurements of physical function and frailty are used to screen older populations and identify high risk individuals for whom interventions could be avoided, or where preventive measures or services could be implemented. More recently, many of these measures have also been integrated into different subspecialties to assist in identifying higher risk individuals even in younger age groups, including people with HIV (PWH). With the marked advances in antiretroviral therapy (ART) over the last three decades, the lifespan of those living with HIV has increased dramatically [9–11]. Several studies have shown that frailty occurs earlier than expected in PWH compared to demographically similar controls without HIV [12–14], and describe a higher than expected prevalence of frailty in middle-aged populations with HIV using a variety of assessments [15–19]. Some studies do suggest that middle-aged PWH with frailty or function impairment do have an increased incidence of co-morbidities such as cardiovascular disease or diabetes, falls, and mortality [20–23]. However, many of these frailty and functional assessments were initially validated in populations aged 65 or older, thus it is unclear which tools may be most useful and predictive of poor outcomes in middle-aged (i.e., 45–65 years of age) individuals with chronic disease [24]. The goal of this study was to compare measures of physical function or frailty (or a combination of two measures) and their association with mortality in a population of viral suppressed middle-aged PWH. We also compared these measures to a previously validated mortality prediction tool, the Veterans Aging Cohort Study (VACS) Index [25].

Methods

Between 2009–2010 (baseline visit), we conducted a cross-sectional study of 359 PWH, aged 45–65 years of age on ART for at least 6 months with at least 1 undetectable plasma HIV-1 RNA (<48 copies/mL) and no plasma HIV-1 RNA >200 copies/mL during the 6

months prior [15]. At the baseline visit, each study participant provided a medical history, demographics, completed questionnaires, and completed an assessment of frailty and physical function.

In 2018, the vital status of each original participant was determined through examination of electronic health records. Participants were classified as alive if the chart contained evidence of patient interaction in the past year (i.e., clinical encounters, laboratory work, refill requests, and correspondence by email or phone). Participants were classified as deceased if there was documentation of death including hospital records, phone calls from family or caregivers, or coroner reports. Individuals whose chart indicated a relocation or a provider change outside of the University of Colorado Health system were considered lost to follow up. The endpoint of the observation period was whichever event occurred first: death, last date of follow-up, or August 2018.

Predictors of Mortality

Frailty was measured using the Fried frailty phenotype (FFP). As previously described [15], the FFP utilizes five criteria of weak hand grip strength, exhaustion, slow gait speed, low physical activity, and unintentional weight loss. Participants with three of five criteria were considered frail, one or two criteria were considered pre-frail, and no criteria were non-frail. We dichotomized study participants into groups of non-frail and pre-frail or frail individuals. The Short Physical Performance Battery (SPPB) incorporates combined performance on three components of gait speed on a 4-meter walk, time to rise from a chair five times, and tandem stand. Each component is scored from zero to four points, with four points indicating the highest function, and a combined maximum total score of 12 [4]. A score of less than 10 is considered indicative of a high risk for subsequent disability. In addition to the composite SPPB, time to rise from the chair was converted to pace (rises/second) and included as a continuous outcome. Time to complete a 400-meter walk was measured in a non-carpeted long corridor; participants were encouraged to complete the test while walking as quickly as possible. The 400-meter walk time was converted to pace (meters/second) and included as a continuous outcome, with higher numbers indicating a greater distance completed per second. Participants were also asked about a fall during the prior 12 months [26]; a fall was defined as “unintentionally coming to rest on the ground or other lower level, not as a result of a major intrinsic event or external hazard”. The Veterans Aging Cohort Study (VACS) Index was calculated using age and laboratory values from the most recent clinic visit for CD4 count, HIV-1 RNA count, hemoglobin, Fibrosis-4 Index for Liver Fibrosis (FIB-4 Index), estimated glomerular filtration rate, and the presence of hepatitis C co-infection [25]. A higher score on the VACS index is indicative of increased risk of all-cause 5-year mortality.

