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

Deborah R Gustafson, Qiuhu Shi, Susan Holman, Howard Minkoff, Mardge H Cohen, Michael W Plankey, Richard Havlik, Anjali Sharma, Stephen Gange, Monica Gandhi, Joel Milam, Donald R Hoover

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, Center for Epidemiologic Studies-Depression (CES-D). Proportional hazards regression analyses were used to predict death and included relevant covariates.

Design Prospective, observational cohort.

Setting Multicentre, across six sites in the USA.

Participants 1385 multirace/ethnic ART-experienced HIV+ women 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, χ²=69.04, p<0.0001), and later than 3 years (HR=1.55, 95% CI 1.30, 1.84, χ²=23.88, p<0.0001); followed by FFI within 3 years (HR=2.06, 95% CI 1.19, 3.57, χ²=6.73, p=0.01) and later than 3 years (HR=2.43, 95% CI 1.58, 3.75, χ²=16.18, p=0.0001), CES-D score was not independently associated with mortality.

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

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 ageing, accompanied by multiple morbidities and rising healthcare costs. The North American AIDS Cohort Collaboration on Research and Design observed that life expectancy of HIV-infected (HIV+) adults increased from 36 to 51 years between 2000 and 2007, primarily due to treatment advances. In 2015, over half of HIV+ Americans are ≥50 years old. 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 minimise 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 Center 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 antiretroviral therapy (HAART) users in the Women’s Interagency HIV Study (WIHS). The VACS Index creates a clinical HIV mortality risk score by summing preassigned points for age, routinely monitored indicators of HIV disease and general

Strengths and limitations of this study

- Longitudinal cohort study with follow-up of almost 10 years.
- Reputable standardised and validated physical, biological and mental health indices.
- Somewhat limited generalisability 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 midlife, a period when risk of death is low.
indicators of organ system function. The FFI is most commonly used when describing ageing in both general and HIV+ populations. Frailty is a common comorbidity of HIV infection, observed even during middle age. The FFI includes measures of gait speed, handgrip strength, body weight loss, physical activity, and exhaustion and predicts death. The CES-D score measures mental health and has been independently associated with mortality, particularly among women with HIV infection on HAART in the WIHS.

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 related and non-AIDS related). All indices were measured in midlife (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 to ~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 ageing. 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. 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 subject 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 were antiretroviral therapy (ART)-experienced and had measures of both VACS Index and CES-D. These women are included in the current analyses.

**Inclusion criteria**

Women included in these analyses are HIV+ members of the WIHS cohort who 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 subcategorised into 0–3 and >3 to ~8 years), subsequent to measurement of the health indices, was the primary outcome. The US National Death Index identified numbers and causes of death from 1 January 2005 through 31 December 2013. Causes of death were subdivided into AIDS and non-AIDS deaths based on consensus panels comprised of WIHS investigators (see figure 1). AIDS deaths included: pneumonia, progressive multifocal leukoencephalopathy (PML), pneumocystis pneumonia (PCP), wasting syndrome, central nervous system (CNS) lymphoma, candida, cytomegalovirus (CMV), Cryptococcus, toxoplasmosis, tuberculosis (TB)/mycobacterium, cervical cancer, pulmonary hypertension, dementia/neurologic, renal failure, multiorgan 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, haemorrhage, 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 than the total number of deaths during the follow-up period.

**Primary predictors of death**

There were three primary predictors of interest: VACS Index, FFI and CES-D score. The VACS Index facilitates a mortality risk score created by summing preassigned 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 haemoglobin, FIB-4 and estimated glomerular filtration rate, eGFR (mL/min). We calculated eGFR based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. The VACS Index has a maximum score of 164. The FFI was defined using well-described criteria. 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 m 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 handheld 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 lost weight by at least 5% of your total body weight?’. Poor performance on VACS, FFI and CES-D indices were measured in midlife (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 to ~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.

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you had unintentional weight loss of at least 10 pounds?"
If at least three 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 totalling 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 midlife in this
sample of HIV+ women, best predicted AIDS, non-AIDS
and all deaths. 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 curve for standard binomial outcomes
(range 0.5–1.0). It describes the probability of death asso-
ciated with a higher health index score or combination of
higher health index scores in a randomly selected partici-
pant compared with those who do not die.18

Covariates found to be significantly associated with
mortality were included in these analyses.4 These covari-
ates included race/ethnicity, education, smoking, annual
income, alcohol drinking, intravenous drug use (IDU)
history, body mass index, prior AIDS-defining illness,
pneumonia, cancer, diabetes and hypertension. Methods
for determining HIV and HCV infection status, AIDS
diagnosis, CD4 cell count, HIV viral load, ART use and
IDU were described previously.9

