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An adapted frailty-related phenotype and the VACS Index as predictors of hospitalization and mortality in HIV-infected and uninfected individuals

Kathleen M. Akgün, M.D., M.S.,

Department of Internal Medicine and General Internal Medicine, VA Connecticut Healthcare System, West Haven, CT, USA; and Department of Internal Medicine, Yale University School of Medicine, New Haven, CT, USA

Janet P. Tate, Sc.D., M.P.H.,

Department of Internal Medicine, VA Connecticut Healthcare System, West Haven, CT, USA; and Department of Internal Medicine, Yale University School of Medicine, New Haven, CT, USA

Kristina Crothers, M.D.,

Department of Medicine, University of Washington School of Medicine, Seattle, WA, USA

Stephen Crystal, Ph.D.,

Institute for Health, Healthcare Policy and Aging Research, Rutgers University, New Brunswick, NJ, USA

David A. Leaf, M.D., M.P.H.,

Department of Medicine, VA Greater Los Angeles Healthcare System, U.C.L.A. School of Medicine, Los Angeles, CA, USA

Julie Womack, Ph.D.,

Yale School of Nursing, New Haven, CT, USA

Todd T. Brown, M.D., Ph.D.,

Division of Endocrinology, Diabetes, and Metabolism, Johns Hopkins University, Baltimore, MD, USA

Amy C. Justice, M.D., Ph.D., and

Department of Internal Medicine, VA Connecticut Healthcare System, West Haven, CT, USA; and Department of Internal Medicine, Yale University School of Medicine, New Haven, CT, USA

Krisann K. Oursler, M.D. Sc.M.

Department of Medicine, VA Maryland Health Care System, University of Maryland SOM, Baltimore, MD, USA

Corresponding author: Kathleen M. Akgün, MD, Assistant Professor, VA Connecticut-West Haven and Yale University School of Medicine, Department of Internal Medicine, Section of Pulmonary, Critical Care & Sleep Medicine, 950 Campbell Ave., MS 11 ACSLG, West Haven, CT 06516, kathleen.akgun@yale.edu, Office Telephone: 203-932-5711 x 5491, Fax number: 203-937-4926.

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Abstract

Background—Frailty is a geriatric syndrome of decreased physiologic reserve and a risk factor for hospitalization and mortality. We hypothesized that an adapted, survey-based frailty-related phenotype (aFRP) predicts hospitalization and mortality among HIV-infected and uninfected individuals in adjusted models but is uncommon among those achieving undetectable HIV-1 RNA.

Methods—Defined from self-reported domains of physical shrinking, exhaustion, slowness and low physical activity in Veterans Aging Cohort Study (VACS) participants, aFRP was considered present with 3 domains and pre-frailty with 1-2 domains. Cox survival analysis determined hazard ratios (HR) for 5-year hospitalization and mortality risk adjusting for frailty states, demographics, health behaviors, comorbidities, and a validated risk index incorporating HIV-specific and general organ system biomarkers, the VACS Index. Model discrimination was assessed.

Results—Participants with complete data were included (6515/7324 (89%)). Of these, 3.9% of HIV-infected with HIV-1 RNA >400copies/ml; 2.0% of HIV-infected with HIV-1 RNA 400copies/ml; and 2.8% of uninfected individuals met aFRP criteria ($p=0.01$). After adjustment for other covariates, aFRP was associated with hospitalization (HR=1.78, 95% CI [1.48, 2.13]) and mortality (HR=1.75, 95% CI [1.28, 2.40]). C-statistics for the VACS Index for hospitalization (0.633) and for mortality (0.756) were higher than for aFRP frailty (0.565 and 0.584, respectively). C-statistic for hospitalization improved modestly when VACS Index and aFRP were both included (0.646) and minimally for mortality (0.761).

Conclusions—aFRP was independently associated with adverse health outcomes among HIV-infected and uninfected individuals. aFRP modestly improved prediction for hospitalization. However, the aFRP is rare among HIV-infected individuals with undetectable HIV-1 RNA.

