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HIV, Aging, and Frailty: *Cannonball?*

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Protecting Health, Saving Lives—*Millions at a Time*

Disclosures

- None

Funding

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  - K01-AI093197 from the NIAID
  - An HIV and Aging pilot grant by the NIH funded program 1R24AG044325

Objectives

- To describe the aging with HIV epidemic and previous work of frailty in HIV
- To describe the challenges to studying frailty in HIV+ adults
- To suggest frailty and physical function measurements among those with HIV

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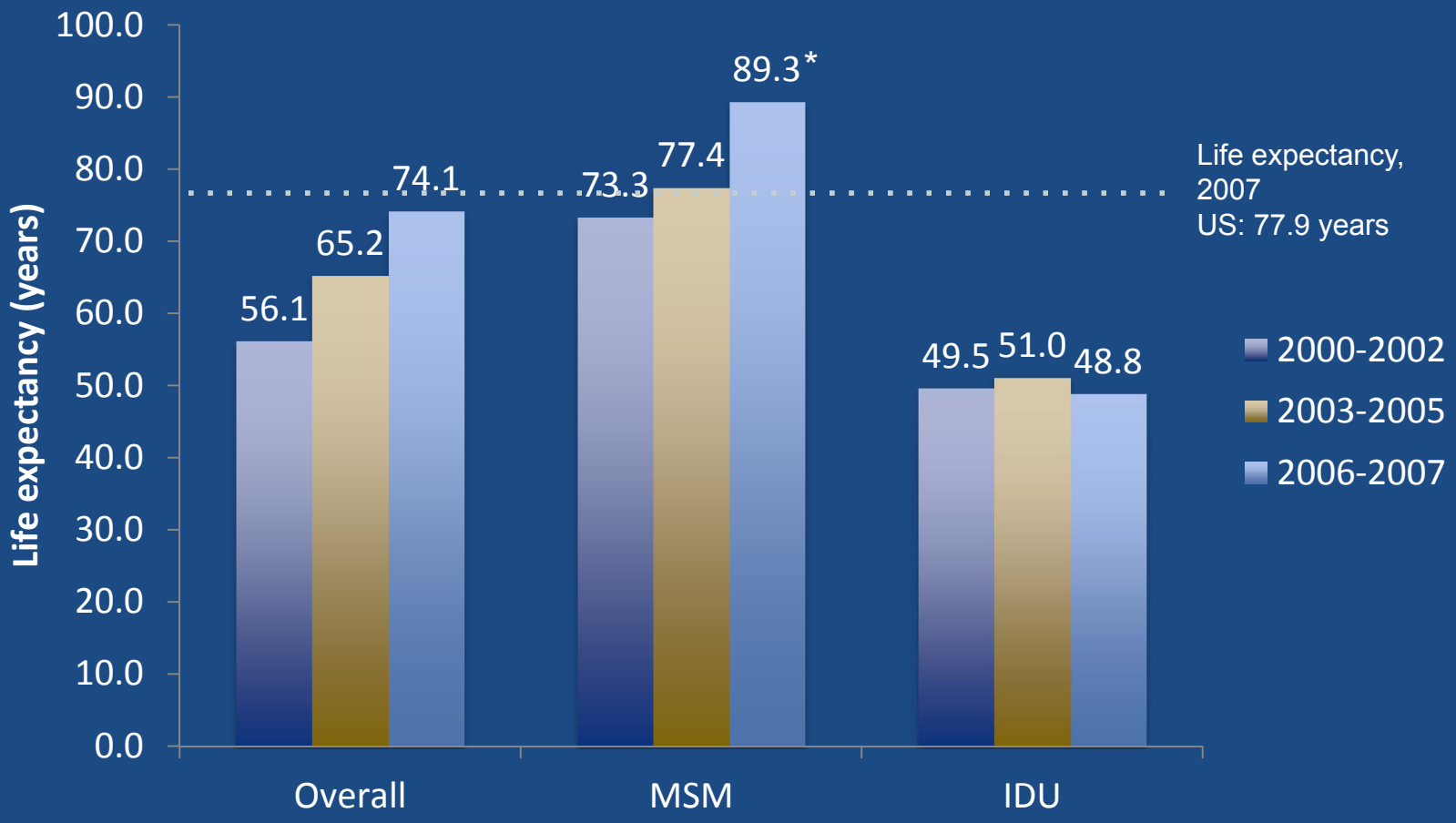
EPIDEMIOLOGY OF AGING WITH HIV

Prevalence of disease = Duration * Incidence

Life expectancy is increasing



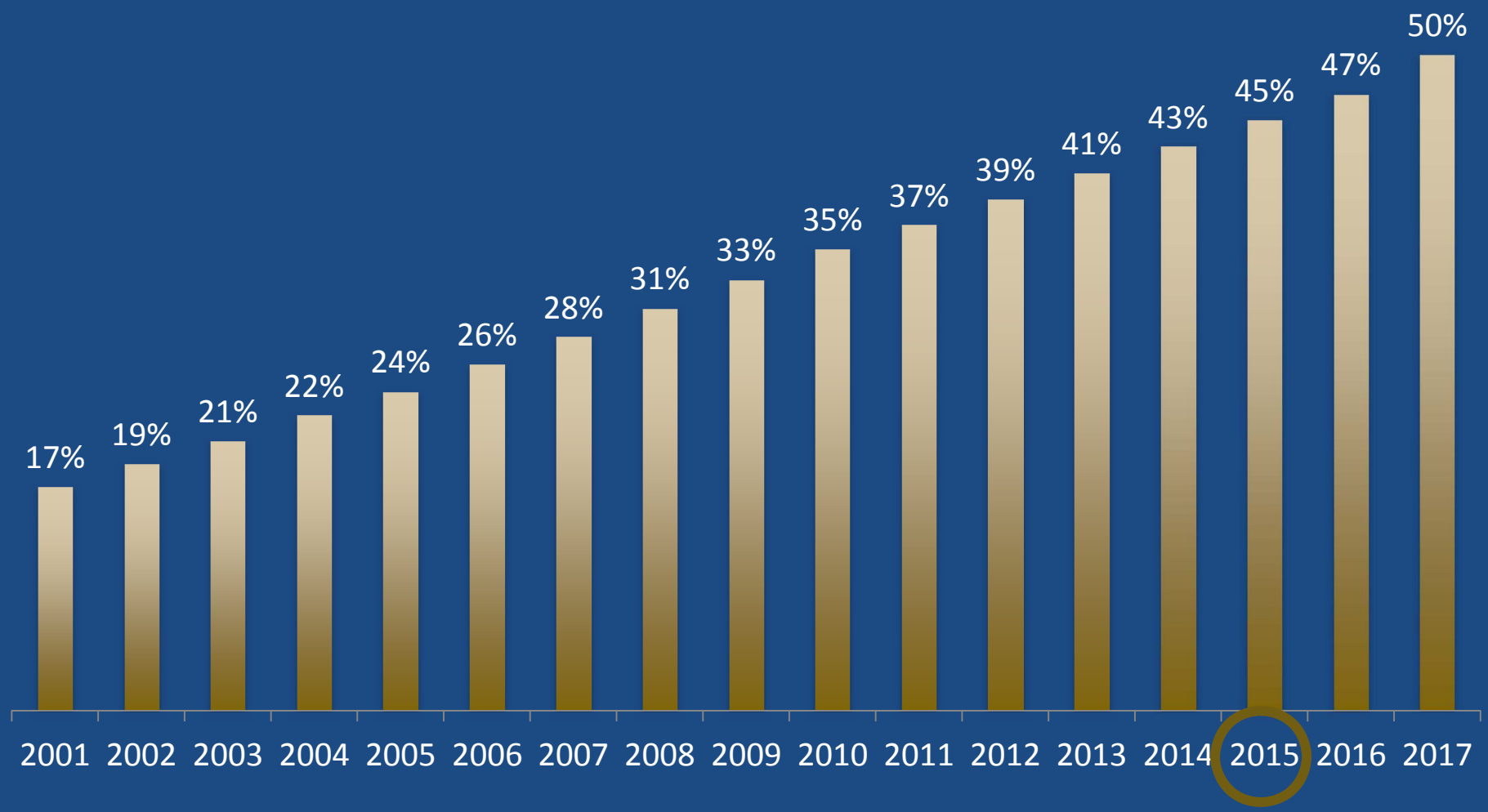
*Likely an overestimation due to a small number of deaths among those aged >60 years and a decreasing number of deaths at younger ages.