We refit models (1) restricting follow-up time to the
first 3 years after measurement (ie, censoring at 3 years),
and (2) starting follow-up time at 3 years after the health
indices measurements (ie, 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 HRs with 95% CI. The \( \chi^2 \)
statistic is also presented to facilitate comparison of strength of
association between models since the HR scale of each
ageing vulnerability index is not the same. Data anal-
yses were accomplished using SAS V.9.4. C-statistics were
calculated using STATA V.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 modi-
ified CES-D score resulted from excluding two CES-D
symptoms that overlap with the FFI. The excluded CES-D

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**Figure 1** WIHS participants with the VACS Index, FFI and CES-D measured in 2005 and follow-up over approximately 8
years. ART, antiretroviral therapies; CES-D, Center for Epidemiologic Studies-Depression; FFI, Fried Frailty Index; HIV+, HIV-
infected; VACS, Veterans Aging Cohort Study; WIHS, Women’s Interagency HIV Study.
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 history of 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 two missing components. The three indices, as well as individual VACS components, demographic/health behaviour, infectious disease, chronic ageing-related disease variables, number and types of deaths are presented in table 1. The crude HR (95% CI) for all deaths by health indices and demographic/health behaviours, infectious diseases and chronic ageing-related disease variables are presented in table 2.

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

Using multivariable proportional hazards regression 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 modelled 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 HRs 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, χ²=69.04, p<0.0001), followed by FFI (HR=2.06, 95% CI 1.19, 3.57, χ²=6.73, p=0.01). For deaths occurring later than 3 years after baseline measurement,...
baseline measures (table 5B), the relative influence of the VACS Index decreased (HR=1.55, 95% CI 1.30, 1.84, $\chi^2=23.88$, $p<0.0001$), and the FFI increased (HR=2.43, 95% CI 1.58, 3.75, $\chi^2=16.18$, $p=0.0001$).

**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, $\chi^2=80.32$, $p<0.0001$) of AIDS deaths; for AIDS death after 3 years (table 5D), both VACS Index (HR=1.75, 95% CI 1.31, 2.35, $\chi^2=13.97$, $p=0.0002$) and FFI (HR=3.38, 95% CI 1.55, 7.37, $\chi^2=9.40$, $p=0.002$) 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, $\chi^2=9.15$, $p=0.003$) and later (table 5F) than 3 years post baseline (HR=3.20, 95% CI 1.66, 6.20, $\chi^2=11.95$, $p=0.0005$). The VACS Index predicted death later than 3 years (HR=1.41, 95% CI 1.07, 1.86, $\chi^2=5.84$, $p=0.016$), but was not quite as robust as the FFI.

**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 to ~8 years) among women with HIV infection. Overall, based on comparative $\chi^2$ and C-statistics,

### Table 1 Continued

<table>
<thead>
<tr>
<th>Variables</th>
<th>N (%) or mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average age (years, mean ± SD)</td>
<td>42.6±8.8</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>324 (23.4)</td>
</tr>
<tr>
<td>Black</td>
<td>806 (58.2)</td>
</tr>
<tr>
<td>Others</td>
<td>255 (18.4)</td>
</tr>
<tr>
<td>Education</td>
<td></td>
</tr>
<tr>
<td>&lt;High school</td>
<td>536 (38.7)</td>
</tr>
<tr>
<td>≥High school</td>
<td>847 (61.2)</td>
</tr>
<tr>
<td>Mission</td>
<td>2 (0.1)</td>
</tr>
<tr>
<td>Smoking history</td>
<td></td>
</tr>
<tr>
<td>Not current smoking</td>
<td>786 (56.8)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>599 (43.2)</td>
</tr>
<tr>
<td>Income</td>
<td></td>
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<tr>
<td>&lt;$12,000</td>
<td>669 (48.3)</td>
</tr>
<tr>
<td>≥$12,000</td>
<td>668 (48.2)</td>
</tr>
<tr>
<td>Missing</td>
<td>48 (3.5)</td>
</tr>
<tr>
<td>Current alcohol drinking</td>
<td></td>
</tr>
<tr>
<td>Abstainer/none</td>
<td>743 (53.6)</td>
</tr>
<tr>
<td>Low</td>
<td>490 (35.4)</td>
</tr>
<tr>
<td>Moderate</td>
<td>129 (9.3)</td>
</tr>
<tr>
<td>High</td>
<td>23 (1.7)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td></td>
</tr>
<tr>
<td>BMI&lt;30</td>
<td>916 (66.1)</td>
</tr>
<tr>
<td>BMI≥30 (obesity)</td>
<td>461 (33.3)</td>
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<tr>
<td>Missing</td>
<td>8 (0.6)</td>
</tr>
<tr>
<td>Current ART use</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>400 (28.9)</td>
</tr>
<tr>
<td>Yes (HAART)</td>
<td>984 (71.0)</td>
</tr>
<tr>
<td>Missing</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>Prior AIDS-defining illness</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>802 (57.9)</td>
</tr>
<tr>
<td>Yes</td>
<td>583 (42.1)</td>
</tr>
<tr>
<td>Injection drug use ever</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>305 (22.0)</td>
</tr>
<tr>
<td>No</td>
<td>1071 (77.3)</td>
</tr>
<tr>
<td>Missing</td>
<td>9 (0.6)</td>
</tr>
<tr>
<td>Prior pneumonia</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1080 (78.0)</td>
</tr>
<tr>
<td>Yes</td>
<td>305 (22.0)</td>
</tr>
<tr>
<td>Current/prior hypertension</td>
<td></td>
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<tr>
<td>No</td>
<td>964 (69.6)</td>
</tr>
<tr>
<td>Yes</td>
<td>421 (30.4)</td>
</tr>
<tr>
<td>History of diabetes</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1195 (86.3)</td>
</tr>
</tbody>
</table>