Covariates

Covariates that were considered individually in analytic models included gender (females vs males), smoking status (current or never/former smoker), age (≤ 50 vs >50 years) and physical activity recall for the previous two weeks using the Minnesota Leisure Time Physical Activity [LTPA] questionnaire [27, 28]. Physical activity was dichotomized using

an equivalent weekly activity of less than versus greater than or equal to five 20-minute walks (approximately 500 Kcal/week).

The study was approved by the Colorado Multiple Institutional Review Board; all participants previously provided written, informed consent for participation.

Statistical Analysis

Frequency and percent were calculated for categorical variables overall and by vital status in 2018 (alive, deceased, or loss to follow-up). Means and standard deviations or median and interquartile ranges were reported for continuous variables. Kaplan-Meier analyses and Cox proportional hazards models were used in time-to-event analyses. Cox proportional hazards models were adjusted for smoking status, sex, and physical activity separately. Due to the non-proportional effect of age, models were also stratified by categorical age (<50 and ≥50) which allows the baseline hazards to differ by age category. Participants without a confirmed date of death were censored at last follow-up visit. Integrated time-dependent area under the ROC (ROC-AUC) curves were estimated using the conditional Kaplan-Meier (KM) method to compare the predictive accuracy of mortality (vs survival) between each physical function in single variable models. Bootstrap confidence intervals were computed for the integrated time-dependent ROC-AUC [29]. Two-variable models were compared to the single-variable model with the highest integrated time-dependent ROC-AUC value to determine if the AUC increases with the addition of individual physical function variables. Two-variable models were compared to single-variable models by assessing the difference in their Uno's concordance statistics [30, 31]. Optimal cut-off values were calculated for the physical function variable with the highest integrated time-dependent ROC-AUC by comparing the AUC values for different cut-offs [32]. All comparisons assumed a significance level of 0.05 with no adjustment for multiple comparisons. However, all comparisons were reported, so that the reader can informally account for multiple comparisons [33]. Statistical analyses were conducted in SAS v9.4 (Carey, NC).

Results

Of 359 PWH that were enrolled in 2010, 249 (69%) were alive, 35 (10%) were deceased and 75 (21%) were lost to follow-up by the time of re-assessment in 2018. The median follow-up time was 7.9 (IQR 6.1, 8.1) years, mean (standard deviation) for age was 52 (5.2) years, the mean CD4⁺ T-cell count was 594 (303) cells/uL, and 95% had HIV-1 RNA below the limits of detection. The majority of the PWH were male (85%), white (74%), and identified as former or never smokers (66%). Study groups (alive, dead, loss to follow-up) varied in their initial characteristics recorded at the study enrollment period. Compared to those who died, those who were alive at follow-up had greater proportion of never or former smokers and non-frail individuals, faster 400-m walk pace, stronger grip strength, lower VACS Index score, fewer falls, and a higher SPPB score. Other characteristics at the time of enrollment are shown in Table 1.

As shown in Table 2, frail or pre-frail status ($p=0.006$), SPPB ($p=0.002$), 400-m walk pace ($p<0.001$), chair rise pace ($p=0.03$), VACS Score ($p<0.001$), and falls ($p<0.001$) were associated with increased hazard of mortality. For example, for every 0.1 m/sec decrease in

the 400-m walk pace, the hazard of mortality was 1.17 times higher (95% CI: 1.11, 1.24). Many of these associations persisted after adjusting singly for smoking, gender, or self-reported physical activity. Grip strength ($p=0.03$) was predictive of mortality only in the sex-adjusted models.

In ROC-AUC models exploring the best single predictor of mortality, the VACS index and the 400-m walk pace were the best predictors of mortality (integrated time-dependent ROC-AUC of 0.82 [95% bootstrap CI: 0.70, 0.96] and 0.82 [95% bootstrap CI: 0.70, 0.93], respectively). Other tools of physical function did not perform as well (Figure 1) in predicting mortality, with ROC-AUC of SPPB 0.73 (95% bootstrap CI: 0.59, 0.90), chair rise pace 0.68 (95% bootstrap CI: 0.57, 0.92), falls 0.65 (95% bootstrap CI: 0.35, 0.80), frailty 0.63 (95% bootstrap CI: 0.51, 0.74), and grip strength 0.55 (95% CI: 0.33, 0.70).