Introduction

HIV-infected individuals (HIV+) with access to antiretroviral therapy (ART) are living longer. Older HIV+ develop more multimorbidity and experience a greater burden of disease compared with demographically and behaviorally similar uninfected individuals¹⁻⁵. In the general population, frailty correlates with age, burden of disease and organ dysfunction and is associated with hospitalization and mortality. The frailty phenotype was originally validated in the general geriatric population and includes physical shrinking, exhaustion, slowness, low physical activity and weakness⁶. Among those with HIV, the frailty phenotype and impairments in physical function may be seen at younger ages and are associated with low muscle mass and falls^{4, 7-10}. However, these HIV studies are small and lack an uninfected comparison group. The Multicenter AIDS Cohort Study (MACS) used survey responses measuring the first four of these frailty phenotype domains to create a “frailty-related phenotype (FRP)”¹¹. Using the survey-based FRP, MACS investigators found that HIV+ may be at increased risk for frailty, especially those with former AIDS-defining illness¹¹. This initial study of survey-based FRP in MACS suggested that FRP may develop at an earlier age compared with uninfected individuals¹¹. FRP has also been associated with hospitalization and progression to AIDS or death, even after adjusting for

HIV viral load, nadir CD4 count, nadir hemoglobin and liver and kidney function among HIV+¹².

The Veterans Aging Cohort Study (VACS) Risk Index (VACS Index) predicts hospitalization and all-cause mortality in HIV+ and uninfected individuals¹³⁻¹⁷. It includes age and routinely collected clinical biomarkers (CD4 count, HIV viral load, hemoglobin, renal function (estimated glomerular filtration rate (eGFR), liver fibrosis (FIB4) and hepatitis C infection). Among uninfected individuals, CD4 is assumed to be >500 cells/mm³ and HIV-1 RNA is assumed to be undetectable^{13, 18}. Among HIV+ and uninfected patients, the VACS Index score at intensive care unit admission has been shown to predict 30-day mortality¹³. Similarly, the VACS Index predicts 1-year hospitalization and 1-year and 5-year mortality in HIV+ and uninfected patients¹⁸. Risk increases with score. The VACS Index is strongly correlated with inflammatory biomarkers^{16, 19}. Among HIV+ men, the VACS Index predicts fragility fractures, and is associated with muscle mass and physical function as well as neurocognitive function²⁰⁻²² and may be a marker of physiologic frailty, somewhat akin to Rockwood's conceptualization of frailty²³⁻²⁵.

The objectives of this study are to compare prevalence of a survey-based frailty-related phenotype adapted from the MACS (aFRP) among HIV+ with detectable HIV-1 RNA (HIV + detectable), HIV+ with undetectable HIV-1 RNA (HIV+ undetectable), and uninfected; to determine whether aFRP independently predicts 5-year hospitalization and mortality risk after adjustment for VACS Index, demographics, health behaviors, pre-specified comorbidities, and HIV status; then to test whether aFRP improves model discrimination with the VACS Index for hospitalization and mortality prediction.

Methods

Participants

HIV+ and uninfected participants enrolled between 2002 and 2012 in the multicenter Veterans Aging Cohort Study (VACS-8) were included in these analyses if baseline data was available for VACS Index scores, aFRP ascertainment and body mass index (BMI)³. Briefly, VACS-8 is an ongoing prospective study conducted in infectious disease and general medicine clinics at eight Veterans Administration (VA) Medical Centers located in Atlanta, Baltimore, the Bronx, Houston, Los Angeles, Manhattan/Brooklyn, Pittsburgh, and Washington, D.C. Written informed consent is obtained from participants and is approved by each site Institutional Review Board. HIV+ participants are group matched 1:1 by age, race, sex and site-of-care to uninfected participants.

Frailty ascertainment

Frailty was measured by the aFRP based on survey items available in VACS at enrollment. The aFRP was adapted from MACS-based survey items that approximated four of the five domains of the Fried frailty phenotype validated in the Cardiovascular Health Study⁶: physical shrinking, exhaustion, slowness, and decreased physical activity¹¹ (Appendix Table 1).