*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.*
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 from 3 to ~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. Ten years later, the first report on a validated VACS Index specific for those with HIV infection was published. The VACS Index has, since then, been used to predict mortality in HIV-infected and uninfected populations and has been associated with the FFI. In the WIHS, the VACS Index and CES-D score considered together have been independently reported to predict mortality over a 5-year period. Here we show that with addition of the FFI, these relationships change.

The FFI predicts death, particularly among elderly (65 years and older). More recently, the FFI has been measured in younger adult populations who may be at risk for premature or earlier ageing, such as those with HIV infection. These studies have shown that adults with HIV infection, even in midlife, experience a prevalence of frailty equivalent to, and greater than, that observed in more elderly adults. 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) and/or other lifestyle habits that may be common among those with HIV infection, such as smoking and substance use. While interesting, FFI fluctuations cannot be addressed in these analyses, but will be in the future with the reinitiation of

### Table 2

<table>
<thead>
<tr>
<th>Variable</th>
<th>Crude HR (95% CI)</th>
<th>( \chi^2 )</th>
<th>( p ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VACS score (0–164), per 20 points</td>
<td>2.20 (1.98 to 2.45)</td>
<td>214.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>FFI 3–5 vs 0–2</td>
<td>3.92 (2.92 to 5.26)</td>
<td>83.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CES-D (&lt;16 vs &gt;16)</td>
<td>2.07 (1.55 to 2.77)</td>
<td>24.0</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

### Table 3

<table>
<thead>
<tr>
<th>Variables</th>
<th>All deaths</th>
<th>AIDS deaths</th>
<th>Non-AIDS deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>CES-D + VACS Index + FFI + demographics*</td>
<td>0.83</td>
<td>0.89</td>
<td>0.81</td>
</tr>
<tr>
<td>VACS Index + FFI + demographics</td>
<td>0.83</td>
<td>0.89</td>
<td>0.81</td>
</tr>
<tr>
<td>VACS Index + CES-D + demographics</td>
<td>0.82</td>
<td>0.89</td>
<td>0.78</td>
</tr>
<tr>
<td>FFI + CES-D + demographics</td>
<td>0.78</td>
<td>0.80</td>
<td>0.80</td>
</tr>
<tr>
<td>VACS Index + demographics</td>
<td>0.81</td>
<td>0.89</td>
<td>0.77</td>
</tr>
<tr>
<td>FFI + demographics</td>
<td>0.77</td>
<td>0.78</td>
<td>0.80</td>
</tr>
<tr>
<td>CES-D + demographics</td>
<td>0.75</td>
<td>0.77</td>
<td>0.75</td>
</tr>
<tr>
<td>Demographics only*</td>
<td>0.74</td>
<td>0.74</td>
<td>0.76</td>
</tr>
</tbody>
</table>

*Demographic variables included were: age, body mass index, race/ethnicity, income, education, cigarette smoking and alcohol use.

ART, antiretroviral therapies; BMI, body mass index; CES-D, Center for Epidemiologic Studies-Depression; df, degrees of freedom; FFI, Fried Frailty Index; HIV+, HIV-infected; VACS, Veterans Aging Cohort Study.
FFI assessments in the WIHS in Fall 2015. As the FFI is a marker of the slower process of physical ageing, 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. 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. 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 these health indices in middle-aged HIV+ 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. Midlife physical, biological and/or mental health indicators against the background of HIV infection may be associated with earlier death.