Samji, et al, for the NA-ACCORD of IeDEA. Closing the gap: Increasing life expectancy among treated HIV positive individuals in the United States and Canada. PLoS ONE 2013; e81355.

Arias E. United States Life Tables, 2007. National Vital Statistics Reports 2011;59:1-61.

The World Bank. Available at http://www.google.com/publicdata/explore ds=d5bncppjof8f9_&met_y=sp_dyn_le00_in&idim=country:BRA:GBR:ITA&hl=en&dl=en

Percent of PLWH ≥50yo will exceed 50%



Data from 2011 onward projected based on 2001-2010 trends (calculated by KN Althoff), 2001-20010 data from CDC Surveillance Reports 2005, 2008, 2011

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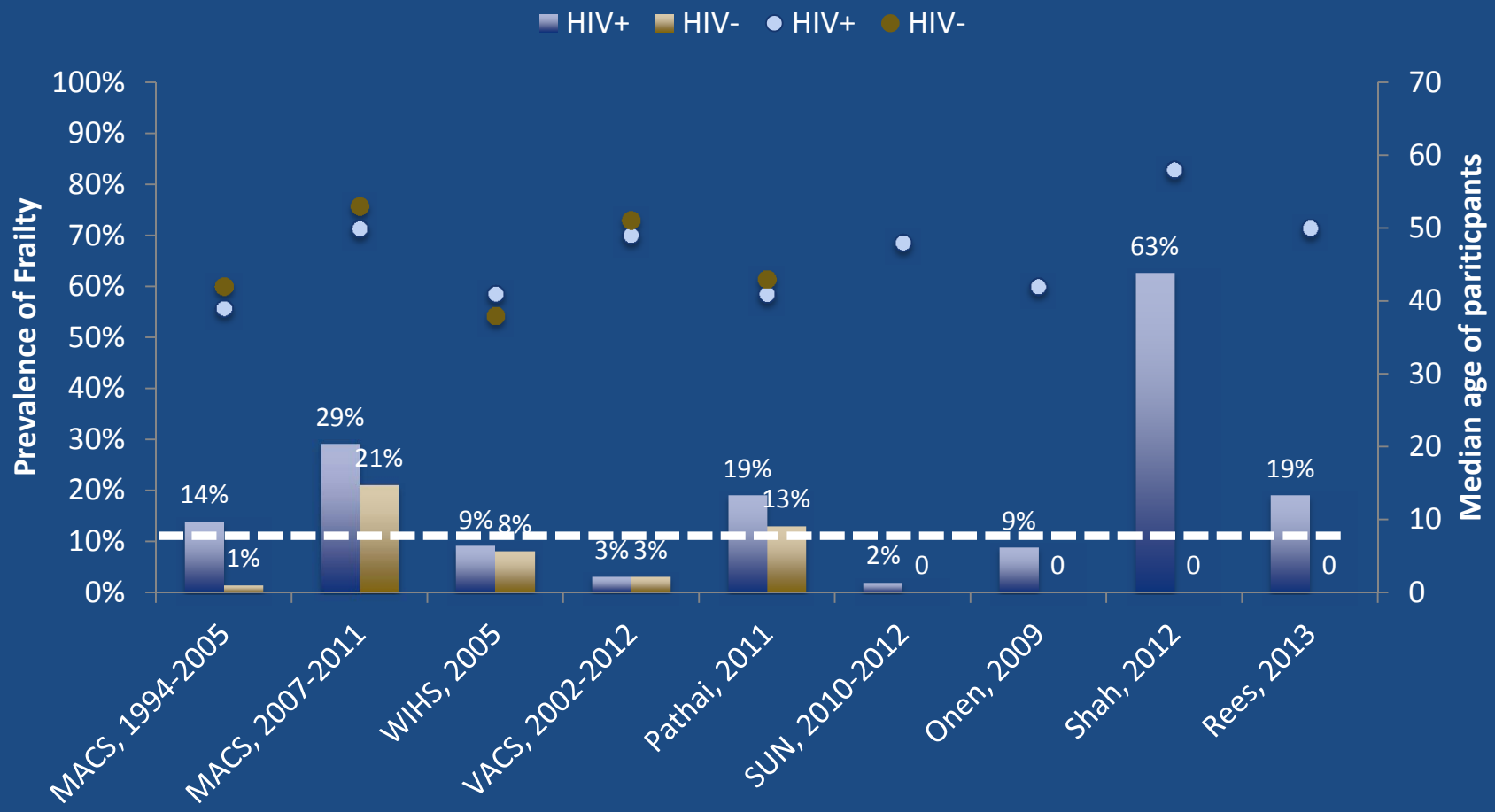
STUDIES OF FRAILTY IN HIV

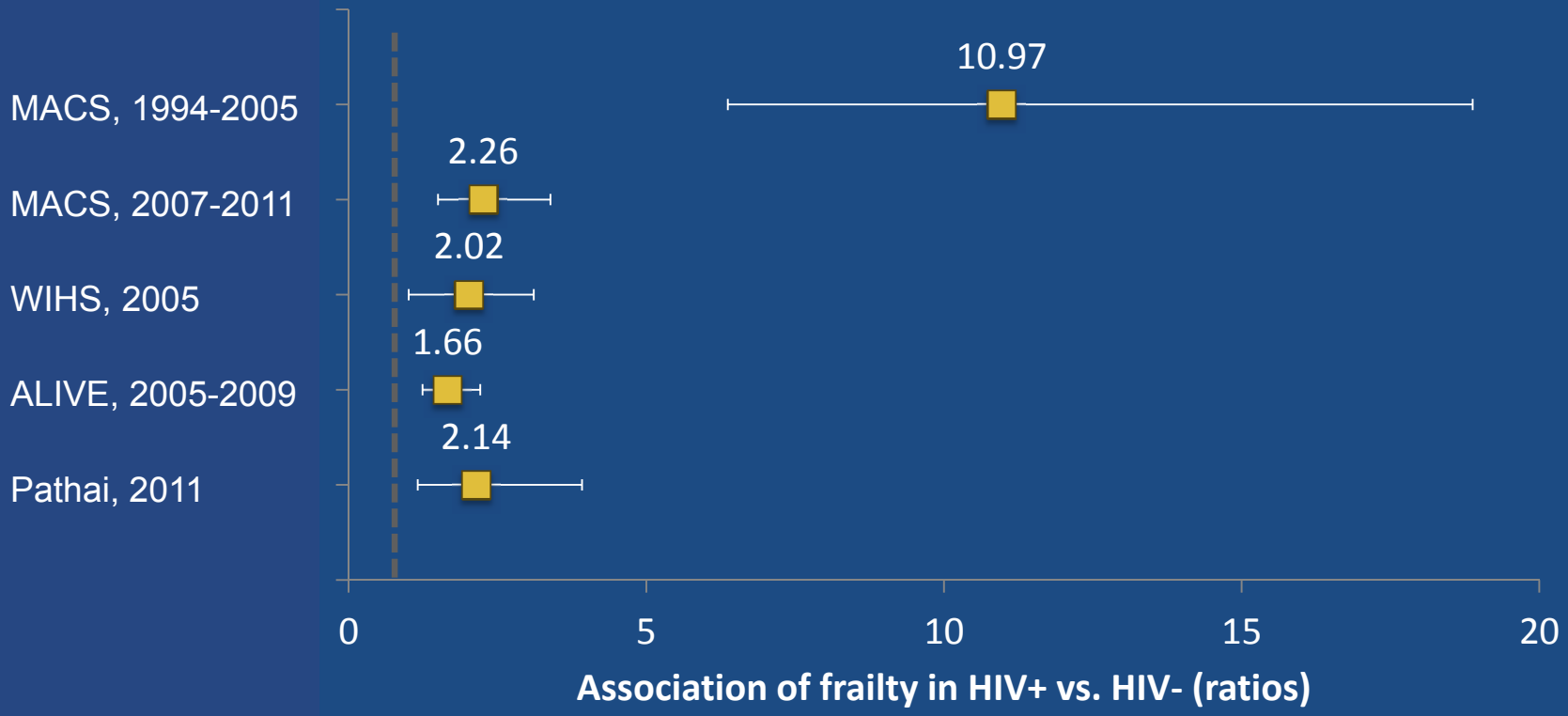
Prevalence of frailty in HIV+



Cardiovascular Health Study (12%) Women's Health and Aging Study (11%)