Participants were classified as having the following frailty states based on survey responses: aFRP=3-4 domains; pre-frail=1-2 domains; not frail=zero domains. Of note, these items closely resemble those used in MACS with the exception of exhaustion. The item used to define exhaustion in MACS related to difficulty performing work or other activities due to physical health.

VACS Index

VACS Index scores were calculated for participants with available laboratory data within +/- 1 year of study enrollment. Ninety percent of participants had scores within 180 days of VACS enrollment. Categorization, point assignment and scoring for the VACS Index was done as previously described (Appendix Table 2)^{16, 26}.

Outcome

Our primary outcomes were first non-psychiatric hospitalization and mortality within 5 years of enrollment. Hospitalizations were identified from the VA inpatient bedsection codes and MedPar data. Mortality was determined from the VA vital status file which combines information from inpatient mortality, social security data and national death benefits data, a method previously shown to provide excellent mortality ascertainment²⁷. Time-to-event was defined starting with date of VACS enrollment until the date of first hospitalization, date of death or participant's last follow up, whichever came first. Cause of death (COD) was obtained from death certificates coded by the National Death Index according to *International Classification of Diseases*, 10th Edition (ICD-10) codes and grouped into mutually exclusive categories of HIV, non-HIV, accidental and unknown. HIV-related deaths were ICD-10 B20-B24. COD data was available for deaths occurring through December 31, 2009 and was completed for 94% of decedents (HIV+ detectable=357/370 (96.5%); HIV+ undetectable=240/259 (92.7%); uninfected=225/244 (92.2%); p=0.04).

Other covariates

Age (in years) was divided into four categories: <40, 40-49, 50-59 and ≥ 60. BMI was calculated from mass in kilograms/height (in meters)². HIV+ were stratified by HIV RNA-1 >400 copies/ml (HIV+ detectable) or HIV RNA-1 ≤ 400 copies/ml (HIV+ undetectable).

Comorbidities were identified by at least one inpatient or two outpatient ICD-9 codes for the condition. This approach has been used extensively in VA data and improves specificity of these codes³. We included comorbidities *a priori* based on prior associations between risk for hospitalization or associations with aFRP domains^{6, 13}. Comorbidities included were hypertension, depression, chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF) and cancer history. Use of ART (≥ 3 antiretroviral medications from at least two classes) was determined from VA pharmacy databases at study enrollment.

Smoking status was based on enrollment surveys. Current smokers were those who reported smoking within 4 weeks of questionnaire completion. Former smokers quit smoking ≥ 4 weeks prior to completion of the questionnaire. Participants with unreported smoking history were included in the former categories for modeling purposes because of similar

overall mortality. Alcohol misuse was a mutually exclusive categorical variable including current alcohol abuse/dependence (ICD-9 codes), former alcohol use (survey items for ever having had a drink but more than 12 months ago) and hazardous or binge alcohol use from survey-based Alcohol Use Disorders Identification Test (AUDIT-C) scores²⁸. Hazardous alcohol use was defined as AUDIT-C score ≥ 4 for men or ≥ 3 for women²⁹. Non-hazardous alcohol use referred to participants without ICD-9 codes for current or former abuse/dependence or specified AUDIT-C scores. Participants with unreported alcohol use history by ICD-9 codes or AUDIT-C scores were categorized separately as missing for modeling purposes ($n=72$).

Statistical analysis

We compared characteristics for participants in VACS-8 stratified by HIV status and among HIV+, by detectable and undetectable HIV-1 RNA. Test for trend (Cochran-Armitage for $2 \times k$ variables and Jonckheere-Terpstra for $n \times k$ variables, where n and $k > 2$) were performed to compare demographic variables, health behaviors, comorbidities, frailty states and outcomes stratified by HIV+ detectable, HIV+ undetectable and uninfected.