Because the VACS Index and 400-m walk pace had the highest integrated time-dependent ROC-AUC in the single-variable models, we then tested whether combinations of these variables with other tools significantly improved prediction of survival in two-variable models. The only significant improvement in the prediction of survival was the addition of the 400-m walk to the VACS index compared to the VACS alone (Difference in Uno's concordance statistic=0.10, integrated time-dependent ROC-AUC=0.89, p -value=0.04, Figure 2, Supplemental Table 1). Similarly, the addition of the VACS index to the 400-m walk resulted in a slight improvement in prediction (Difference in Uno's concordance statistic=0.05, AUC=0.89, p -value=0.08) compared to the 400-m walk alone (Figure 3, Supplemental Table 2). The optimal cut-off for the 400-m walk was 1.3 m/s with an integrated time-dependent ROC-AUC of 0.76. The optimal cut-off score for the VACS index was 23 with an integrated time-dependent ROC-AUC of 0.77.

Discussion

Measures of frailty and physical function are increasingly used in populations of middle-aged and older people with HIV, but to the best of our knowledge, no prior studies have compared the ability of these measures to predict outcomes, nor compared the performance of these measures to validated measures such as the VACS Index. Here we compared the ability of several different measures of frailty and physical function to predict all-cause mortality. Although we found that several of our measures of frailty and physical function were associated with mortality over eight years, the VACS index and 400-m walk pace either singly or in combination were the strongest predictors of mortality in a cohort of middle-aged PWH on suppressive ART.

The VACS Index utilizes patient age and routinely measured biomarkers of HIV disease and organ function (e.g., hemoglobin, liver fibrosis), to estimate mortality in people with or without HIV [27]. Thus, unlike physical function measures that must be collected prospectively, the ability to calculate VACS score from routine laboratory assessments is particularly useful for clinical practice or cohorts where physical function testing is not available. The VACS has been established as a strong predictor of mortality or poor outcomes (falls, hospitalizations) across a variety of populations in both U.S.-based and international cohorts [28], including women [29], people 50 years and older, and those with

low or undetectable HIV-1 RNA [27]. Here we include the VACS Index as a “gold standard” measurement for prediction of mortality. Indeed, as expected, the VACS Index was the best single predictor of mortality.

However, for the first time, we also found that many of our physical function markers predicted mortality quite similarly to the VACS, and some may further improve upon the ability of the VACS index to predict mortality in middle-aged PWH. Of the physical function measures, the 400-m walk pace was the strongest predictor of mortality in our cohort, with the same ROC value as the VACS Index. Prior studies have found that the 400-m walk is valid across a wide range of physical capacity and detects reduced performance even among individuals who self-report no difficulty walking [3]. As a test of endurance, the 400-m walk may uncover reduced physical function not apparent by shorter, less intensive evaluation methods. The ability to include 400-m walk pace as a continuous, rather than categorical, measure of performance may also improve its predictive power in middle-aged adults.

Furthermore, to the best of our knowledge, we present the first comparison between several markers of physical function with the VACS to provide clinicians and researchers with data on the ability of these indices to predict mortality in middle-aged PWH, key information to select the most appropriate instruments for implementation in various clinical or research settings. For example, the 400-m walk requires more space and approximately 10 minutes time to complete, and thus presents a challenge to implement in a busy clinic. Although the chair rise pace did not perform as well as the 400-m walk in predicting mortality, the chair rise test can be completed in a clinic room in less than a minute and requires only a chair and stopwatch. Slow chair rise impairment was predictive of subsequent disability and mortality in both middle-aged and older populations of persons without HIV [4, 8]. Importantly, we have previously shown that both 400-m walk and chair rise pace are amenable to interventions: significant improvements in both tests were seen among PWH and uninfected adults with a 24-week exercise intervention [34]. Thus, clinicians with limited time and space to complete a 400-m walk may opt to include a chair rise test, balancing the knowledge of test performance with feasibility.