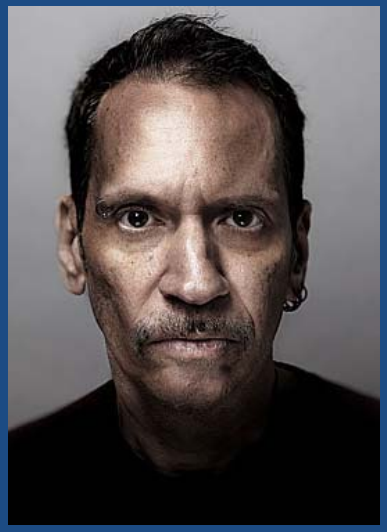
Desquilbet, et al., J Gerontol A Biol Sci Med Sci, 2007. Althoff, et al., J Gerontol A Biol Sci Med Sci, 2014. Terzian, et al., J Women's Health, 2009. Akung, et al., AIDS, 2014. Pathai, et al., JAIDS 2013. Escota, et al. AIDS Res Hum Retroviruses, 2014. Onen, et al., J Infect, 2009. Shah,et al., JAGS, 2012. Rees, et al., J Vis Exp, 2013. Newman, et al., J of Geronotology, 2001. Bandeen-Roche, et al., J of Gerontology, 2006.

Association of frailty in HIV+ vs. HIV-



Desquilbet, et al., J Gerontol A Biol Sci Med Sci, 2007. Althoff, et al., J Gerontol A Biol Sci Med Sci, 2014. Terzian, et al., J Women's Health, 2009. Piggott, PLoS ONE, 2013. Pathai, et al., JAIDS 2013

Factors associate with frailty in HIV+



Enrico McLane
Age: 52
HIV: 17 years
short-term memory loss
two hip replacements

Norma Martinez.
Age: 61
HIV: 12 years
lipodystrophy, fatigue

Joe Westmoreland
Age: 53
HIV: 27 years
memory loss, fatigue, peripheral neuropathy in feet and hands

From New York Magazine, Nov 2009.

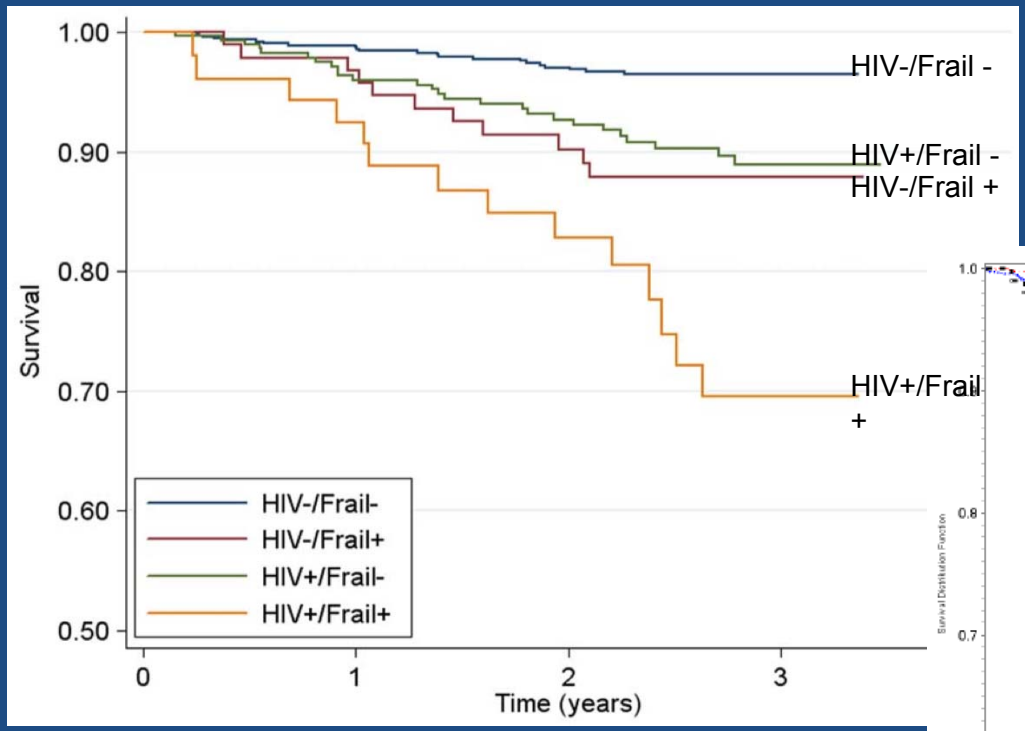
Table 2. Summary of Factors Associated With Frailty Among HIV-positive Individuals on Antiretroviral Therapy

Age [12, 13, 17, 32–34]
HIV-related measures
Longer time since diagnosis [12]
Lower current CD4 count [12, 13, 31–34, 44]
Lower nadir CD4 count [12]
Low CD4/CD8 ratio [31]
Detectable viral load [13, 32]
Longer duration of HAART [13]
Protease inhibitor-containing HAART regimen [12]
Comorbidities
Hepatitis C coinfection [33]
Low BMI [12, 34]
High BMI [38]
Lipodystrophy [38]
Diabetes [13]
Kidney disease [13]
Depressive symptoms [12, 13, 32]
Cognitive impairment [12, 45]
Inflammation [6]
Weak upper and lower extremities [42]
History of falls [36]
Social factors
Lower education [12, 13, 32]
Current unemployment [12, 35]
Low income in past year [12]

Brothers TD, Rockwood K. Cur Opin HIV AIDS 2014;9:412-8.

Frailty predicts mortality in HIV+ adults

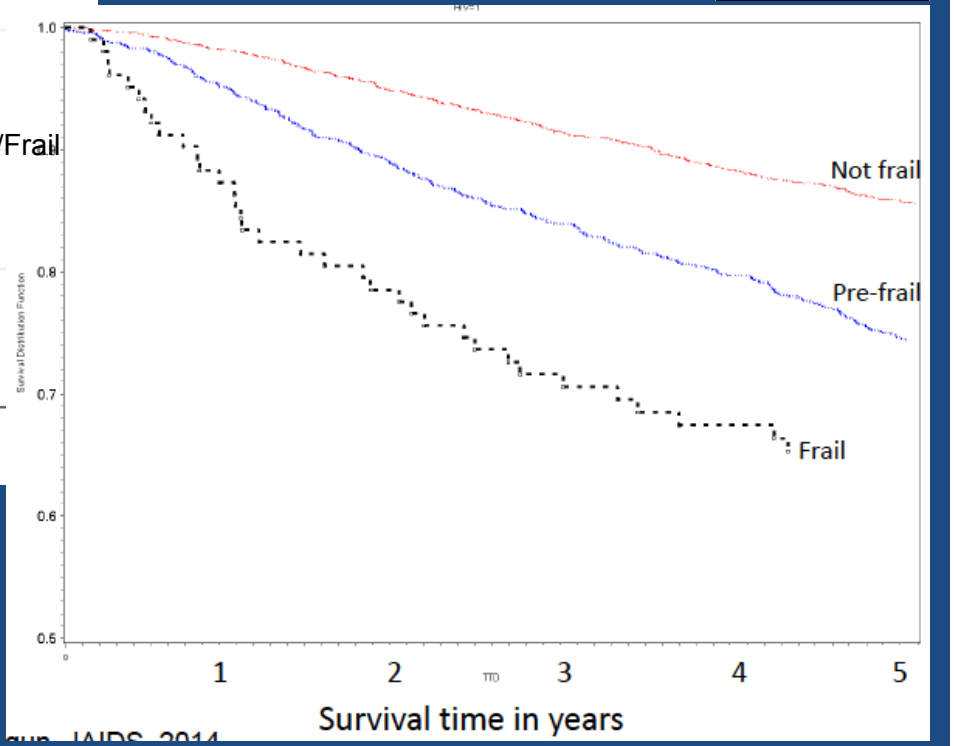
HIV+ and HIV-



Piggott, et al. PLoS ONE 2013:8(1):e54910.

AIDS Linked to the IntraVenous Experience

HIV+ only



Akgun, et al. AIDS 2014;67:397-404.

