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What types of frailty predict death in HIV-infected women? The Women's Interagency HIV Study

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ABSTRACT

Objectives. Predicting mortality in middle-aged HIV-infected (HIV+) women on antiretroviral therapies (ART) is important for understanding the impact of HIV infection. Several indices have been used to predict mortality in women with HIV infection. We evaluated: 1) a modified HIV biological index, Veterans Aging Cohort Study (mVACS); 2) physical index, Fried Frailty Index (FFI); and 3) modified mental health index, Centers for Epidemiologic Studies-Depression (mCES-D). Proportional hazards regression analyses was used to predict death and included relevant covariates.

Design. Prospective, observational cohort

Setting. Multicenter, across 6 sites in the United States

Participants. 1385 multirace/ethnic HIV+ women on ART in 2005

Primary and secondary outcomes. All deaths, AIDS-deaths and non-AIDS deaths up to ~8 years from baseline

Results. Included together in one model, mVACS Index was the dominant, significant independent predictor of all deaths within 3 years (HR=2.21, 95% CI 1.84, 2.65, χ^2=72.5 , p<0.0001), and later than 3 years (HR=1.59, 95% CI 1.33, 1.89 X^2=26.8, p<0.0001); followed by FFI within 3 years (HR=2.11, 95% CI 1.23, 3.59, χ^2=7,46, p<0.0063) and later than 3 years (HR=2.44, 95% CI 1.59, 3.73, X^2=16.9, p<0.0001). CES-D score was not associated with mortality.

Conclusions and Relevance. This is the first simultaneous evaluation of three common mortality indices in HIV infected adults. Indices reflecting physical and biological aging were associated with death.

Article summary

Strengths and limitations of this study

- Longitudinal cohort study with follow-up of almost 10 years
- Well-phenotyped White, African American and Latina HIV+ women
- Reputable standardized and validated physical, biological and emotional frailty indices

INTRODUCTION

HIV infection continues as a major global health issue affecting approximately 36 million people worldwide. HIV infection has evolved from a fatal infection to a treatable, chronic condition of aging,[1,2] accompanied by multiple morbidities and rising healthcare costs. The North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD), observed that life expectancy of HIV infected adults increased from 36 to 51 years between 2000 and 2007,[3] primarily due to treatment advances. In 2015, over half of HIV-infected Americans are ≥50 years old.[3] Therefore HIV infection may prove to represent a modern-day phenomenon of achieving healthy old age accompanied by improved longevity.

Predicting death in chronic HIV infection may assist in the design of interventions to understand, prevent, cure or minimize age-related impairments, improve health and increase lifespan. Several indices predict death in adults with HIV infection - the Veterans Aging Cohort Study (VACS) Index; Fried Frailty Index (FFI); and the Centers for Epidemiologic Studies – Depression (CES-D) score. Each index can be considered an index of frailty, since each worsens with age and denotes weakness. The only HIV-specific mortality index is the VACS Index, which has been reproduced in North American and European patient populations including Highly Active ART (HAART) users in the Women's Interagency HIV Study (WIHS).[4,5] The VACS Index creates a clinical HIV mortality risk score by summing pre-assigned points for age, routinely monitored indicators of HIV disease and general indicators of organ system function.[5,6] The Fried Frailty Index (FFI) is most commonly used when describing aging in both general and HIV-infected populations.[7,8] Frailty is a common co-morbidity of HIV infection, observed even during middle age.[4,9] The FFI includes measures of gait speed, handgrip strength, body weight loss, physical activity, and exhaustion and predicts death.[10-12] The Centers for Epidemiologic Studies –

Depression (CES-D) score measures mental health[13] and has been independently associated with mortality, particularly among women with HIV infection on HAART in the WIHS.[4]

The objective of our analyses was to evaluate, among HIV-infected women, the association of the aforementioned indices: VACS, FFI, and CES-D, with death (both AIDS-and non-AIDS related). All indices were measured in mid-life (average age 39 years) in our analyses and evaluated for prediction of mortality for up to ~8 years. This follow-up period was further broken down into short-term (within 0-3 years) and long-term (>3- ~8 years) deaths, since studies show that prediction of death may vary depending on the exposure being evaluated by more immediate precipitating diseases, conditions or longer term exposures.

METHODS

Study Population. WIHS is a prospective, observational cohort suitable to study the intersection of HIV-infection and aging. WIHS participants enrolled at six sites (Bronx/Manhattan, Brooklyn, Chicago, Los Angeles, San Francisco and Washington DC); methods, and baseline cohort characteristics have been described previously.[14] Participants have visits every 6 months, which include an extensive face-to-face interview by trained interviewers, medical examinations, and laboratory specimen collection. Of the HIV-infected women actively enrolled in 2005, 1395 completed an assessment of the FFI. Of these, 1385 women reported current use of antiretroviral therapy and had measures of both VACS index and CES-D and are included in the current analyses.

Inclusion criteria. Women included in these analyses are members of the WIHS cohort and had to have adequately completed all indices (VACS, FFI, CES-D) in 2005 for evaluation in association with mortality.

Primary outcome. Mortality over the ~8 years, 2005-2013 (also subcategorized into 0-3 and >3 - ~8 years) subsequent to measurement of the aging vulnerability indices, was the primary outcome. The US National Death Index identified numbers and causes of death from Jan 1, 2005 through Dec 31, 2013. Causes of death were subdivided into AIDS and non-AIDS deaths based on consensus opinion from a panel of WIHS investigators. (See Figure 1) AIDS deaths included: pneumonia, PML, PCP, wasting syndrome, CNS lymphoma, candida, CMV, Cryptococcus, toxoplasmosis, TB/mycobacterium, cervical cancer, pulmonary hypertension, dementia/neurologic, renal failure, multi-organ failure and pancreatitis. Non-AIDS deaths included: non-AIDS related malignancy, gastrointestinal, trauma, drug/alcohol overdose, heart disease, lung disease, liver disease, kidney disease, neurologic/stroke, hemorrhage, pneumonia, psychiatric, surgical complication, or pregnancy complication. For some, cause of death could not be classified as AIDS or non-AIDS, thus the sum of these two subcategories is less that the total number of deaths during the follow-up period.

Primary Predictors of Death. There were three primary predictors of interest: VACS score, FFI, and CES-D score. The VACS Index facilitates a mortality risk score created by summing pre-assigned points for age, routinely monitored indicators of HIV disease (CD4 count and HIV-1 RNA), and viral hepatitis C infection (HCV); and general indicators of organ system injury including hemoglobin, FIB-4, and estimated glomerular filtration rate, eGFR (ml/min). We

calculated eGFR based on the CKD-EPI equation.[15] The VACS Index has a maximum score of 164. Our modified VACS Index (mVACS) totaled a maximum score of 136 since VACS age groups were not included in our derivation of the algorithm due to the younger age of our sample (VACS Index lowest age group is <50 years). Instead we adjusted for age as age decades that reflected our sample as a separate covariate in multivariate analyses.

The FFI was defined using well-described criteria.[7] A woman was classified as frail if she exhibited three or more of five characteristics: 1) impaired mobility, 2) reduced grip strength, 3) physical exhaustion, 4) unintentional weight loss and 5) low physical activity. At each site, mobility was measured using a 3-4 meter timed gait test, and impaired mobility was defined as the lowest quintile of performance among HIV negatives. Similarly, grip strength was measured using a dominant hand-held dynamometer with maximum force; reduced grip strength was the lowest quintile of performance among HIV negatives. Physical exhaustion was a "Yes" to the question: "During the past four weeks, as a result of your physical health, have you had difficulty performing your work or other activities (for example, it took extra efforts)"? Low physical activity was a "Yes" to "Does your health now limit you in vigorous activities, such as running, lifting heavy objects, or participating in strenuous sports?" Unintentional weight loss was a "Yes" to: "Since your last visit, have you had unintentional weight loss of at least 10 pounds?" If at least 3 components were available, the total out of 3 (or 4) was calculated.

The 20-item CES-D, is a depressive symptom screening tool. For these analyses, we excluded two CES-D symptoms that overlap with the FFI. The excluded CES-D symptoms were 'this past week I could not get going' (overlaps with low physical activity in the FFI) and 'this past week

everything was an effort' (overlaps with exhaustion in the FFI). Thus, the maximum total points possible on our modified CES-D (mCES-D) were 54 instead of 60), and a cut point of 15 (instead of the typical 16) was used to denote symptoms of clinical relevance.

Statistical analyses. We used single variable and multivariable proportional hazards models to address the questions of which indices (of FFI, mVACS or mCES-D), when measured at mid-life in this sample of HIV+ women, best predicted AIDS, non-AIDS and all death. Tested covariates were those found to be significant in cross-sectional analyses.[4] These covariates included race/ethnicity, education, smoking, annual income, alcohol drinking, intravenous drug use (IDU) history, body mass index (BMI), prior AIDS defining illness, pneumonia, cancer, diabetes and hypertension. Methods for determining HIV and HCV infection status, Acquired Immunodeficiency Syndrome (AIDS) diagnosis, CD4 cell count, HIV viral load, ART use, and IDU were described previously.[9] In addition, in relation to the frailty measures, we refit models i) restricting follow up time to the first 3 years after measurement (i.e. censoring at 3 years), and ii) starting follow up time at 3 years after the frailty measurement (i.e. truncating prior to 3 years). Results of proportional hazards regression models are presented as Hazards Ratios (HR) with 95% Confidence Intervals (CI). The χ^2 statistic is also presented to facilitate comparison of strength of association between models since the HR scale of each aging vulnerability index is not the same. Data analyses were accomplished using SAS 9.4.

RESULTS

Data were available for all indices on 1385 HIV+ women (average age 42.6±8.8 years) who reported ART use. The average mVACS score was 26.3 ±18.2 (possible range 0-136);

prevalence of frailty (defined as FFI = 3-5) was 17.5%; and 37.3% had a mCES-D score of at least 15 points indicating a clinically relevant depression phenotype. With regard to calculating the FFI, of 1385 women, 1166 (84.2%) had no missing components, 94 (6.8%) had one missing component and 125 (9.0%) had 2 missing components. The three indices, as well as individual mVACS components, demographic/health behavior, infectious disease, chronic aging-related disease variables, number and types of deaths are presented in Table 1. The crude HR (95% CI) for all deaths by aging vulnerability indices and demographic/health behavior, infectious disease and chronic aging-related disease variables are presented in Table 2. When evaluated separately in univariate and multivariable models, worse (higher) FFI, mVACS, and mCES-D scores were each significantly associated with a more rapid onset of mortality, as was higher age and several other covariates.

Using multivariable models that included all indices, we separately evaluated all deaths up to ~8 years from baseline (Table 3) and subdivided by timing of death (short-term, 0 - 3 years *vs* long-term, >3 to ~8 years from baseline, Table 4). We also modeled AIDS and non-AIDS deaths separately over the same time periods. Over the entire follow-up period, FFI was a stronger predictor of non-AIDS deaths than was the mVACS Index, while mVACS was a stronger predictor of AIDS deaths than was FFI. Yet, all HR were significant for both indices. mCES-D was not an independently significant predictor of death.

All deaths. When considering all deaths, within the first 3 years after baseline measurement (Table 4A) the mVACS Index was the dominant, significant independent predictor of all deaths (HR=2.21, 95% CI 1.84, 2.65, χ^2=72.50, p<0.0001), followed by FFI (HR=2.11, 95% CI 1.23,

3.59, χ^2=7.46, p=0.0063). For deaths occurring later than 3 years after baseline measures (Table 4B), the relative influence of the mVACS Index decreased (HR=1.59, 95% CI 1.33, 1.89, χ^2=26.75, p<0.0001), and the FFI increased (HR=2.44, 95% CI 1.59, 3.73, χ^2=16.85, p<0.0001).

AIDS deaths. Within 3 years after baseline (Table 4C), mVACS Index was the only statistically significant independent predictor (HR=3.27, 95% CI 2.53, 4.22, χ^2=82.38, p=<0.0001) of AIDS deaths; for AIDS death after 3 years (Table 4D), both mVACS Index (HR=1.80, 95% CI 1.34, 2.42, χ^2=15.49 p=0.0001) and FFI (HR=3.27, 95% CI 1.53, 7.00, χ^2=9.28, p=0.002) were independently significant.

Non-AIDS deaths. FFI was the most significant predictor of non-AIDS death both within (Table 3E) (HR=3.35, 95% CI 1.52, 7.35, χ^2=9.03, p=0.003), and later (Table 4F) than 3 years post baseline (HR=3.11, 95% CI 1.62, 5.95, χ^2=11.66, p=0.0006). The mVACS Index predicted death later than 3 years (HR=1.45, 95% CI 1.10, 1.92, χ^2=6.87, p=0.009), but was not quite as robust as the FFI.

mCES-D score was not an independently significant (at $P < 0.05$) predictor in any AIDS or non-AIDS death model after adjusting for FFI and mVACS Index. Also of note, inclusion of ART-naïve participants (n=54, for a total N of 1439) did not change these findings.