In contrast to the 400-m walk, grip strength and Fried’s frailty phenotype had lower predictive ability in this study. Grip strength has been associated with mortality in both middle-aged and elderly populations of people without HIV [7], and was predictive of cognition, mortality, functional status, and mortality in adults aged 60 or older [35]. In contrast to lower extremity strength measured by chair rise, grip strength is heavily influenced by neuropathy, arthritis, BMI, and manual labor. Indeed, average grip strength among healthy young adults has declined over the last two decades [36] with the technology boom and less manual labor. Variability in grip strength may have been more reflective of these underlying factors, decreasing the prediction of mortality in our population. Fried’s Frailty Phenotype, which includes hand grip strength, is consistently associated with increased risk of mortality, or poor health outcomes (e.g., disability), in both middle-aged and older populations of people with and without HIV [6, 21, 23]. We also found greater odds of death among those with recurrent falls in the prior year. Falls occur at a similar rate among middle-aged PWH as much older populations of people without HIV [26], thus

further emphasizing the clinical relevance of falling in younger PWH. Interventions to decrease falls may not only decrease fall-related injuries but decrease the risk of death.

In contrast to many studies of physical function and frailty, our follow-up duration of eight years and the variety of baseline assessments for comparison strengthened the findings despite a small sample size of individuals with impairments and loss to follow up. The male predominance of the study (85%) reflects the male predominance of the HIV epidemic in the US [37], and our findings should be validated in studies with more women. Although the focus for this analysis was on mortality, other outcomes such as decline in mobility, institutionalization, or hospitalization should also be explored as important endpoints. These tools may perform differently when predicting hospitalization or disability rather than mortality.

In summary, this study contributes to the growing body of literature on the role of frailty and physical function assessments in middle-aged PWH. We provide guidance as to the tests that are most discriminatory for increased mortality. Further choice of test can be based on availability, time, and setting. The VACS index can be easily obtained through routine laboratory data. Addition of the 400-m walk test to the VACS Index improved performance and can provide further insight into the ability to complete endurance activities that are common in community living but has space and time limitations. Routine incorporation of assessments such as the VACS Index and the 400-m walk in the clinical or research setting will aid in identification of individuals at increased risk of poor outcomes to allow for early intervention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements/Funding:

This study was supported by National Institute of Health, National Institute on Aging (R01 AG054366) and National Center for Advancing Translational Sciences Colorado CTSA Grant Number UL1 TR002535. Contents are the authors' sole responsibility and do not necessarily represent official NIH views.

Conflict of Interest:

KME has received grant funding from Gilead Sciences, and has received consultation fees (paid to the University of Colorado) from Gilead Sciences and ViiV Pharmaceuticals.

References:

1. Dent E, Kowal P, Hoogendijk EO. Frailty measurement in research and clinical practice: A review. *European journal of internal medicine* 2016; 31: 3–10. [PubMed: 27039014]
2. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001; 56(3): M146–56. [PubMed: 11253156]
3. Newman AB, Simonsick EM, Naydeck BL, et al. Association of long-distance corridor walk performance with mortality, cardiovascular disease, mobility limitation, and disability. *Jama* 2006; 295(17): 2018–26. [PubMed: 16670410]
4. Guralnik JM, Simonsick EM, Ferrucci L, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. *J Gerontol* 1994; 49(2): M85–94. [PubMed: 8126356]