Frailty predicts hospitalizations in HIV+ adults

TABLE 3. Multivariable Models for Hospitalization and Mortality*

		Hospitalization		Mortality	
N = 6515	Reference	HR	95% CI	HR	95% CI
HIV		1.22	1.13–1.33	1.45	1.22–1.72
Frailty states	Not frail				
aFRP		1.78	1.48–2.13	1.75	1.28–2.40
Prefrail		1.44	1.33–1.54	1.44	1.25–1.66

Akgun, et al. AIDS 2014;67:397-404.

	AIDS hospitalization	Non-AIDS infectious disease hospitalization
aHR (95% CI) comparing frail vs. non-frail HIV+ adults	6.30 (1.20, 33.1)	2.21 (1.40, 3.50)

Piggott et al. Abstract #738, 23rd CROI, 2015.

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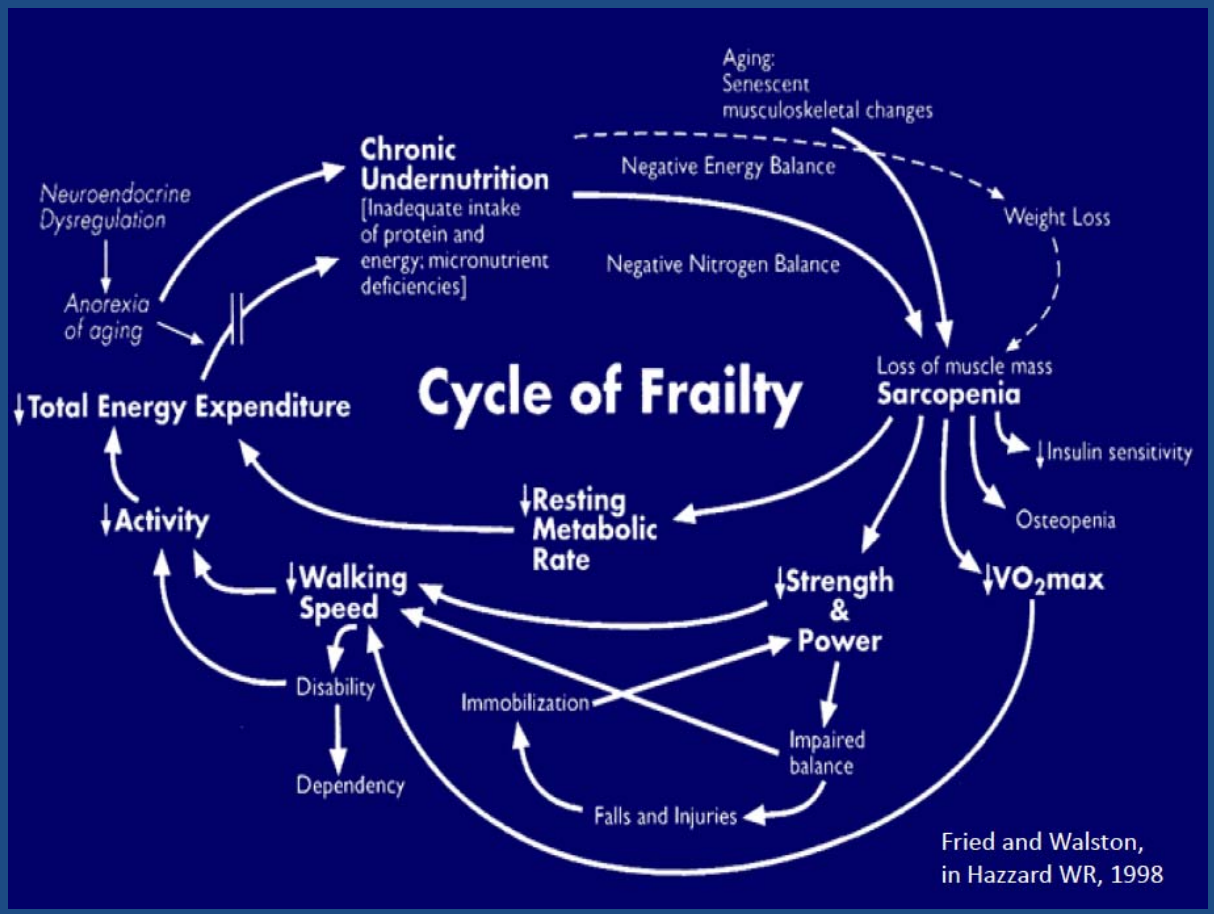
CLARIFYING THE CONCEPT OF FRAILTY IN ADULTS AGING WITH HIV