DISCUSSION

We evaluated the ability of three common indices representing physical, biological and mental health status to predict mortality in adults with HIV infection. These indices - mVACS, a

biological HIV index; the FFI, a physical index; and the mCES-D, a mental health index - were evaluated concurrently in association with mortality over approximately 8 years (and repeated for 0-3 and >3 - ~8 years) among women with HIV infection. Overall, based on comparative $\chi 2$ statistics, the mVACS Index was the strongest predictor of death, particularly of AIDS-related deaths and early deaths within 3 years after index assessments. The FFI was also additively informative, a better predictor of non-AIDS deaths than the mVACS and a realtively more important predictor of deaths from 3 - ~ 8 years after index assessments.

First published in 2003, the FFI has been a useful construct by which to predict poor quality of life, cognitive impairment, dementia and death.[16] Ten years later, the first report on a validated VACS index specific for those with HIV infection was published.[5] The VACS Index has, since then, been used to predict mortality in infected and uninfected populations and has been associated with the FFI.[6] In the WIHS, the VACS Index and CES-D score considered together have been independently reported to predict mortality over a 5 year period.[4] Here we show that with addition of the FFI, these relationships change.

The FFI predicts death, particularly among elderly (65 years and older).[10] More recently the FFI has been measured in younger adult populations who may be at risk for premature or earlier aging, such as those with HIV infection.[6,17] These studies have shown that adults with HIV infection, even in mid-life, experience a prevalence of frailty equivalent to, and greater than, that observed in more elderly patients.[4,9] The reason for this early manifestation of the frailty phenotype may be a consequence of HIV infection itself, including suboptimal medication and control of infection early on, comorbid diseases (infectious or non-infectious)[4,18] and/or other

lifestyle habits that may be common among those with HIV infection, such as smoking and substance use.[11] While interesting, FFI fluctuations cannot be addressed in these analyses, but will be in the future with the re-initiation of FFI assessments in the WIHS in Fall 2015. As the FFI is a marker of the slower process of physical aging, it may continue to be more strongly associated with non-AIDS and later deaths as was seen in this analysis.

The mCES-D was significantly associated with death in models that did not adjust for mVACS and FFI (i.e. p=0.0017 and χ^2=9.9 in Table 2), however it was not associated with death once mVACS and FFI indices were included in the same model. Several studies that do not consider FFI and/or VACS, including those from the WIHS, have found CES-D to be a significant "independent" predictor of mortality.[4,19-23] This study calls into question whether CES-D is a surrogate for other vulnerabilities rather than being independently causally associated with death. Other studies or analyses of CES-D in relation to death tend to not include other frailty indices in their models or only include VACS.[4] It should be noted that our mCES-D excludes two items overlapping with the FFI (low physical activity and exhaustion). However, adding these two items back to the mCES-D did not qualitatively change the failure of CES-D to be significant in the multivariate models (data not shown). Evaluating vulnerabilities in middle-aged HIV-infected women (the average age of infected women today) is important to understanding the impact of HIV infection on mortality over the life course. This approach has been shown for other diseases of later-life.[24] Midlife physical, biological and/or mental indicators against the background of HIV infection may be associated with earlier death.

Why are multi-dimensional frailty indices associated with mortality in adults with HIV infection? Throughout adult life, HIV infection is synergistic with adverse aging influences on the immune, vascular, reproductive, and central nervous systems, thereby intensifying the aging process.[25,26] In our previous cross-sectional analysis of the FFI, we showed that the FFI is associated with infectious, demographic, chronic disease, and biological factors, including individual components of the VACS Index,[4] lending support to this observation.

We chose to assess deaths occurring within 3 years versus those occurring ≥ 3 years after the indices were measured. Studies in uninfected populations have shown that deaths occurring within a short period of time (e.g., 3 years) tend to be those due to more rapid biological triggers of death such as infections (e.g., HIV, pneumonia) or other acute illnesses, while longer term deaths reflect delayed consequences of deteriorating biological and physical health.[27] Non-AIDS deaths were predicted by FFI, whether those deaths occurred within or later than 3 years. mVACS was more significant for AIDS deaths and deaths occurring within 3 years. Notably, both mVACS and FFI were stronger predictors of death (all, AIDS, non-AIDS) than age and other variables considered in the multivariable models reflecting that these indices, more than age, carried the consequences of deteriorating biological and physical health.

Aging with HIV infection is associated with geriatric morbidities or syndromes, including frailty,[28] however these aging morbidities often occur earlier among those with HIV infection compared to uninfected individuals.[29-31] The question is whether HIV infection leads to more severe aging phenotypes, or accelerates their onset leading to earlier age of death.[32] These analyses show that two indices, the mVACS (biological) index and the FFI (physical),

independently predict mortality in middle-aged women with HIV infection. Inclusion of mCES-D, a depressive symptom scale, was not independently informative once both the biological and physical frailty measures were considered. This is the first published report on the simultaneous evaluation of these important indices in association with mortality in women with HIV infection. These analyses point to the importance of designing interventions to address components of multifaceted indices in the hopes of extending the lifespan of patients living with chronic HIV.

Author Contributions

All authors contributed to this work. Hypothesis generation and manuscript drafting was led by DG and DH; statistical analyses and interpretation was led by DH and QS; participant recruitment and retention were accomplished by the WIHS Principal Investigators, DG, HM, MC, MP, AS, SG, MG, and JM and project staff, SH. Manuscript editing was performed by all.

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Competing Interest

There are no competing interests to declare.

STROBE Criteria

This manuscript meets the STROBE criteria for longitudinal cohort studies.

Data Sharing

Technical appendix, statistical code, and dataset are available from the WIHS Statistical Analysis Center, WD-MAC.

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Table 1. Baseline characteristics of HIV-infected WIHS participants who are not ART-naive

Variables	N (%)
Indices	
Fried Frailty Index (FFI)	
0-2	1143 (82.5)
3-5	242 (17.5)
mVACS Score (0-136)[a]	26.3 ±18.2
mCES-D score >= 15[b]	
No	869 (62.9)
Yes	516 (37.1)
Outcomes	
All Deaths	
3 Years or Less	73 (5.3)
> 3-8 years	111 (8.0)
AIDS deaths[c]	
3 Years or Less	39 (2.8)
> 3-8 years	35 (2.5)
Non-AIDS deaths[c]	
3 Years or Less	32 (2.3)
> 3-8 years	45 (3.2)
HIV variables	
CD4 count (cells/mm3)	
>= 500	554 (40.0)
200-499	614 (44.3)
< 200	217 (15.7)
Viral Load (copies/ml)	
< 500	820 (59.2)
500-100,000	510 (36.8)
>100,000	55 (4.0)
Hemoglobin (g/dl)	
≥14	209 (15.1)
12-13.9	743 (53.6)
10-11.9	362 (26.1)
<10	71 (5.1)
FIB4	
< 1.45	1018 (73.5)
1.45-3.25	280 (20.2)
> 3.25	87 (6.3)
eGFR (ml/min)	
>=60	1277 (92.2)
45-59.9	71 (5.1)
30-44.9	15 (1.1)
< 30	22 (1.6)
Hepatitis C Co-infection	298 (21.5)

Demographic Variables	
Average age (years, mean ± SD)	42.6 ±8.8
Race/Ethnicity	
White	324 (23.4)
Black	806 (58.2)
Others	255 (18.4)
Education	
< High School	536 (38.7)
>= High School	847 (61.2)
Mission	2 (0.1)
Smoking History	
Not current smoking	786 (56.8)
Current smoking	599 (43.2)
Income	
< $12,000	669 (48.3)
>=$12,000	668 (48.2)
Missing	48 (3.5)
Current Alcohol Drinking	
Abstainer/None	743 (53.6)
Low	490 (35.4)
Moderate	129 (9.3)
High	23 (1.7)
Body Mass Index (BMI), kg/m^2	
BMI < 30	916 (66.1)
BMI >=30 (Obesity)	461 (33.3)
Missing	8 (0.6)
Current ART use	
No	400 (28.9)
Yes (HAART)	984 (71.0)
Missing	1 (0.1)
Prior AIDS Defining Illness	
No	802 (57.9)
Yes	583 (42.1)
Injection Drug Use Ever	
Yes	305 (22.0)
No	1071 (77.3)
Missing	9 (0.6)
Prior Pneumonia	
No	1080 (78.0)
Yes	305 (22.0)
Current / Prior Hypertension	
No	964 (69.6)
Yes	421 (30.4)
History of Diabetes	

No	1195 (86.3)
Yes	190 (13.7)
Prior Cancer Diagnosis	
No	1220 (88.1)
Yes	165 (11.9)

[a]mVACS Index without VACS-specific age strata; usual sum is 163, without age category the maximum possible sum is 136. The VACS Index includes older age groups not adequately represented in the WIHS. Thus, we adjust for age category in the analysis and leave age group out of the VACS score, resulting in a lower total VACS score.

[b]mCES-D is a CES-D score calculated without inclusion of 2 items that could overlap with FFI

[c]For some deaths, cause of death could not be classified as AIDS / non-AIDS, thus the number of AIDS + non-AIDS deaths does not sum to total deaths.

Table 2. Proportional Hazards models of time to all deaths by FFI, mVACS, mCESD, age group, and potential confounders among women with HIV infection

Variable	Crude HR (95% CI)	χ^2	P-value
Univariate Analyses of Indices			
mVACS Score (0-136), per 20 units[a]	2.21 (1.99, 2.46)	209.7	< 0.0001
FFI 3-5 vs 0-2	3.92 (2.92, 5.26)	83.2	< 0.0001
mCESD, modified (< 15 vs ≥ 15)[b]	2.01 (1.50, 2.68)	22.2	<0.0001
Univariate Analyses of Potential Confounders			
Age per Decade	1.62 (1.38, 1.89)	36.14	<0.0001
Race/ethnicity		8.95 (2 df)	0.011
White vs black	0.55 (0.37, 0.83)	8.02	0.005
Others vs black	0.74 (0.49, 1.11)	2.15	0.140
Education ≥ high school vs < high school	0.68 (0.51, 0.90)	6.96	0.008
Smoking (current vs no)	3.41 (2.49, 4.69)	57.5	<0.0001
Income (< $12,000 vs ≥ $12,000)	2.03 (1.49, 2.77)	19.8	<0.0001
Drinking		27.25 (3 df)	<0.0001
Low vs Abstainer/None	0.59 (0.42, 0.84)	8.59	0.003
Moderate vs Abstainer/None	1.27 (0.82, 1.98)	1.14	0.290
High vs Abstainer/None	3.48 (1.76, 6.87)	12.9	0.0003
BMI, kg/m^2 (>= 30 vs <30)	0.57 (0.41, 0.81)	10.2	0.001

[a]mVACS Index score without VACS-specific age strata; [b]mCES-D without FFI overlap

Table 3. mVACS Index, FFI, and mCES-D individually predict time to all, AIDS and non-AIDS deaths over ~8 years follow-up among women with HIV infection.

	All deaths			AIDS deaths			Non-AIDS deaths		
Index	**X2**	**HR[c] (95% CI)**	**P-value**	**X2**	**HR (95% CI)**	**P-value**	**X2**	**HR (95% CI)**	**P-value**
FFI	26.15	2.36 (1.79, 3.28)	< 0.0001	9.76	2.34 (1.37, 3.98)	0.002	20.806	3.20 (1.94, 5.26)	< 0.0001
mVACS[a]	97.07	1.85 (1,64, 2.09)	< 0.0001	100.12	2.54 (2.12, 3.05)	0.000	7.0126	1.33 (1.08, 1.65)	0.008
mCES-D[b]	1.84	1.24 (0.91, 1.70)	0.188	4.29	1.75 (1.03, 2.96)	0.038	0.0211	0.96 (0.59, 1.57)	0.885
Age per decade	10.22	1.37 (1.13, 1.66)	0.001	0.0027	0.99 (0.72, 1.36)	0.959	11.133	1.63 (1.22, 2.17)	0.001

[a]mVACS Index score without VACS-specific age strata
[b]mCES-D is a CES-D score calculated without inclusion of 2 items that could overlap with FFI
[c]Multivariate models included race/ethnicity; education less than or equal to vs greater than high school; smoking current vs no; income less than vs greater than or equal to $12,000 annually; drinking low, moderate or high vs none; and BMI at least than vs less 30 kg/m^2

Table 4. Multivariable proportional hazards models of time to all, AIDS and non-AIDS deaths within 3 years vs greater than 3 years by mVACS Index, FFI, mCES-D and age among women with HIV infection.