5. Kojima G, Iliffe S, Walters K. Frailty index as a predictor of mortality: a systematic review and meta-analysis. *Age Ageing* 2018; 47(2): 193–200. [PubMed: 29040347]
6. Hanlon P, Nicholl BI, Jani BD, Lee D, McQueenie R, Mair FS. Frailty and pre-frailty in middle-aged and older adults and its association with multimorbidity and mortality: a prospective analysis of 493 737 UK Biobank participants. *Lancet Public Health* 2018; 3(7): e323–e32. [PubMed: 29908859]
7. Sasaki H, Kasagi F, Yamada M, Fujita S. Grip strength predicts cause-specific mortality in middle-aged and elderly persons. *Am J Med* 2007; 120(4): 337–42. [PubMed: 17398228]
8. Dodds RM, Kuh D, Sayer AA, Cooper R. Can measures of physical performance in midlife improve the clinical prediction of disability in early old age? Findings from a British birth cohort study. *Exp Gerontol* 2018; 110: 118–24. [PubMed: 29885357]
9. Vella S, Schwartlander B, Sow SP, Eholie SP, Murphy RL. The history of antiretroviral therapy and of its implementation in resource-limited areas of the world. *Aids* 2012; 26(10): 1231–41. [PubMed: 22706009]
10. Survival of HIV-positive patients starting antiretroviral therapy between 1996 and 2013: a collaborative analysis of cohort studies. *Lancet HIV* 2017; 4(8): e349–e56.
11. Ray M, Logan R, Sterne JA, et al. The effect of combined antiretroviral therapy on the overall mortality of HIV-infected individuals. *Aids* 2010; 24(1): 123–37. [PubMed: 19770621]
12. Althoff KN, Jacobson LP, Cranston RD, et al. Age, Comorbidities, and AIDS Predict a Frailty Phenotype in Men Who Have Sex With Men. *J Gerontol A Biol Sci Med Sci* 2013.
13. Piggott DA, Muzaale AD, Mehta SH, et al. Frailty, HIV infection, and mortality in an aging cohort of injection drug users. *PLoS One* 2013; 8(1): e54910. [PubMed: 23382997]
14. Greene M, Covinsky K, Astemborski J, et al. The relationship of physical performance with HIV disease and mortality. *Aids* 2014; 28(18): 2711–9. [PubMed: 25493597]
15. Erlandson KM, Allshouse AA, Jankowski CM, et al. Comparison of functional status instruments in HIV-infected adults on effective antiretroviral therapy. *HIV Clin Trials* 2012; 13(6): 324–34. [PubMed: 23195670]
16. Erlandson KM, Wu K, Koletar SL, et al. Association Between Frailty and Components of the Frailty Phenotype With Modifiable Risk Factors and Antiretroviral Therapy. *J Infect Dis* 2017; 215(6): 933–7. [PubMed: 28453849]
17. Erlandson KM, Schrack JA, Jankowski CM, Brown TT, Campbell TB. Functional impairment, disability, and frailty in adults aging with HIV-infection. *Curr HIV/AIDS Rep* 2014; 11(3): 279–90. [PubMed: 24966138]
18. Onen NF, Patel P, Baker J, et al. Frailty and Pre-Frailty in a Contemporary Cohort of HIV-Infected Adults. *J Frailty Aging* 2014; 3(3): 158–65. [PubMed: 27050062]
19. Gustafson DR, Shi Q, Thurn M, et al. Frailty and Constellations of Factors in Aging HIV-infected and Uninfected Women - The Women's Interagency HIV Study. *J Frailty Aging* 2016; 5(1): 43–8. [PubMed: 26980368]
20. Kelly SG, Wu K, Tassiopoulos K, Erlandson KM, Koletar SL, Palella FJ. Frailty Is an Independent Risk Factor for Mortality, Cardiovascular Disease, Bone Disease, and Diabetes Among Aging Adults With Human Immunodeficiency Virus. *Clin Infect Dis* 2019; 69(8): 1370–6. [PubMed: 30590451]
21. Erlandson KM, Perez J, Abdo M, et al. Frailty, Neurocognitive Impairment, or Both in Predicting Poor Health Outcomes Among Adults Living With Human Immunodeficiency Virus. *Clin Infect Dis* 2019; 68(1): 131–8. [PubMed: 29788039]
22. Sharma A, Hoover DR, Shi Q, et al. Frailty as a predictor of falls in HIV-infected and uninfected women. *Antivir Ther* 2019; 24(1): 51–61. [PubMed: 30604692]
23. Verheij E, Kirk GD, Wit FW, et al. Frailty is associated with mortality and incident comorbidity among middle-aged HIV-positive and HIV-negative participants. *J Infect Dis* 2020.
24. Lachman ME. Development in midlife. *Annu Rev Psychol* 2004; 55: 305–31. [PubMed: 14744218]
25. Justice AC, McGinnis KA, Skanderson M, et al. Towards a combined prognostic index for survival in HIV infection: the role of 'non-HIV' biomarkers. *HIV Med* 2010; 11(2): 143–51. [PubMed: 19751364]