Why are multidimensional health indices associated with mortality in adults with HIV infection? Throughout adult life, HIV infection is synergistic with adverse ageing influences on the immune, vascular, reproductive and central nervous systems, thereby intensifying the ageing process. 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, lending support to this observation. We chose to assess deaths occurring within 3 years versus those occurring $\geq 3$ years after the indices were measured. Studies in HIV-uninfected populations have shown that deaths occurring within a short period of time (eg, 3 years) tend to be those due to more rapid biological triggers of death such as infections (eg, HIV, pneumonia) or other acute illnesses, while longer term deaths reflect delayed consequences of deteriorating biological and physical health. 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

| Table 4: VACS index, FFI and CES-D individually predict time to all deaths, AIDS deaths and non-AIDS deaths over ~8 years of follow-up among HIV+ women who were ART-experienced. |
|-----------------|------------------|------------------|------------------|
| **VACS Index** | **FFI** | **CES-D** | **Age** |
| Index | HR (95% CI) | $\chi^2$ | p Value | HR (95% CI) | $\chi^2$ | p Value | HR (95% CI) | $\chi^2$ | p Value |
| VACS score (0-164), per 20 points | 0.75 | 2.70 | 0.01 | 0.75 | 2.70 | 0.01 | 0.75 | 2.70 | 0.01 |
| FFI 3-5 vs 0-2 | 2.06 | 3.28 | 0.01 | 2.06 | 3.28 | 0.01 | 2.06 | 3.28 | 0.01 |
| CES-D (<16, 16 vs >16) | 0.83 | 1.90 | 0.01 | 0.83 | 1.90 | 0.01 | 0.83 | 1.90 | 0.01 |
| Age per decade | 2.03 | 1.39 | 0.01 | 2.03 | 1.39 | 0.01 | 2.03 | 1.39 | 0.01 |

*Multivariate models included race/ethnicity; education less than equal to high school; smoking current versus never; income less than versus greater than or equal to $12,000 annually; alcohol: low, moderate or high versus none; and body mass index <30 vs 30 kg/m². ART, antiretroviral therapies; CES-D, Center for Epidemiologic Studies Depression; FFI, Fried Frailty Index; HIV+, HIV-infected; VACS, Veterans Aging Cohort Study.
to predict mortality in HIV+ persons, and that the FFI was designed to be descriptive of a clinically recognisable phenotype. Therefore, the VACS Index may be expected to have more explanatory power in multivariable analyses of HIV-related ageing morbidities often occur earlier among those with HIV infection compared with uninfected individuals. The question is whether HIV infection leads to more severe ageing phenotypes, or accelerates their onset leading to earlier age of death. 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.

### Table 5  Multivariable proportional hazards models of time to all deaths, AIDS deaths and non-AIDS deaths within 3 years versus greater than 3 years by VACS Index, FFI, CES-D and age among HIV+ women who were ART-experienced.

<table>
<thead>
<tr>
<th>Variable</th>
<th>A. All deaths within 3 years after FFI visit</th>
<th>B. All deaths later than 3 years after FFI visit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( \chi^2 )</td>
<td>Multivariate-adjusted HR* (95% CI)</td>
</tr>
<tr>
<td>VACS Index per 20 points</td>
<td>69.04</td>
<td>2.20 (1.83 to 2.65)</td>
</tr>
<tr>
<td>FFI (3–5 vs 0–2 points)</td>
<td>6.73</td>
<td>2.06 (1.19 to 3.57)</td>
</tr>
<tr>
<td>CES-D (&lt;16vs ≥16 points)</td>
<td>1.01</td>
<td>1.32 (0.77 to 2.28)</td>
</tr>
<tr>
<td>Age per decade</td>
<td>0.09</td>
<td>1.05 (0.77 to 1.42)</td>
</tr>
</tbody>
</table>

*Multivariate models included race/ethnicity; education less than or equal to versus greater than high school; smoking current versus no; income less than versus greater than or equal to $12,000 annually; alcohol use: low, moderate or high versus none; and body mass index <30 vs ≥30 kg/m².

ART, antiretroviral therapies; CES-D, Center for Epidemiologic Studies-Depression; FFI, Fried Frailty Index; HIV+, HIV-infected; VACS, Veterans Aging Cohort Study.
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Data sharing statement
Technical appendix, code books, statistical code and dataset are available at the WIHS Statistical Analysis Center, WD-MAC in Baltimore, MD, USA.

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