	A. All Deaths Within 3 Years After FFI Visit			B. All Deaths Later Than 3 Years After FFI Visit		
Variable	χ^2	**Multivariate-Adjusted HR[b] (95% CI)**	**P-value**	χ^2	**Multivariate-Adjusted HR[b] (95% CI)**	**P-Value**
mVACS Index per 20	72.50	2.21 (1.84, 2.65)	0.0000	26.75	1.59 (1.33, 1.89)	<0.0001
FFI (3-5 vs 0-2)	7.46	2.11 (1.23, 3.59)	0.006	16.85	2.44 (1.59, 3.73)	<0.0001
mCES-D[c] (< 15 vs >=15)	1.74	1.42 (0.84, 2.40)	0.187	0.35	1.13 (0.75, 1.69)	0.550
Age per Decade	3.23	1.33 (0.97, 1.83)	0.072	7.89	1.42 (1.11, 1.82)	0.005
	C. AIDS Deaths Within 3 Years or Less After FFI Visit			**D. AIDS Deaths Later Than 3 Years After FFI Visit**		
	χ^2	**Multivariate-Adjusted HR[b] (95% CI)**	**P-value**	χ^2	**Multivariate-Adjusted HR[b] (95% CI)**	**P-Value**
mVACS Index per 20	82.38	3.27 (2.53, 4.22)	0.0000	15.49	1.80 (1.34, 2.42)	0.0001
FFI (3-5 vs 0-2)	1.88	1.68 (0.80, 3.54)	0.171	9.28	3.27 (1.53, 7.00)	0.002
mCES-D[c] (< 15 vs >=15)	2.25	1.75 (0.84, 3.64)	0.133	2.13	1.76 (0.82, 3.78)	0.140
Age per Decade	0.001	0.99 (0.64, 1.54)	0.971	0.14	1.10 (0.68, 1.76)	0.710
	E. Non-AIDS Deaths Within 3 Years or Less After FFI Visit			**F. Non-AIDS Deaths Later Than 3 Years After FFI Visit**		
	χ^2	**Multivariate-Adjusted HR[b] (95% CI)**	**P-value**	χ^2	**Multivariate-Adjusted HR[b] (95% CI)**	**P-Value**
mVACS Index per 20	0.87	1.17 (0.84, 1.65)	0.350	6.87	1.45 (1.10, 1.92)	0.009

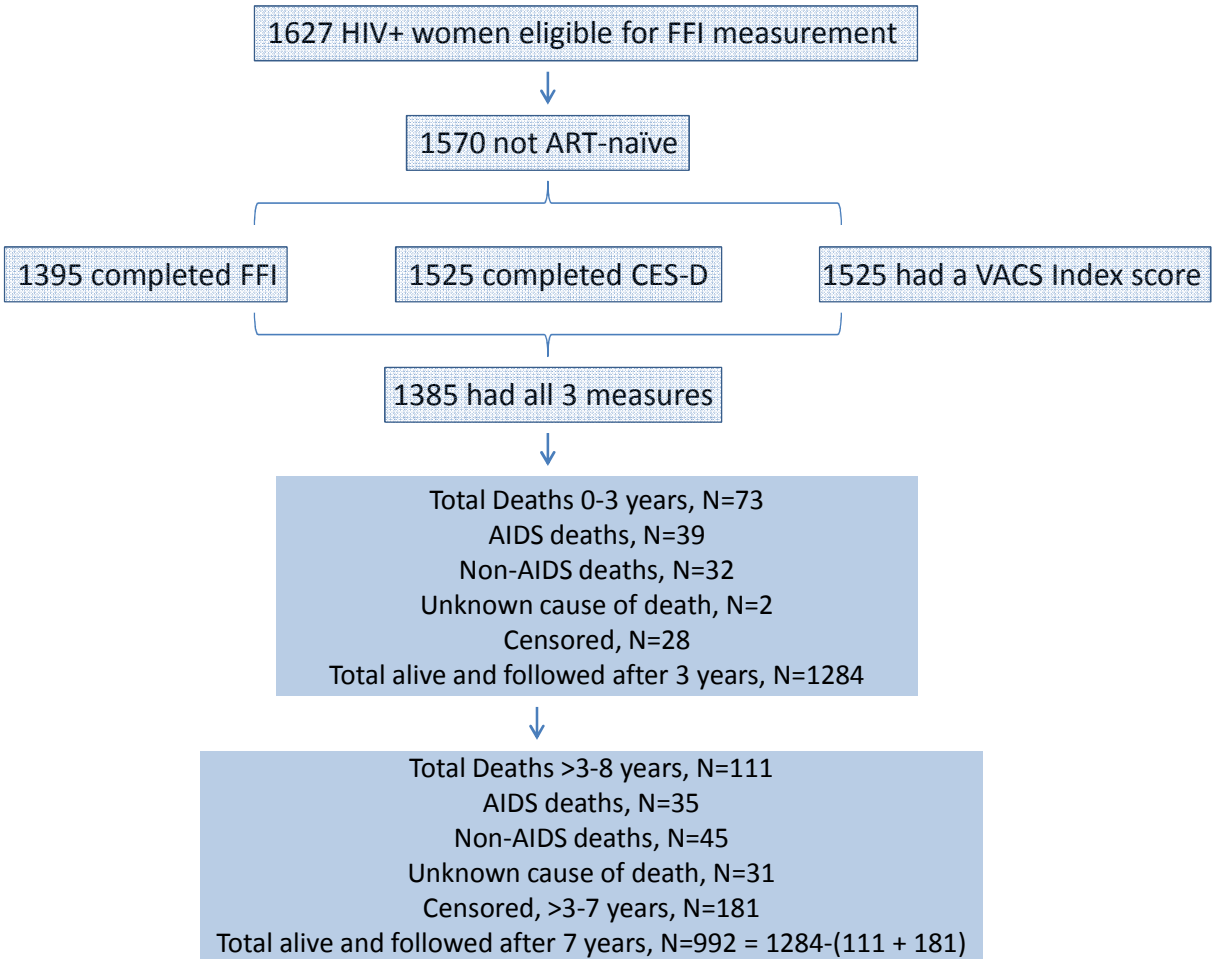
FFI (3-5 vs 0-2)	9.03	3.35 (1.52, 7.35)	0.003	11.66	3.11 (1.62, 5.95)	0.0006
mCES-D[c] (< 15 vs >=15)	0.16	1.17 (0.54, 2.52)	0.690	0.23	0.86 (0.45, 1.62)	0.630
Age per Decade	9.25	2.00 (1.28, 3.14)	0.002	2.89	1.38 (0.95, 2.01)	0.089

[a]mVACS Index score without VACS-specific age strata

[b]Multivariate models included race/ethnicity; education less than or equal to vs greater than high school; smoking current vs no; income less than vs greater than or equal to $12,000 annually; drinking low, moderate or high vs none; and BMI at least than vs less 30 kg/m^2

[c]mCES-D is a CES-D score calculated without inclusion of 2 items that could overlap with FFI

Figure 1. WIHS participants with mVACS, FFI, and mCES-D measured in 2005 and follow-up over approximately 8 years



****All items in the STROBE checklist have been accomplished.**

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Predicting death over 8 years in a prospective cohort of HIV-infected women. The Women's Interagency HIV Study

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ABSTRACT

Objectives. Predicting mortality in middle-aged HIV-infected (HIV+) women on antiretroviral therapies (ART) is important for understanding the impact of HIV infection. Several health indices have been used to predict mortality in women with HIV infection. We evaluated: 1) an HIV biological index, Veterans Aging Cohort Study (VACS); 2) a physical index, Fried Frailty Index (FFI); and 3) a mental health index, Centers for Epidemiologic Studies-Depression (CES-D). Proportional hazards regression analyses were used to predict death and included relevant covariates.

Design. Prospective, observational cohort

Setting. Multicenter, across 6 sites in the United States

Participants. 1385 multirace/ethnic HIV+ women on ART in 2005

Primary and secondary outcomes. All deaths, AIDS-deaths and non-AIDS deaths up to ~8 years from baseline

Results. Included together in one model, VACS Index was the dominant, significant independent predictor of all deaths within 3 years (HR=2.20, 95% CI 1.83, 2.65, χ^2=69.04 , p<0.0001), and later than 3 years (HR=1.55, 95% CI 1.30, 1.84 X^2=23.88, p<0.0001); followed by FFI within 3 years (HR=2.06, 95% CI 1.19, 3.57, χ^2=6.73, p=0.01) and later than 3 years (HR=2.43, 95% CI 1.58, 3.75, X^2=16.18, p=0.0001). CES-D score was not associated with mortality.

Conclusions and Relevance. This is the first simultaneous evaluation of three common health indices in HIV infected adults. Indices reflecting physical and biological aging were associated with death.

Article summary

Strengths and limitations of this study

- Longitudinal cohort study with follow-up of almost 10 years
- Well-phenotyped White, African American and Latina HIV+ women
- Reputable standardized and validated physical, biological and emotional health indices
- Somewhat limited generalizability since a survivor sample of urban women with strong, consistent research study-related HIV care and social support
- Health indices and mortality were examined at mid-life, a period when risk of death is low.

INTRODUCTION

HIV infection continues as a major global health issue affecting approximately 36 million people worldwide. HIV infection has evolved from a fatal infection to a treatable, chronic condition of aging,[1,2] accompanied by multiple morbidities and rising healthcare costs. The North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD), observed that life expectancy of HIV infected (HIV+) adults increased from 36 to 51 years between 2000 and 2007,[3] primarily due to treatment advances. In 2015, over half of HIV+ Americans are ≥50 years old.[3] Therefore, HIV infection may prove to represent a modern-day phenomenon of achieving healthy old age accompanied by improved longevity.

Predicting death in chronic HIV infection may assist in the design of interventions to understand, prevent, cure or minimize age-related impairments, improve health and increase lifespan. Several health indices predict death in adults with HIV infection - the Veterans Aging Cohort Study (VACS) Index; Fried Frailty Index (FFI); and the Centers for Epidemiologic Studies – Depression (CES-D) score. These indices represent biological, physical and mental health vulnerabilities that worsen with age. The only HIV-specific mortality index is the VACS Index, which has been reproduced in North American and European patient populations including Highly Active ART (HAART) users in the Women's Interagency HIV Study (WIHS).[4,5] The VACS Index creates a clinical HIV mortality risk score by summing pre-assigned points for age, routinely monitored indicators of HIV disease and general indicators of organ system function.[5,6] The FFI is most commonly used when describing aging in both general and HIV+ populations.[7,8] Frailty is a common co-morbidity of HIV infection, observed even during middle age.[4,9] The FFI includes measures of gait speed, handgrip strength, body weight loss, physical activity, and exhaustion and predicts death.[10-12] The Centers for Epidemiologic Studies – Depression (CES-D)

score measures mental health[13] and has been independently associated with mortality, particularly among women with HIV infection on HAART in the WIHS.[4]

The objective of our analyses was to evaluate, among HIV+ women, the association of the aforementioned, frequently used health indices: VACS, FFI, and CES-D, with death (both AIDS- and non-AIDS related). All indices were measured in mid-life (average age 39 years) in our analyses and evaluated for prediction of mortality for up to ~8 years. This follow-up period was further broken down into short-term (within 0-3 years) and long-term (>3- ~8 years) deaths, since studies show that prediction of death may vary depending on the exposure being evaluated in relation to more immediate precipitating diseases or conditions versus chronic outcomes.

METHODS

Study Population. WIHS is a prospective, observational cohort suitable to study the intersection of HIV-infection and aging. WIHS participants enrolled at six sites (Bronx/Manhattan, Brooklyn, Chicago, Los Angeles, San Francisco and Washington DC); methods, and baseline cohort characteristics have been described previously.[14] Participants have visits every 6 months, which include an extensive face-to-face interview by trained interviewers, medical examinations, and laboratory specimen collection. Written informed consent was provided by all WIHS participants via human subjects protocols that were approved by institutional review committees at each affiliated institution (Albert Einstein College of Medicine and Montefiore Medical Center Institutional Review Board, #03-07-174; Cook County Bureau of Health Services Institutional Review Board, #15-084; Georgetown University Institutional Review Board Protocol #1993-077; State University of New York - Downstate Medical Center Institutional Review Board,

#266921; University of California San Francisco Committee on Human Research, #1003720; and University of Southern California Institutional Review Board HS-944027.

Of the HIV+ women actively enrolled in 2005, 1395 completed an assessment of the FFI. Of these, 1385 women reported current use of antiretroviral therapy and had measures of both VACS index and CES-D and are included in the current analyses.

Inclusion criteria. Women included in these analyses are members of the WIHS cohort and had to have adequately completed all indices (VACS, FFI, CES-D) in 2005 for evaluation in association with mortality.