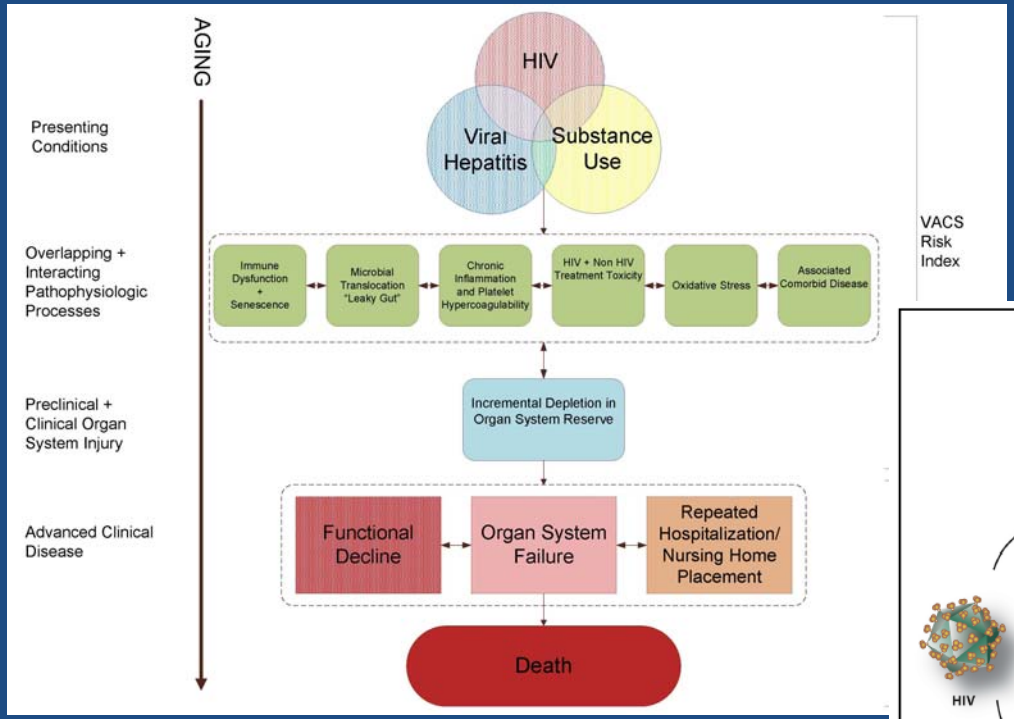
Frailty in HIV: Clarifying the concept

- Frailty, defined as a loss of physiologic reserve and increased vulnerability

- Mechanisms of frailty in the elderly general population



Frailty in HIV: Clarifying the concept



Justice AC. Curr HIV/AIDS Rep. 2010 May;7(2):69-76

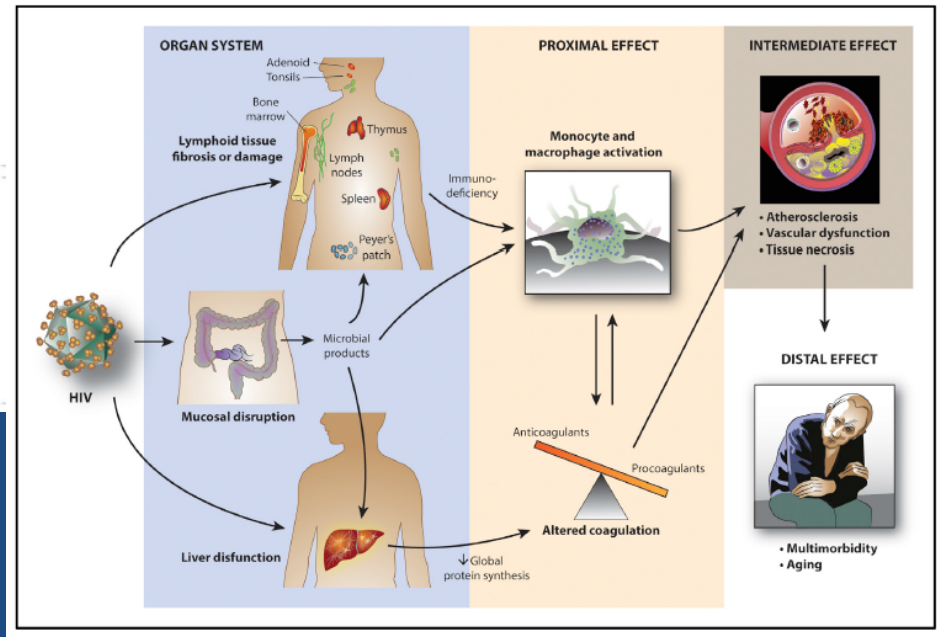


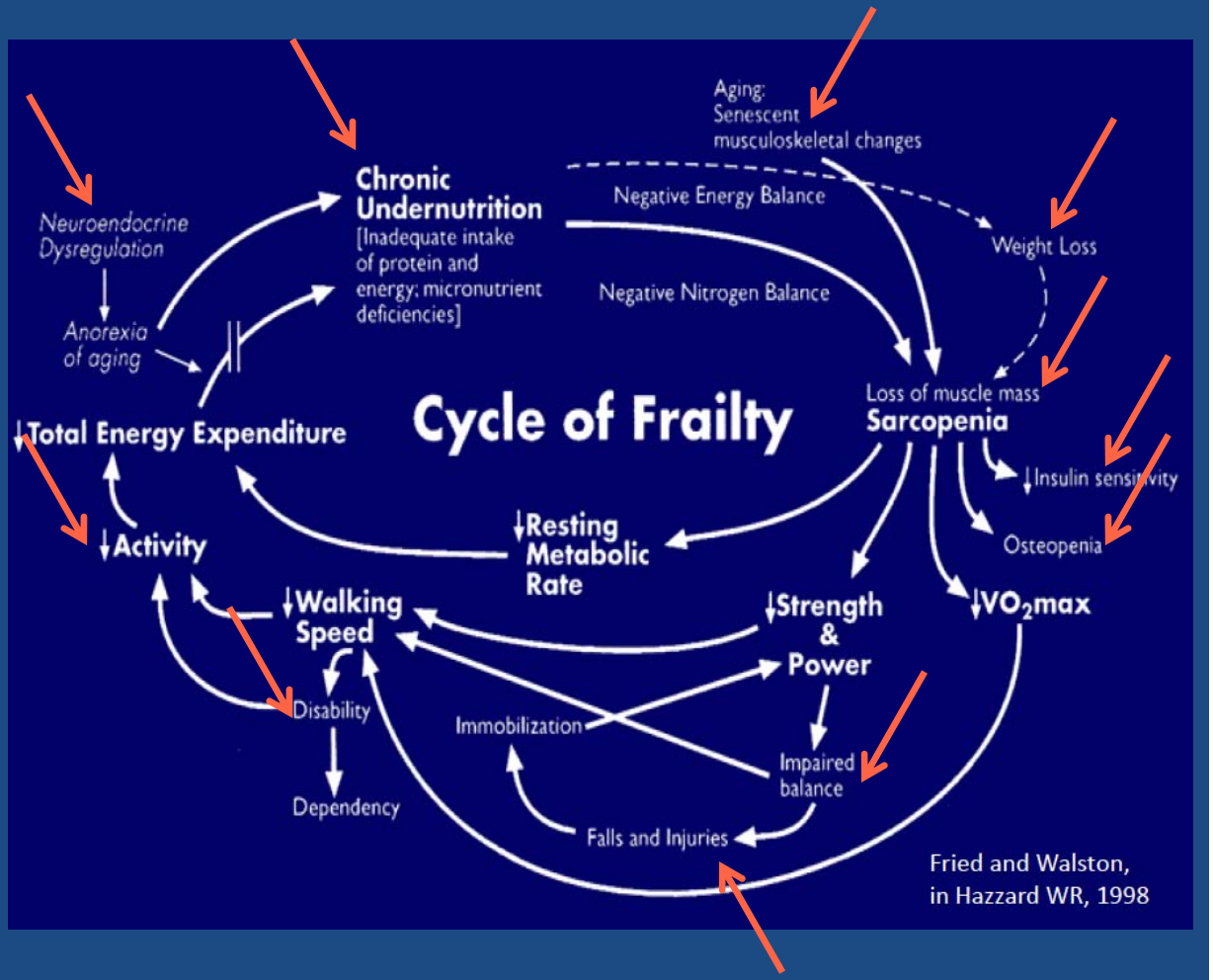
Figure 1. Pathogenesis of Inflammation-Associated Disease in HIV-Infected Adults
HIV infection causes damage to lymphoid and mucosa tissues, leading to progressive immunodeficiency, excess levels of pathogens (including HIV), and inflammation. HIV also damages the mucosa of the gut, leading to microbial translocation. HIV and its treatment also affect liver function through a variety of mechanisms. The collective effect of these initial insults is chronic monocyte and macrophage activation and hypercoagulation. These processes lead directly to vascular harm, end-organ tissue damage, and multimorbidity, all of which theoretically may manifest later in life with the onset of a variety of geriatric syndromes.

Deeks, et al. Cell 2013;39:633-645.

Frailty in HIV: Clarifying the concept

- Frailty, defined as a loss of physiologic reserve and increased vulnerability
- Mechanisms of frailty in the elderly general population

- Does HIV modify these mechanisms?
- Are there other mechanisms in HIV?
  - Chronic viral infection(s)
  - HIV treatment



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CHALLENGES TO MEASUREMENT IN HIV

The case of Althoff, *et al*. J Gerontol A Biol Sci Med Sci. 2014;69(2):189-198.

Althoff KN, et al. J Gerontol A Biol Sci Med Sci. 2014;69(2):189-198.

So an investigator walks into my office…

…and says "Do you have any interest in helping with a project on frailty in the MACS? It should take 6 weeks maximum."

- 2 years later…

Journals of Gerontology: MEDICAL SCIENCES
Cite journal as: J Gerontol A Biol Sci Med Sci 2014 February;69(2):189–198
doi:10.1093/gerona/glt148

Advance Access publication October 14, 2013

Age, Comorbidities, and AIDS Predict a Frailty Phenotype in Men Who Have Sex With Men

Keri N. Althoff,[1] Lisa P. Jacobson,[1] Ross D. Cranston,[2] Roger Detels,[3] John P. Phair,[4] Xiuhong Li,[1] and Joseph B. Margolick[5]; for the Multicenter AIDS Cohort Study (MACS)

[1]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland.
[2]Department of Medicine, University of Pittsburgh School of Medicine, Pennsylvania.
[3]Department of Epidemiology, Fielding School of Public Health, University of California, Los Angeles.
[4]Department of Medicine, The Feinberg School of Medicine, Northwestern University, Chicago, Illinois.
[5]Department of Molecular Microbiology and Immunology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland.

Althoff KN, et al. J Gerontol A Biol Sci Med Sci. 2014;69(2):189-198.

Why Fried criteria to define frailty phenotype (FP)?

Pros

- A recognized tool with utility among the elderly
- Previous MACS publication used this definition

Cons

- This measure has not been validated in younger or HIV+ populations
- Concerns about translating the components
  - Could there be social constructs or ART effects that need to be considered when evaluating unintentional weight loss?
  - Could self report of exhaustion be influenced by recent drug use behaviors among people who inject drugs?
- Accumulation of deficits definition may better fit this special population

Measuring frailty in the MACS

Visit 21

Data collection initiated using questionnaire

Frailty-related phenotype: ≥3 of the following 4: physical shrinking, exhaustion, slowness, low physical activity

Desquillbet, et al. J Gerontol A Biol Sci Med Sci. 2007;62A(11):1279-1286.