Kaplan-Meier estimates were generated to compare unadjusted time-to-death within 5 years by frailty state stratified by HIV status and among HIV+, by detectable HIV-1 RNA. Multivariable regression models were used to assess the association between frailty states and outcomes. We used Cox proportional hazard models to determine adjusted hazard ratios (HR) with 95% CI for time-to-event (hospitalization and death) in years. In these models, we used HIV as the predictor because, after adjusting for the VACS Index, hazard ratios for detectable and undetectable HIV-1 RNA (referent uninfected) were the same (data not shown). We also ran the models stratified by HIV status to determine whether the associations between frailty states and outcomes varied with HIV status. To compare discrimination between the aFRP and the VACS Index for predicting hospitalization and mortality, we calculated Harrel's c-statistic for models including frailty states alone (treated as a 3-level variable), the VACS Index alone, and frailty states with the VACS Index. Statistical analyses were performed using SAS 9.2 (SAS Institute, Cary, North Carolina, USA). C-statistics were run using STATA 11 (StataCorp; College Station, TX). Statistical significance was defined as $p < 0.05$.

Results

From 2002-2012, 3472/3602 (96.4%) HIV+ and 3043/3639 (83.6%) uninfected VACS-8 participants with VACS Index scores, aFRP ascertainment and BMI³ data were included in the analysis. Missing VACS Index score accounted for the majority of exclusions (8.9% of all participants). VACS Index scores were available for 97.8% HIV+ and 84.5% uninfected ($p < 0.0001$). Nearly all participants were male. Among HIV+, half had detectable HIV-1 RNA. HIV+ detectable were younger and more likely to identify themselves as Black race/ethnicity (Table 1).

VACS Index scores were highest in HIV+ detectable. The median and interquartile ranges (IQR) were 35 (23, 52) in HIV+ detectable, 23 (12, 38) in HIV+ undetectable and 12 (6, 23) in uninfected (p trend < 0.0001). This reflects lower CD4 count, higher HIV-1 RNA and

higher prevalence and severity of anemia and liver fibrosis despite younger age and less kidney dysfunction compared with HIV+ undetectable and undetectable (Appendix Table 3). Hepatitis C infection was much more common among HIV+ but did not vary with detectable HIV-1 RNA status (data not shown). Five-year hospitalization and mortality were most common among HIV+ detectable (hospitalization=58.8%, HIV+ undetectable= 51.8%, uninfected=44%; p-trend<0.0001; mortality: HIV+ detectable=21.3%, HIV+ undetectable=14.9%, uninfected=8%; p-trend<0.001).

aFRP and HIV

The aFRP, pre-frailty and aFRP domains varied with HIV status and with detectable HIV-1 RNA. The aFRP was most common among HIV+ detectable (67/1736 (3.9%)) and less common in HIV+ undetectable (35/1736 (2.0%); uninfected=86/3043 (2.8%); p=0.01) (Table 2). Among HIV+ detectable, 549 (31.6%) were pre-frail compared with 572 (33.0%) HIV+ undetectable and 1038 (34.1%) uninfected. There were also major differences by HIV status and detectable HIV-1 RNA for all aFRP domains except slowness. Shrinking and exhaustion were most common among HIV+ detectable and low physical activity most common among uninfected individuals (p<0.01 in all cases).

aFRP and Outcomes

Hospitalization—In unadjusted analysis, risk for hospitalization was approximately doubled among participants with aFRP (reference not frail) (HR=2.16, 95% CI [1.80, 2.59]). Pre-frailty was also associated with hospitalization risk (HR=1.62, 95% CI [1.51, 1.74]). The effects were similar in models stratified by HIV status (data not shown). Because pre-frailty was much more common than aFRP, the population attributable risk percent (PAR%) for hospitalization was substantially higher. Using unadjusted hazard ratios, 17.0% of hospitalizations could have been prevented if pre-frailty was completely eliminated compared with 3.2% of hospitalizations if aFRP was eliminated.