Primary outcome. Mortality over the ~8 years, 2005-2013 (also subcategorized into 0-3 and >3 - ~8 years) subsequent to measurement of the aging vulnerability indices, was the primary outcome. The US National Death Index identified numbers and causes of death from Jan 1, 2005 through Dec 31, 2013. Causes of death were subdivided into AIDS and non-AIDS deaths based on consensus opinion from a panel of WIHS investigators.[15] (See Figure 1) AIDS deaths included: pneumonia, PML, PCP, wasting syndrome, CNS lymphoma, candida, CMV, Cryptococcus, toxoplasmosis, TB/mycobacterium, cervical cancer, pulmonary hypertension, dementia/neurologic, renal failure, multi-organ failure and pancreatitis. Non-AIDS deaths included: non-AIDS related malignancy, gastrointestinal, trauma, drug/alcohol overdose, heart disease, lung disease, liver disease, kidney disease, neurologic/stroke, hemorrhage, pneumonia, psychiatric, surgical complication, or pregnancy complication. For some, cause of death could

not be classified as AIDS or non-AIDS, thus the sum of these two subcategories is less that the total number of deaths during the follow-up period.

Primary Predictors of Death. There were three primary predictors of interest: VACS score, FFI, and CES-D score. The VACS Index facilitates a mortality risk score created by summing pre-assigned points for age, routinely monitored indicators of HIV disease (CD4 count and HIV-1 RNA), and viral hepatitis C infection (HCV); and general indicators of organ system injury including hemoglobin, FIB-4, and estimated glomerular filtration rate, eGFR (ml/min). We calculated eGFR based on the CKD-EPI equation.[16] The VACS Index has a maximum score of 164.

The FFI was defined using well-described criteria.[7] A woman was classified as frail if she exhibited three or more of five characteristics: 1) impaired mobility, 2) reduced grip strength, 3) physical exhaustion, 4) unintentional weight loss and 5) low physical activity. At each site, mobility was measured using a 3-4 meter timed gait test, and impaired mobility was defined as the lowest quintile of performance among HIV negatives. Similarly, grip strength was measured using a dominant hand-held dynamometer with maximum force; reduced grip strength was the lowest quintile of performance among HIV negatives. Physical exhaustion was a "Yes" to the question: "During the past four weeks, as a result of your physical health, have you had difficulty performing your work or other activities (for example, it took extra efforts)"? Low physical activity was a "Yes" to "Does your health now limit you in vigorous activities, such as running, lifting heavy objects, or participating in strenuous sports?" Unintentional weight loss was a

"Yes" to: "Since your last visit, have you had unintentional weight loss of at least 10 pounds?" If at least 3 components were available, the total out of 3 (or 4) was calculated.

The 20-item CES-D, is a depressive symptom screening tool comprised of 20 items and totaling 60 points. A cut point of 16 was used to denote a symptom burden of clinical relevance.[17]

Statistical analyses. We used single variable and multivariable proportional hazards models to address the questions of which indices (of FFI, VACS or CES-D), when measured at mid-life in this sample of HIV+ women, best predicted AIDS, non-AIDS and all death. Concordance statistics (C-statistics) were also calculated. Besides FFI, VACS and CES-D, tested covariates were those found to be significant in cross-sectional analyses.[4] These covariates included race/ethnicity, education, smoking, annual income, alcohol drinking, intravenous drug use (IDU) history, body mass index (BMI), prior AIDS defining illness, pneumonia, cancer, diabetes and hypertension. Methods for determining HIV and HCV infection status, Acquired Immunodeficiency Syndrome (AIDS) diagnosis, CD4 cell count, HIV viral load, ART use, and IDU were described previously.[9] In addition, in relation to the health indices, we refit models i) restricting follow up time to the first 3 years after measurement (i.e. censoring at 3 years), and ii) starting follow up time at 3 years after the health indices measurements (i.e. truncating prior to 3 years). In addition, the interaction between FFI and CES-D was considered. Results of proportional hazards regression models are presented as Hazards Ratios (HR) with 95% Confidence Intervals (CI). The χ^2 statistic is also presented to facilitate comparison of strength of association between models since the HR scale of each aging vulnerability index is not the same.

Data analyses were accomplished using SAS 9.4 C-statistics were calculated using STATA Version 12.1.

Modified VACS and CES-D Indices. While not reported here, as a sensitivity analysis, we reran the statistical models using a modified VACS Index and a modified CES-D. Our modified VACS Index did not include VACS age groups in the derivation of total points due to the younger age of our sample (VACS Index lowest age group is <50 years). Thus, a maximum score of 136 was attainable. We then adjusted for age as age decades that reflected our sample as a separate covariate in multivariate analyses. Our modified CES-D score resulted from excluding two CES-D symptoms that overlap with the FFI. The excluded CES-D symptoms were 'this past week I could not get going' (overlaps with low physical activity in the FFI) and 'this past week everything was an effort' (overlaps with exhaustion in the FFI).

RESULTS

Data were available for all indices on 1385 HIV+ women (average age 42.6±8.8 years) who reported ART use. The average VACS score was 28.9 ±19.4 (possible range 0-164); prevalence of frailty (defined as FFI = 3-5) was 17.5%; and 39.1% had a CES-D score of at least 16 points indicating a clinically relevant depressive symptom burden. With regard to calculating the FFI, of 1385 women, 1166 (84.2%) had no missing components, 94 (6.8%) had one missing component and 125 (9.0%) had 2 missing components. The three indices, as well as individual VACS components, demographic/health behavior, infectious disease, chronic aging-related disease variables, number and types of deaths are presented in Table 1. The crude HR (95% CI)

for all deaths by aging vulnerability indices and demographic/health behavior, infectious disease and chronic aging-related disease variables are presented in Table 2.

C-Statistics. When evaluated in multivariable models, worse (higher) FFI, VACS, and CES-D scores were each significantly associated with a more rapid onset of mortality, additive to higher age and several other covariates (Table 3). As a single index added on to demographics, the VACS performed best for all and AIDS deaths, however the FFI was best for non-AIDS deaths. The C-statistics were qualitatively higher for AIDS death reaching 0.89 with demographics and VACS in the model and remaining at 0.89 in the full model than for non-AIDs death which reached 0.80 with VACS and FFI in the model and only improving to 0.81 in the full model.

Using multivariable models that included all indices, we separately evaluated all deaths up to ~8 years from baseline (Table 4) and subdivided by timing of death (short-term, 0 - 3 years *vs* long-term, >3 to ~8 years from baseline, Table 5). We also modeled AIDS and non-AIDS deaths separately over the same time periods. Over the entire follow-up period, FFI was a stronger predictor of non-AIDS deaths than was the VACS Index, while VACS was a stronger predictor of AIDS deaths than was FFI. Yet, all HR were significant for both indices. CES-D was not an independently significant predictor of death.

All deaths. When considering all deaths, within the first 3 years after baseline measurement (Table 5A) the VACS Index was the dominant, significant independent predictor of all deaths (HR=2.20, 95% CI 1.83, 2.65, χ^2=69.04, p<0.0001), followed by FFI (HR=2.06, 95% CI 1.19, 3.57, χ^2=6.73, p=0.01). For deaths occurring later than 3 years after baseline measures (Table

5B), the relative influence of the VACS Index decreased (HR=1.55, 95% CI 1.30, 1.84, χ^2=23.88, p<0.0001), and the FFI increased (HR=2.43, 95% CI 1.58, 3.75, χ^2=16.18, p=0.0001).

AIDS deaths. Within 3 years after baseline (Table 4C), VACS Index was the only statistically significant independent predictor (HR=3.33, 95% CI 2.56, 4.33, χ^2=80.32, p=<0.0001) of AIDS deaths; for AIDS death after 3 years (Table 4D), both VACS Index (HR=1.75, 95% CI 1.31, 2.35, χ^2=13.97 p=0.0002) and FFI (HR=3.38, 95% CI 1.55, 7.37, χ^2=9.40, p=0.002) were independently significant.

Non-AIDS deaths. FFI was the most significant predictor of non-AIDS death both within (Table 5E) (HR=3.37, 95% CI 1.53, 7.40, χ^2=9.15, p=0.003), and later (Table 5F) than 3 years post baseline (HR=3.20, 95% CI 1.66, 6.20, χ^2=11.95, p=0.0005). The VACS Index predicted death later than 3 years (HR=1.41, 95% CI 1.07, 1.86, χ^2=5.84, p=0.016), but was not quite as robust as the FFI.

CES-D score was not an independently significant (at $P < 0.05$) predictor in any AIDS or non-AIDS death model after adjusting for FFI and VACS Index. Also of note, inclusion of ART-naïve participants (n=54, for a total N of 1439), the use of modified VACS and CES-D Indices or including an interaction term for FFI x CES-D as described in the Methods Section in the regression model, did not change our findings.

DISCUSSION

We systematically evaluated the ability of three common indices representing physical, biological and mental health status to predict mortality in women with HIV infection. These

indices - VACS, a biological HIV index; the FFI, a physical index; and the CES-D, a mental health index - were evaluated concurrently in association with mortality over approximately 8 years (and repeated for 0-3 and >3 - ~8 years) among women with HIV infection. Overall, based on comparative $\chi 2$ and C-statistics, the VACS Index was the strongest predictor of death, particularly of AIDS-related deaths and early deaths within 3 years after index assessments. The FFI was additively informative, a better predictor of non-AIDS deaths than the VACS and a relatively more important predictor of deaths from 3 - ~ 8 years after index assessments.

First published in 2003, the FFI has been a useful construct by which to predict poor quality of life, cognitive impairment, dementia and death.[18] Ten years later, the first report on a validated VACS index specific for those with HIV infection was published.[5] The VACS Index has, since then, been used to predict mortality in infected and uninfected populations and has been associated with the FFI.[6] In the WIHS, the VACS Index and CES-D score considered together have been independently reported to predict mortality over a 5 year period.[4] Here we show that with addition of the FFI, these relationships change.

The FFI predicts death, particularly among elderly (65 years and older).[10] More recently the FFI has been measured in younger adult populations who may be at risk for premature or earlier aging, such as those with HIV infection.[6,19] These studies have shown that adults with HIV infection, even in mid-life, experience a prevalence of frailty equivalent to, and greater than, that observed in more elderly adults.[4,9] The reason for this early manifestation of the frailty phenotype may be a consequence of HIV infection itself, including suboptimal medication and control of infection early on, comorbid diseases (infectious or non-infectious)[4,20] and/or other

lifestyle habits that may be common among those with HIV infection, such as smoking and substance use.[11] While interesting, FFI fluctuations cannot be addressed in these analyses, but will be in the future with the re-initiation of FFI assessments in the WIHS in Fall 2015. As the FFI is a marker of the slower process of physical aging, it may continue to be more strongly associated with non-AIDS and later deaths as was seen in this analysis.

The CES-D was significantly associated with death in models that did not adjust for VACS and FFI (HR=2.07, 95% CI 1.55, 2.7, p<0.0001, χ^2=24.0 in Table 2), however it was not associated with death once VACS and FFI indices were included in the same model. Several studies that do not consider FFI and/or VACS, including those from the WIHS, have found CES-D to be a significant "independent" predictor of mortality.[4,15,21-24] This study calls into question whether CES-D is a surrogate for other vulnerabilities rather than being independently and causally associated with death. Other studies or analyses of CES-D in relation to death tend to not include other health indices in their models or only include VACS.[4] It should be noted that modifying the CES-D to exclude two items potentially overlapping with the FFI (low physical activity and exhaustion) did not change the failure of CES-D to be significant in the multivariate models (data not shown). Evaluating vulnerabilities in middle-aged HIV-infected women (the average age of infected women today) is important to understanding the impact of HIV infection on mortality over the life course. This approach has been shown for other diseases of later-life.[25] Midlife physical, biological and/or mental indicators against the background of HIV infection may be associated with earlier death.

Why are multi-dimensional health indices associated with mortality in adults with HIV infection? Throughout adult life, HIV infection is synergistic with adverse aging influences on the immune, vascular, reproductive, and central nervous systems, thereby intensifying the aging process.[26,27] In our previous cross-sectional analysis of the FFI, we showed that the FFI is associated with infectious, demographic, chronic disease, and biological factors, including individual components of the VACS Index,[4] lending support to this observation.

We chose to assess deaths occurring within 3 years versus those occurring ≥ 3 years after the indices were measured. Studies in uninfected populations have shown that deaths occurring within a short period of time (e.g., 3 years) tend to be those due to more rapid biological triggers of death such as infections (e.g., HIV, pneumonia) or other acute illnesses, while longer term deaths reflect delayed consequences of deteriorating biological and physical health.[28] Non-AIDS deaths were predicted by FFI, whether those deaths occurred within versus later than 3 years. VACS was more significant for AIDS deaths and deaths occurring within 3 years. Notably, both VACS and FFI were stronger predictors of death (all, AIDS, non-AIDS) than age and other variables considered in the multivariable models reflecting that these indices, more than age, carried the consequences of deteriorating biological and physical health.