26. Erlandson KM, Allshouse AA, Jankowski CM, et al. Risk factors for falls in HIV-infected persons. *J Acquir Immune Defic Syndr* 2012; 61(4): 484–9. [PubMed: 23143526]
27. Conway JM, Irwin ML, Ainsworth BE. Estimating energy expenditure from the Minnesota Leisure Time Physical Activity and Tecumseh Occupational Activity questionnaires - a doubly labeled water validation. *J Clin Epidemiol* 2002; 55(4): 392–9. [PubMed: 11927208]
28. Taylor HL, Jacobs DR Jr., Schucker B, Knudsen J, Leon AS, Debacker G. A questionnaire for the assessment of leisure time physical activities. *J Chronic Dis* 1978; 31(12): 741–55. [PubMed: 748370]
29. Heagerty PJ, Lumley T, Pepe MS. Time-dependent ROC curves for censored survival data and a diagnostic marker. *Biometrics* 2000; 56(2): 337–44. [PubMed: 10877287]
30. Uno H, Cai T, Pencina MJ, D'Agostino RB, Wei LJ. On the C-statistics for evaluating overall adequacy of risk prediction procedures with censored survival data. *Stat Med* 2011; 30(10): 1105–17. [PubMed: 21484848]
31. Guo C, So YC, Jang W. Evaluating predictive accuracy of survival models with PROC PHREG. Accessed 1/15/2020 <https://support.sas.com/resources/papers/proceedings17/SAS0462-2017.pdf>. In: SAS Institute, Inc, 2017.
32. Kamarudin AN, Cox T, Kolamunnage-Dona R. Time-dependent ROC curve analysis in medical research: current methods and applications. *BMC medical research methodology* 2017; 17(1): 53. [PubMed: 28388943]
33. Rothman KJ. No adjustments are needed for multiple comparisons. *Epidemiology* 1990; 1(1): 43–6. [PubMed: 2081237]
34. Erlandson KM, MaWhinney S, Wilson M, et al. Physical function improvements with moderate or high-intensity exercise among older adults with or without HIV infection. *Aids* 2018; 32(16): 2317–26. [PubMed: 30134299]
35. Rijk JM, Roos PR, Deckx L, van den Akker M, Buntinx F. Prognostic value of handgrip strength in people aged 60 years and older: A systematic review and meta-analysis. *Geriatrics & gerontology international* 2016; 16(1): 5–20. [PubMed: 26016893]
36. Fain E, Weatherford C. Comparative study of millennials' (age 20–34 years) grip and lateral pinch with the norms. *J Hand Ther* 2016; 29(4): 483–8. [PubMed: 26869476]
37. Center for Disease Control and Prevention. HIV Surveillance Report: Diagnoses of HIV Infection in the United States and Dependent Areas, 2018 (30): 1–129.

Figure 1:

Time-Dependent Area Under the Curve for One-Variable Models. Receiver operating characteristic (ROC) curves are compared, with increased area under the curve indicating increased test accuracy in predicting mortality. VACS and 400-m walk had greatest AUC values for the one-variable model, while average grip and frailty had the lowest AUC values.

Figure 2:

Time-Dependent Area Under the Curve for Two-Variable Models, with all models including the VACS Index. Receiver operating characteristic (ROC) curves are compared, with increased area under the curve indicating increased test accuracy in predicting mortality. Addition of each test to the VACS Index resulted in highest AUC value for the combination of 400-m walk + VACS Index and lowest value for Frailty Phenotype + VACS Index.

Figure 3:

Time-Dependent Area Under the Curve for Two-Variable Models, with all models including the 400-m walk. Receiver operating characteristic (ROC) curves are compared, with increased area under the curve indicating increased test accuracy in predicting mortality. Addition of each test to the 400-m walk resulted in highest AUC value for VACS Index + 400-m walk and lowest value for falls + 400-m walk.

Table 1.