After adjusting for HIV, demographics, health behaviors, comorbidities and VACS Index, the effects of aFRP and pre-frailty were attenuated although remained substantial (aFRP HR=1.78, 95% CI [1.48, 2.13]; pre-frailty HR=1.44, 95% CI [1.33, 1.54]) (Table 3). Population attributable risk using adjusted hazard ratios remained higher for pre-frailty compared with aFRP (pre-frailty PAR%=12.7% vs. aFRP PAR%=2.2%). HIV infection was associated with 22% increased risk for hospitalization (HR=1.22, 95% CI [1.13, 1.33]). VACS Index, current smoking, alcohol misuse, hypertension, depression, COPD, CHF and cancer history were also associated with increased risk for hospitalization. In separate models stratified by HIV status, the associations between frailty states and hospitalization were unchanged (Appendix Table 4).

We next compared discrimination of models for predicting hospitalization including aFRP only, VACS Index only and aFRP + VACS Index. Model discrimination for hospitalization was better with the VACS Index than the aFRP based on c-statistic (c-stat). For the VACS Index alone, c-stat was 0.633 (95% CI [0.623, 0.643]). For aFRP states alone, c-stat was 0.565 (95% CI [0.556, 0.573]). When aFRP was added to the VACS Index, the c-stat improved modestly compared with the VACS Index alone (0.646, 95% CI [0.637, 0.656]).

Mortality—In unadjusted survival models for the overall sample stratified by HIV status and among HIV+, detectable and undetectable HIV-1 RNA, there was a strong gradient observed between frailty state and mortality in each group (Figure 1). Among HIV+ detectable with aFRP, approximately 63% of patients were alive after 5 years compared with approximately 83% of non-frail HIV+ detectable. A similar trend was observed for HIV+ undetectable and uninfected patients. The unadjusted PAR% for mortality from pre-frailty was 22.0% compared with 4.9% for aFRP. HIV-related COD was reported for 212/357 (59.4%) of deaths in HIV+ with detectable HIV-1 RNA and 96/240 (40%) for HIV+ with undetectable HIV-1 RNA while non-HIV-related deaths were reported for 31.9% and 48.3%, respectively ($p < 0.0001$; data not otherwise shown).

In adjusted models, aFRP and pre-frailty were associated with 75% and 44% increased risk for 5-year mortality, respectively (aFRP HR=1.75, 95% CI [1.28, 2.40], pre-frailty HR=1.44, 95% CI [1.25, 1.66]) (Table 3). PAR% for mortality using adjusted hazard ratios was 12.7% from pre-frailty and 2.1% for aFRP. HIV infection was associated with 45% increased mortality risk. VACS Index, current smoking, alcohol abuse/dependence, hypertension, COPD, CHF and cancer history were also risk factors for mortality. In separate models stratified by HIV, the point estimates for aFRP/pre-frailty and mortality were essentially unchanged (Appendix Table 5).

Model discrimination was better with the VACS Index than aFRP for mortality. The c-stat for the VACS Index alone was 0.756 (95% CI [0.740, 0.772]). For aFRP states alone, c-stat was 0.584 (95% CI [0.567, 0.601]). The c-stat minimally improved when adding aFRP states to the VACS Index compared with the VACS Index alone (0.761, 95% CI [0.745, 0.777]).

Discussion

Frailty, as measured by the aFRP, was rare among veterans currently in care with HIV infection, particularly among those with undetectable HIV-1 RNA. While VACS Index scores varied substantially among HIV-infected individuals with and without detectable HIV-1 RNA and compared with uninfected individuals, frailty states were less variable. Frailty states were associated with 5-year hospitalization and mortality risk. Finally, we show that the VACS Index provides better discrimination of risk of hospitalization and of mortality than the aFRP. These findings, in conjunction with prior research, support the use of the VACS Index as a measure of physiologic frailty.