Some limitations of our approach may be that the VACS Index was specifically designed and statistically weighted to predict mortality in HIV infected persons, and that the FFI was designed to be descriptive of a clinically recognizable phenotype. Therefore the VACS Index may be expected to have more explanatory power in multivariate analyses of survival. Furthermore, there exist other frailty measures than FFI that also predict mortality.[29,30] However, the VACS,

FFI and CES-D health indices were selected because they are typically reported in the literature as being predictive of death in HIV+ samples. The point of our analyses was not to identify the best mortality index *de novo*, but rather to systematically compare the three health indices that have been reported in the literature. An additional limitation of these health indices, particularly the FFI, is the blatant lack of standardization across studies. Our goal in these analyses, as aforementioned, was to harmonize the WIHS FFI with that of another large HIV cohort study in the US - the Male Aging Cohort Study (MACS). This will facilitate our future of working together and comparing the natural history of frailty among those with HIV infection by sex and gender. Finally, the WIHS is a prospective cohort study of women (and for these analyses, HIV+ women on ART), with a defined demographic profile (See Table 1). This limits generalizability to other groups with and without HIV infection.

Aging with HIV infection is associated with geriatric morbidities or syndromes, including frailty and other health indices denoting vulnerability,[31] however these aging morbidities often occur earlier among those with HIV infection compared to uninfected individuals.[32-34] The question is whether HIV infection leads to more severe aging phenotypes, or accelerates their onset leading to earlier age of death.[35] These analyses show that two health indices, the VACS (biological) index and the FFI (physical), independently predict mortality in middle-aged women with HIV infection; in particular VACS predicted AIDS death while FFI predicted non-AIDS death. Inclusion of CES-D, a depressive symptom scale, was not independently informative once both the biological and physical health indices were considered. This is the first published report on the simultaneous evaluation of these important indices in association with mortality in women with HIV infection. These analyses point to the importance of designing interventions to address

components of multifaceted indices in the hopes of extending the lifespan of patients living with chronic HIV.

Author Contributions

All authors contributed to this work. Hypothesis generation and manuscript drafting was led by DG and DH; statistical analyses and interpretation was led by DH and QS; participant recruitment and retention were accomplished by the WIHS Principal Investigators, DG, HM, MC, MP, AS, SG, MG, and JM and project staff, SH. Manuscript editing was performed by all.

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Competing Interest

There are no competing interests to declare.

STROBE Criteria

This manuscript meets the STROBE criteria for longitudinal cohort studies.

Data Sharing

Technical appendix, statistical code, and dataset are available from the WIHS Statistical Analysis Center, WD-MAC.

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Table 1. Baseline characteristics of HIV+ WIHS participants who are not ART-naïve

Variables	N (%) or Mean ± SD
Indices	
Fried Frailty Index (FFI)	
0-2 points	1143 (82.5)
3-5 points	242 (17.5)
VACS Index Score	
(0-164 points)	28.9 ±19.4
CES-D score >= 16 points	
No	844 (60.9)
Yes	541 (39.1)
Outcomes	
All Deaths	
3 Years or Less	73 (5.3)
> 3-8 years	111 (8.0)
AIDS deaths[a]	
3 Years or Less	39 (2.8)
> 3-8 years	35 (2.5)
Non-AIDS deaths[a]	
3 Years or Less	32 (2.3)
> 3-8 years	45 (3.2)
HIV variables	
CD4 count (cells/mm3)	
>= 500	554 (40.0)
200-499	614 (44.3)
< 200	217 (15.7)
Viral Load (copies/ml)	
< 500	820 (59.2)
500-100,000	510 (36.8)
>100,000	55 (4.0)
Hemoglobin (g/dl)	
≥14	209 (15.1)
12-13.9	743 (53.6)
10-11.9	362 (26.1)
<10	71 (5.1)
FIB4	
< 1.45	1018 (73.5)
1.45-3.25	280 (20.2)
> 3.25	87 (6.3)
eGFR (ml/min)	
>=60	1277 (92.2)
45-59.9	71 (5.1)
30-44.9	15 (1.1)
< 30	22 (1.6)
Hepatitis C Co-infection	298 (21.5)

Demographic Variables	
Average age (years, mean ± SD)	42.6 ±8.8
Race/Ethnicity	
White	324 (23.4)
Black	806 (58.2)
Others	255 (18.4)
Education	
< High School	536 (38.7)
>= High School	847 (61.2)
Mission	2 (0.1)
Smoking History	
Not current smoking	786 (56.8)
Current smoking	599 (43.2)
Income	
< $12,000	669 (48.3)
>=$12,000	668 (48.2)
Missing	48 (3.5)
Current Alcohol Drinking	
Abstainer/None	743 (53.6)
Low	490 (35.4)
Moderate	129 (9.3)
High	23 (1.7)
Body Mass Index (BMI), kg/m^2	
BMI < 30	916 (66.1)
BMI >=30 (Obesity)	461 (33.3)
Missing	8 (0.6)
Current ART use	
No	400 (28.9)
Yes (HAART)	984 (71.0)
Missing	1 (0.1)
Prior AIDS Defining Illness	
No	802 (57.9)
Yes	583 (42.1)
Injection Drug Use Ever	
Yes	305 (22.0)
No	1071 (77.3)
Missing	9 (0.6)
Prior Pneumonia	
No	1080 (78.0)
Yes	305 (22.0)
Current / Prior Hypertension	
No	964 (69.6)
Yes	421 (30.4)
History of Diabetes	

No	1195 (86.3)
Yes	190 (13.7)
Prior Cancer Diagnosis	
No	1220 (88.1)
Yes	165 (11.9)

[a]For some deaths, cause of death could not be classified as AIDS / non-AIDS, thus the number of AIDS + non-AIDS deaths does not sum to total deaths

Table 2. Proportional Hazards models of time to all deaths by FFI, VACS Index, CES-D, age group, and potential confounders among HIV+ women who are not ART naïve.

Variable	Crude HR (95% CI)	χ^2	P-value
Univariate Analyses of Indices			
VACS Score (0-164), per 20 points	2.20 (1.98, 2.45)	214.6	< 0.0001
FFI 3-5 vs 0-2	3.92 (2.92, 5.26)	83.2	< 0.0001
CES-D (< 16 vs ≥ 16)	2.07 (1.55, 2.77)	24.0	<0.0001
Univariate Analyses of Potential Confounders			
Age per Decade	1.62 (1.38, 1.89)	36.14	<0.0001
Race/ethnicity		8.95 (2 df)	0.011
White vs black	0.55 (0.37, 0.83)	8.02	0.005
Others vs black	0.74 (0.49, 1.11)	2.15	0.140
Education ≥ high school vs < high school	0.68 (0.51, 0.90)	6.96	0.008
Smoking (current vs no)	3.41 (2.49, 4.69)	57.5	<0.0001
Income (< $12,000 vs ≥ $12,000)	2.03 (1.49, 2.77)	19.8	<0.0001
Drinking		27.25 (3 df)	<0.0001
Low vs Abstainer/None	0.59 (0.42, 0.84)	8.59	0.003
Moderate vs Abstainer/None	1.27 (0.82, 1.98)	1.14	0.290
High vs Abstainer/None	3.48 (1.76, 6.87)	12.9	0.0003
BMI, kg/m^2 (>= 30 vs <30)	0.57 (0.41, 0.81)	10.2	0.001

Table 3. Concordance statistics from Proportional hazards models for health indices used to predict death among HIV+ women who were not ART naïve.

Variables	All deaths	AIDS deaths	Non-AIDS deaths
CES-D + VACS Index + FFI + Demographics[a]	0.83	0.89	0.81
VACS Index + FFI + Demographics	0.83	0.89	0.81
VACS Index + CES- D+ Demographics	0.82	0.89	0.78
FFI + CES-D + Demographics	0.78	0.80	0.80
VACS Index + Demographics	0.81	0.89	0.77
FFI + Demographics	0.77	0.78	0.80
CES-D+ Demographics	0.75	0.77	0.75
Demographics Only[*]	0.74	0.74	0.76

[a]Demographic variables included were: age, BMI, race/ethnicity, income, education, cigarette smoking & alcohol use.

Table 4. VACS Index, FFI, and CES-D individually predict time to all, AIDS and non-AIDS deaths over ~8 years follow-up among HIV+ women who are not ART naïve.

All deaths				AIDS deaths			Non-AIDS deaths		
Index	**χ^2**	**HR[a] (95% CI)**	**P-value**	**χ^2**	**HR (95% CI)**	**P-value**	**χ^2**	**HR (95% CI)**	**P-value**
VACS Score (0-164), per 20 points	89.81	1.82 (1.61, 2.06)	<0.0001	94.95	2.52 (2.09, 3.04)	>0.0001	21.22	3.27 (1.97, 5.40)	<0.0001
FFI 3-5 vs 0-2	24.70	2.35 (1.68, 3.28)	<0.0001	8.44	2.27 (1.30, 3.93)	0.004	6.13	1.31 (1.06, 1.62)	0.013
CES-D (< 16 vs ≥ 16)	0.75	1.16 (0.83, 1.60)	0.38	2.04	1.49 (0.86, 2.59)	0.15	0.17	0.90 (0.55, 1.48)	0.68
Age per decade	2.03	1.15 (0.95, 1.39)	0.15	2.88	0.77 (0.56, 1.04)	0.09	7.48	1.50 (1.12, 2.01)	0.006

[a]Multivariate models included race/ethnicity; education less than or equal to vs greater than high school; smoking current vs no; income less than vs greater than or equal to $12,000 annually; drinking low, moderate or high vs none; and BMI at least than vs less 30 kg/m^2

Table 5. Multivariable proportional hazards models of time to all, AIDS and non-AIDS deaths within 3 years vs greater than 3 years by VACS Index, FFI, CES-D and age among HIV+ women who are not ART naïve.

	A. All Deaths Within 3 Years After FFI Visit			B. All Deaths Later Than 3 Years After FFI Visit		
Variable	**χ^2**	**Multivariate-Adjusted HR[a] (95% CI)**	**P-value**	**χ^2**	**Multivariate-Adjusted HR[a] (95% CI)**	**P-Value**
VACS Index per 20 points	69.04	2.20 (1.83, 2.65)	<0.0001	23.88	1.55 (1.30, 1.84)	<0.0001
FFI (3-5 vs 0-2 points)	6.73	2.06 (1.19, 3.57)	0.01	16.18	2.43 (1.58, 3.75)	0.0001
CES-D (< 16 vs >=16 points)	1.01	1.32 (0.77, 2.28)	0.31	0.11	1.07 (0.71, 1.62)	0.74
Age per Decade	0.09	1.05 (0.77, 1.42)	0.76	3.24	1.26 (0.98, 1.61)	0.07
	C. AIDS Deaths Within 3 Years or Less After FFI Visit			**D. AIDS Deaths Later Than 3 Years After FFI Visit**		
	χ^2	**Multivariate-Adjusted HR[a] (95% CI)**	**P-value**	**χ^2**	**Multivariate-Adjusted HR[a] (95% CI)**	**P-Value**
VACS Index per 20 points	80.32	3.33 (2.56, 4.33)	0.0000	13.97	1.75 (1.31, 2.35)	0.0002
FFI (3-5 vs 0-2 points)	0.88	1.45 (0.67, 3.14)	0.34	9.40	3.38 (1.55, 7.37)	0.002
CES-D (< 16 vs >=16 points)	1.96	1.73 (0.80, 3.73)	0.17	0.81	1.43 (0.65, 3.14)	0.37
Age per Decade	2.42	0.72 (0.47, 1.09)	0.12	0.09	0.93 (0.58, 1.50)	0.77

	E. Non-AIDS Deaths Within 3 Years or Less After FFI Visit			F. Non-AIDS Deaths Later Than 3 Years After FFI Visit		
	χ^2	Multivariate-Adjusted HR[a] (95% CI)	P-value	χ^2	Multivariate-Adjusted HR[a] (95% CI)	P-Value
VACS Index per 20 points	0.80	1.16 (0.83, 1.62)	0.37	5.84	1.41 (1.07, 1.86)	0.016
FFI (3-5 vs 0-2 points)	9.15	3.37 (1.53, 7.40)	0.003	11.95	3.20 (1.66, 6.20)	0.0005
CES-D (< 16 vs >=16 points)	0.15	1.17 (0.54, 2.54)	0.70	0.60	0.77 (0.40, 1.48)	0.44
Age per Decade	7.43	1.90 (1.20, 3.02)	0.006	1.44	1.26 (0.86, 1.84)	0.23

[a]Multivariate models included race/ethnicity; education less than or equal to vs greater than high school; smoking current vs no; income less than vs greater than or equal to $12,000 annually; drinking low, moderate or high vs none; and BMI at least than vs less 30 kg/m^2

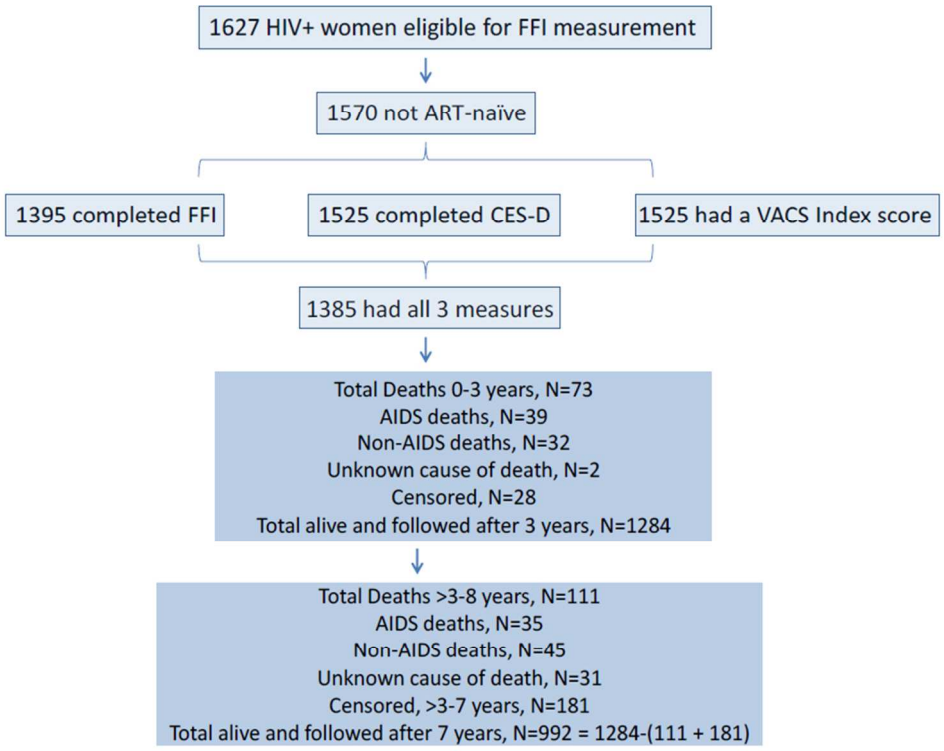

Figure 1. WIHS participants with the VACS Index, FFI, and CES-D measured in 2005 and follow-up over approximately 8 years.