Visit 48

Dynamometer and 4m walk data collection initiated

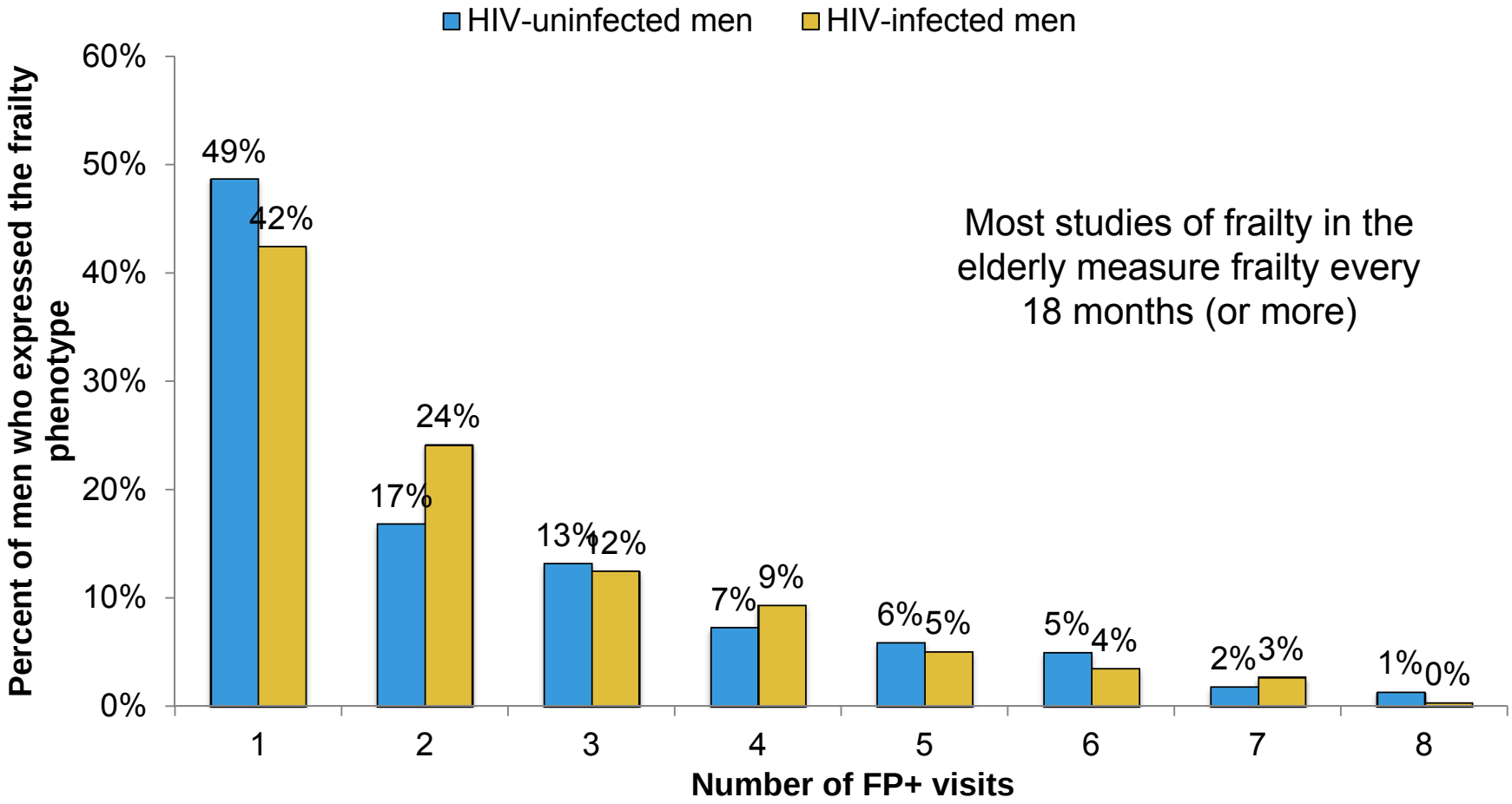
Frailty phenotype: ≥3 of the following 4: physical shrinking, exhaustion, slowness, low physical activity, weakness

Althoff et al. J Gerontol A Biol Sci Med Sci. 2014;69(2):189-198.

Measuring frailty in the MACS

- ≥3 of 5 FP criteria collected during semi-annual study visits
  - Weakness
    - present if grip strength measured using a dynamometer is ≤20th percentile of HIV-uninfected men
  - Slowness
    - present if time to walk 15 feet is ≥80th percentile of HIV-uninfected men
  - Unintentional weight loss
    - "Since your last visit, have you had unintentional weight loss of at least 10 pounds?" **– YES**
  - Exhaustion
    - "During the past 4 weeks, as a result of your physical health, have you had difficulty performing your work or other activities (for example, it took extra effort)?" **– YES**
  - Low physical activity
    - "Does your health now limit you in vigorous activities, such as running, lifting heavy objects, participating in strenuous sports?" **– YES, limited a lot**

Fluctuation in the expression of FP



Number of men (N=477)

HIV-uninfected:	107	37	29	16	13	11	4	3
HIV-infected:	109	62	32	24	13	9	7	1

Althoff KN, et al. J Gerontol A Biol Sci Med Sci. 2014;69(2):189-198.

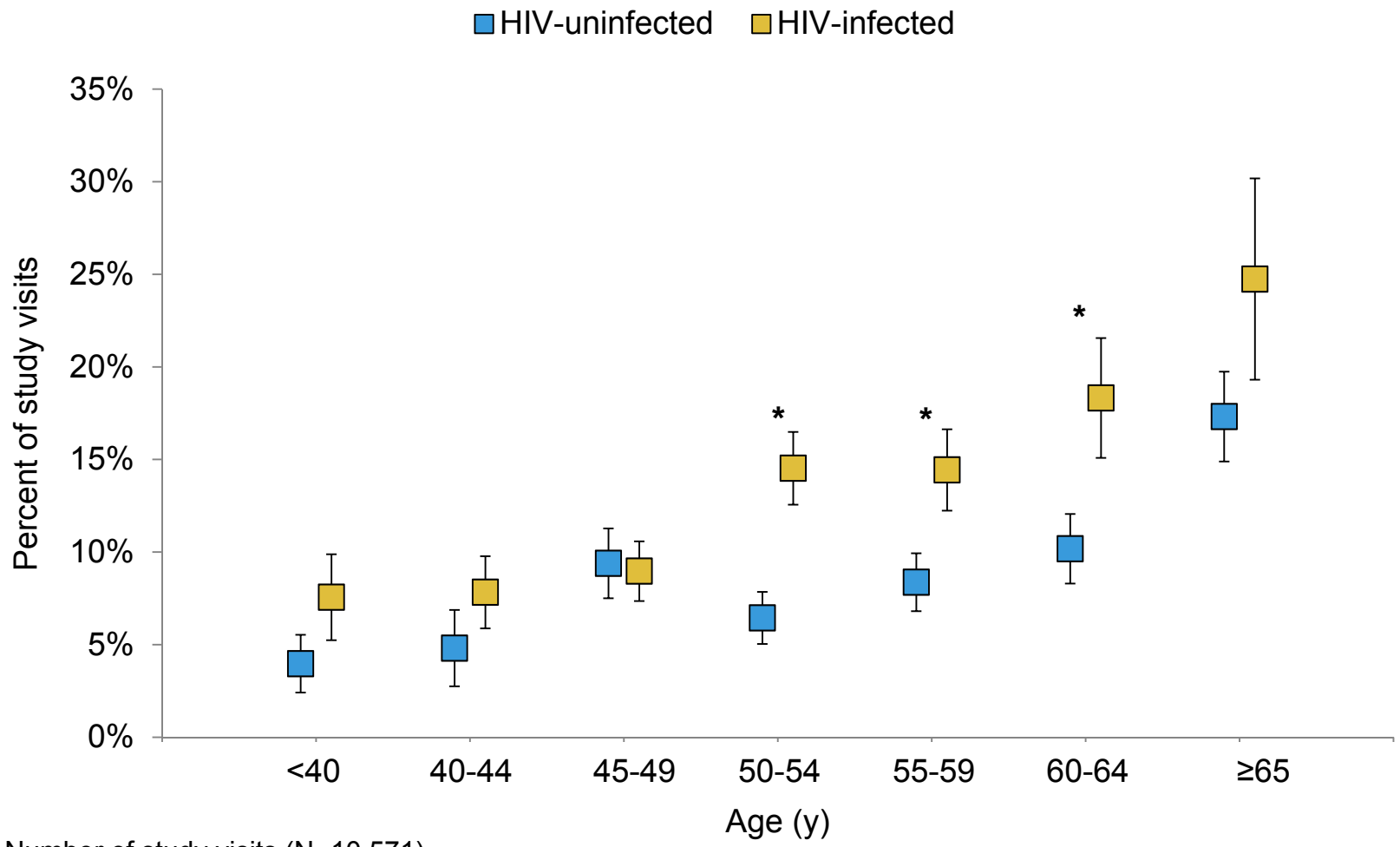
Prevalence or incidence?