Baseline Participant Characteristics

	Overall (n=359)	Alive (n=249)	Deceased (n=35)	Loss to Follow Up (n=75)
Follow-up time (Years) *	7.9 (6.1,8.1)	8.1 (7.9,8.2)	4.0 (2.2,6.2)	3.2 (1.4, 5.0)
Male sex	305 (85%)	210 (84%)	29 (83%)	66 (88%)
Baseline Age (Years)	52.0 (5.2)	51.9 (5.2)	54.9 (5.7)	51.3 (4.6)
Race				
White	265 (74%)	183 (73%)	25 (71%)	57 (76%)
Smoking Status				
Never or Former Smoker	236 (66%)	165 (66%)	21 (60%)	50 (67%)
Current Smoker	123 (34%)	84 (34%)	14 (40%)	25 (33%)
HIV-1 Viral Load >48 copies/mL	17 (5%)	13 (5%)	0(0%)	4 (5%)
Current CD4 T-cell count (cells/μL)	594.4 (302.7)	601.5 (304.8)	484.1 (270.3)	622.1 (303.0)
Body Mass Index (kg/m²)	26.4 (6.0)	26.5 (5.2)	25.2 (4.8)	26.4 (8.5)
400-meter walk (m/sec)	1.4 (0.4)	1.5 (0.3)	1.1 (0.5)	1.4 (0.4)
Chair rise (rises/sec)	0.5 (0.2)	0.5 (0.2)	0.4 (0.2)	0.5 (0.2)
Grip strength (kg)	39.0 (9.3)	39.5 (9.2)	35.8 (9.2)	39.1 (9.1)
Veterans Aging Cohort Study Index Score *	18 (6,24)	17 (6,23)	29 (17,40)	17 (10,24)
Frailty				
Non-Frail	166 (46%)	123 (49%)	8 (23%)	35 (47%)
Pre-Frail	166 (46%)	106 (43%)	23 (66%)	37 (49%)
Frail	27 (8%)	20 (8%)	4 (11%)	3 (4%)
Falls				
None	250 (70%)	183 (73%)	15 (43%)	52 (69%)
One	43 (12%)	26 (10%)	8 (23%)	9 (12%)
Two or more	66 (18%)	40 (16%)	12 (34%)	14 (19%)
Short Physical Performance Battery	11.1 (1.6)	11.3 (1.5)	10.1 (1.8)	10.9 (1.7)

Values are presented as mean (standard deviation) or number (frequency) with the exception of those indicated by * where the value is the median (interquartile range)

Unadjusted and Adjusted Survival Models Predicting All-cause Mortality by Measures of Frailty/Physical Function in Persons Living with HIV

Table 2:

Models	Unadjusted HR (95%CI)	P-value	Smoking-Adjusted HR (95%CI)	P-value	Sex-Adjusted HR (95%CI)	P-value	Physical Activity- Adjusted HR (95% CI)	P-value
Frail or prefrail (ref = Non-Frail)	3.03 (1.38,6.68)	0.006	2.94 (1.32,6.54)	0.008	3.03 (1.38,6.68)	0.006	2.65 (1.12,6.25)	0.03
SPPB per 1 unit decrease	1.22 (1.08,1.39)	0.002	1.22 (1.06,1.39)	0.004	1.24 (1.09,1.41)	0.002	1.14 (0.99,1.30)	0.06
Grip strength per 1 kg decrease	1.03 (0.99,1.07)	0.08	1.03 (0.99,1.06)	0.10	1.04 (1.00,1.09)	0.03	1.03 (0.99,1.06)	0.16
400-m walk per 0.1 m/sec decrease	1.17 (1.11,1.24)	<0.001	1.18 (1.11,1.26)	<0.001	1.18 (1.11,1.25)	<0.001	1.15 (1.08,1.23)	<0.001
Chair rise per 0.5 rises/sec decrease	2.48 (1.09,5.65)	0.03	2.33 (1.00,5.44)	0.05	2.48 (1.08,5.68)	0.03	1.56 (0.66,3.69)	0.31
VACS Index per 10-unit increase	1.62 (1.33,1.98)	<0.001	1.60 (1.31,1.96)	<0.001	1.63 (1.33,2.00)	<0.001	1.57 (1.28,1.92)	<0.001
Falls (ref = no falls)	3.34 (1.71,6.53)	<0.001	3.26 (1.65,6.46)	<0.001	3.39 (1.73,6.65)	<0.001	2.90 (1.44,5.84)	0.003

HR, hazard ratio; CI, confidence interval; SPPB, Short Physical Performance Battery; VACS, Veterans Aging Cohort Study