245x183mm (96 x 96 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

All items in the STROBE checklist are accomplished, see page numbers by items listed below.

	Item No & Page#	Recommendation
Title and abstract	1, P1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
	P3	(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2, P5-6	Explain the scientific background and rationale for the investigation being reported
Objectives	3, P6	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4, P6	Present key elements of study design early in the paper
Setting	5, P6-9	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6, P6-7	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7, P7-9	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*, P7-9	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias, NA
Study size	10, P7	Explain how the study size was arrived at
Quantitative variables	11, P9-10	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
	P9-10	(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed, NA
		(*d*) *Cohort study*—If applicable, explain loss to follow-up was addressed, NA *Case-control study*—If applicable, explain how matching of cases and controls was addressed, NA *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy, NA
	P10	(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13*, P31	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage, NA
	P31	(c) Consider use of a flow diagram
Descriptive data	14*, P23-25	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest, NA
	P31	(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*, P7-9, P31	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure, NA
		Cross-sectional study—Report numbers of outcome events or summary measures, NA
Main results	16, P10-13	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
	P8-9	(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period, NA
Other analyses	17, P11	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18, P12-13	Summarise key results with reference to study objectives
Limitations	19, P15-16	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20, P12-17	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21, P4, P12-17	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22, P17-18	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Predicting death over 8 years in a prospective cohort of HIV-infected women. The Women's Interagency HIV Study

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Predicting death over 8 years in a prospective cohort of HIV-infected women. The Women's Interagency HIV Study

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ABSTRACT

Objectives. Predicting mortality in middle-aged HIV-infected (HIV+) women on antiretroviral therapies (ART) is important for understanding the impact of HIV infection. Several health indices have been used to predict mortality in women with HIV infection. We evaluated: 1) an HIV biological index, Veterans Aging Cohort Study (VACS); 2) a physical index, Fried Frailty Index (FFI); and 3) a mental health index, Centers for Epidemiologic Studies-Depression (CES-D). Proportional hazards regression analyses were used to predict death and included relevant covariates.

Design. Prospective, observational cohort

Setting. Multicenter, across 6 sites in the United States

Participants. 1385 multirace/ethnic HIV+ women on ART in 2005

Primary and secondary outcomes. All deaths, AIDS-deaths and non-AIDS deaths up to ~8 years from baseline

Results. Included together in one model, VACS Index was the dominant, significant independent predictor of all deaths within 3 years (HR=2.20, 95% CI 1.83, 2.65, χ^2=69.04 , p<0.0001), and later than 3 years (HR=1.55, 95% CI 1.30, 1.84 X^2=23.88, p<0.0001); followed by FFI within 3 years (HR=2.06, 95% CI 1.19, 3.57, χ^2=6.73, p=0.01) and later than 3 years (HR=2.43, 95% CI 1.58, 3.75, X^2=16.18, p=0.0001). CES-D score was not associated with mortality.

Conclusions and Relevance. This is the first simultaneous evaluation of three common health indices in HIV infected adults. Indices reflecting physical and biological aging were associated with death.

Article summary

Strengths and limitations of this study

- Longitudinal cohort study with follow-up of almost 10 years
- Well-phenotyped White, African American and Latina HIV+ women
- Reputable standardized and validated physical, biological and emotional health indices
- Somewhat limited generalizability since a survivor sample of urban women with strong, consistent research study-related HIV care and social support
- Health indices and mortality were examined at mid-life, a period when risk of death is low.

INTRODUCTION

HIV infection continues as a major global health issue affecting approximately 36 million people worldwide. HIV infection has evolved from a fatal infection to a treatable, chronic condition of aging,[1,2] accompanied by multiple morbidities and rising healthcare costs. The North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD), observed that life expectancy of HIV infected (HIV+) adults increased from 36 to 51 years between 2000 and 2007,[3] primarily due to treatment advances. In 2015, over half of HIV+ Americans are ≥50 years old.[3] Therefore, HIV infection may prove to represent a modern-day phenomenon of achieving healthy old age accompanied by improved longevity.

Predicting death in chronic HIV infection may assist in the design of interventions to understand, prevent, cure or minimize age-related impairments, improve health and increase lifespan. Several health indices predict death in adults with HIV infection - the Veterans Aging Cohort Study (VACS) Index; Fried Frailty Index (FFI); and the Centers for Epidemiologic Studies – Depression (CES-D) score. These indices represent biological, physical and mental health vulnerabilities that worsen with age. The only HIV-specific mortality index is the VACS Index, which has been reproduced in North American and European patient populations including Highly Active ART (HAART) users in the Women's Interagency HIV Study (WIHS).[4,5] The VACS Index creates a clinical HIV mortality risk score by summing pre-assigned points for age, routinely monitored indicators of HIV disease and general indicators of organ system function.[5,6] The FFI is most commonly used when describing aging in both general and HIV+ populations.[7,8] Frailty is a common co-morbidity of HIV infection, observed even during middle age.[4,9] The FFI includes measures of gait speed, handgrip strength, body weight loss, physical activity, and exhaustion and predicts death.[10-12] The Centers for Epidemiologic Studies – Depression (CES-D)

score measures mental health[13] and has been independently associated with mortality, particularly among women with HIV infection on HAART in the WIHS.[4]

The objective of our analyses was to evaluate, among HIV+ women, the association of the aforementioned, frequently used health indices: VACS, FFI, and CES-D, with death (both AIDS- and non-AIDS related). All indices were measured in mid-life (average age 39 years) in our analyses and evaluated for prediction of mortality for up to ~8 years. This follow-up period was further broken down into short-term (within 0-3 years) and long-term (>3- ~8 years) deaths, since studies show that prediction of death may vary depending on the exposure being evaluated in relation to more immediate precipitating diseases or conditions versus chronic outcomes.

METHODS

Study Population. WIHS is a prospective, observational cohort suitable to study the intersection of HIV-infection and aging. WIHS participants enrolled at six sites (Bronx/Manhattan, Brooklyn, Chicago, Los Angeles, San Francisco and Washington DC); methods, and baseline cohort characteristics have been described previously.[14] Participants have visits every 6 months, which include an extensive face-to-face interview by trained interviewers, medical examinations, and laboratory specimen collection. Written informed consent was provided by all WIHS participants via human subjects protocols that were approved by institutional review committees at each affiliated institution (Albert Einstein College of Medicine and Montefiore Medical Center Institutional Review Board, #03-07-174; Cook County Bureau of Health Services Institutional Review Board, #15-084; Georgetown University Institutional Review Board Protocol #1993-077; State University of New York - Downstate Medical Center Institutional Review Board,

#266921; University of California San Francisco Committee on Human Research, #1003720; and University of Southern California Institutional Review Board HS-944027.)

Of the HIV+ women actively enrolled in 2005, 1395 completed an assessment of the FFI. Of these, 1385 women reported current use of antiretroviral therapy and had measures of both VACS index and CES-D and are included in the current analyses.

Inclusion criteria. Women included in these analyses are members of the WIHS cohort and had to have adequately completed all indices (VACS, FFI, CES-D) in 2005 for evaluation in association with mortality.

Primary outcome. Mortality over the ~8 years, 2005-2013 (also subcategorized into 0-3 and >3 - ~8 years) subsequent to measurement of the aging vulnerability indices, was the primary outcome. The US National Death Index identified numbers and causes of death from Jan 1, 2005 through Dec 31, 2013. Causes of death were subdivided into AIDS and non-AIDS deaths based on consensus opinion from a panel of WIHS investigators.[15] (See Figure 1) AIDS deaths included: pneumonia, PML, PCP, wasting syndrome, CNS lymphoma, candida, CMV, Cryptococcus, toxoplasmosis, TB/mycobacterium, cervical cancer, pulmonary hypertension, dementia/neurologic, renal failure, multi-organ failure and pancreatitis. Non-AIDS deaths included: non-AIDS related malignancy, gastrointestinal, trauma, drug/alcohol overdose, heart disease, lung disease, liver disease, kidney disease, neurologic/stroke, hemorrhage, pneumonia, psychiatric, surgical complication, or pregnancy complication. For some, cause of death could

not be classified as AIDS or non-AIDS, thus the sum of these two subcategories is less that the total number of deaths during the follow-up period.

Primary Predictors of Death. There were three primary predictors of interest: VACS score, FFI, and CES-D score. The VACS Index facilitates a mortality risk score created by summing pre-assigned points for age, routinely monitored indicators of HIV disease (CD4 count and HIV-1 RNA), and viral hepatitis C infection (HCV); and general indicators of organ system injury including hemoglobin, FIB-4, and estimated glomerular filtration rate, eGFR (ml/min). We calculated eGFR based on the CKD-EPI equation.[16] The VACS Index has a maximum score of 164.

The FFI was defined using well-described criteria.[7] A woman was classified as frail if she exhibited three or more of five characteristics: 1) impaired mobility, 2) reduced grip strength, 3) physical exhaustion, 4) unintentional weight loss and 5) low physical activity. At each site, mobility was measured using a 3-4 meter timed gait test, and impaired mobility was defined as the lowest quintile of performance among HIV negatives. Similarly, grip strength was measured using a dominant hand-held dynamometer with maximum force; reduced grip strength was the lowest quintile of performance among HIV negatives. Physical exhaustion was a "Yes" to the question: "During the past four weeks, as a result of your physical health, have you had difficulty performing your work or other activities (for example, it took extra efforts)"? Low physical activity was a "Yes" to "Does your health now limit you in vigorous activities, such as running, lifting heavy objects, or participating in strenuous sports?" Unintentional weight loss was a

"Yes" to: "Since your last visit, have you had unintentional weight loss of at least 10 pounds?" If at least 3 components were available, the total out of 3 (or 4) was calculated.

The 20-item CES-D, is a depressive symptom screening tool comprised of 20 items and totaling 60 points. A cut point of 16 was used to denote a symptom burden of clinical relevance.[17]

Statistical analyses. We used single variable and multivariable proportional hazards models to address the questions of which indices (of FFI, VACS or CES-D), when measured at mid-life in this sample of HIV+ women, best predicted AIDS, non-AIDS and all death. Concordance statistics (C-statistics) were also calculated. The C-statistic for time to event outcomes is equivalent to the area under the Receiver Operating Characteristic (ROC) curve for standard binomial outcomes (range 0.5-1.0). It describes the probability of death associated with a higher health index score or combination of higher health index scores in a randomly selected participant compared to those who do not die.[18] Besides FFI, VACS and CES-D, tested covariates were those found to be significant in cross-sectional analyses.[4] These covariates included race/ethnicity, education, smoking, annual income, alcohol drinking, intravenous drug use (IDU) history, body mass index (BMI), prior AIDS defining illness, pneumonia, cancer, diabetes and hypertension. Methods for determining HIV and HCV infection status, Acquired Immunodeficiency Syndrome (AIDS) diagnosis, CD4 cell count, HIV viral load, ART use, and IDU were described previously.[9] In addition, in relation to the health indices, we refit models i) restricting follow up time to the first 3 years after measurement (i.e. censoring at 3 years), and ii) starting follow up time at 3 years after the health indices measurements (i.e. truncating prior to 3 years). In addition, the interaction between FFI and CES-D was considered. Results of

proportional hazards regression models are presented as Hazards Ratios (HR) with 95% Confidence Intervals (CI). The χ^2 statistic is also presented to facilitate comparison of strength of association between models since the HR scale of each aging vulnerability index is not the same. Data analyses were accomplished using SAS 9.4. C-statistics were calculated using STATA Version 12.1.