- Due to the fluctuation, it did not seem as though we were truly capturing “incident” frailty phenotype expressions
  - Almost half the participant expressed FP at only 1 study visit
- Frailty phenotype expression has been shown to fluctuate in studies in the elderly, but not in 80% of the population
  - We were really measuring frailty as we know it in elderly populations?
- Decision: Report the following
  - The proportion of study visits where the FP was expressed, by age and HIV status
  - Correlates of conversion to the FP (FP- to FP+ at next completed visit)
  - Correlates of reversion from the FP (FP+ to FP- at the next completed visit)

Methods

- Outcomes (visit pairs)
  - Conversion: FP- → FP+
  - Reversion: FP+ → FP-
- Factors of interest
  - Time fixed
    - race/ethnicity, education, HIV status
  - Time varying, measured at first visit in visit pair
    - age, cigarette smoking, injection drug use, Hepatitis C infection, depressive symptoms, high blood pressure, diabetes, dyslipidemia, kidney disease, cancer (at, or within a year of study visit), CD4 count, HIV RNA, HAART use, history of a clinical AIDS diagnosis
- Logistic regression with repeated measures (GEE) to estimate odds ratios of conversion and reversion

Proportion of FP+ study visits



Number of study visits (N=10,571)							
HIV-uninfected:	579	395	841	1,102	1,111	904	797
HIV-infected:	463	677	1,104	1,081	859	464	194

Althoff KN, et al. J Gerontol A Biol Sci Med Sci. 2014;69(2):189-198.

Correlates of FP+ conversion (FP- to FP+)

Correlate	HIV+ and HIV- aOR (95%CI)	HIV+ only aOR (95%CI)
HIV+ (vs. HIV-)		
HIV+ no AIDS	**1.31 (1.05, 1.64)**	Ref
HIV+ with AIDS	**2.56 (1.75, 3.75)**	**1.57 (1.06, 2.34)**
Black (vs. White)	**1.87 (1.48, 2.36)**	1.31 (0.89, 1.91)
≥ College degree (vs. <)	**0.56 (0.45, 0.69)**	**0.60 (0.43, 0.84)**
Current cigarette smoking	**1.81 (1.46, 2.26)**	1.19 (0.86, 1.65)
Hepatitis C	**3.38 (2.44, 4.68)**	**1.48 (0.89, 2.47)**
Depressive symptoms	**2.83 (2.31, 3.47)**	**3.17 (2.35, 4.30)**
History of diabetes	**2.44 (1.84, 3.23)**	**1.87 (1.25, 2.80)**
Kidney disease	**2.36 (1.85, 3.01)**	**1.46 (1.02, 2.08)**

The model in the HIV+ and HIV- study population was adjusted for age, race/ethnicity, education, smoking, injection drug use, HIV and AIDS status, hepatitis C, depressive symptoms, diabetes, kidney disease, and completed number of study visits (max=8).
The model in the HIV+ only study population was adjusted for age, race/ethnicity, education, smoking, injection drug use, HIV and AIDS status, hepatitis C, depressive symptoms, diabetes, kidney disease, nadir CD4, current CD4, and completed number of study visits (max=8).

Althoff KN, et al. J Gerontol A Biol Sci Med Sci. 2014;69(2):189-198.

Correlates of FP+ reversion (FP+ to FP-)

Correlate	HIV+ and HIV- aOR (95%CI)	HIV+ only aOR (95%CI)
HIV+ (vs. HIV-) HIV+ no AIDS HIV+ with AIDS	 1.23 (0.81, 1.85) 0.82 (0.47, 1.46)	 Ref 0.68 (0.38, 1.20)
Black (vs. White)	1.37 (0.87, 2.14)	1.76 (1.00, 3.10)
Injection drug use	4.04 (0.99, 16.45)	2.98 (0.80, 11.70)
Kidney disease	**0.65 (045, 0.94)**	0.66 (0.41, 1.06)

Both the models in the HIV+ and HIV- study population and HIV+ only study population was adjusted for age, race/ethnicity, injection drug use, HIV and AIDS status, kidney disease, and completed number of study visits (max=8).

Althoff KN, et al. J Gerontol A Biol Sci Med Sci. 2014;69(2):189-198.

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PROPOSED MEASURES

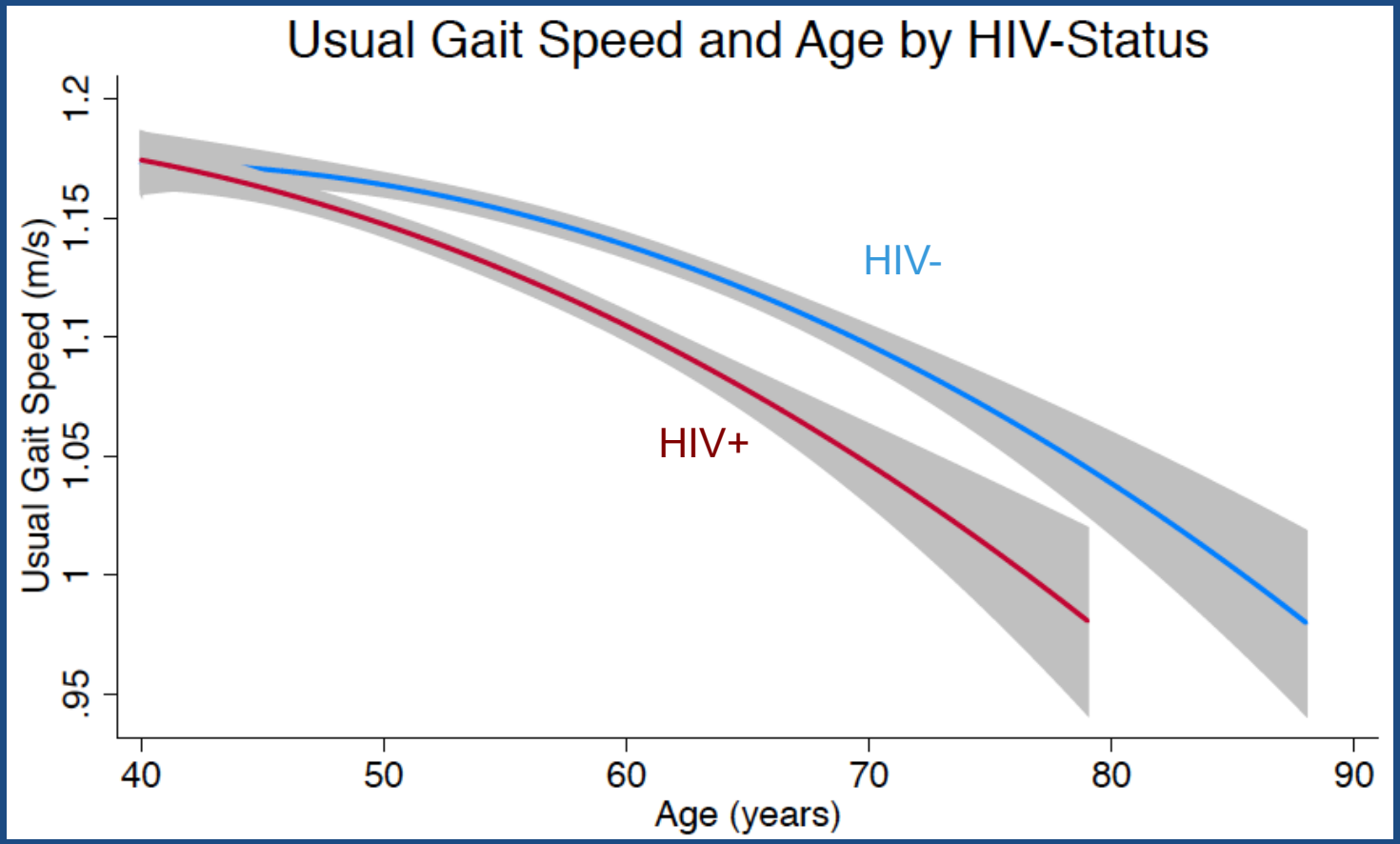
Grip Strength

TABLE 2. ASSOCIATIONS OF MARKERS OF IMMUNOSUPPRESSION WITH GRIP STRENGTH (KG) IN HIV-NEGATIVE AND HIV-POSITIVE WOMEN WITH HISTORY OF HAART ($N = 1639$)