Similar with prior survey-based analyses conducted in the MACS, aFRP prevalence was low. aFRP prevalence was as high as 15% in HIV+ with AIDS in MACS but after excluding AIDS-related person visits, was only present in 2.8% of HIV+³⁰. Of note, although the cross-sectional prevalence of aFRP in VACS was 3.9% in HIV+ with detectable HIV-1 RNA, aFRP prevalence in HIV+ undetectable was lower than in uninfected participants (2.0% compared with 2.8%, respectively). There are significant differences between FRP studies in MACS and aFRP in VACS that are worth noting. First, the majority of MACS participants were enrolled during the pre-ART era, with 71% of participants enrolled in 1984-1985. VACS represents a more contemporary sample of HIV+, having begun

enrollment in 2002 with ongoing enrollment since. Second, only 48% of MACS participants were on ART when FRP prevalence was first measured³⁰ compared with more than 70% of VACS participants. Third, MACS measured FRP prevalence per person-visits over an 11 year period. We measured aFRP cross-sectionally at VACS enrollment. Despite these differences and differences in sociodemographic and HIV risk behaviors between MACS and VACS, the associations between HIV+ and frailty states are quite similar. Specifically, uncontrolled HIV disease, measured as prior AIDS illness in MACS^{11, 30} and detectable HIV-1 RNA in VACS, but not HIV infection alone, is associated with a frailty-related phenotype.

Similar to our findings, survey-based FRP predicts hospitalization and mortality in prior analyses^{12, 31}, suggesting internal validity. However, compared with the aFRP which varied only modestly by HIV status and detectable HIV-1 RNA (absolute difference <2%), the VACS Index varied substantially by HIV status and detectable viral load (median scores HIV+ detectable, undetectable and uninfected: 35, 23, and 12, respectively). Based on prior work, a 5-point difference in VACS Index score suggests an approximate 20% difference in mortality risk³². Thus based on VACS Index scores alone, we expected a large difference in risk of hospitalization and mortality among these groups and this was borne out in our analyses. The VACS Index was substantially better at discriminating hospitalization and mortality risk than the aFRP.

Prior work has demonstrated that the VACS Index accurately predicts risk of mortality among HIV+ individuals in North America and Europe^{15, 32}, predicts mortality among veterans with and without HIV infection^{13, 18}, is responsive to changes in antiretroviral treatment³³, predicts fragility fracture²⁰, and is strongly associated with biomarkers of inflammation¹⁶, cognitive function²², and functional performance²¹. In conjunction with the current study, the VACS Index appears to offer major advantages in estimating the level of physiologic frailty or vulnerability among those aging with HIV infection compared with the aFRP. Of note, while the VACS Index is not very consistent with the Fried phenotypic conceptualization of frailty⁶, it bears much in common with Rockwood's cumulative deficit approach²⁴. Rockwood's measure has not been as widely applied, likely due to the added burden of measurement (30 specific deficits), but the VACS Index, based on routinely monitored clinical variables, does not suffer from this limitation. We propose using the VACS index as an objective, clinical measure of physiologic vulnerability (frailty) in patients with HIV that accounts for subclinical as well as frank organ dysfunction^{24, 34}.

Prior studies examining frailty in HIV-infected persons using objective measurement of physical function had a substantially higher prevalence of frailty states than we observed in VACS^{8, 10}. VACS does not routinely collect objective measurements of physical function for all participants. However, in VACS substudies, the prevalence of low grip strength according to previously described thresholds for defining frailty phenotype⁶ was low (6/53 (11%)²¹). Another substudy with chair stands is ongoing. Based on these findings, it is unlikely that the addition of objective measures of physical function would have changed the prevalence of frailty states in this population. Whether incorporating domains of aFRP or, ideally, objective measurements of physical function would further improve the performance

of the VACS Index in predicting frailty-related health outcomes could be explored in future studies.