Modified VACS and CES-D Indices. While not reported here, as a sensitivity analysis, we reran the statistical models using a modified VACS Index and a modified CES-D. Our modified VACS Index did not include VACS age groups in the derivation of total points due to the younger age of our sample (VACS Index lowest age group is <50 years). Thus, a maximum score of 136 was attainable. We then adjusted for age as age decades that reflected our sample as a separate covariate in multivariate analyses. Our modified CES-D score resulted from excluding two CES-D symptoms that overlap with the FFI. The excluded CES-D symptoms were 'this past week I could not get going' (overlaps with low physical activity in the FFI) and 'this past week everything was an effort' (overlaps with exhaustion in the FFI).

RESULTS

Data were available for all indices on 1385 HIV+ women (average age 42.6±8.8 years) who reported ART use. The average VACS score was 28.9 ±19.4 (possible range 0-164); prevalence of frailty (defined as FFI = 3-5) was 17.5%; and 39.1% had a CES-D score of at least 16 points indicating a clinically relevant depressive symptom burden. With regard to calculating the FFI, of 1385 women, 1166 (84.2%) had no missing components, 94 (6.8%) had one missing component and 125 (9.0%) had 2 missing components. The three indices, as well as individual

VACS components, demographic/health behavior, infectious disease, chronic aging-related disease variables, number and types of deaths are presented in Table 1. The crude HR (95% CI) for all deaths by aging vulnerability indices and demographic/health behavior, infectious disease and chronic aging-related disease variables are presented in Table 2.

C-Statistics. When evaluated in multivariable models, worse (higher) FFI, VACS, and CES-D scores were each significantly associated with a more rapid onset of mortality, additive to higher age and several other covariates (Table 3). As a single index added on to demographics, the VACS performed best for all and AIDS deaths, however the FFI was best for non-AIDS deaths. The C-statistics were qualitatively higher for AIDS death reaching 0.89 with demographics and VACS in the model and remaining at 0.89 in the full model than for non-AIDs death which reached 0.80 with VACS and FFI in the model and only improving to 0.81 in the full model.

Using multivariable models that included all indices, we separately evaluated all deaths up to ~8 years from baseline (Table 4) and subdivided by timing of death (short-term, 0 - 3 years *vs* long-term, >3 to ~8 years from baseline, Table 5). We also modeled AIDS and non-AIDS deaths separately over the same time periods. Over the entire follow-up period, FFI was a stronger predictor of non-AIDS deaths than was the VACS Index, while VACS was a stronger predictor of AIDS deaths than was FFI. Yet, all HR were significant for both indices. CES-D was not an independently significant predictor of death.

All deaths. When considering all deaths, within the first 3 years after baseline measurement (Table 5A) the VACS Index was the dominant, significant independent predictor of all deaths

(HR=2.20, 95% CI 1.83, 2.65, χ^2=69.04, p<0.0001), followed by FFI (HR=2.06, 95% CI 1.19, 3.57, χ^2=6.73, p=0.01). For deaths occurring later than 3 years after baseline measures (Table 5B), the relative influence of the VACS Index decreased (HR=1.55, 95% CI 1.30, 1.84, χ^2=23.88, p<0.0001), and the FFI increased (HR=2.43, 95% CI 1.58, 3.75, χ^2=16.18, p=0.0001).

AIDS deaths. Within 3 years after baseline (Table 5C), VACS Index was the only statistically significant independent predictor (HR=3.33, 95% CI 2.56, 4.33, χ^2=80.32, p<0.0001) of AIDS deaths; for AIDS death after 3 years (Table 5D), both VACS Index (HR=1.75, 95% CI 1.31, 2.35, χ^2=13.97 p=0.0002) and FFI (HR=3.38, 95% CI 1.55, 7.37, χ^2=9.40, p=0.002) were independently significant.

Non-AIDS deaths. FFI was the most significant predictor of non-AIDS death both within (Table 5E) (HR=3.37, 95% CI 1.53, 7.40, χ^2=9.15, p=0.003), and later (Table 5F) than 3 years post baseline (HR=3.20, 95% CI 1.66, 6.20, χ^2=11.95, p=0.0005). The VACS Index predicted death later than 3 years (HR=1.41, 95% CI 1.07, 1.86, χ^2=5.84, p=0.016), but was not quite as robust as the FFI.

CES-D score was not an independently significant (at P < 0.05) predictor in any AIDS or non-AIDS death model after adjusting for FFI and VACS Index. Also of note, inclusion of ART-naïve participants (n=54, for a total N of 1439), the use of modified VACS and CES-D Indices or including an interaction term for FFI x CES-D as described in the Methods Section in the regression model, did not change our findings.

DISCUSSION

We systematically evaluated the ability of three common indices representing physical, biological and mental health status to predict mortality in women with HIV infection. These indices - VACS, a biological HIV index; the FFI, a physical index; and the CES-D, a mental health index - were evaluated concurrently in association with mortality over approximately 8 years (and repeated for 0-3 and >3 - ~8 years) among women with HIV infection. Overall, based on comparative $\chi 2$ and C-statistics, the VACS Index was the strongest predictor of death, particularly of AIDS-related deaths and early deaths within 3 years after index assessments. The FFI was additively informative, a better predictor of non-AIDS deaths than the VACS and a relatively more important predictor of deaths from 3 - ~ 8 years after index assessments.

First published in 2003, the FFI has been a useful construct by which to predict poor quality of life, cognitive impairment, dementia and death.[19] Ten years later, the first report on a validated VACS index specific for those with HIV infection was published.[5] The VACS Index has, since then, been used to predict mortality in infected and uninfected populations and has been associated with the FFI.[6] In the WIHS, the VACS Index and CES-D score considered together have been independently reported to predict mortality over a 5 year period.[4] Here we show that with addition of the FFI, these relationships change.

The FFI predicts death, particularly among elderly (65 years and older).[10] More recently the FFI has been measured in younger adult populations who may be at risk for premature or earlier aging, such as those with HIV infection.[6,20] These studies have shown that adults with HIV infection, even in mid-life, experience a prevalence of frailty equivalent to, and greater than, that

observed in more elderly adults.[4,9] The reason for this early manifestation of the frailty phenotype may be a consequence of HIV infection itself, including suboptimal medication and control of infection early on, comorbid diseases (infectious or non-infectious)[4,21] and/or other lifestyle habits that may be common among those with HIV infection, such as smoking and substance use.[11] While interesting, FFI fluctuations cannot be addressed in these analyses, but will be in the future with the re-initiation of FFI assessments in the WIHS in Fall 2015. As the FFI is a marker of the slower process of physical aging, it may continue to be more strongly associated with non-AIDS and later deaths as was seen in this analysis.

The CES-D was significantly associated with death in models that did not adjust for VACS and FFI (HR=2.07, 95% CI 1.55, 2.7, $p<0.0001$, $\chi^2=24.0$ in Table 2), however it was not associated with death once VACS and FFI indices were included in the same model. Several studies that do not consider FFI and/or VACS, including those from the WIHS, have found CES-D to be a significant "independent" predictor of mortality.[4,15,22-25] This study calls into question whether CES-D is a surrogate for other vulnerabilities rather than being independently and causally associated with death. Other studies or analyses of CES-D in relation to death tend to not include other health indices in their models or only include VACS.[4] It should be noted that modifying the CES-D to exclude two items potentially overlapping with the FFI (low physical activity and exhaustion) did not change the failure of CES-D to be significant in the multivariate models (data not shown). Evaluating vulnerabilities in middle-aged HIV-infected women (the average age of infected women today) is important to understanding the impact of HIV infection on mortality over the life course. This approach has been shown for other diseases of later-life.[26]

Midlife physical, biological and/or mental indicators against the background of HIV infection may be associated with earlier death.

Why are multi-dimensional health indices associated with mortality in adults with HIV infection? Throughout adult life, HIV infection is synergistic with adverse aging influences on the immune, vascular, reproductive, and central nervous systems, thereby intensifying the aging process.[27,28] In our previous cross-sectional analysis of the FFI, we showed that the FFI is associated with infectious, demographic, chronic disease, and biological factors, including individual components of the VACS Index,[4] lending support to this observation.

We chose to assess deaths occurring within 3 years versus those occurring ≥ 3 years after the indices were measured. Studies in uninfected populations have shown that deaths occurring within a short period of time (e.g., 3 years) tend to be those due to more rapid biological triggers of death such as infections (e.g., HIV, pneumonia) or other acute illnesses, while longer term deaths reflect delayed consequences of deteriorating biological and physical health.[29] Non-AIDS deaths were predicted by FFI, whether those deaths occurred within versus later than 3 years. VACS was more significant for AIDS deaths and deaths occurring within 3 years. Notably, both VACS and FFI were stronger predictors of death (all, AIDS, non-AIDS) than age and other variables considered in the multivariable models reflecting that these indices, more than age, carried the consequences of deteriorating biological and physical health.

Some limitations of our approach may be that the VACS Index was specifically designed and statistically weighted to predict mortality in HIV infected persons, and that the FFI was designed

to be descriptive of a clinically recognizable phenotype. Therefore the VACS Index may be expected to have more explanatory power in multivariate analyses of survival. Furthermore, there exist other frailty measures than FFI that also predict mortality.[30,31] However, the VACS, FFI and CES-D health indices were selected because they are typically reported in the literature as being predictive of death in HIV+ samples. The point of our analyses was not to identify the best mortality index *de novo*, but rather to systematically compare the three health indices that have been reported in the literature. An additional limitation of these health indices, particularly the FFI, is the blatant lack of standardization across studies. Our goal in these analyses, as aforementioned, was to harmonize the WIHS FFI with that of another large HIV cohort study in the US - the Male Aging Cohort Study (MACS). This will facilitate our future of working together and comparing the natural history of frailty among those with HIV infection by sex and gender. Finally, the WIHS is a prospective cohort study of women (and for these analyses, HIV+ women on ART), with a defined demographic profile (See Table 1). This limits generalizability to other groups with and without HIV infection.

Aging with HIV infection is associated with geriatric morbidities or syndromes, including frailty and other health indices denoting vulnerability,[32] however these aging morbidities often occur earlier among those with HIV infection compared to uninfected individuals.[33-36] The question is whether HIV infection leads to more severe aging phenotypes, or accelerates their onset leading to earlier age of death.[37] These analyses show that two health indices, the VACS (biological) index and the FFI (physical), independently predict mortality in middle-aged women with HIV infection; in particular VACS predicted AIDS death while FFI predicted non-AIDS death. Inclusion of CES-D, a depressive symptom scale, was not independently informative once both

the biological and physical health indices were considered. This is the first published report on the simultaneous evaluation of these important indices in association with mortality in women with HIV infection. These analyses point to the importance of designing interventions to address components of multifaceted indices in the hopes of extending the lifespan of patients living with chronic HIV.

Author Contributions

All authors contributed to this work. Hypothesis generation and manuscript drafting was led by DRG, DRH, and RH; statistical analyses and interpretation were led by DRH and QS; data base management was led by SG; participant recruitment and retention and collection of site-specific health indices, covariates and outcomes data, were actively accomplished by the WIHS Principal Investigators, DRG, HM, MHC, MWP, AS, MG, and JM and project staff, SH. Attainment of funding and manuscript editing was performed by all.

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Competing Interest

There are no competing interests to declare.

STROBE Criteria

This manuscript meets the STROBE criteria for longitudinal cohort studies.

Data Sharing

Technical appendix, statistical code, and dataset are available from the WIHS Statistical Analysis Center, WD-MAC.

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Figure 1. WIHS participants with the VACS Index, FFQ, and CES-D measured in 2005 and follow-up over approximately 8 years.