	n	*Median strength (kg)*	*Age-adjusted univariate β (95% CI)*[a]	*Multivariate model 1*[b] *β (95% CI)*	*Multivariate model 2*[c] *β (95% CI)*
HIV-negative (Ref)	534	30			
$CD4^+$					
<100	78	28	−3.29 (−5.17-−1.42)*	2.75 (−4.61-−0.89)*	−1.53 (−3.56-0.49)
100–199	102	28	−1.48 (−3.17-0.20)	−0.86 (−2.56-0.84)	−0.83 (−2.67-1.01)
200–349	246	28	−1.23 (−2.43-−0.03)*	−0.52 (−1.74-0.69)	−0.16 (−1.45-1.13)
350–499	237	28	−1.06 (−2.27-0.15)	−0.11 (−1.35-1.13)	0.16 (−1.15-1.46)
≥500	425	30	−0.26 (−1.27-0.75)	0.22 (−0.81-1.25)	0.53 (−0.55-1.61)
AUC $CD4^{+d}$					
<100	135	26	−3.01 (−4.50-−1.52)*	−2.03 (−4.63-0.56)	−2.47 (−5.19-0.25)
100–199	239	28	−1.89 (−3.10-−0.68)*	−0.81 (−3.39-1.76)	−2.18 (−4.91-0.54)
200–349	370	29	−1.18 (−2.23-−0.13)*	−0.36 (−2.87-2.15)	−1.70 (−4.32-0.91)
350–499	239	30	0.03 (−1.17-1.23)	0.67 (−1.93-3.28)	−0.32 (−3.04-2.40)
≥500	106	30	−0.43 (−2.07-1.20)	−0.10 (−2.97-2.77)	−1.46 (−4.45-1.53)
$CD4^+/CD8^{+e}$					
≤0.29	234	28	−2.02 (−3.23-−0.80)*	−1.36 (−2.59-−0.13)*	−0.57 (−1.88-0.74)
0.30–0.46	216	28	−0.91 (−2.16-0.35)	<−0.01 (−1.27-1.26)	0.30 (−1.04-1.64)
0.47–0.63	223	28	−1.68 (−2.91-−0.45)*	−0.92 (−2.17-0.32)	−0.66 (−1.95-0.64)
0.64–0.93	212	28	−0.54 (−1.80-0.71)	0.16 (−1.11-1.42)	0.39 (−0.93-1.71)
≥0.94	202	30	0.41 (−0.86-1.69)	0.79 (−0.50-2.07)	1.19 (−0.16-2.53)
AIDS					
Yes	454	28	−1.94 (−2.96-−0.91)*	−1.25 (−2.31-−0.19)*	−0.51 (−1.64-0.63)
No	651	30	−0.51 (−1.42-0.39)	0.10 (−0.84-1.04)	0.33 (−0.65-1.31)

Terzian, et al. Journal of Women's Health, 2009.

Gait Speed



Adjusted hazard ratio of HIV+ vs. HIV- = 1.57 (1.27, 1.91)

Adjusted for age, weight, height, race, education, smoking, history of drug use, history of alcohol use, diabetes, kidney disease, liver disease, hypertension, arthritis, hepatitis B and C infections.

Schrack J, Althoff KN, et al. Submitted.

Balance (or perception of balance)

Table 3. Clinical Predictors of Falling Status in Older HIV-infected and HIV-uninfected Men

	Fallers		*Recurrent Fallers*	
	Multivariate OR (95% CI)	*p-value*	*Multivariate OR (95% CI)*	*p-value*
Balance Confidence				
ABC ≤80% vs. >80%	1.54 (0.78,3.04)	0.209	4.03 (1.79,9.06)	**0.001**
ABC ≤90% vs. >90%	2.1 (1.32,3.34)	**0.002**	2.82 (1.50,5.31)	**0.001**
ABC -6 ≤80% vs. >80%	2.24 (1.38,3.66)	**0.001**	2.67 (1.38,5.16)	**0.003**
ABC -6 ≤90% vs. >90%	1.69 (1.11,2.57)	**0.014**	1.96 (1.06,3.61)	**0.031**
Balance				
Completing standing balance, no vs. yes	1.26 (0.82,1.94)	0.30	0.83 (0.44,1.55)	0.56
Functional reach, per -1 SD (8 cm)	0.95 (0.74,1.22)	0.67	0.95 (0.67,1.35)	0.78
Strength				
Time to do 10 chair stands, per +1 SD (7 s)	1.13 (0.91,1.42)	0.27	1.08 (0.78,1.49)	0.65
Grip strength, per -1 SD (9 kg)	0.94 (0.75,1.18)	0.62	0.95 (0.67,1.33)	0.76
Speed				
Gait speed, per -1 SD (0.2 m/s)	1.1 (0.88,1.39)	0.40	1.26 (0.89,1.79)	0.19
Composite Physical Function				
SPPB ≤9 vs. >9	1.28 (0.52,3.15)	0.59	2.03 (0.62,6.65)	0.24
SPPB ≤10 vs. >10	1 (0.53,1.89)	0.99	1.62 (0.68,3.83)	0.27

Adjusted for age, race, study visit site, education, BMI, and HIV status.

Brown TT,… Althoff KN. Abstract #786. 23rd CROI, 2015.

VACS Index

- VACS Index to predict 5-year mortality
  - Age
  - HIV RNA
  - CD4
  - Hepatitis C
  - Hemoglobin
  - FIB-4 (liver)
  - eGFR (renal)
- VACS Index correlates with functional performance

(Erlandson KM, et al. HIV Clin Trials 2012;13:324-34.)

Appendix 1: List of variables used by the Canadian Study of Health and Aging to construct the 70-item CSHA Frailty Index

- Changes in everyday activities
- Head and neck problems
- Poor muscle tone in neck
- Bradykinesia, facial
- Problems getting dressed
- Problems with bathing
- Problems carrying out personal grooming
- Urinary incontinence
- Toileting problems
- Bulk difficulties
- Rectal problems
- Gastrointestinal problems
- Problems cooking
- Sucking problems
- Problems going out alone
- Impaired mobility
- Musculoskeletal problems
- Bradykinesia of the limbs
- Poor muscle tone in limbs
- Poor limb coordination
- Poor coordination, trunk
- Poor standing posture
- Irregular gait pattern
- Falls
- Mood problems
- Feeling sad, blue, depressed
- History of depressed mood
- Tiredness all the time
- Depression (clinical impression)
- Sleep changes
- Restlessness
- Memory changes
- Short-term memory impairment
- Long-term memory impairment
- Changes in general mental functioning
- Onset of cognitive symptoms
- Clouding or delirium
- Paranoid features
- History relevant to cognitive impairment or loss
- Family history relevant to cognitive impairment or loss
- Impaired vibration
- Tremor at rest
- Postural tremor
- Intention tremor
- History of Parkinson's disease
- Family history of degenerative disease
- Seizures, partial complex
- Seizures, generalized
- Syncope or blackouts
- Headache
- Cerebrovascular problems
- History of stroke
- History of diabetes mellitus
- Arterial hypertension
- Peripheral pulses
- Cardiac problems
- Myocardial infarction
- Arrhythmia
- Congestive heart failure
- Lung problems
- Respiratory problems
- History of thyroid disease
- Thyroid problems
- Skin problems
- Malignant disease
- Breast problems
- Abdominal problems
- Presence of snout reflex
- Presence of the palmomental reflex
- Other medical history

Rockwood K, et al. CMAJ, 2005.

Other measures

Proposed tests to investigate frailty and HIV in large cohorts

Operational Definition	Domains	Objective Data In HIV	Proposed Test
Frailty Index	Deficits	VACS Index	VACS Index
Frailty phenotype	Weakness	Grip strength Chair stands	Chair stands
	Weight loss	Muscle mass Sarcopenic obesity	DEXA
	Exhaustion	VO2peak	6-MWD
	Slowness	Short distance walk	
	Low activity	Accelerometer	Accelerometer

Oursler, KA. HIV & Aging: from Mitochondrial to Metropolis. Atlanta, GA, 2014.
Erlandson, et al. Curr HIV/AIDS Rep, 2014.

Summary

- Frailty studies are increasing in number among HIV+ adults
  - Prevalence estimates vary
  - Frailty has been associated with hospitalizations and death
  - HIV+ adults seem to be at higher risk for frailty as compared to similar HIV- adults
- Numerous challenges to the measurement and interpretation of frailty in HIV+ adults
  - Frailty has not been validated in a younger or HIV+ population
  - The expression of the frailty phenotype fluctuates
- Recommendations for future research include measures of physical function and the VACS Index

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