There are several limitations to this study. VACS participants are predominantly men who are younger than the general geriatric population where frailty measures were originally developed and validated. Mean age for VACS participants included in this study was approximately 50 years. The frailty phenotype and the deficit accumulation concept for frailty has been characterized in persons age 65 years and older^{6, 23, 24, 35}. Further, in these geriatric cohorts, more than 50% of participants (and up to 64% in one cohort) were women who experienced more frailty than men^{6, 23, 24, 35}. It remains to be seen if the rates of frailty will be higher among women with HIV. Additionally, it will be important to monitor incident frailty as HIV cohorts age beyond median ages in the 50s to the 60s and 70s. In addition, our aFRP is adapted from the MACS FRP. We used survey items that approximated the four domains used in MACS but the items are not exactly the same as those used in the MACS (Appendix Table 1)¹¹. Of note, most items were very similar with the possible exception of our measure of exhaustion. The MACS measure asks about ability to perform work and other activities. The VACS measure asks about the symptom of fatigue. We also did not include pain in the current study. This would be an important area for future work. The VACS Index has not been used to predict psychiatric hospitalizations which may also represent frailty-related health events. However, the relative weights of the VACS Index are likely to be different for psychiatric admissions. This would be an additional area for future research. Finally, as a cross-sectional study we are unable to determine the temporal changes in frailty states in VACS. Prior studies suggest that frailty states are dynamic but that important health events such as hospitalization can impact frailty state transitions^{36, 37}. Longitudinal studies are warranted to determine how frailty states change over time in VACS, particularly in light of the high population attributable risk for both outcomes associated with pre-frailty. VACS is well suited to characterize a frailty-related phenotype in HIV+ with and without detectable viral load and for comparing aFRP with uninfected patients.

Conclusion

Despite HIV-infected individuals with undetectable HIV-1 RNA having higher hospitalization and mortality rates than uninfected individuals, the aFRP was less common among HIV+ undetectable than uninfected. In contrast, VACS Index scores were substantially higher even among HIV+ undetectable individuals compared to uninfected subjects. The VACS Index performs better than the aFRP in predicting hospitalization and mortality. Further studies are required to determine whether specific domains of aFRP improve the VACS Index. As in the general geriatric population, strategies to improve physiologic reserve and reduce frailty in HIV+ patients must be a priority for successful aging.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Kaplan-Meier survival curves among a) HIV+ detectable, b) HIV+ undetectable and c) uninfected stratified by frailty state. Dashed dark lines are not frail, gray lines are pre-frail and solid lines are adapted frailty-related phenotype (aFRP).

Table 1

Characteristics of patients in VACS8 evaluated for aFRP and with VACS Index scores available.

N=6515	HIV + (N=3472)				Uninfected (N=3043)				p trend
	VL> 400 (n=1736)		VL 400 (n=1736)						
	No.	%	No.	%	No.	%	No.	%	
Demographics									
Age in years									
Mean (SD)	47.6	(8.5)	50.8	(8.8)	50.9	(9.6)			<0.0001
< 40	286	16.5	152	8.8	314	10.3			
40-49	749	43.1	602	34.7	1063	34.9			
50-59	578	33.3	745	42.9	1200	39.4			
60	123	7.1	237	13.6	466	15.3			
Race / ethnicity									
Black	1205	69.4	1117	64.3	1923	63.2			0.02
White / non-Hispanic	310	17.9	386	21.2	693	22.8			
Hispanic	143	8.2	190	10.9	327	10.7			
Other/unknown	78	4.5	61	3.5	100	3.3			
Male Gender									
	1689	97.3	1694	97.6	2810	92.3			<0.0001
BMI, kg/m ² , median (IQR)	24.8	(22.3-27.8)	25.3	(22.8-28.2)	28.9	(25.5-32.9)			<0.0001
Clinical Characteristics									
Smoking status									
Current	968	55.8	872	50.2	1396	45.9			0.9
Former	353	20.3	481	27.7	808	26.6			
Never	411	23.7	373	21.5	784	25.8			
Missing	4	0.2	10	0.6	55	1.8			
Alcohol use*									
Non-hazardous	588	33.9	592	34.1	886	29.1			<0.0001
Hazardous (AUDIT score > 4)	427	24.6	370	21.3	633	20.8			
Abuse/dependence (ICD9)	303	17.4	251	14.5	722	23.7			