Table 1. Baseline characteristics of HIV+ WIHS participants who are not ART-naïve

Variables	N (%) or Mean ± SD
Indices	
Fried Frailty Index (FFI)	
0-2 points	1143 (82.5)
3-5 points	242 (17.5)
VACS Index Score	
(0-164 points)	28.9 ±19.4
CES-D score ≥ 16 points	
No	844 (60.9)
Yes	541 (39.1)
Outcomes	
All Deaths	
3 Years or Less	73 (5.3)
> 3-8 years	111 (8.0)
AIDS deaths[a]	
3 Years or Less	39 (2.8)
> 3-8 years	35 (2.5)
Non-AIDS deaths[a]	
3 Years or Less	32 (2.3)
> 3-8 years	45 (3.2)
HIV variables	
CD4 count (cells/mm3)	
≥ 500	554 (40.0)
200-499	614 (44.3)
< 200	217 (15.7)
Viral Load (copies/ml)	
< 500	820 (59.2)
500-100,000	510 (36.8)
>100,000	55 (4.0)
Hemoglobin (g/dl)	
≥ 14	209 (15.1)
12-13.9	743 (53.6)
10-11.9	362 (26.1)
<10	71 (5.1)
FIB4	
< 1.45	1018 (73.5)
1.45-3.25	280 (20.2)
> 3.25	87 (6.3)
eGFR (ml/min)	
≥ 60	1277 (92.2)
45-59.9	71 (5.1)
30-44.9	15 (1.1)
< 30	22 (1.6)
Hepatitis C Co-infection	298 (21.5)

Demographic Variables	
Average age (years, mean ± SD)	42.6 ±8.8
Race/Ethnicity	
White	324 (23.4)
Black	806 (58.2)
Others	255 (18.4)
Education	
< High School	536 (38.7)
≥ High School	847 (61.2)
Mission	2 (0.1)
Smoking History	
Not current smoking	786 (56.8)
Current smoking	599 (43.2)
Income	
< $12,000	669 (48.3)
≥ $12,000	668 (48.2)
Missing	48 (3.5)
Current Alcohol Drinking	
Abstainer/None	743 (53.6)
Low	490 (35.4)
Moderate	129 (9.3)
High	23 (1.7)
Body Mass Index (BMI), kg/m^2	
BMI < 30	916 (66.1)
BMI ≥ 30 (Obesity)	461 (33.3)
Missing	8 (0.6)
Current ART use	
No	400 (28.9)
Yes (HAART)	984 (71.0)
Missing	1 (0.1)
Prior AIDS Defining Illness	
No	802 (57.9)
Yes	583 (42.1)
Injection Drug Use Ever	
Yes	305 (22.0)
No	1071 (77.3)
Missing	9 (0.6)
Prior Pneumonia	
No	1080 (78.0)
Yes	305 (22.0)
Current / Prior Hypertension	
No	964 (69.6)
Yes	421 (30.4)
History of Diabetes	

No	1195 (86.3)
Yes	190 (13.7)
Prior Cancer Diagnosis	
No	1220 (88.1)
Yes	165 (11.9)

[a]For some deaths, cause of death could not be classified as AIDS / non-AIDS, thus the numbers of AIDS + non-AIDS deaths do not sum to total deaths

Table 2. Proportional Hazards models of time to all deaths by FFI, VACS Index, CES-D, age group, and potential confounders among HIV+ women who are not ART naïve.

Variable	Crude HR (95% CI)	χ^2	P-value
Univariate Analyses of Indices			
VACS Score (0-164), per 20 points	2.20 (1.98, 2.45)	214.6	< 0.0001
FFI 3-5 vs 0-2	3.92 (2.92, 5.26)	83.2	< 0.0001
CES-D (< 16 vs ≥ 16)	2.07 (1.55, 2.77)	24.0	<0.0001
Univariate Analyses of Potential Confounders			
Age per Decade	1.62 (1.38, 1.89)	36.14	<0.0001
Race/ethnicity		8.95 (2 df)	0.011
White vs black	0.55 (0.37, 0.83)	8.02	0.005
Others vs black	0.74 (0.49, 1.11)	2.15	0.140
Education ≥ high school vs < high school	0.68 (0.51, 0.90)	6.96	0.008
Smoking (current vs no)	3.41 (2.49, 4.69)	57.5	<0.0001
Income (< $12,000 vs ≥ $12,000)	2.03 (1.49, 2.77)	19.8	<0.0001
Drinking		27.25 (3 df)	<0.0001
Low vs Abstainer/None	0.59 (0.42, 0.84)	8.59	0.003
Moderate vs Abstainer/None	1.27 (0.82, 1.98)	1.14	0.290
High vs Abstainer/None	3.48 (1.76, 6.87)	12.9	0.0003
BMI, kg/m^2 (≥ 30 vs <30)	0.57 (0.41, 0.81)	10.2	0.001

Table 3. Concordance statistics from Proportional hazards models for health indices used to predict death among HIV+ women who were not ART naïve.

Variables	All deaths	AIDS deaths	Non-AIDS deaths
CES-D + VACS Index + FFI + Demographics[a]	0.83	0.89	0.81
VACS Index + FFI + Demographics	0.83	0.89	0.81
VACS Index + CES- D + Demographics	0.82	0.89	0.78
FFI + CES-D + Demographics	0.78	0.80	0.80
VACS Index + Demographics	0.81	0.89	0.77
FFI + Demographics	0.77	0.78	0.80
CES-D + Demographics	0.75	0.77	0.75
Demographics Only*	0.74	0.74	0.76

[a]Demographic variables included were: age, BMI, race/ethnicity, income, education, cigarette smoking & alcohol use.

Table 4. VACS Index, FFI, and CES-D individually predict time to all, AIDS and non-AIDS deaths over ~8 years follow-up among HIV+ women who are not ART naïve.

All deaths				AIDS deaths			Non-AIDS deaths		
Index	χ^2	HR[a] (95% CI)	P-value	χ^2	HR (95% CI)	P-value	χ^2	HR (95% CI)	P-value
VACS Score (0-164), per 20 points	89.81	1.82 (1.61, 2.06)	<0.0001	94.95	2.52 (2.09, 3.04)	>0.0001	21.22	3.27 (1.97, 5.40)	<0.0001
FFI 3-5 vs 0-2	24.70	2.35 (1.68, 3.28)	<0.0001	8.44	2.27 (1.30, 3.93)	0.004	6.13	1.31 (1.06, 1.62)	0.013
CES-D (< 16 vs ≥ 16)	0.75	1.16 (0.83, 1.60)	0.38	2.04	1.49 (0.86, 2.59)	0.15	0.17	0.90 (0.55, 1.48)	0.68
Age per decade	2.03	1.15 (0.95, 1.39)	0.15	2.88	0.77 (0.56, 1.04)	0.09	7.48	1.50 (1.12, 2.01)	0.006

[a]Multivariate models included race/ethnicity; education less than or equal to vs greater than high school; smoking current vs no; income less than vs greater than or equal to $12,000 annually; alcohol use: low, moderate or high vs none; and BMI at least than vs less 30 kg/m^2

Table 5. Multivariable proportional hazards models of time to all, AIDS and non-AIDS deaths within 3 years vs greater than 3 years by VACS Index, FFI, CES-D and age among HIV+ women who are not ART naïve.

	A. All Deaths Within 3 Years After FFI Visit			B. All Deaths Later Than 3 Years After FFI Visit		
Variable	**χ^2**	**Multivariate-Adjusted HR[a] (95% CI)**	**P-value**	**χ^2**	**Multivariate-Adjusted HR[a] (95% CI)**	**P-Value**
VACS Index per 20 points	69.04	2.20 (1.83, 2.65)	<0.0001	23.88	1.55 (1.30, 1.84)	<0.0001
FFI (3-5 vs 0-2 points)	6.73	2.06 (1.19, 3.57)	0.01	16.18	2.43 (1.58, 3.75)	0.0001
CES-D (< 16 vs >=16 points)	1.01	1.32 (0.77, 2.28)	0.31	0.11	1.07 (0.71, 1.62)	0.74
Age per Decade	0.09	1.05 (0.77, 1.42)	0.76	3.24	1.26 (0.98, 1.61)	0.07
	C. AIDS Deaths Within 3 Years or Less After FFI Visit			**D. AIDS Deaths Later Than 3 Years After FFI Visit**		
	χ^2	**Multivariate-Adjusted HR[a] (95% CI)**	**P-value**	**χ^2**	**Multivariate-Adjusted HR[a] (95% CI)**	**P-Value**
VACS Index per 20 points	80.32	3.33 (2.56, 4.33)	0.0000	13.97	1.75 (1.31, 2.35)	0.0002
FFI (3-5 vs 0-2 points)	0.88	1.45 (0.67, 3.14)	0.34	9.40	3.38 (1.55, 7.37)	0.002
CES-D (< 16 vs >=16 points)	1.96	1.73 (0.80, 3.73)	0.17	0.81	1.43 (0.65, 3.14)	0.37
Age per Decade	2.42	0.72 (0.47, 1.09)	0.12	0.09	0.93 (0.58, 1.50)	0.77

	E. Non-AIDS Deaths Within 3 Years or Less After FFI Visit			F. Non-AIDS Deaths Later Than 3 Years After FFI Visit		
	χ^2	**Multivariate-Adjusted HR[a] (95% CI)**	**P-value**	χ^2	**Multivariate-Adjusted HR[a] (95% CI)**	**P-Value**
VACS Index per 20 points	0.80	1.16 (0.83, 1.62)	0.37	5.84	1.41 (1.07, 1.86)	0.016
FFI (3-5 vs 0-2 points)	9.15	3.37 (1.53, 7.40)	0.003	11.95	3.20 (1.66, 6.20)	0.0005
CES-D (< 16 vs >=16 points)	0.15	1.17 (0.54, 2.54)	0.70	0.60	0.77 (0.40, 1.48)	0.44
Age per Decade	7.43	1.90 (1.20, 3.02)	0.006	1.44	1.26 (0.86, 1.84)	0.23

[a]Multivariate models included race/ethnicity; education less than or equal to vs greater than high school; smoking current vs no; income less than vs greater than or equal to $12,000 annually; alcohol use: low, moderate or high vs none; and BMI at least than vs less 30 kg/m^2

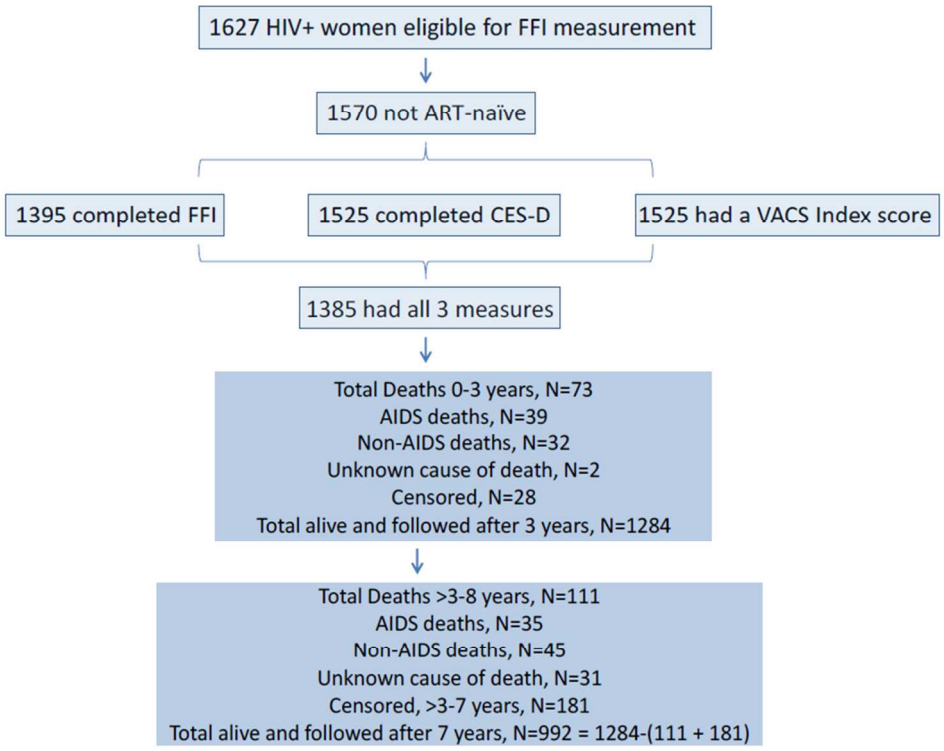

Figure 1. WIHS participants with the VACS Index, FFI, and CES-D measured in 2005 and follow-up over approximately 8 years.

245x183mm (96 x 96 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

All items in the STROBE checklist are accomplished, see page numbers by items listed below.

	Item No & Page#	Recommendation
Title and abstract	1, P1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
	P3	(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2, P5-6	Explain the scientific background and rationale for the investigation being reported
Objectives	3, P6	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4, P6	Present key elements of study design early in the paper
Setting	5, P6-9	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6, P6-7	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7, P7-9	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*, P7-9	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias, NA
Study size	10, P7	Explain how the study size was arrived at
Quantitative variables	11, P9-10	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12 P9-10	(*a*) Describe all statistical methods, including those used to control for confounding
	P9-10	(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed, NA
		(*d*) *Cohort study*—If applicable, explain loss to follow-up was addressed, NA *Case-control study*—If applicable, explain how matching of cases and controls was addressed, NA *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy, NA
	P10	(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13*, P31	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage, NA
	P31	(c) Consider use of a flow diagram
Descriptive data	14*, P23-25	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest, NA
	P31	(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*, P7-9, P31	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure, NA
		Cross-sectional study—Report numbers of outcome events or summary measures, NA
Main results	16, P10-13	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
	P8-9	(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period, NA
Other analyses	17, P11	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18, P12-13	Summarise key results with reference to study objectives
Limitations	19, P15-16	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20, P12-17	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21, P4, P12-17	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22, P17-18	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.