N=6515	HIV + (N=3472)				Uninfected (N=3043)			
	VL> 400 (n=1736)		VL 400 (n=1736)					
	No.	%	No.	%	No.	%	No.	p trend
Former	394	22.7	504	29.0	773	25.4		
VACS Index score, median (IQR) Comorbidities	35	(23, 52)	23	(12, 38)	12	(6, 23)		<0.0001
Hypertension	420	24.2	482	27.8	1514	49.8		<0.0001
Depression	188	10.8	201	11.6	418	13.7		0.002
COPD	71	4.1	81	4.7	159	5.2		0.08
Congestive heart failure	25	1.4	34	2.0	98	3.2		<0.0001
Cancer history	9	0.5	13	0.8	23	0.8		0.4
Outcome (within 5 years)								
Non-psychiatric hospitalization	1021	58.8	900	51.8	1339	44.0		<0.0001
Died	370	21.3	259	14.9	244	8.0		<0.0001

* 72 respondents had missing responses for AUDIT-C scores and no ICD-9 code for abuse/dependence.

Table 2

Frailty states and domains stratified by HIV status and detectable HIV-1 RNA among HIV+.

	HIV + (N=3472)				Uninfected (N=3043)			
	VL> 400 (n=1736)		VL 400 (n=1736)					
	No.	%	No.	%	No.	%	No.	%
Frailty states								
aFRP	67	3.9	35	2.0	86	2.8	0.01	0.3
Pre-frail	549	31.6	572	33.0	1038	34.1		
Not frail	1120	64.5	1129	65.0	1919	63.1		
aFRP domains								
Shrinking	165	9.6	134	7.8	194	6.5	<0.0001	
Exhaustion	269	15.6	203	11.8	379	12.6	0.009	
Slowness	70	4.0	67	3.9	146	4.8	0.2	
Low physical activity	415	23.9	441	25.4	864	28.5	0.0004	

Table 3

Multivariable models for hospitalization and mortality.*

N=6515	Reference	Hospitalization		Mortality	
		HR	(95 % CI)	HR	(95 % CI)
HIV		1.22	(1.13, 1.33)	1.45	(1.22, 1.72)
Frailty states	Not frail				
aFRP		1.78	(1.48, 2.13)	1.75	(1.28, 2.40)
Pre-frail		1.44	(1.33, 1.54)	1.44	(1.25, 1.66)
VACS Risk Index	Per 5 points	1.10	(1.09, 1.11)	1.18	(1.17, 1.20)
Black race/ethnicity	White	1.01	(0.94, 1.09)	0.86	(0.74, 0.99)
Female gender	Male	0.84	(0.70, 1.02)	0.70	(0.45, 1.10)
Smoking status	Never				
Current smoker		1.27	(1.15, 1.39)	1.54	(1.26, 1.87)
Former		1.01	(0.91, 1.21)	1.04	(0.83, 1.30)
Alcohol misuse**	Non-hazardous				
Abuse/dependence		1.62	(1.46, 1.80)	1.45	(1.19, 1.76)
Hazardous		1.07	(0.97, 1.19)	1.02	(0.83, 1.25)
Former		1.11	(1.03, 1.23)	1.17	(0.97, 1.40)
Comorbidities					
Hypertension		1.42	(1.32, 1.53)	1.38	(1.20, 1.59)
Depression		1.20	(1.08, 1.33)	0.99	(0.81, 1.20)
COPD		1.67	(1.46, 1.92)	1.61	(1.29, 2.01)
CHF		1.89	(1.58, 2.27)	2.54	(1.95, 3.31)
Cancer history		1.90	(1.36, 2.65)	1.90	(1.07, 3.38)

*The VACS Index includes age and HIV-1 RNA. After adjustment for the VACS Index, these variables were no longer significant.

**Alcohol use missing for 72 respondents who were included as missing category in the model.